Low-Dose Ramipril Reduces Microalbuminuria in Type 1 Diabetic Patients Without Hypertension

Results of a randomized controlled trial

The ATLANTIS Study Group

OBJECTIVE — To assess if low (1.25 mg) and/or standard (5 mg) doses of the ACE inhibitor ramipril could prevent progression of microalbuminuria (incipient diabetic nephropathy) in normotensive type 1 diabetic patients.

RESEARCH DESIGN AND METHODS — This study, using a multicenter randomized placebo-controlled double-blind parallel group, was conducted over 2 years in 28 outpatient diabetic clinics in the U.K. and Ireland. We screened 334 type 1 diabetic patients with suspected microalbuminuria and normal blood pressure; of these, 140 patients 18–65 years of age with a diagnosis of type 1 diabetes and persistent microalbuminuria, defined as urinary albumin excretion rate (AER) of 20–200 µg/min, were enrolled in the study.

RESULTS — The proportion of patients progressing to macroalbuminuria was reduced in the ramipril groups but did not reach statistical significance over 2 years. AER was significantly lower at year 2 in the combined ramipril-treated patients versus placebo (P = 0.013). More patients on ramipril regressed to normoalbuminuria (<20 µg/min), with 11% for 1.25 mg ramipril, 20% for 5 mg ramipril, and 4% for placebo (P = 0.053). Blood pressure was significantly reduced to a similar extent with both 1.25 and 5 mg ramipril. Supine systolic blood pressure increased from 130 to 134 mmHg in the placebo group and fell in the 1.25 mg ramipril group (from 132 to 129 mmHg) and in the 5 mg ramipril group (from 134 to 130 mmHg) (P = 0.003, compared with placebo). No statistically significant changes were observed in glomerular filtration rate (GFR) between the placebo- and ramipril-treated groups during the 2-year period.

CONCLUSIONS — Microalbuminuria is reduced significantly by ramipril treatment in type 1 diabetic patients without hypertension. Although the magnitude of the response was greater, there is no significant difference between responses to 1.25 or 5 mg ramipril. Small but highly significant reductions in systolic and mean arterial pressures occur in ramipril-treated patients. GFR is stable at this stage of the evolution of diabetic nephropathy and is unaffected by ramipril treatment for 2 years.

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Abbreviations: AER, albumin excretion rate; ANCOVA, analysis of covariance; ATLANTIS, Ace-Inhibitor Trial to Lower Albuminuria in Normotensive Insulin-Dependent Subjects; DCCT, Diabetes Control and Complications Trial; GFR, glomerular filtration rate; ITT, intention to treat; PP, per-protocol.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
Low-dose ramipril reduces microalbuminuria

(25,26) and Stornello et al. (27) have however claimed in small studies that low doses of ACE inhibitors can reduce microalbuminuria without apparent changes in blood pressure.

The ATLANTIS (Ace-Inhibitor Trial to Lower Albuminuria in Normotensive Insulin-Dependent Subjects) Study aimed to test the hypothesis that 2 years of treatment with low (1.25 mg) or standard (5 mg) doses of ramipril, as compared with placebo, would slow the progression from microalbuminuria to clinical diabetic nephropathy in normotensive type 1 diabetic patients.

Figure 1—The trial profile.
RESEARCH DESIGN AND METHODS — We carried out a placebo-controlled double-blind parallel group study in 28 outpatient diabetic clinics in the U.K. and Ireland. The primary efficacy variable was progression of AER from microalbuminuria (AER 20–200 µg/min) to macroalbuminuria (AER >200 µg/min). Secondary efficacy variables were progression to normoalbuminuria (AER <20 µg/min) as well as changes of AER, serum creatinine, GFR (plasma iohexol clearance), and blood pressure (supine, standing, and mean) from baseline.

