

Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria

The EUCLID study group*

Summary

Background Renal disease in people with insulin-dependent diabetes (IDDM) continues to pose a major health threat. Inhibitors of angiotensin-converting enzyme (ACE) slow the decline of renal function in advanced renal disease, but their effects at earlier stages are unclear, and the degree of albuminuria at which treatment should start is not known.

Methods We carried out a randomised, double-blind, placebo-controlled trial of the ACE inhibitor lisinopril in 530 men and women with IDDM aged 20–59 years with normoalbuminuria or microalbuminuria. Patients were recruited from 18 European centres, and were not on medication for hypertension. Resting blood pressure at entry was at least 75 and no more than 90 mm Hg diastolic, and no more than 155 mm Hg systolic. Urinary albumin excretion rate (AER) was centrally assessed by means of two overnight urine collections at baseline, 6, 12, 18, and 24 months.

Findings There were no differences in baseline characteristics by treatment group; mean AER was 8.0 $\mu\text{g}/\text{min}$ in both groups; and prevalence of microalbuminuria was 13% and 17% in the placebo and lisinopril groups, respectively. On intention-to-treat analysis at 2 years, AER was 2.2 $\mu\text{g}/\text{min}$ lower in the lisinopril than in the placebo group, a percentage difference of 18.8% (95% CI 2.0–32.7, $p=0.03$), adjusted for baseline AER and centre, absolute difference 2.2 $\mu\text{g}/\text{min}$. In people with normoalbuminuria, the treatment difference was 1.0 $\mu\text{g}/\text{min}$ (12.7% [–2.9 to 26.0], $p=0.1$). In those with microalbuminuria, however, the treatment difference was 34.2 $\mu\text{g}/\text{min}$ (49.7% [–14.5 to 77.9], $p=0.1$; for interaction, $p=0.04$). For patients who completed 24 months on the trial, the final treatment difference in AER was 38.5 $\mu\text{g}/\text{min}$ in those with microalbuminuria at baseline ($p=0.001$), and 0.23 $\mu\text{g}/\text{min}$ in those with normoalbuminuria at baseline ($p=0.6$). There was no treatment difference in hypoglycaemic events or in metabolic control as assessed by glycated haemoglobin.

Interpretation Lisinopril slows the progression of renal disease in normotensive IDDM patients with little or no

Correspondence to: Dr Nish Chaturvedi, EURODIAB, Department of Epidemiology and Public Health, University College, London WC1E 6BT, UK

*Writing committee, study organisation, and participants listed at end of article

albuminuria, though greatest effect was in those with microalbuminuria (AER ≥ 20 $\mu\text{g}/\text{min}$). Our results show that lisinopril does not increase the risk of hypoglycaemic events in IDDM.

Lancet 1997; **349**: 1787–92
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Introduction

Rates of morbidity and mortality continue to be higher among people with insulin-dependent diabetes mellitus (IDDM) than in the general population.^{1,2} Much of this increased risk results from renal and cardiovascular complications of IDDM; a strong predictor of these complications is the appearance of even small amounts of protein (mainly albumin) in the urine.^{3,4} Blood pressure is an important modifiable risk factor for the progression of renal disease.⁵ Of all antihypertensive agents, inhibitors of angiotensin-converting enzyme (ACE) are regarded as particularly effective in limiting renal-disease progression, because of possible beneficial influences on kidney function, which are separate from the effects on systemic blood pressure.⁶ ACE inhibitors significantly limit the progression of renal disease in patients with macroalbuminuria,⁷ and, at the time our trial was designed, there were indications that this beneficial effect also occurred in patients with microalbuminuria.^{8,9} If ACE inhibitors can slow the relentless decline of renal function in patients with microalbuminuria, it is reasonable to investigate whether use of ACE inhibitors in patients with normoalbuminuria may also be beneficial. However, previous trials of ACE inhibitors in normoalbuminuric patients are few,^{10–12} and have either lacked power,¹² or have not been designed as randomised and controlled.^{10,11} Consequently, the degree of albuminuria at which treatment with ACE inhibitors should start is unclear.

We carried out, therefore, a 2-year randomised, placebo-controlled trial of the ACE inhibitor lisinopril in patients with both normoalbuminuria and microalbuminuria. Our aim was to assess whether early-stage intervention in patients without hypertension would limit progression of renal disease, and whether this effect differed according to degree of albuminuria.

Methods

The EURODIAB controlled trial of lisinopril in insulin dependent diabetes (EUCLID) was a double-blind, randomised, parallel-design clinical trial of lisinopril and placebo in 18 European centres. The trial was done according to the

Declaration of Helsinki. All centres obtained approval from local ethics authorities, and obtained written consent from participants.

