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).

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 pravastatin 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. 

RESEARCH DESIGN AND METHODS

Study population and design. Fifty-one hypercholesterolemic patients (LDL cholesterol levels $\geq$130 mg/dL) participated in this study. We excluded patients with overt liver disease, chronic renal failure, uncontrolled diabetes (HbA1c $>$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 hypertensive, 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 RIA bead II; SRL, Inc, Tokyo, Japan) and assays for HbA1c 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 difference of ≥1.7% in FMD between baseline and pravastatin, with α = 0.05 based on previous studies (9). The comparison of endothelium-dependent vasodilation 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/dL (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 = 0.002), 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 2A 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 2B 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 2C and Table 1). The three therapies did not significantly change fasting glucose or HbA1c 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 = 0.379; 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 significant 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.

| Variables                                      | Diastolic BP | Systolic BP | hsCRP (mg/L) | Lipids (mg/dL) | Glucose (mg/dL) | Insulin (µU/ml) | QUICKI | ADP (µM) |
|------------------------------------------------|--------------|-------------|--------------|----------------|-----------------|-----------------|--------|----------|
| Diabetic Retinopathy                           |              |             |              |                |                 |                 |        |          |
| Diabetic Nephropathy                            |              |             |              |                |                 |                 |        |          |
| Diabetic Neuropathy                             |              |             |              |                |                 |                 |        |          |
| Total Cholesterol                              |              |             |              |                |                 |                 |        |          |
| HDL Cholesterol                                |              |             |              |                |                 |                 |        |          |
| Triglycerides                                  |              |             |              |                |                 |                 |        |          |
| Apolipoprotein A1                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein B                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein A                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein E                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein D                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein C                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein H                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein I                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein K                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein M                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein N                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein O                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein P                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein Q                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein R                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein S                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein T                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein U                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein V                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein W                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein X                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein Y                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein Z                                |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AA                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AB                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AC                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AD                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AE                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AF                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AG                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AH                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AI                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AJ                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AK                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AL                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AM                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AN                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AO                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AP                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AQ                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AR                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AS                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AT                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AU                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AW                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AX                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AY                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AZ                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AA                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AB                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AC                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AD                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AE                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AF                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AG                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AH                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AI                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AJ                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AK                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AL                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AM                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AN                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AO                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AP                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AQ                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AR                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AS                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AT                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AU                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AW                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AX                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AY                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AZ                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AA                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AB                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AC                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AD                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AE                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AF                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AG                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AH                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AI                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AJ                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AK                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AL                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AM                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AN                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AO                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AP                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AQ                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AR                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AS                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AT                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AU                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AW                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AX                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AY                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AZ                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AA                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AB                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AC                               |              |             |              |                |                 |                 |        |          |
| Apolipoprotein AD                               |              |             |              |                |                 |                 |        |          |
TABLE 2
Effects of pravastatin, combination, and valsartan in 23 hypercholesterolemic patients with metabolic syndrome

| Variables               | Pravastatin (P) | Pravastin plus valsartan (C) | Valsartan (V) | ANOVA | P/C | C/V | P/V |
|-------------------------|-----------------|------------------------------|---------------|-------|-----|-----|-----|
| Age (years)             | 58 ± 2          | 27.29 ± 0.58                 | 27.29 ± 0.58  | 0.649 |     |     |     |
| Sex (male/female)       | 12/11           | 81 ± 2                       | 78 ± 2        | 0.963 |     |     |     |
| BMI (kg/m²)             | 27.33 ± 0.56    | 27.12 ± 0.56                 | 27.29 ± 0.58  |       |     |     |     |
| Heart rate              | 81 ± 2          | 80 ± 2                       | 78 ± 2        | 0.05  |     |     |     |
| Systolic BP             | 130 ± 3         | 134 ± 3*                     | 136 ± 4       | 0.124 |     |     |     |
| Diastolic BP            | 87 ± 2          | 84 ± 2*                      | 84 ± 2        | 0.528 |     |     |     |
| Lipids (mg/dL)          | 243 ± 9         | 194 ± 7‡                     | 236 ± 9       | 0.001 |     |     |     |
| Total cholesterol       | 100 ± 14        | 160 ± 19                     | 190 ± 20      | 0.231 |     |     |     |
| Triglycerides           | 49 ± 3          | 49 ± 2                       | 51 ± 3        | 0.589 |     |     |     |
| LDL cholesterol         | 110 ± 6‡        | 108 ± 5‡                     | 108 ± 5‡      |       |     |     |     |
| Apolipoprotein B        | 97 ± 4‡         | 96 ± 3‡                      | 122 ± 4       |       |     |     |     |
| HDL cholesterol         | 51 ± 2          | 49 ± 2                       | 49 ± 2        | 0.389 |     |     |     |
| Apolipoprotein A1       | 144 ± 4         | 143 ± 4                      | 144 ± 4       | 0.006 |     |     |     |
| FMD dilation (%)        | 5.86 ± 0.37     | 7.70 ± 0.36‡                 | 5.85 ± 0.33   | <0.05 |     |     |     |
| NTG dilation (%)        | 17.47 ± 0.65    | 18.23 ± 0.88                 | 17.74 ± 0.71  | 0.05  |     |     |     |
| Inflammation            |                 |                              |               |       |     |     |     |
| hsCRP (mg/L)            | 1.00 (0.60–1.90) | 0.60 (0.50–1.30)‡ | 1.10 (0.70–1.80) | NS    |     |     |     |
| Insulin resistance      | 2.73 (1.81–6.38) | 2.91 (2.25–6.29) | 2.64 (1.78–5.44) |       |     |     |     |
| ADP (µg/mL)             | 11.4 (6.3–17.5) | 9.6 (8.3–16.0)               | 10.7 (6.3–16.2) | 0.065 |     |     |     |
| Glucose (mg/dL)         | 106 ± 2         | 107 ± 2                      | 106 ± 2       | 0.751 |     |     |     |
| QUICKI                  | 0.33 (0.31–0.35) | 0.33 (0.31–0.35) | 0.33 (0.31–0.35) |     |     |     |     |
| HbA1c [% (mmol/mol)]    | 5.86 ± 0.09     | 5.97 ± 0.11                  | 5.97 ± 0.12   | 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). P, 0.05, ‡P < 0.001, +P < 0.01 for comparison with each baseline value.
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.
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., D.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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