Patients were seen at baseline and monthly intervals for blood pressure (supine and erect), blood samples, and two overnight timed urine collections for AER. Blood pressure was measured by the study nurses taking phase 1 and phase 2 Korokhoff sounds to the nearest 2 mm and a mean of two readings using a Hawksley random zero sphygmomanometer in the patients’ diabetes centers. At the sixth monthly visit, plasma iohexol clearance studies were performed as a measurement for GFR. Before the iohexol injection, patients had blood glucose tests to exclude hypoglycemia. A small dose of the radio contrast agent iohexol was injected after taking baseline samples, and the clearance was calculated over a 4-h period by measuring the plasma concentration (with high-performance liquid chromatography) and using a two-compartment model on samples taken at 0, 45, 180, 210, and 240 min. This method has been shown to compare favorably with radioactive chromium EDTA measurement of GFR (28). Blood and urine samples were sent to a centralized laboratory (West Middlesex, U.K.). Urine albumin was measured by the particl-enhanced immunoturbometric method using the Technicon RA systems (method ID-2478-F91). The coefficient of variation for this assay at a level of 120 mg/dl was 2.5%. HbA1c was measured by chromatography (Abbott IMX). The normal range for the assay is 4.0–6.5%.

Table 1—Baseline demographic and clinical characteristics of 134 type 1 diabetic patients in the three study groups

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ramipril 1.25 mg</th>
<th>Ramipril 5 mg</th>
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<tbody>
<tr>
<td>Men</td>
<td>46 (87)</td>
<td>44 (70)</td>
<td>44 (55)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40 ± 12 (19–64)</td>
<td>40 ± 11 (18–62)</td>
<td>40 ± 13 (21–65)</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>23 ± 12 (0.5–55)</td>
<td>20 ± 9 (2–37)</td>
<td>18 ± 12 (2–49)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79 ± 13 (50–108)</td>
<td>77 ± 15 (46–112)</td>
<td>78 ± 16 (52–123)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174 ± 10 (149–193)</td>
<td>171 ± 9 (158–187)</td>
<td>170 ± 10 (154–187)</td>
</tr>
<tr>
<td>Supine systolic BP (mmHg)</td>
<td>130 ± 11 (108–160)</td>
<td>132 ± 13 (95–160)</td>
<td>134 ± 16 (100–160)</td>
</tr>
<tr>
<td>Supine diastolic BP (mmHg)</td>
<td>76 ± 8 (60–92)</td>
<td>76 ± 10 (55–95)</td>
<td>77 ± 8 (60–90)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>10.7 ± 2.4 (7.1–17.3)</td>
<td>11.3 ± 2.2 (6.7–16.5)</td>
<td>12.1 ± 2.5 (6.5–19.9)</td>
</tr>
<tr>
<td>AER (µg/min)</td>
<td>10.7 ± 2.4 (7.1–17.3)</td>
<td>11.3 ± 2.2 (6.7–16.5)</td>
<td>12.1 ± 2.5 (6.5–19.9)</td>
</tr>
<tr>
<td>GFR (iohexol) (ml/min)</td>
<td>100 ± 23 (61–173)</td>
<td>104 ± 26 (41–147)</td>
<td>109 ± 29 (33–191)</td>
</tr>
</tbody>
</table>

Data are n (%), means ± SD (range), or geometric mean (range). BP, blood pressure.

Subjects
The study comprised an open-placebo screening phase of 4 weeks followed by a 2-year double-blind phase. Patients were eligible for randomization to active (1.25 or 5 mg ramipril once a day) or placebo treatment if they met the following inclusion criteria: type 1 diabetes; microalbuminuria, defined as overnight AER on screening of 20–200 µg/min in two of three collections; and untreated blood pressure <150/90 mmHg for patients <50 years of age and <165/90 mmHg for patients 50–65 years of age. (This pragmatic definition of hypertension followed guidelines prevalent at the time of the study design [21].)

A total of 334 potential patients with an albumin-to-creatinine ratio >3.0 or positive Micral test were screened formally for microalbuminuria between 1992 and 1995. Of these, 141 patients were found to have an AER <20 µg/min; 30 had an AER of >200 µg/min. Twenty-three patients declined further screening.

Individuals excluded from study consideration were those who were pregnant or lactating; were women of child-bearing potential and not using adequate contraception; were on concomitant therapy for hypertension; were on one or more nonsteroidal anti-inflammatory drugs; had a history of drug or alcohol abuse; had other known renal diseases or raised creatinine levels (>120 µmol/l) or liver function twice that of normal on repeat testing; or had iodine sensitivity, making them unable to partake in GFR measurements.