Men and women aged between 20 and 59 years who had IDDM—which we defined as a diagnosis before age 36 and the need for continuous insulin therapy within a year of diagnosis—were recruited if resting blood pressure was at least 75 and no more than 90 mm Hg diastolic, and no more than 155 mm Hg systolic. Women were only eligible if they were postmenopausal or using medically accepted contraceptives.

Exclusion criteria included a history of renal-artery stenosis, cardiac-valve obstruction, or accelerated hypertension; recent (within the previous 3 months) myocardial infarction, coronary bypass surgery, stroke, or congestive cardiac failure; abnormal renal function—a plasma creatinine of more than 150 $\mu\text{mol/L}$ (>1.8 mg/dL) in the previous 6 months, persistent proteinuria (Albustix positive or an albumin excretion rate [AER] >250 $\mu\text{g/min}$) or persistent haematuria (“stick” positive haematuria) on three occasions within the previous 12 months; or postural hypotension, medication that affects blood pressure, a previous idiosyncratic reaction to ACE inhibitors, or seropositivity for hepatitis B or HIV.

At the initial visit, blood pressure was taken twice after 5 min rest with a random zero sphygmomanometer; we used the average of these readings to assess eligibility. Eligible patients were issued with 1 month’s supply of placebo tablets, and made two consecutive timed overnight urine collections just before the randomisation visit, 1 month after the initial visit.

At the randomisation visit, blood pressure was measured twice to ensure it conformed to entry criteria. The patient was allowed to continue if a tablet count revealed that 70% or more of the medication had been taken. We used a Nephur test strip (Boehringer Mannheim) to test each urine collection for infection. Patients with positive tests were treated and repeated urine collections.

Randomisation was stratified by centre and albuminuric status. To assess the latter, we used a Micral strip (Boehringer Mannheim) to test each urine collection for albumin. Provisional assignment was made to the normoalbuminuric group if the average of the two results indicated that albumin concentration was below 15 mg/L. Patients with higher average concentrations were assigned to the microalbuminuric group for randomisation. Local investigators telephoned the coordinating centre with the provisional albuminuric status, and were given an identification number that matched numbers on pill boxes. Patients were randomly assigned to lisinopril or placebo with a block size of four. Separate schemes were created for each stratum (microalbuminuric and normoalbuminuric), with a FORTRAN computer program validated against the SAS RANUNI random-number generator. This scheme was generated by Zeneca Pharmaceuticals, so that both the coordinating centre and the local investigators were unaware of the allocation. Sealed envelopes were supplied to each centre and the coordinating centre so that the code could be broken in an emergency.

At randomisation, clinical measurements included blood pressure, height, and weight, and blood samples were taken for measurement of glycated haemoglobin (HbA_{1c}). Separate aliquots of urine from the two overnight collections were frozen with the blood samples, and sent to a central laboratory for analysis.

Patients were re-examined at 1, 3, 6, 12, 18, and 24 months after randomisation. We assessed HbA_{1c} and AER every 6 months, the latter by two overnight urine collections. Blood pressure was measured at each visit. No change was made to the patients’ diet, and diabetes control was managed according to usual clinical practice. Tablet counts were done at each visit to assess compliance. The starting dose was either 10 mg of lisinopril or matching placebo per day, which could be increased to 20 mg at 3 months and at subsequent visits to achieve a target blood pressure of less than 75 mm Hg diastolic.

We asked about adverse events at each visit. Serious adverse events were defined as: withdrawal for any serious medical

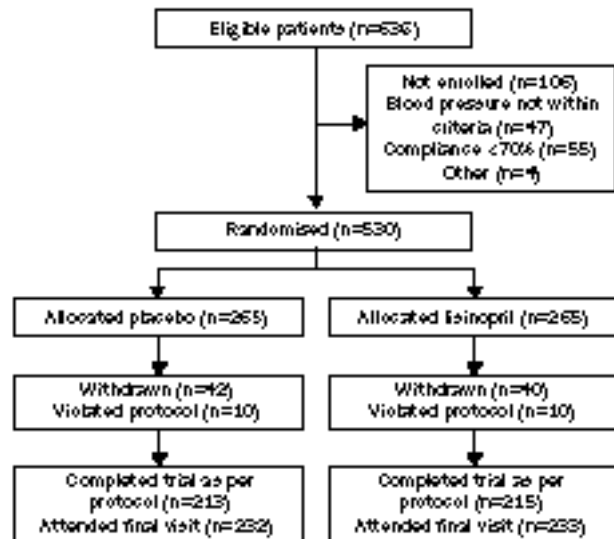


Figure 1: Trial profile

reason; death; any major morbid event or hospital admission for any reason; and any abnormal laboratory value associated with signs or symptoms or requiring treatment. Hypoglycaemic events were defined as events requiring the assistance of another person. Withdrawal from treatment could result from a serious adverse event or from the patient’s wishes. Whenever possible, those who had withdrawn were encouraged to attend the final study visit.

