Vascular and Metabolic Effects of Combined Therapy With Ramipril and Simvastatin in Patients With Type 2 Diabetes

Kwang Kon Koh, Michael J. Quon, Seung Hwan Han, Jeong Yeal Ahn, Dong Kyu Jin, Hyung Sik Kim, Dae Sung Kim, Eak Kyun Shin

Abstract—Mechanisms underlying biological effects of statin and angiotensin-converting enzyme inhibitor therapies differ. Therefore, we compared vascular and metabolic responses to these therapies either alone or in combination in patients with type 2 diabetes. This was a randomized, double-blind, placebo-controlled crossover trial with 3 treatment arms (each 2 months) and 2 washout periods (each 2 months). Fifty patients with type 2 diabetes were given simvastatin 20 mg and placebo, simvastatin 20 mg and ramipril 10 mg, or ramipril 10 mg and placebo daily during each 2-month treatment period. Ramipril alone or combined therapy significantly reduced blood pressure when compared with simvastatin alone. When compared with ramipril alone, simvastatin alone or combined therapy significantly improved the lipoprotein profile. All 3 treatment arms significantly improved flow-mediated dilator response to hyperemia and reduced plasma levels of malondialdehyde relative to baseline measurements. However, these parameters were changed to a greater extent with combined therapy when compared with simvastatin or ramipril alone (P<0.001 by ANOVA). When compared with simvastatin or ramipril alone, combined therapy significantly reduced high-sensitivity C-reactive protein levels (P=0.004 by ANOVA). Interestingly, combined therapy or ramipril alone significantly increased plasma adiponectin levels and insulin sensitivity relative to baseline measurements. These changes were significantly greater than in the group treated with simvastatin alone (P<0.015 by ANOVA). Ramipril combined with simvastatin had beneficial vascular and metabolic effects when compared with monotherapy in patients with type 2 diabetes.

Key Words: angiotensin-converting enzyme ■ diabetes mellitus ■ endothelium ■ insulin resistance ■ statins

Hypcholesterolemia and type 2 diabetes are major public health problems that are frequently treated with statins and angiotensin-converting enzyme inhibitors. Although the mechanisms of action for these 2 classes of drugs differ, both classes of agents have been shown to reduce the rate of major cardiovascular events in patients with diabetes. The mechanisms of the benefit may relate, in part, to the ability of these therapies to reduce insulin resistance and endothelial dysfunction. However, studies with simvastatin and atorvastatin suggest that statins may worsen insulin resistance.

Inhibition of the production of superoxide anions may limit oxidation of low-density lipoprotein (LDL) and contribute to increased nitric oxide (NO) bioactivity by limiting oxidative degradation of NO. Statins improve endothelial function via stimulation of NO synthase activity and mediate antioxidant effects that result in enhanced NO bioactivity. angiotensin-converting enzyme inhibition also improves endothelial function. This may be caused, in part, by diminished intracellular production of superoxide anions via reduced activity of angiotensin II-dependent oxidases.

The endothelial dysfunction associated with diabetes is characterized by impaired NO release from endothelium. 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. In humans, plasma levels of adiponectin are negatively correlated with adiposity and decreased plasma adiponectin levels are observed in patients with type 2 diabetes. Thus, decreased levels of adiponectin may play a key role in the development of insulin resistance. In addition, adiponectin also possesses anti-atherogenic properties.

Because the impact of simvastatin and ramipril therapies on NO bioactivity, oxidant stress, inflammation, endothelial function, and insulin resistance may differ, we hypothesized that combined therapy may have additive beneficial effects that are greater than those observed with either simvastatin or ramipril therapy alone in hypercholesterolemic patients with type 2 diabetes.
TABLE 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variables</th>
<th>N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (M:F)</td>
<td>59±1</td>
</tr>
<tr>
<td>Sex (F:M)</td>
<td>30:20</td>
</tr>
<tr>
<td>BMI</td>
<td>25.5±0.4</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>13 (26)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>31 (62)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>38 (76)</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>β-Adrenergic blockers</td>
<td>25 (50)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>28 (56)</td>
</tr>
<tr>
<td>Long-acting nitrates</td>
<td>33 (66)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>34 (68)</td>
</tr>
</tbody>
</table>

Values are expressed as means±SEM or no. (%).

