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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It is estimated that 30–40% of type 1 diabetic patients will develop clinical diabetic nephropathy (1,2). Incipient diabetic nephropathy can be identified in those individuals with early signs of albumin leakage or microalbuminuria, defined as an albumin excretion rate (AER) of 30–300 mg in 24 h or of 20–200 µg/min in a timed overnight sample. Microalbuminuria identifies a subgroup of type 1 diabetic patients with a high probability of developing the full manifestations of diabetic nephropathy (3–6). Microalbuminuria is a marker for not only nephropathy, but patients with this complication have a very high risk of cardiovascular disease as well (7).

The ability to detect patients at risk of developing clinical nephropathy provides the possibility of developing therapies that may arrest, or slow down, its progression. Several studies (8–10) and, most notably, the Diabetes Control and Complications Trial (DCCT) (10) have suggested that strict glycemic control prevents the development of microalbuminuria and may slow progression (9,10). In clinical practice, the diabetic patients most at risk may well be those in whom efforts to tighten glycemic control in the past have proven unsuccessful and therefore need additional strategies.

Blood pressure is an important modifiable risk factor for the progression of renal disease; to that effect, ACE inhibitors have been shown to slow glomerular filtration rate (GFR) decline in patients with proteinuria of both diabetic and nondiabetic origin (11,12) and to prevent glomerular sclerosis in animal models (13,14).

Clinical studies in humans have shown that converting enzyme inhibition may reduce the proteinuria of established diabetic nephropathy (15–17). Most of these studies claimed a specific effect on the reduction of proteinuria and have, at the same time, reduced blood pressure (18,19). Some small studies (17,18) have compared ACE inhibitors with β-blockers and have claimed that, despite similar blood pressure reduction, ACE inhibitors produced a greater reduction in proteinuria.

Other studies using high doses of ACE inhibitors in normotensive patients with microalbuminuria (20–24) have demonstrated that progression of microalbuminuria (and thus nephropathy) has been postponed. In these studies, there was a significant reduction in blood pressure even though the groups studied were usually described as normotensive. Marre et al.

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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.