Blood and urine samples were sent to the laboratory of the Royal London Hospital, UK. Laboratory investigators were given the identification number only of the patient. Urine albumin was estimated by the particle-enhanced immunoturbidimetric assay,¹³ which was also used for calculation of AER. We estimated HbA_{1c} by an EIA with monoclonal antibody raised against HbA_{1c} (Dako Ltd, Ely, UK); the normal range for this assay is 2.9–4.8%.¹⁴

We estimated from the EURODIAB study¹⁵ that 40% of patients in our study population would have microalbuminuria (AER ≥ 20 $\mu\text{g/min}$). The rate of change of AER per month for this population in the placebo group was estimated to be 1.9 $\mu\text{g/min/month}$ (SD 10). With 90% power and 5% significance, 500 patients would be required in total (250 in each group) for us to detect a difference in AER change per month of 3 $\mu\text{g/min/month}$ between treatment and placebo groups.

Data were analysed at the coordinating centre. The randomisation code was kept at Zeneca Pharmaceuticals for the duration of the study, and access to it was allowed only when the final data had been received by the coordinating centre. The rate of change in AER was the primary endpoint of the study, and was derived with a summary measures approach,^{16–18} by calculation of the regression through the origin estimate for each patient (S Senn: personal communication). The mean of the two AERs from the overnight urine collections at each available visit was plotted, and a regression line drawn between these points. The slope of this line is equivalent to the rate of change in AER. This technique is similar to that of least-squares estimation, but applies sequentially increasing weights, beginning with 0 for the baseline measurement, 1 for the first follow-up measurement, and so on to each successive observation, so that the final observation has the greatest weight. The baseline measurement is used as a covariate in the analysis. This method has advantages over least-squares estimation in that all follow-up data contribute to the model, and is particularly applicable to growth curves that have a substantial plateau period. Analysis of covariance was used to measure the treatment effect on rate of change in AER, and successive terms for baseline AER and centre were added to the model, as stated in the protocol. Further adjustments were made for other potential confounders, such as sex, duration of diabetes, and glycaemic control. Interactions with treatment for key confounders—such as

	Placebo (n=265)	Lisinopril (n=265)
Median (IQR) age in years	33 (28-41)	33 (27-40)
Median (IQR) diabetes duration in years	13 (9-20)	13 (8-19)
M/F	167/98	155/110
Median (IQR) body-mass index (kg/m ²)	24.3 (22.9-26.3)	24.3 (22.8-26.0)
Median (IQR) blood pressure (mm Hg)		
Diastolic	80 (77-83)	79 (76-84)
Systolic	121 (114-130)	122 (116-130)
Geometric mean (IQR) AER* (µg/min)	8.0 (4.7-14.0)	8.0 (4.4-14.8)
Number with		
Normoalbuminuria	227 (86%)	213 (80%)
Microalbuminuria	34 (13%)	45 (17%)
Macroalbuminuria	2 (1%)	4 (2%)
Median (IQR) HbA _{1c} (%)†	7.0 (6.0-8.4)	6.9 (5.6-8.2)

*Data missing for two patients in placebo group and three patients in lisinopril group.
†10-90th centiles=4.9-10.0% for placebo group; 4.8-9.8% for lisinopril group.

Table 1: Baseline characteristics by treatment status

albuminuric status, sex, glycaemic control, duration of diabetes, and blood pressure—were also tested. AER was positively skewed and log transformed effectively for parametric analysis. Mean rates of change in AER were compared by treatment group to derive an absolute and relative treatment difference in AER at 2 years. Cox's proportional-hazards modelling was used by treatment group to compare rates of progression to microalbuminuria or macroalbuminuria from normoalbuminuria. All analyses were done by intention to treat unless otherwise stated.

Results

530 patients were randomly assigned active treatment (265) or placebo (figure 1). Factors associated with severity of diabetes and likelihood of complications, such as glycaemic control and duration of diabetes, showed a broad distribution within the study sample (table 1). HbA_{1c} ranged from 2.5% to 14.4%, and diabetes duration from 1 to 51 years. However, there were no between-group differences in baseline measures (table 1).

At 1 month, mean diastolic blood pressure was 74 mm Hg on active treatment and 77 mm Hg on placebo ($p=0.0001$). This blood-pressure difference was maintained throughout the rest of the trial (figure 2). Mean HbA_{1c} was similar in the two groups for the duration of the trial (figure 2).

The intention-to-treat analysis required that baseline AER and at least one follow-up AER were available. Thus, data on 244 patients in the treatment group and 246 in the placebo group were available for analysis. The difference in mean AER between placebo and treatment groups increased during the study (figures 2 and 3); after 2 years, AER was 2.2 µg/min lower in the treatment than in the placebo group (adjusted for baseline AER and centre, as per protocol). The crude relative treatment difference in AER at 2 years was 24% (95% CI 4.1-39.8%; $p=0.02$). When adjustment was made for baseline AER and centre, this difference persisted; at 2 years, AER was 18.8% lower in the lisinopril than in the placebo group (2.0, 32.7; $p=0.03$). These values did not significantly alter when adjustment was made for sex and baseline HbA_{1c}.