A sequence of subject numbers was assigned to each study center, and the study medication was randomly assigned to the participant numbers in advance by Hoechst Marion Rousell on a 1:1:1 basis. Participants who, after consenting to the study, decided not to take part before administration of the first dose of study medication, and those who discontinued or were withdrawn from the study during the treatment or double-blind phase, all kept their numbers. The next study subject enrolled was given the next number. The randomization schedule was stored with the Drug Safety Department and with the Clinical Trial Supplies Department of Hoechst Marion Rousell in a set of sealed envelopes. Investigators received an identical set of envelopes for each participant number, each containing information on the study medication; the envelopes were only to be opened under circumstances when it was medically imperative to know what the subject was receiving. All envelopes were collected intact by the sponsor at the end of the study.

The treatment was packed in presealed white plastic childproof pots (one of which was dispensed at each visit). Each contained the number of capsules required for the 12-week intervisit interval plus an additional 2 weeks’ supply (98 capsules total).

Persistent microalbuminuria was present in 140 patients; these patients were randomized as follows: 48 to placebo, 47 to Placebo

<table>
<thead>
<tr>
<th>n</th>
<th>Patients who progressed</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>46</td>
<td>5 (10.9)</td>
</tr>
<tr>
<td>Ramipril 1.25 mg</td>
<td>44</td>
<td>2 (4.5)</td>
</tr>
<tr>
<td>Ramipril 5 mg</td>
<td>44</td>
<td>4 (9.1)</td>
</tr>
</tbody>
</table>

Data are n (%), unless otherwise indicated. *P* = 0.42 (placebo vs. pooled active treatment groups).
1.25 mg ramipril, and 45 to 5 mg ramipril. After randomization, six of these participants were withdrawn either as protocol violators or because of adverse events that took place before first measurements. A total of 134 (46 on placebo, 44 on 1.25 mg ramipril, and 44 on 5 mg ramipril) were actually entered into the study and available for an intention-to-treat (ITT) analysis (Fig. 1).

Diabetic neuropathy, defined as sensory loss or dysthesia, and retinopathy, defined as the presence of microvascular lesions, were determined at baseline by clinical examination and ophthalmoscopy; they were equally present between groups. No systematic attempt was made to follow the progression of retinopathy or neuropathy during the course of the study. Approximately 19% of each group had retinopathy, and 6% had neuropathy.

Statistical analysis
Based on previous reports (5,6,8,18) at the time of the study design, a 30% progression from micro- to macroalbuminuria in the placebo group and a 5% progression in the 1.25 and 5 mg ramipril groups was assumed. To detect a clinically relevant difference between the placebo and 1.25 mg ramipril groups and between the placebo and 5 mg ramipril groups with 80% power and \( \alpha = 0.025 \) (two-tailed), a total of 120 patients were calculated to be required. The study was not powered to directly contrast the 1.25 and 5 mg groups. An initial recruitment target of 162 was based on a 25% anticipated withdrawal rate; after the study began, however, only 140 were available for randomization.

The statistical methods of analysis included the Mantel-Haenszel test on pooled centers and analysis of covariance (ANCOVA). Wilcoxon's rank-sum test was performed for individual comparisons of single-treatment group versus placebo group where appropriate and based on ANCOVA. Both an ITT analysis, with the last observation carried forward, and a per-protocol (PP) analysis, including only those patients with complete 2-year follow up, were performed.

Ethics
Permission was obtained from local district ethics committees, and all individuals screened gave written informed consent. The trial was carried out according to the principles set forth in the Declaration of Helsinki and conformed to the standards of the Good Clinical Practice Guidelines of the European Union.
RESULTS — There were no significant differences in age or weight between groups, but significant differences in sex and height were found, largely due to female overrepresentation in the 5 mg ramipril treatment group (Table 1). Overall mean duration of diabetes was 20.3 years (range 6 months to 59 years). Of the study participants, 37 (77%) completed 2 years on placebo, 33 (70%) completed 2 years on 1.25 mg ramipril, and 28 (62.2%) completed 2 years on 5 mg ramipril. A total of 42 patients withdrew: 11 from the placebo group, 14 from the 1.25 mg ramipril group, and 17 from the 5 mg ramipril group (Fig. 1). Adverse events led to 21 of these withdrawals, but only 5 were related to ramipril treatment. The adverse events included five progressions to hypertension; 21 patients withdrew for personal reasons, or their clinicians opted for treatment with ACE inhibitors. Compliance by tablet count was high, with 93% on placebo, 90% on 1.25 mg ramipril, and 95% on 5 mg ramipril.