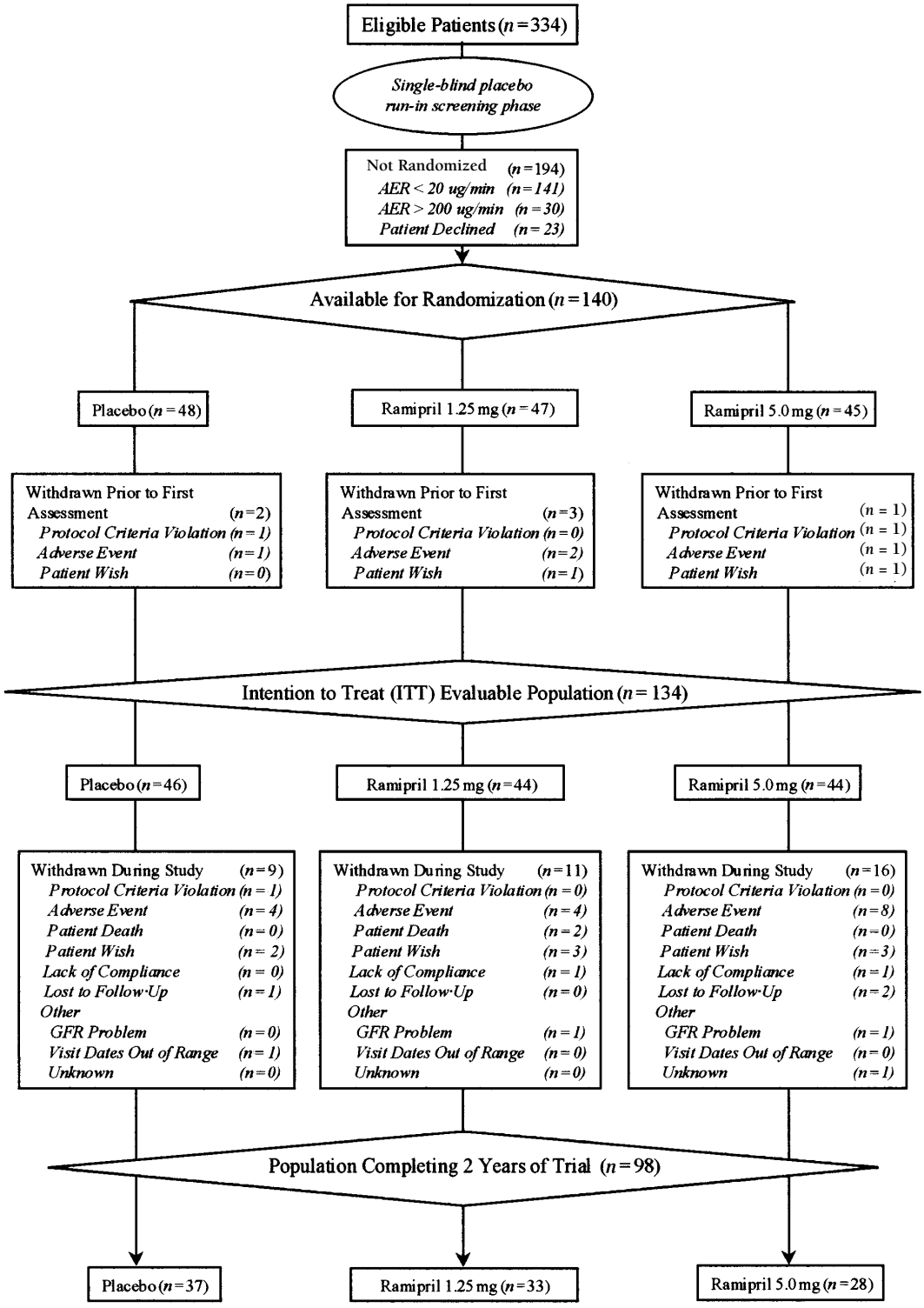

Figure 1—*The trial profile.*

(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.

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

	Placebo	Ramipril 1.25 mg	Ramipril 5 mg
Men	46 (87)	44 (70)	44 (55)
Age (years)	40 ± 12 (19–64)	40 ± 11 (18–62)	40 ± 13 (21–65)
Duration of diabetes (years)	23 ± 12 (0.5–55)	20 ± 9 (2–37)	18 ± 12 (2–49)
Weight (kg)	79 ± 13 (50–108)	77 ± 15 (46–112)	78 ± 16 (52–123)
Height (cm)	174 ± 10 (149–193)	171 ± 9 (158–187)	170 ± 10 (154–187)
Supine systolic BP (mmHg)	130 ± 11 (108–160)	132 ± 13 (95–160)	134 ± 16 (100–160)
Supine diastolic BP (mmHg)	76 ± 8 (60–92)	76 ± 10 (55–95)	77 ± 8 (60–90)
HbA_{1c} (%)	10.7 ± 2.4 (7.1–17.3)	11.3 ± 2.2 (6.7–16.5)	12.1 ± 2.5 (6.5–19.9)
AER (μg/min)	59 (22–182)	50 (18–168)	50 (22–174)
GFR (iohexol) (ml/min)	100 ± 23 (61–173)	104 ± 26 (41–147)	109 ± 29 (33–191)

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

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 regression 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 I and phase V Korotkoff 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 particle-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%. HbA_{1c} was measured by chromatography (Abbot IMX). The normal range for the assay is 4.0–6.5%.

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

Table 2—*Number and percentage of patients who progressed to macroalbuminuria, defined as AER >200 μg/min at two consecutive visits during the study*

	n	Patients who progessed	95% CI
Placebo	46	5 (10.9)	3.6–23.6%
Ramipril 1.25 mg	44	2 (4.5)	0.6–15.5%
Ramipril 5 mg	44	4 (9.1)	2.5–21.7%

Data are *n* (%), unless otherwise indicated. $P = 0.42$ (placebo vs. pooled active treatment groups).