We adjusted for diastolic blood pressure at 1 month to assess whether the effects of lisinopril on AER could be accounted for by its effects on blood pressure. This adjustment reduced the percentage difference in AER at 2 years to 17.3% (0.2, 31.5; $p=0.05$). Adjustment for systolic blood pressure at 1 month instead of diastolic had identical results.

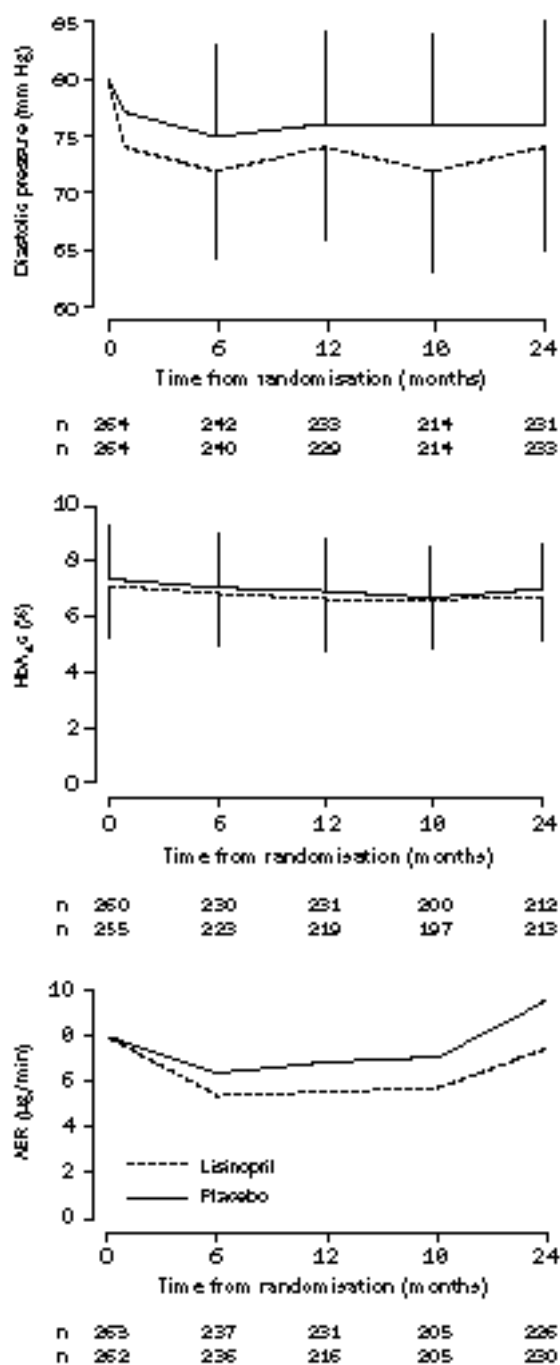


Figure 2: Blood pressure HbA_{1c} and AER over time
Vertical bars show SDs.

A second per-protocol analysis was also done, which excluded patients who violated the protocol, or who withdrew ($n=20$ and 82 , respectively). The percentage treatment difference in rate of change in AER, adjusted for baseline AER and centre, was now 20.1% (4.3, 33.3; $p=0.02$).

The effect of treatment differed according to baseline AER ($p=0.001$ for interaction with AER as a continuous variable). Among patients who were normoalbuminuric at baseline, AER at 2 years was 12.7% (-2.9 to 26.0; $p=0.1$) lower in the treatment than in the placebo group, whereas this difference was 49.7% (-14.5 to 77.9; $p=0.1$) in the microalbuminuric group (adjusted for baseline AER and centre, $p=0.04$ for the interaction). Absolute treatment differences were 1.0 µg/min in the

