Comparison of the Effects of *Ramipril* Versus *Telmisartan* in Reducing Serum Levels of High-Sensitivity C-Reactive Protein and Oxidized Low-Density Lipoprotein Cholesterol in Patients With Type 2 Diabetes Mellitus

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The effect of ramipril (an angiotensin [AT]-converting enzyme inhibitor), telmisartan (an AT-II type 1 receptor blocker), or their combination on inflammation and lipid peroxidation was assessed in 37 patients with type 2 diabetes who were free of coronary artery disease. All regimens were associated with a significant reduction of C-reactive protein and oxidized low-density lipoprotein cholesterol serum levels ($p < 0.001$). These results further enlighten the mechanisms underlying the cardiovascular beneficial effect of renin-AT system inhibition.

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Agents that inhibit the renin–angiotensin (AT) system (RAS), such as AT-converting enzyme (ACE) inhibitors and AT-II type 1 receptor blockers, have a well-established beneficial role in the treatment of patents with diabetes, hypertension, and congestive heart failure.[1–3] Moreover, because several studies have shown that AT-II has a high level of atherogenic potency by promoting vasoconstriction, inflammation, oxidative stress, thrombosis, and plaque rupture,[4–6] a potential antiatherogenic effect of RAS inhibition has been implicated.[7,8] However, direct comparisons between these 2 drug categories regarding their biologic or clinical effects against atherosclerosis have been scarce. Thus, we conducted a clinical trial to assess and compare the antioxidant and anti-inflammatory effects of ramipril (an ACE inhibitor) and telmisartan (an AT-II type 1 receptor blocker) in a group of diabetic patients without overt atherosclerosis.

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Forty patients (17 men and 23 women) with type 2 diabetes mellitus were enrolled in this study. Their baseline characteristics are listed in Table 1. No patient had a history of hypertension, myocardial infarction, angina, or congestive heart failure. Additional exclusion criteria included renal impairment, presence of microalbuminuria (urinary albumin excretion rate >20 μg/min), systolic blood pressure >150 mm Hg, diastolic blood pressure >90 mm Hg, glycosylated hemoglobin $>8\%$, and positive exercise stress test results (Bruce protocol). No subject had taken either ACE inhibitors or AT-II type 1 receptor blockers for ≥ 6 months before beginning the study. The local research ethics committee approved the protocol, and all subjects gave written informed consent.

TABLE 1 Baseline Characteristics of Study Patients (n = 37)

Characteristic	Value
Age (yrs)	55 ± 14.6
Men/women	17/20
Body mass index (kg/m^2)	27.7 ± 0.5
Waist-to-hip ratio	0.91 ± 0.1
Duration of diabetes (yrs)	8.5 ± 0.8
Drug-controlled diabetes	70%
Insulin treatment	14%
Smokers	22%
Systolic blood pressure (mm Hg)	126 ± 14
Diastolic blood pressure (mm Hg)	77 ± 4

Values are expressed as number of patients (percentage) or mean ± SD.

This study was designed as a randomized, open-label, crossover trial. The patients began randomly receiving ramipril 2.5 mg/day or telmisartan 40 mg/day or their combination for 3 months. Subsequently, they were randomly crossed over to the alternative treatment. A 2-week washout period was allowed between treatments. A detailed medical history was taken and a complete physical examination performed at baseline. A clinical follow-up visit was performed each month. Blood draws for biochemistry measurements were done at baseline and at the end of each treatment period (i.e., at 3, 6, and 9 months). Total cholesterol, triglycerides, and high-density lipoprotein cholesterol were measured using conventional enzymatic methods (Roche Diagnostics GmbH, Mannheim, Germany). Low-density lipoprotein (LDL) cholesterol levels were calculated according to the Friedwald formula. Apolipoprotein A-I, apolipoprotein B-100, and lipoprotein(a) were assessed with

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TABLE 2 Variable Changes With Various Treatments