Methods

Study Population and Design

Fifty-three hypercholesterolemic patients with type 2 diabetes (LDL cholesterol levels >100 mg/dL) participated in this study. The diagnosis of diabetes was based on a history of diabetes or criteria according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.15 Patients with angina were in Canadian Cardiovascular Society class I or II. We excluded patients with severe hypertension (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥120 mm Hg), unstable angina, or acute myocardial infarction. No patient had taken any cholesterol-lowering agent, hormone replacement therapy, or anti-oxidant vitamin supplements during the preceding 2 months. Blood pressure was measured from the right arm in the sitting position, using a standard sphygmomanometer, and was recorded as the mean of 2 successive readings with the subject having sat for at least 10 minutes. To minimize acute side effects to ramipril, study medication was titrated from 5 to 10 mg upwards over a 2-week period unless hypotension (systolic blood pressure <100 mm Hg) was noted. At the end of this time, participants were receiving either placebo or ramipril 10 mg per day. Fifty among 53 patients tolerated ramipril 10 mg with regard to maintaining systolic blood pressure >100 mm Hg for 3 hours after drug administration, and experienced no adverse effects from therapy. Three patients had dry cough and withdrew from the study. Thus, data were analyzed from a total of 50 patients. The clinical characteristics of these patients are summarized in Table 1. Data from some participants have been reported previously.16

Patients were randomly assigned to one of the 3 initial treatment arms: simvastatin 20 mg and placebo, simvastatin 20 mg combined with ramipril 10 mg, or ramipril 10 mg and placebo daily during 2 months. This study design was randomized, double-blind, placebo-controlled, with 3 treatment arms (each 2 months), and crossover with 2 washout periods (each 2 months). The patients were seen at 8:00 AM after 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, plasma malondialdehyde (MDA), and adiponectin were performed in duplicate by enzyme-linked immunosorbent assay (INSULIN-RIABEAD II; Abbott Japan, 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 μU/mL and glucose in mg/dL): QUICKI=1/[log(insulin)+log(glucose)].18

Laboratory Assays

Blood samples for laboratory assays were obtained at ~8:00 AM after 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, plasma malondialdehyde (MDA), and adiponectin were performed in duplicate by enzyme-linked immunosorbent assay (BIOXYTECH LPO-586; OxiRes Search, Portland, Ore; and R & D Systems, Inc, Minneapolis, Minn), and assays for high-sensitivity C-reactive protein (hsCRP) levels by latex agglutination (CRP-Latex II; Denka-Seiken, Tokyo, Japan) as previously described.8,17 Assays for plasma insulin levels were performed in duplicates by immunoradiometric assay (INSULIN-RIABEAD II; Abbott Japan, 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 μU/mL and glucose in mg/dL): QUICKI=1/[log(insulin)+log(glucose)].18

Vascular Studies

Imaging studies of the right brachial artery were performed using an ATL HDI 3000 ultrasound machine equipped with a 10-MHz linear array transducer, based on a previously published technique.8,17,19

Statistical Analysis

Data are expressed as mean±SEM or median (range, 25% to 75%). After testing data for normality, we used Student paired t or Wilcoxon Signed Rank test to compare values before and after each treatment, as reported in Table 2. The effects of the 3 therapies were analyzed by 1-way repeated measures ANOVA or Friedman repeated ANOVA on ranks by comparing the relative changes in values in response to treatment. 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 difference of absolute increase, 2.1% or greater flow-mediated dilatation of the brachial artery between baseline and simvastatin, with α=0.05 based on our previous studies.19 The comparison of endothelium-dependent dilatation among the 3 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 2). To rule out the possibility of a carryover effect from one treatment period to the next treatment period, 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

Resting heart rate was similar after each treatment. Ramipril alone or combined therapy significantly reduced systolic and diastolic blood pressure after 2 months administration compared with baseline. These reductions were significantly greater than that observed with simvastatin alone (P=0.003 and P=0.040 by ANOVA, respectively). Simvastatin alone or combined therapy significantly lowered total cholesterol (both P<0.001), triglycerides (both P<0.001), LDL cholesterol (both P<0.001), and apolipoprotein B levels (both P<0.001) compared with baseline. These reductions were significantly greater than those observed with ramipril alone (P<0.001 by ANOVA). However, there were no significant differences between simvastatin alone and combined therapy for these parameters (Table 2).