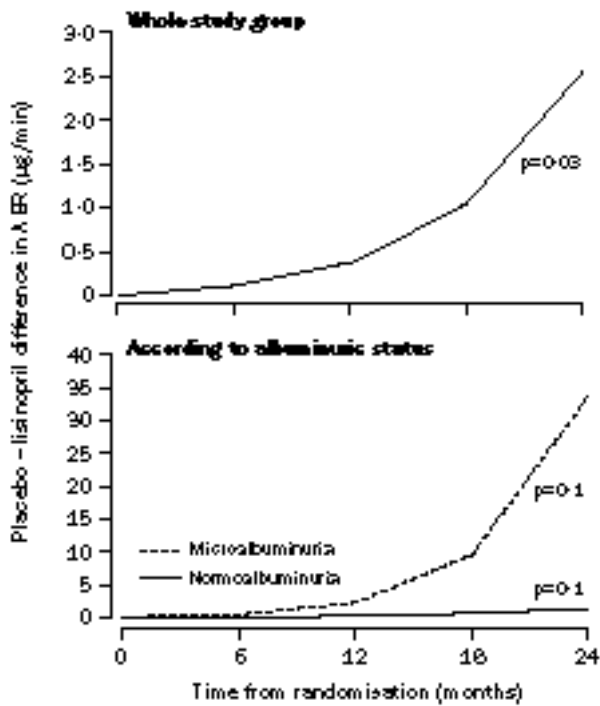
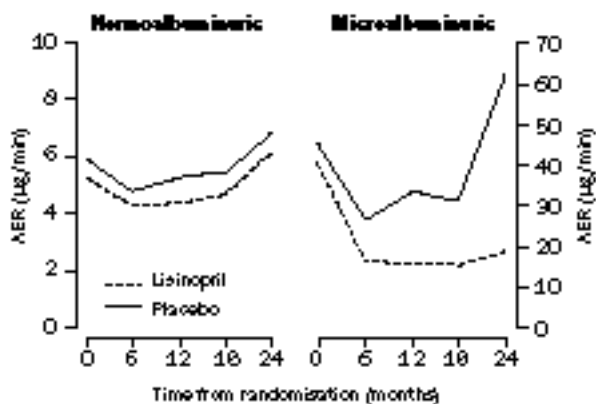


Figure 3: Absolute treatment difference (placebo-lisinopril) in AER ($\mu\text{g}/\text{min}$) adjusted for baseline AER and centre and according to albuminuric status

normoalbuminuric group, and $34.2 \mu\text{g}/\text{min}$ in the microalbuminuric group (figure 3). A stratified analysis (table 2) showed little treatment benefit at baseline AERs of $5 \mu\text{g}/\text{min}$ and below; above this value, the treatment effect increased substantially.

A separate analysis was done to compare actual mean AER at the 2-year visit, adjusted for baseline AER and centre. Thus, only patients who attended the final visit are included in this analysis (figure 1). Among patients with normoalbuminuria at baseline, the treatment difference in mean AER was $0.23 \mu\text{g}/\text{min}$ ($p=0.6$); among those with microalbuminuria at baseline, the difference was $38.5 \mu\text{g}/\text{min}$ ($p=0.001$; figure 4).

Progression to microalbuminuria or macroalbuminuria was assessed by exclusion of patients with an AER of $20 \mu\text{g}/\text{min}$ or higher at baseline, and by comparison of those



n 227 202 201 179 193 34 33 29 25 32
 n 213 196 179 170 191 45 37 34 32 37

Figure 4: Albumin excretion rate (AER) over time in EUCLID by initial microalbuminuric status

AER ($\mu\text{g}/\text{min}$)	Placebo/treatment (n)	% difference in AER (95% CI)	p
<5	72/82	-3.3 (-35.9 to 21.5)	0.8
5-<10	89/81	21.3 (-1.9 to 39.3)	0.07
10-<20	47/41	18.8 (-25.1 to 44.7)	0.4
20-200	34/39	49.7 (-14.5 to 77.9)	0.1

% difference is percentage by which AER is lower in lisinopril than in placebo group, adjusted for baseline AER as continuous variable and centre.

Table 2: Treatment effect (lisinopril vs placebo) at different baseline AER values

with a mean AER of $20 \mu\text{g}/\text{min}$ or higher on two consecutive visits or at their final visit by treatment group. 18 (8%) of 227 patients in the placebo group and 13 (6%) of 213 in the lisinopril group progressed to an AER of $20 \mu\text{g}/\text{min}$ or higher. The rate ratio for progression in placebo versus lisinopril groups was 1.30 (95% CI 0.64-2.70; $p=0.5$).

Interactions with centre, sex, initial glycaemic control, duration of diabetes, and initial blood pressure were also tested. Only the interaction with sex was statistically significant ($p=0.04$). When men and women were examined separately, the treatment difference in AER at 2 years was $0.40 \mu\text{g}/\text{min}$ ($p=0.6$) in men, and $6.52 \mu\text{g}/\text{min}$ ($p=0.01$) in women. At baseline, the most striking difference between the sexes was in mean AER. Women in both groups had slightly higher AERs than men (7.5 vs $9.0 \mu\text{g}/\text{min}$ in men and women in the placebo group, $p=0.2$; and 7.2 vs $9.3 \mu\text{g}/\text{min}$ in the lisinopril group, $p=0.09$). These mean values are derived from different distributions of AER by sex; although 27% of all men at baseline had an AER of $4 \mu\text{g}/\text{min}$ or less, only 13% of women had an AER in this category. Baseline AER is a clear determinant of treatment effect, and further inclusion of a baseline AER by treatment interaction rendered the sex-by-treatment interaction non-significant (from $p=0.04$ to 0.1).