The baseline median AERs were similar in the three groups (50–59 µg/min) (Table 1), and the percentage progression of AER to macroalbuminuria in the placebo group was 11%. The proportion of patients progressing to macroalbuminuria within 2 years was reduced in the ramipril-treated groups (6 of 88 [7%] in 1.25 and 5 mg ramipril groups vs. 5 of 46 placebo [11%]) but did not reach statistical significance (Table 2).

On the basis of the ITT analysis with the last observation carried forward, there was a significant difference in AER from baseline at 2 years in the placebo group, increasing from 54 to 70 µg/min; however, the ramipril groups decreased from 49 to 36 µg/min on 1.25 mg and from 45 to 38 µg/min on 5 mg (P = 0.032). Albumin excretion rose steadily in the placebo-treated group but fell significantly after 6 months in the 1.25 and 5 mg ramipril groups and was sustained over the subsequent 18 months (Fig. 2). Because of the effect of subject withdrawal on a PP analysis, however, statistical significance at 2 years was reduced (e.g., placebo vs. pooled ramipril, P = 0.053).

More patients on ramipril regressed to an AER <20 µg/min (macroalbuminuria), defined strictly as three of the last four consecutive AERs; 4% did so for placebo, 11% for 1.25 mg ramipril, and 20% for 5 mg ramipril (P = 0.053) (Table 3).

Baseline GFR was performed on 114 subjects; 101 (37 placebo, 32 1.25 mg ramipril, and 32 5 mg ramipril) had repeat determinations. GFR (corrected for age, sex, and baseline GFR) did not change significantly with ramipril treatment or between groups (Fig. 2) on either ITT or PP analysis.

Mean blood pressure at baseline was 130/76 mmHg for the placebo group, 132/76 mmHg for the 1.25 mg ramipril group, and 134/77 mmHg for the 5 mg ramipril group and was not significantly different between the groups (Table 1). Both groups on ramipril showed a highly significant difference at 2 years in supine systolic blood pressure on ITT (P = 0.018) and PP (P = 0.016) analyses. Placebo rose from 130 mmHg at baseline to 134 mmHg; those on 1.25 mg ramipril experienced falls from 132 to 129 mmHg (P = 0.003) and those on 5 mg ramipril from 134 to 130 mmHg (Table 4). There was no significant change in diastolic blood pressure (Table 5).

Glycemic control was similar for the three groups, with HbA1c (means ± SD) of 10.7 ± 2.4% for the placebo group, 11.3 ± 2.2% for the 1.25 mg ramipril group, and 12.1 ± 2.5% for the 5 mg ramipril group. There was a small but statistically significant decline in the HbA1c in the 5 mg ramipril group (P < 0.01) (Fig. 2).

There was no significant difference in the reporting of adverse events between groups. There were a similar number of reported cardiovascular adverse events in the placebo group (17%) as opposed to the 1.25 (17%) and 5 mg (18%) ramipril groups. There were five deaths over the course of the trial, all in the ramipril groups, but none were considered to be directly related to the treatment.

There were four episodes of myocardial infarction (one in placebo, two in 1.25 mg ramipril, and one in 5 mg ramipril) and eight episodes of chest pain/angina (five in placebo, three in 1.25 mg ramipril, and one in 5 mg ramipril).

CONCLUSIONS — We have shown that the ACE inhibitor ramipril, at low and standard doses, lowers urinary AER progression significantly and restores normoalbuminuria more often than placebo in type 1 diabetic patients with microalbuminuria and without arterial hypertension.

We were unable to demonstrate a significant difference in progression to macroalbuminuria, probably because of the slower- than-expected progression rate of the placebo-treated group. Previous studies (19,24,25), on which our study was based, had higher thresholds for the definition of hypertension and higher baseline AERs. The progression of microalbuminuria in our placebo-treated group was not dissimilar to the published data from the Capptori Collaborative Study (20,23), which was 14%, or in the Euclid Study (21), which was 13%.