Effects of Therapies on Vasomotor Function and Malondialdehyde

Simvastatin, combined therapy, or ramipril significantly improved the percent flow-mediated dilator response to hyper-
TABLE 2. Effects of Simvastatin, Combined Therapy, and Ramipril on Endothelial Function, Adiponectin Levels, and Insulin Resistance in 50 Patients With Type 2 Diabetes

<table>
<thead>
<tr>
<th>Variables</th>
<th>Simvastatin ($)</th>
<th>Simvastatin + Ramipril ($)</th>
<th>Ramipril ($)</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 1</td>
<td>Treatment</td>
<td>Baseline 2</td>
<td>Treatment</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>73±2</td>
<td>72±1</td>
<td>75±2</td>
<td>74±2</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>134±2</td>
<td>135±2</td>
<td>135±2</td>
<td>124±2‡</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>80±1</td>
<td>80±2</td>
<td>80±1</td>
<td>75±2‡</td>
</tr>
<tr>
<td>Lipids, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>229±6</td>
<td>163±5‡</td>
<td>227±6</td>
<td>163±5‡</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>236±25</td>
<td>174±14</td>
<td>231±17</td>
<td>167±14</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>135±6</td>
<td>80±5§</td>
<td>134±5</td>
<td>83±4‡</td>
</tr>
<tr>
<td>ApoB</td>
<td>124±4</td>
<td>85±3‡</td>
<td>127±4</td>
<td>85±3‡</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>46±2</td>
<td>45±2</td>
<td>47±1</td>
<td>47±2</td>
</tr>
<tr>
<td>ApoA-I</td>
<td>147±3</td>
<td>151±3</td>
<td>150±4</td>
<td>152±4</td>
</tr>
<tr>
<td>Vasomotor, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMD dilation, %</td>
<td>4.10±0.16</td>
<td>5.84±0.20‡</td>
<td>4.12±0.18</td>
<td>6.83±0.21‡</td>
</tr>
<tr>
<td>NTG dilation, %</td>
<td>12.67±0.69</td>
<td>13.03±0.62</td>
<td>13.19±0.53</td>
<td>13.36±0.56</td>
</tr>
<tr>
<td>MDA, µmol</td>
<td>0.85±0.41</td>
<td>0.72±0.31‡</td>
<td>0.83±0.36</td>
<td>0.60±0.31‡</td>
</tr>
<tr>
<td>Inflammation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>1.10 (0.60–2.90)</td>
<td>0.85 (0.40–2.00)</td>
<td>1.60 (0.60–3.50)</td>
<td>0.75 (0.40–1.30‡)</td>
</tr>
</tbody>
</table>
| Adiponectin levels relative to baseline measurements by 47±5%, 74±6%, and 36±4%, respectively (all P<0.001); however, combined therapy significantly improved this response more than simvastatin or ramipril alone (P<0.001 by ANOVA; Table 2). The brachial artery dilator response to nitroglycerin was similar for all therapies and was not significantly changed from respective baseline values. Simvastatin, combined therapy, or ramipril significantly decreased the plasma MDA levels relative to baseline measurements by 10±4% (P<0.001), 26±3% (P<0.001), and 7±3% (P=0.017), respectively; however, combined therapy significantly reduced MDA levels more than simvastatin or ramipril alone (P<0.001 by ANOVA; Figure 1; Table 2).

Effects of Therapies on Markers of Inflammation

Simvastatin or ramipril did not significantly change plasma hsCRP levels relative to baseline measurements from 1.10 to 0.85 (P=0.138) and 1.30 to 1.00 mg/L (P=0.690), respectively; however, combined therapy significantly lowered plasma hsCRP levels relative to baseline measurements from 1.60 to 0.75 (P<0.0001). The magnitude of these decreases with combined therapy were significantly more than with simvastatin or ramipril alone (P=0.004 by ANOVA; Figure 1; Table 2).

Effects of Therapies on Adiponectin and Insulin Resistance

There were significant inverse correlations between baseline adiponectin levels and baseline triglyceride levels (r=−0.422, P=0.002 before simvastatin; r=−0.320, P=0.024 before combined therapy; r=−0.319, P=0.024 before ramipril). There were significant correlations between baseline adiponectin levels and baseline high-density lipoprotein cholesterol levels (r=0.274, P=0.054 before simvastatin; r=0.446, P=0.001 before combined therapy; r=0.383, P=0.006 before ramipril).