Patients withdrew for various reasons, including a wish not to continue with the trial, pregnancy, and major operations or illnesses unconnected with trial medication. There were 477 minor adverse events (266 in the lisinopril group, and 211 in the placebo group), and 108 serious adverse events (56 in the lisinopril group, and 52 in the placebo group). There were ten reports of hypoglycaemic episodes in eight people in the placebo group, and 12 reports in 12 people in the lisinopril group. The only major difference in adverse events between groups was cough; seven episodes reported in seven individuals in the placebo group, and 24 episodes in 21 individuals in the lisinopril group.

Compliance with trial medication was 95% at the beginning of the study and 90% at the end. Data for the calculation of compliance were missing for 9% of those who attended visits. Compliance did not vary significantly by treatment group or sex.

Discussion

We show that the ACE inhibitor lisinopril slows the progression of AER in a mixed population of normoalbuminuric and microalbuminuric normotensive IDDM patients. After 2 years, AER was 18.8% lower on active treatment than on placebo—an absolute difference of $2.2 \mu\text{g}/\text{min}$. Our findings apply to IDDM patients with a broad range of glycaemic control and duration of diabetes, and the treatment effect did not appear to differ according to the key confounders, except sex and

baseline albuminuric status. The sex difference seems to be explained by the sex difference in AER at baseline. There was little beneficial effect in those who started the trial with an AER of 5 $\mu\text{g}/\text{min}$ or less; but those who started with microalbuminuria (AER ≥ 20 $\mu\text{g}/\text{min}$) benefited more from lisinopril than did those in the normoalbuminuric range. Thus, after 2 years, the absolute and relative treatment differences in AER were 34.2 $\mu\text{g}/\text{min}$ (49.7%) in the microalbuminuric group; and 1.0 $\mu\text{g}/\text{min}$ (12.7%) in the normoalbuminuric group. The treatment difference for microalbuminuric people was not statistically significant, since the number of people in this subgroup was small; nevertheless, the final AER in the lisinopril group is about half that in the placebo group, which suggests this difference may represent an important clinical effect. We must emphasise that the prevalence of microalbuminuria in this trial was much smaller than anticipated (15 vs 40%), and smaller than that on which the study power was calculated.

Studies of microalbuminuric patients have shown large changes in AER after 6 weeks,¹⁹ 1 year, 2 years^{20,21} and 4 years,⁹ despite the small number of study participants in some cases. The choice of statistical test to analyse the primary endpoint may account for some of the variability in magnitude of treatment effect in our study, and for the variability of results between studies. Many studies presented a comparison of mean AER at the final visit as the main outcome,²⁰ thus including only patients who completed the study, and producing a more optimistic result than a true intention-to-treat analysis. This effect is confirmed when we compare our findings in the microalbuminuric subgroup by these different approaches. A true intention-to-treat analysis, with a summary measures approach, produces a result in microalbuminuric patients that is clinically important but not statistically significant. However, a simple comparison of mean AER at the final visit—as in other studies—produces a statistically significant effect. It is interesting that a combination of the two trials with the largest participant numbers^{20,21} showed a more modest treatment difference (about 33 $\mu\text{g}/\text{min}$,²² a result close to our own) in AER than earlier, smaller studies.

Previous studies of normoalbuminuric patients had conflicting results. A comparison of ten IDDM patients with eight non-diabetic participants showed a statistically significant difference in AER of 1.3 $\mu\text{g}/\text{min}$ after 3 months' treatment.¹¹ By contrast, an uncontrolled antihypertensive study of 11 diabetic patients on enalapril showed a clinically significant fall of AER from 50.5 to 12.2 mg/24 h, which was dismissed because it was not significant.¹⁰ Similarly, a randomised controlled trial of enalapril in 18 people, 12 of whom were normoalbuminuric, showed a treatment difference in AER of 31.4 $\mu\text{g}/\text{min}$ at 3 months—again not significant in conventional terms, and results for the normoalbuminuric group¹² were not presented separately. None of these earlier studies conform to the design requirements of adequately-powered, double-blind, randomised, controlled, clinical trials. Although the absolute treatment effect we have shown in AER in normoalbuminuric people is small, this effect represents a 13% relative difference in 2 years. Furthermore, a stratified analysis shows that much of this beneficial effect occurs in patients with AER above 5 $\mu\text{g}/\text{min}$. This treatment difference may be of clinical importance in limiting the progression of renal disease, and reducing the proportion of people who

ultimately require renal-replacement therapy.

There are indications that ACE inhibitors may improve insulin sensitivity,^{23,24} possibly resulting in an increased number of hypoglycaemic events in people with diabetes.²⁵ These findings have been vigorously challenged.^{26,27} Criticism mainly targeted the case-control study design, notoriously prone to bias. In our randomised controlled trial, one of the largest of an ACE inhibitor in people with IDDM, there was no treatment difference in hypoglycaemic events or glycaemic control throughout the study. The EUCLID study provides clear evidence, therefore, that ACE inhibitors do not increase the risk of hypoglycaemia in people with IDDM.