Variable	Baseline (n = 37)	Ramipril (n = 37)	Telmisartan (n = 37)	Telmisartan + Ramipril (n = 37)	p Value
Systolic blood pressure (mm Hg)	125.6 ± 14.1	125.6 ± 10.3	125.2 ± 10.2	122.4 ± 10.8	0.77
Diastolic blood pressure (mm Hg)	77.2 ± 3.7	76.2 ± 3.2	78.4 ± 3.6	76.6 ± 5.2	0.16
Glucose (mg/dl)	148.3 ± 10.1	152.5 ± 11.4	151.2 ± 8.6	149.1 ± 9.6	0.54
Glycosylated hemglobin A1 (%)	6.9 ± 0.8	7.1 ± 0.7	7 ± 0.5	7 ± 0.4	0.48
Cholesterol (mg/dl)	212.3 ± 30.2	214.6 ± 31.5	214 ± 34.3	216 ± 23.1	0.77
Triglycerides (mg/dl)	140.7 ± 77.1	144.6 ± 54	159.4 ± 80	149.9 ± 54.1	0.22
LDL cholesterol (mg/dl)	135.4 ± 26.4	136.6 ± 24.6	130.4 ± 33.8	137.7 ± 20.4	0.30
HDL cholesterol (mg/dl)	49.5 ± 19.5	49.3 ± 15.5	48.8 ± 11.9	48.5 ± 11	0.30
Apolipoprotein A-I (mg/dl)	162.8 ± 28.9	159.8 ± 24.2	157.4 ± 23.7	151.4 ± 19.2	0.003
Apolipoprotein B-100 (mg/dl)	111.2 ± 27.3	104.2 ± 19.3	106.9 ± 22.2	109.2 ± 17	0.53
Lipoprotein(a) (mg/dl)	12 ± 17.1	12.2 ± 19.1	10.3 ± 14	11.3 ± 15.5	0.13
C-reactive protein (mg/L)	0.21 ± 0.15	0.16 ± 0.15	0.13 ± 0.10	0.12 ± 0.10	<0.001
Oxidized LDL cholesterol (mg/dl)	11.7 ± 4.2	8.5 ± 3.3	9.5 ± 3.3	7.8 ± 2.5	<0.001

Values are expressed as number of patients (percentage) or mean ± SD.
p Values are derived from the analysis of variance.
HDL = high-density lipoprotein.

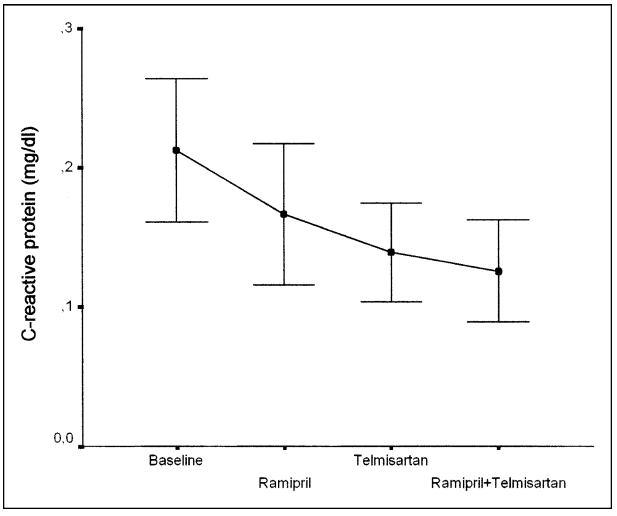

FIGURE 1. Change in C-reactive protein serum levels after treatment with ramipril, telmisartan, or their combination (mean ± 95% confidence intervals of the mean).

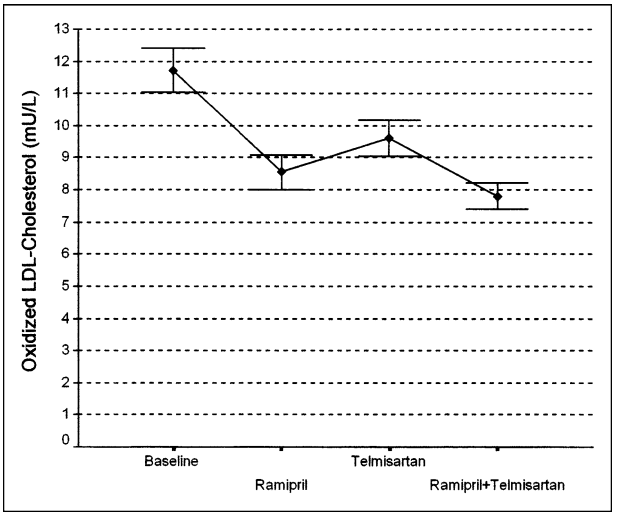

FIGURE 2. Change of oxidized LDL cholesterol serum levels after treatment with ramipril, telmisartan, or their combination (mean ± 95% confidence intervals of the mean).

nephelometry (Dade Behring Holding GmbH, Marburg, Germany). Plasma glucose was measured with the glucose oxidase method (Roche Diagnostics GmbH). Glycosylated hemoglobin A1 was assessed by high-resolution liquid chromatography (A. Menarini Diagnostics, Florence, Italy). High-sensitivity C-reactive protein plasma levels were assessed using a Dade Behring Prospec nephelometric analyzer (Dade Behring Holding GmbH). Circulating levels of oxidized LDL cholesterol were used as an index of lipid peroxidation. The serum titer was measured using a commercially available enzyme-linked immunosorbent assay kit (Mercodia AB, Uppsala, Sweden).