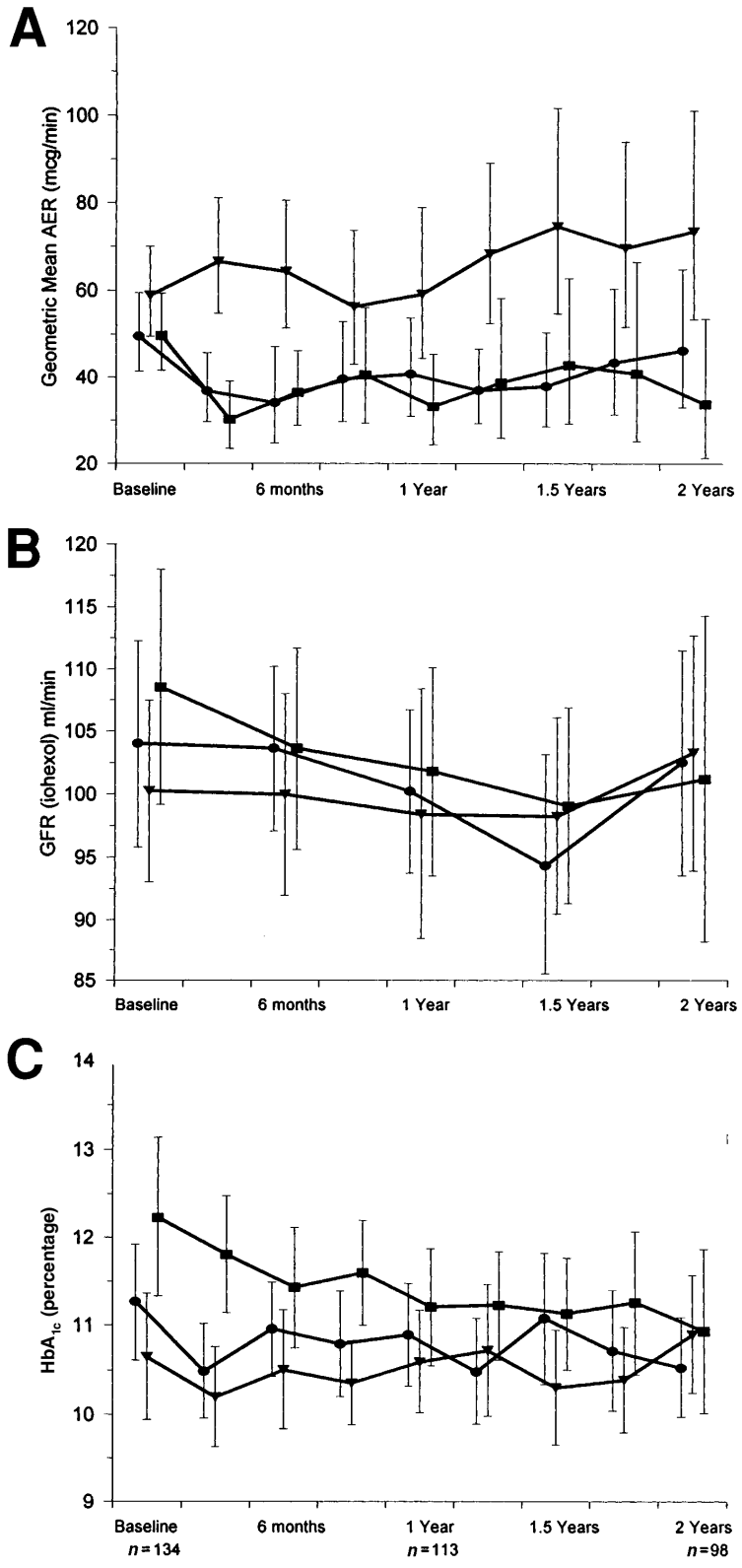

Figure 2—*AER, GFR, and HbA_{1c} over 2 years (mean ± SEM) for placebo (▼), 1.25 mg ramipril (●), or 5 mg ramipril (■). Urinary AER (A), GFR (B), and HbA_{1c} (C) for placebo, 1.25 mg ramipril, and 5 mg ramipril groups over 2 years are shown. AER was significantly lower in the ramipril-treated patients from month 6 and thereafter.*

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.