We conclude that lisinopril is of clinical benefit to people with IDDM who have early signs of renal disease without hypertension. The greatest clinical effect is observed in those with microalbuminuria (AER ≥ 20 $\mu\text{g}/\text{min}$), but the exact threshold at which to start treatment requires long-term follow-up to assess the impact of a modest protective effect in those with normoalbuminuria, particularly those with AER greater than 5 $\mu\text{g}/\text{min}$. Long-term follow-up of microalbuminuric patients is also required to measure the full impact of ACE inhibitor therapy on outcomes such as renal-replacement therapy, and mortality. It is clear, however, that care guidelines for people with IDDM should now include the treatment of early-stage renal disease with ACE inhibitors, even in normotensive patients.

Study Organisation

Writing committee—N Chaturvedi, J Stevenson, J H Fuller, R Rottiers, B Ferriss.

Centres and principal investigators—B Karamanos, A Kofinis, C Petrou (Hippokraton Hospital, Athens, Greece); C Ionescu-Tirgoviste, C Iosif (Clinic of Diabetes Nutrition and Metabolic Diseases, Bucharest, Romania); G Tamas, G Bibok (Semmelweis University, Budapest, Hungary); Z Kervnyi, P Kis-Gombos, J Toth (Szent Imre Teaching Hospital, Budapest, Hungary); J B Ferriss, G Grealay (Cork University Hospital, Wilton, Cork, Ireland); R Rottiers, H Priem (University Hospital, Gent, Belgium); V Koivisto, J Tuominen, E Kostamo (Helsinki University Hospital, Helsinki, Finland); B Idziarz-Walus, B Solnica, D Galicka-Latalie (University School of Medicine, Krakow, Poland); G Michel, M Keipes, A Giuliani, A Herode (Centre Hospitalier de Luxembourg, Luxembourg); F Santusanio, A Buetti, S Bistoni, Dr Cagini (Istituto di Medicina Interna e Scienze Endocrine e Metaboliche, Perugia, Italy); R Navalesi, G Penno, M Nannipieri, L Rizzo, R Miccoli (Istituto di Clinica Medica II, Pisa, Italy); N Ghirlanda, P Cotroneo, A Manto, A Minella, C Saponara (Universita Cattolica del Sacro Cuore, Rome, Italy); J Ward, M Plater, S Ibrahim, S Ibbotson, C Mody (Royal Hallamshire Hospital, Sheffield, UK); N Papazoglou, C Manes, K Soulis, M Voukias (Agios Pavlos General Hospital, Thessaloniki, Greece); M Muggeo, V Cacciatori, ML Gemma, A Delleria, A Castellarin (Ospedale Civile, Verona, Italy); K Irsigler, H Abrahamian, C Gurdet, C Willinger (Hospital Vienna Lainz, Vienna, Austria); A Nelstrop, C Feben (Watford General Hospital, Watford, UK); S Walford, V McLelland, S Hughes (New Cross Hospital, Wolverhampton, UK); Z Metelko, G Roglic, Dr Z Rogulja Pepeonik (Vuk Vrhovak Institute for Diabetes, Zagreb, Croatia).

Steering committee—B Ferriss (Chairman, Cork), J H Fuller (London), B Karamanos (Athens), Z Kerenyi (Budapest), G Michel (Luxembourg), M Muggeo (Verona), J Stephenson (London), N Chaturvedi (London), G C Viberti (London), A K Sjolie (Aarhus).

Coordinating centre—J H Fuller, J Stephenson, N Chaturvedi, J Holloway, M Milne, D Webb.

Safety committee—C Bulpitt, (Hammersmith Hospital); A Fletcher (London School of Hygiene and Tropical Medicine); M Shipley (University College, London).

Central laboratory—G John, D J Newman (Royal London Hospital, London, UK).

Acknowledgments

This study was supported by a grant from Zeneca Pharmaceuticals for designing and coordinating the trial and analysing data. Zeneca did not have access to decoded data.

Lisinopril and matching placebo tablets were supplied to all centres by Zeneca Pharmaceuticals. Micral and Nephur test sticks were supplied by Boehringer Mannheim. We thank Stephen Senn and Lynda Stevens for statistical advice, the EUCLID investigators, and participants in the study.