Simvastatin alone did not significantly change the plasma adiponectin levels relative to baseline measurements from 3.75 to 3.71 (P=0.247). Meanwhile, combined therapy or ramipril alone significantly increased the plasma adiponectin levels relative to baseline measurements from 3.82 to 4.25 (P=0.004) and 3.83 to 4.61 (P=0.003), respectively. These increases were significantly greater than those observed with simvastatin alone (P=0.013 by ANOVA; Figure 2; Table 2). The 3 therapies did not have significantly different baseline insulin and glucose levels. Simvastatin, combined therapy, and ramipril alone did not significantly change insulin levels relative to baseline measurements (29±11% [P=0.261], 1±13% [P=0.130], and 2±8% [P=0.116], respectively). Combined therapy or ramipril alone significantly increased QUICKI relative to baseline measurements by 5±2% (P=0.030) and 3±1% (P=0.045), respectively, whereas simvastatin alone did not. Of interest, these increases were significantly greater than those observed with simvastatin alone (P=0.015 by ANOVA; Figure 2; Table 2). After combined therapy, there were significant correlations between the percent changes in adiponectin and insulin levels

Data are expressed as mean±SEM or median (25th percentile to 75th percentile). There were no significant differences among each baseline values. ADP indicates adiponectin; C/R, combined therapy vs ramipril; S/C, simvastatin vs combined therapy; S/R, simvastatin vs ramipril. Quantitative Insulin-Sensitivity Check Index (QUICKI)=1/{log(insulin)+log(glucose)}18.
($r = -0.402$ and $P = 0.004$) or QUICKI ($r = 0.374$ and $P = 0.008$) and after ramipril alone therapy, there were significant correlations between the percent changes in adiponectin and insulin levels ($r = -0.510$ and $P < 0.001$) or QUICKI ($r = 0.407$ and $P = 0.003$).

We investigated whether ramipril-induced 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 ($r = -0.201$ and $P = 0.276$) or between these changes and reduction of diastolic blood pressure ($r = -0.245$ and $P = 0.266$). After combined therapy, there were significant inverse correlations between the percent changes in flow-mediated dilation and MDA levels ($r = -0.384$ and $P = 0.006$).

### Discussion

In our previous publication with 45 patients, we did not measure hsCRP and only reported the lipoprotein changes and vasomotion. Now we provide the final data from 50 patients with hsCRP, MDA levels, and blood pressure changes. Importantly, we provide additional metabolic characterization by assessing circulating levels of adiponectin, insulin, and glucose as well as QUICKI, a surrogate index of insulin sensitivity. In the present study, we focused on these new metabolic and inflammatory findings that are complementary to our previous report. The effects of statins on insulin sensitivity are controversial. Simvastatin and atorvastatin improve insulin sensitivity in patients with type 2 diabetes; however, others have reported that simvastatin worsens insulin sensitivity in patients. Simvastatin significantly increases serum insulin levels, whereas a modified Mediterranean-type diet counteracts this effect of simvastatin. High-dose statins may increase, rather than decrease, the onset of new diabetes. Atorvastatin 80 mg was associated with a statistically significant increase in the risk for HbA1c $>6\%$ both in non-diabetic subjects (adjusted hazard ratio [HR] 1.78) and in diabetic subjects (adjusted HR 2.36). The pooled adjusted HR was 1.84 ($P < 0.0001$).