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*

	n	Patients who regressed	95% CI
Placebo	46	2 (4.3)	0.6–15.5%
Ramipril 1.25 mg	44	5 (11.4)	3.8–24.6%
Ramipril 5 mg	44	9 (20.5)	9.8–35.3%

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

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 55 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 withdrawls, 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 (normoalbuminuria), 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 HbA_{1c} (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 HbA_{1c} 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 Captopril 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 4—*Supine systolic blood pressure (mmHg) at baseline and at 2 years in the three treatment groups*

	n	Baseline*	Year 2†
Placebo	46	130 ± 11 (108–160)	134 ± 15 (100–190)
Ramipril 1.25 mg	44	132 ± 13 (95–160)	129 ± 14 (110–166)
Ramipril 5 mg	44	134 ± 16 (100–160)	127 ± 18 (100–160)

Data are means ± SD (range). *$P = 0.41$ between groups; †$P = 0.018$ between groups.

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

	n	Baseline*	Year 2†
Placebo	46	76 ± 8 (60–92)	79 ± 10 (53–98)
Ramipril 1.25 mg	44	76 ± 10 (55–95)	74 ± 9 (52–90)
Ramipril 5 mg	44	77 ± 8 (60–90)	77 ± 10 (60–100)

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 that was not thought to be hypotensive. The results of our present study suggest that even at low doses, a small reduction in blood pressure occurs; a separation between the proteinuria-lowering and the blood pressure–lowering effects is not possible to obtain.

Our results differ from a smaller study using similar doses of ramipril (1.25 and 5 mg) conducted in Sweden (30). That group failed to detect any significant difference in progression of AER between placebo- and ramipril-treated groups, despite effective ACE inhibition. Plasma renin activity levels were measured during this study, and maximum inhibition of ACE was apparent at both low and high ramipril doses. The study differed in design and patient selection from ours, and, importantly, the mean HbA_{1c} for the Swedish study patients was only 7.4% compared with 10.4% for the study patients in the ATLANTIS Study. The higher HbA_{1c} level in our study may reflect the differences in health care interventions in Sweden or in assay methodology, but is more likely due to differences in patient selection for the trial, as patients with the full range of HbA_{1c} seen in clinical practice were included in our study. The conclusion of the Prima group (30) was that the addition of ACE inhibitors in type 1 diabetic patients with microalbuminuria, in whom strict glycemic control was being achieved, did not effect progression of AER. The rate of change of AER in their placebo group was minimal, and the numbers in their study (14 in each group) were also small; therefore, a type 2 error perhaps cannot be excluded. The small but significant decline in the HbA_{1c} level in the 5 mg ramipril group in our study is of interest in the light of recent large studies (31), which suggest that ACE inhibitors may improve insulin sensitivity, but our study was not designed to evaluate this.

Progression of albuminuria is a surrogate end point in diabetic nephropathy, but it has been widely accepted and was used in the DCCT as the only measurable end point at this stage of incipient nephropathy (10). We also measured GFR using iohexol clearance, but found no significant difference over the period of the study. Either a longer time frame or larger numbers, or both, would be needed in following patients with microalbuminuria to determine any GFR changes at this stage of nephropathy. Some of our patients had low GFRs out of proportion to their levels of microalbuminuria. These subjects were females of low body weight, and other studies have reported similar low GFR in such patients (32).

The results of the DCCT and studies on longer-term use of ACE inhibitors in normotensive microalbuminuric type 1 diabetic patients suggest that both optimizing glycemic control and using an ACE inhibitor can slow the progression of microalbuminuria, a marker for diabetic nephropathy. Taken with previous studies (20–25,29), our results add weight to the recommendation for the use of ACE inhibitors to slow the progression of microalbuminuria in normotensive type 1 diabetic patients.

To the clinician faced with the microalbuminuric patient without hypertension, 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.

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APPENDIX

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