References

- Moss SE, Klein R, Klein BEK. Cause-specific mortality in a population-based study of diabetes. *Am J Public Health* 1991; **81**: 1158-62.
- Wang S-L, Head J, Stevens L, Fuller JH, WHO Multinational Study Group. Excess mortality and its relation to hypertension and proteinuria in diabetic patients: the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetes Care* 1996; **19**: 305-12.
- Viberti GC, Hill RD, Jarrett R J, Argyropoulos A, Mahmud U, Keen H. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. *Lancet* 1982; **i**: 1430-32.
- Messent JWC, Elliott TG, Hill RD, Jarrett RJ, Keen H, Viberti G-C. Prognostic significance of microalbuminuria in insulin-dependent diabetes mellitus: a twenty-three year follow-up study. *Kidney Int* 1992; **41**: 836-39.
- Mogensen CE. Progression of nephropathy in long-term diabetics with proteinuria and effect of initial anti-hypertensive treatment. *Scand J Clin Lab Invest* 1976; **36**: 383-88.
- Kasike BL, Kalil RSN, Ma JZ, Liao M, Keane WF. Effect of antihypertensive therapy on the kidney in patients with diabetes: a meta-regression analysis. *Ann Intern Med* 1993; **118**: 129-38.
- Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin converting enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993; **329**: 1456-62.
- Marre M, Chatellier G, Leblanc H, Guyene TT, Menard J, Passa P. Prevention of diabetic nephropathy with enalapril in normotensive diabetics with microalbuminuria. *BMJ* 1988; **297**: 1092-95.
- Mathiesen ER, Hommel E, Giese J, Parving H-H. Efficacy of captopril in postponing nephropathy in normotensive insulin dependent diabetic patients with microalbuminuria. *BMJ* 1991; **303**: 81-87.
- Passa P, Leblanc H, Marre M. Effects of enalapril in insulin dependent diabetic subjects with mild to moderate uncomplicated hypertension. *Diabetes Care* 1987; **10**: 200-04.
- Pedersen MM, Schmitz A, Pedersen EB, Danielsen H, Christiansen JS. Acute and long-term renal effects of angiotensin converting enzyme inhibition in normotensive, normoalbuminuric insulin-dependent diabetic patients. *Diabet Med* 1988; **5**: 562-69.
- Wiegmann TB, Herron KG, Chonko AM, MacDougall ML, Moore WV. Effect of angiotensin-converting enzyme inhibition on renal function and albuminuria in normotensive type I diabetic patients. *Diabetes* 1992; **41**: 62-67.
- Medcalf E, Newman DJ, Gorman EG, Price CP. Rapid, robust method for measuring low concentrations of albumin in urine. *Clin Chem* 1990; **36** (3): 446-49.
- John GW, Gray MR, Bates DL, Beacham JL. Enzyme immunoassay: a new technique for estimating HbA1c. *Clin Chem* 1993; **39**: 663-66.
- The EURODIAB IDDM Complications Study Group. Microvascular and acute complications in insulin dependent diabetes mellitus: the EURODIAB IDDM Complications Study. *Diabetologia* 1994; **37**: 278-85.
- Matthews JNS, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. *BMJ* 1990; **300**: 230-35.
- Laird NM, Wang F. Estimating rates of change in randomized clinical trials. *Control Clin Trials* 1990; **11**: 405-19.
- Frisson L, Pocock SJ. Repeated measures in clinical trials: analysis using mean summary statistics and its implications for design. *Stat Med* 1992; **11**: 1685-1704.
- Mimran A, Insua A, Ribstein J, Bringer J, Monnier L. Comparative effect of captopril and nifedipine in normotensive patients with incipient diabetic nephropathy. *Diabetes Care* 1988; **11**: 850-53.
- Viberti G, Mogensen CE, Groop LC, Pauls JF. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. *JAMA* 1994; **271**: 275-79.
- Laffel LMB, McGill JB, Gans DJ. The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria. *Am J Med* 1995; **99**: 497-504.
- The Microalbuminuria Captopril Study Group. Captopril reduces the risk of nephropathy in IDDM patients with microalbuminuria. *Diabetologia* 1996; **39**: 587-93.
- Pollare T, Lithell H, Berne C. A comparison of the effects of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. *N Engl J Med* 1989; **321**: 868-73.
- Paolisso G, Gambardella A, Verza M, D'Amore A, Sgambato S, Varricchio M. ACE inhibition improves insulin-sensitivity in aged insulin-resistant hypertension patients. *J Hum Hyperten* 1992; **6**: 175-79.
- Herings RMC, de Boer A, Stricker BHCh, Leufkens HGM, Porsius A. Hypoglycaemia associated with use of inhibitors of angiotensin converting enzyme. *Lancet* 1995; **345**: 1195-98.
- Donnelly R. Angiotensin-converting enzyme inhibitors and insulin sensitivity: metabolic effects in hypertension, diabetes, and heart failure. *J Cardiovasc Pharmacol* 1992; **20** (suppl 11): 38-44.
- Petrie JR, Morris AD, Ueda S, et al. Do ACE inhibitors improve insulin sensitivity? *Lancet* 1995; **346**: 583-84.