It was assumed (25,26) that a low dose of 1.25 mg ramipril would have minimal or no effect on systemic blood pressure and allow an assessment in humans of the effect of ACE inhibition that was independent of any associated antihypertensive action. In fact, the effect of both doses of ramipril on mean and systolic blood pressure in type 1 diabetic patients with microalbuminuria, although small at ∼4–5 mmHg, was highly

Table 3—Number and percentage of patients who regressed to normoalbuminuria, defined as AER <20 µg/min, sustained for at least three of four consecutive visits during the study

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Patients who regressed</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>46</td>
<td>2 (4.3)</td>
<td>0.6–15.5%</td>
</tr>
<tr>
<td>Ramipril 1.25 mg</td>
<td>44</td>
<td>5 (11.4)</td>
<td>3.8–24.6%</td>
</tr>
<tr>
<td>Ramipril 5 mg</td>
<td>44</td>
<td>9 (20.5)</td>
<td>9.8–35.3%</td>
</tr>
</tbody>
</table>

Data are n (%), unless otherwise indicated. P = 0.053 (placebo vs. pooled active treatment groups).

Table 4—Supine systolic blood pressure (mmHg) at baseline and at 2 years in the three treatment groups

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Baseline†</th>
<th>Year 2‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>46</td>
<td>130 ± 11 (108–160)</td>
<td>134 ± 15 (100–190)</td>
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<tr>
<td>Ramipril 1.25 mg</td>
<td>44</td>
<td>132 ± 13 (95–160)</td>
<td>129 ± 14 (110–166)</td>
</tr>
<tr>
<td>Ramipril 5 mg</td>
<td>44</td>
<td>134 ± 16 (100–160)</td>
<td>127 ± 18 (100–160)</td>
</tr>
</tbody>
</table>

Data are means ± SD (range). †P = 0.41 between groups; ‡P = 0.018 between groups.
Low-dose ramipril reduces microalbuminuria

Table 5—Supine diastolic blood pressure (mmHg) at baseline and at 2 years in the three treatment groups

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Baseline*</th>
<th>Year 2†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>46</td>
<td>76 ± 8 (60–92)</td>
<td>79 ± 10 (53–98)</td>
</tr>
<tr>
<td>Ramipril 1.25 mg</td>
<td>44</td>
<td>76 ± 10 (55–95)</td>
<td>74 ± 9 (52–90)</td>
</tr>
<tr>
<td>Ramipril 5 mg</td>
<td>44</td>
<td>77 ± 8 (60–90)</td>
<td>77 ± 10 (60–100)</td>
</tr>
</tbody>
</table>

Data are means ± SD (range). *P = 0.89 between groups; †P = 0.08 between groups.

significant. There was no statistically significant difference between the 1.25- and 5-mg doses in this effect. This study therefore fails to confirm in this group of patients previous reports (25) that low-dose ramipril has no systemic blood pressure–lowering effect.

Conventional statistical significance (P < 0.05) for the reduction in AER was seen only for the 5 mg ramipril group and was significant when data from both ramipril-treated groups are compared with the placebo data. The effect on AER could be directly related to the arresting of the blood pressure rise observed in the placebo-treated patients. There are claims that ACE inhibitors in humans have an effect to reduce proteinuria that is independent of their effect in lowering systemic blood pressure. Such claims are based on studies in which the blood pressure–lowering effects of ACE inhibitors are compared with those of other antihypertensive drugs (22,27,29) or the ACE inhibitor is added to an existing antihypertensive regime (11,12,15). The results of these studies are difficult to interpret because the groups treated with ACE inhibitors had significantly lower blood pressure (29) or the numbers and methodology used in measuring blood pressure cannot exclude an additional blood pressure–lowering effect. No large study has formally tested a low dose of an ACE inhibitor in humans that is effective in lowering systemic blood pressure. Thus, there remains the question of which dose to use to commence treatment. Previous studies have used high doses of ACE inhibitors, such as 50 mg twice a day of captopril (20,23) or 20 mg of lisinopril (21), but our results suggest that the low dose of ramipril (1.25 mg) provides both blood pressure– and microalbuminuria–lowering effects. It seems prudent to recommend in these patients that treatment should commence with a low dose of ACE inhibitor and be titrated if there is progression in systolic blood pressure or further increases in AER. Such a strategy should prove to be rational and more cost-effective for health care budgets.

Acknowledgments — This study was sponsored by Hoechst Marion Roussel (Aventis), who provided £500 per year per patient to support research costs.

APPENDIX

The ATLANTIS Study Group


References