Statistical analysis was performed using the SPSS 10.0 statistical package for Windows (SPSS, Inc., Chicago, Illinois). Data are presented as mean ± SD for continuous variables and as the proportion of patients with a characteristic for categorical variables. All variables were tested for normality using Lilliefors's test. Comparisons among groups were performed with 1-sample, repeated-measures analysis of variance for variables with normal distribution and with Friedman's test for variables without normal distribution. Moreover, for variables demonstrating a significant difference among groups in the analysis of variance, Student's *t* test or Wilcoxon's paired test was used to perform paired comparisons between baseline and each treatment group and among treatment groups. A p value of <0.05 was considered statistically significant.

A significant decrease in systolic blood pressure (>10 mm Hg) associated with dizziness was noted in 2 patients, who did not complete the study and were excluded from the subsequent analysis. Three patients experienced cough with ramipril (7.5%), 1 of whom discontinued as well. The remaining 37 patients completed the study without significant adverse effects. No reduction in blood pressure was noted with

ramipril or telmisartan in the study population. An insignificant decrease of 3.2 ± 3.3 mm Hg in systolic blood pressure was noted with combination therapy. Lipid profile parameters did not change with treatments. The only exception was a significant reduction (7%) of apolipoprotein A-I levels associated with the combined intake of ramipril and telmisartan in comparison with baseline values ($p = 0.018$). All treatments were associated with a significant decrease in C-reactive protein and oxidized LDL cholesterol serum levels (Table 2; Figures 1 and 2). More specifically, compared with baseline, a 24% reduction in C-reactive protein levels was noted with ramipril ($p = 0.012$), a 38% reduction was noted with telmisartan ($p < 0.001$), and a 43% reduction was associated with their combination ($p < 0.001$). Similarly, compared with baseline, oxidized LDL cholesterol levels were reduced by 27% with ramipril ($p < 0.001$), by 19% with telmisartan ($p = 0.008$), and by 33% with their combination ($p < 0.001$). No significant differences were noted among treatments regarding their effect on C-reactive protein or oxidized LDL cholesterol level.

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The findings of our study demonstrate that ramipril and telmisartan are equally effective in suppressing inflammation and LDL cholesterol oxidation in patients with type 2 diabetes. Several in vitro and preclinical data[9,10] suggest that ACE inhibitors and AT-II type 1 receptor blockers protect vasculature from inflammation and oxidative stress by inhibiting the AT-II–mediated stimulation of inflammatory cell functions, such as the promotion of oxidative stress by a nicotinamide adenine dinucleotide or nicotinamide adenine dinucleotide phosphate membrane-bound, oxidase-dependent mechanism and the overexpression of inflammatory adhesion molecules, chemokines, and cytokines. In vivo data regarding the antioxidant and anti-inflammatory effects of RAS inhibition have been scarce. Nevertheless, the results of the few trials published thus far are mostly in agreement with ours.[11–15] Most of these studies included patients with established coronary artery disease, whereas our asymptomatic diabetic patients probably represent a population at high risk but in an earlier stage of the atherosclerotic process. From that point of view, our findings offer some new insight suggesting that the same antioxidant and anti-inflammatory mechanisms underlie the beneficial effect of RAS inhibition in the primary and secondary prevention of atherosclerosis.

A major limitation of our study is the lack of a placebo control treatment arm. However, the crossover design of the trial combined with no lifestyle (dietary, smoking, exercise, etc.) or conventional treatment changes during follow-up make the presence of a confounding factor associated with the observed differences unlikely. This is further supported by the finding of no major changes in the patients' glucose and lipid profiles (Table 2) throughout the study, with the exception of a reduction in apolipoprotein A-I levels associated with the combination treatment. Whether this unfavorable change has any pathophysiologic significance or represents just an incidental finding remains elusive. Another limitation is the small population size, which may have obscured a difference in the antioxidant and anti-inflammatory effect between the 2 drugs. However, the insignificant decrease in blood pressure with the 2 drugs should not be surprising, considering that our population consisted of nonhypertensive subjects, and the doses were small. In a large-scale trial that included hypertensive and nonhypertensive patients, the administration of ramipril 10 mg had a similar minor effect on blood pressure levels.[7]

In conclusion, our study further supports the hypothesis that RAS inhibition by either ramipril or telmisartan suppresses inflammatory and lipid peroxidation markers in nonhypertensive diabetic patients. Major ongoing clinical trials[16] testing these drugs' effects on cardiovascular morbidity and mortality in a high-risk population are expected to further elucidate the issue of the vascular benefits offered by RAS inhibition.

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