We reasoned that distinct biological actions of simvastatin and ramipril therapies on lipoproteins and the angiotensin system may improve endothelium-dependent vascular function by different mechanisms. Whereas monotherapy with simvastatin or ramipril significantly improved endothelial function (assessed by flow-mediated dilation and MDA levels), combined therapy had additional substantial and significant beneficial effects on these parameters over those seen with monotherapy for either drug, which may provide one physiological mechanism to explain the observations of a recent clinical trial, although combined therapy had no additional substantial and significant beneficial effects on metabolic effects over ramipril alone. Simvastatin did not significantly reduce hsCRP levels in the current study. It may be that our sample size was not large enough or the dose was not large enough.
The additional beneficial effects of combined simvastatin/ramipril therapy we observed may be the result of several interacting mechanisms. For example, angiotensin II is very potent endogenous vasoconstrictor, whereas LDL induces upregulation of the angiotensin II type 1 (AT$_1$) receptor.\textsuperscript{22} Hypercholesterolemic rabbits display enhanced vascular expression of AT$_1$ receptors that mediate increased activity of angiotensin II.\textsuperscript{23} Furthermore, the effect of statins to reverse the elevated blood pressure response to angiotensin II infusion is accompanied by downregulated AT$_1$ receptor density.\textsuperscript{24} Angiotensin II promotes superoxide anion generation and endothelial dysfunction.\textsuperscript{17,25} CRP upregulates AT$_1$ receptors in vascular smooth muscle cells and these effects are attenuated by losartan.\textsuperscript{26} In the current study, we observed that combined therapy significantly reduced plasma MDA and hsCRP levels more than monotherapy. We observed significant inverse correlations between the percent changes in flow-mediated dilation and MDA levels after combined therapy. The additive beneficial effects of combined therapy in the present study are consistent with previous experimental and clinical studies.\textsuperscript{21,27}

Ramipril therapy alone resulted in significant elevation of adiponectin levels and increased insulin sensitivity. QUICKI is a reliable surrogate index for insulin sensitivity that has an especially excellent correlation with the reference standard glucose clamp method in insulin resistant subjects with type 2 diabetes, obesity, or hypertension $(r=0.9$ in subjects with these diseases).\textsuperscript{18,28} In addition, test characteristics of QUICKI including coefficient of variation (CV=0.05) and discriminant ratio are significantly better than other simple surrogate indexes and comparable to those of the glucose clamp.\textsuperscript{29} QUICKI can appropriately follow changes in insulin sensitivity after various therapeutic interventions when compared directly with glucose clamp results.\textsuperscript{30} Moreover, a large meta-analysis of insulin resistant subjects demonstrated that QUICKI is among the best surrogate indexes in terms of predictive power for the onset of diabetes.\textsuperscript{31}

The present study is the first report demonstrating that ramipril therapy can increase adiponectin levels. Increasing adiponectin levels is 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 both adiponectin and insulin to stimulate production of NO.\textsuperscript{14} Thus, improvements in endothelial function may increase insulin sensitivity, whereas increased insulin sensitivity may improve endothelial function.\textsuperscript{11} Interestingly, in contrast to effects of combination therapy on flow-mediated dilation, MDA, and hsCRP, the beneficial effects of ramipril therapy on adiponectin levels, insulin levels, and insulin sensitivity did not increase further with combination therapy. This suggests that improving endothelial function per se (as reflected by flow-mediated dilation) may not completely explain effects of ramipril or combined therapy to improve insulin sensitivity. In this regard, angiotensin II receptor cross-talk with insulin signaling pathway may cause insulin resistance.\textsuperscript{1} In addition, there may be direct effects of ramipril on glucose insulin-stimulated glucose uptake or promotion of adipogenic differentiation of preadipocytes.\textsuperscript{32} Angiotensin II inhibits adipogenic differentiation of human adipocytes via the AT$_1$ receptor\textsuperscript{33} and that expression of angiotensin II-forming enzymes in adipose tissue is inversely correlated with insulin sensitivity.\textsuperscript{34} Effects of ramipril or combined therapy to increase adiponectin levels may mediate, in part, improved insulin sensitivity as supported by the significant correlation we observed in the present study. However, combined therapy may reduce insulin resistance by multiple mechanisms such as lipoprotein changes and reduced oxidant stress that improve NO bioavailability.

**Perspectives**

Impaired endothelial vasodilation and insulin resistance are associated with increased cardiovascular event rates. Furthermore, endothelial dysfunction and increased vascular oxidative stress, inflammation, and insulin resistance predict the risk of cardiovascular event rates in patients with coronary artery disease. Statins may worsen insulin resistance, whereas ramipril improves insulin resistance by increasing adiponectin levels. Importantly, we observed that ramipril combined with simvastatin improved endothelial function as reflected by improved flow-mediated dilation, reduced oxidant stress, and decreased inflammatory markers. In addition, reductions in insulin resistance were accompanied by increased adiponectin levels. Accordingly, combined therapy is predicted to be more effective in reducing the rate of cardiovascular events than either simvastatin or ramipril alone in patients with type 2 diabetes.

**Acknowledgments**

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