ANGIOTENSIN CONVERTING ENZYME INHIBITORS IN NORMOTENSIVE DIABETIC PATIENTS WITH MICROALBUMINURIA

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ABSTRACT

Background
Renal disease is a serious complication of diabetes mellitus.

Objectives
To examine whether the progression of early diabetic renal disease to end-stage renal failure may be slowed by the use of angiotensin converting enzyme inhibitors for reasons other than their antihypertensive properties, so that they have value in the treatment of normotensive diabetics with microalbuminuria.

Search Strategy
Medline was searched for English language reviews and randomised controlled trials. Personal reference lists, and reference lists of retrieved studies were also used.

Selection Criteria
Randomised controlled trials with separate identifiable results for initially normotensive diabetic patients, who received angiotensin converting enzyme inhibitors for at least one year and were compared with controls.

Data collection and analysis
Meta-analyses were performed on the results of 12 randomised controlled trials with a variety of patient inclusion and exclusion criteria. One further study met all conditions for inclusion but did not provide data in useable form for meta-analyses.

Main Results
Albumin excretion rate fell for patients on angiotensin converting enzyme inhibition in 12 of the 13 studies but did so for only two of the 13 groups on placebo. Treatment provided a significant reduction in albumin excretion rate in both insulin dependent diabetes mellitus and non insulin dependent diabetes mellitus. Treatment with either captopril, enalapril or lisinopril reduced albumin excretion rate in comparison with control patients.

A significantly greater lowering of blood pressure was experienced by initially normotensive patients in the angiotensin converting enzyme inhibitor than in the placebo group. Average glycosylated haemoglobin fell a little in the treated patients and rose in the controls, the difference being just significant. The difference in changes in glomerular filtration rate did not reach statistical significance.

Reviewers’ conclusions
Inhibition of angiotensin converting enzyme can arrest or reduce the albumin excretion rate in microalbuminuric normotensive diabetics, as well as reduce or prevent an increase in blood pressure. But, given the drop in blood pressure in patients on angiotensin converting
enzyme inhibitors, it is not certain that the reduction of albumin excretion rate is due to a separate renal effect. A direct link with postponement of end-stage renal failure has not been demonstrated. There appear to be no substantial side effects.

This review should be cited as:

BACKGROUND

GLOSSARY
Albustix positive proteinuria: Albustix testing uses a 'stick' that is dipped into a sample of urine to test for protein. It is only positive when there is much more protein than usual.
Angiotensin converting enzyme inhibitors: Drugs that inhibit the conversion of angiotensin I to angiotensin II.
Diabetic nephropathy: A type of kidney disease that may occur in people with diabetes.
End stage renal failure: A deficiency of renal function which is fatal without transplantation or dialysis.
Glomerulus: The filtration unit of the kidney.
Glomerular filtration rate: Rate at which the kidney filters out waste products, usually 125 ml/minute, although it decreases in renal failure. Glomerular filtration rate is therefore used as a measure of renal failure.
Heterogeneity: A measure of the extent to which studies vary. Homogeneous studies are in accord; heterogeneous studies differ from each other.
Meta-analysis: Statistical techniques which combine the results of several trials to produce a joint estimate.
Microalbuminuria: Higher than normal amounts of protein in the urine but not enough to be detected by albustix. Once persistent, is a sign of early renal disease.
Normotensive: Having normal blood pressure.
Renal: Relating to the kidney.

MICROALBUMINURIA
A patient is said to have overt proteinuria if urine tests show more than 300mg/l of albuminuria. Sensitive assays have shown that levels of albuminuria too low to be detected by conventional dipstick urinalysis can be present for months or years before reaching the 300mg/l level. This phenomenon is termed microalbuminuria and is defined as an excretion rate of 20 to 200 micrograms/min (30 to 300mg/day). Assuming an average daily urine output of one to 1.5 litres, this gives concentrations of 20 to 300 mg/l (Liou 1995).

DIABETIC NEPHROPATHY
About 20-35% of diabetic patients develop persistent proteinuria, a decline in glomerular filtration rate, and increased arterial blood pressure, which collectively constitute the clinical syndrome of diabetic nephropathy (Andersen 1983; Borch-Johnsen 1985; Krolewski 1985; Parving 1989; Bilous 1995). The relationship between arterial blood pressure and diabetic nephropathy seems to be a complex one: nephropathy increasing blood pressure and blood pressure accelerating the course of nephropathy (Parving 1993). The presence of nephropathy is closely associated with the increased morbidity and mortality in insulin dependent diabetes mellitus (Knowles 1971; Andersen 1983; Borch-Johnsen 1985; Krolewski 1985; Parving 1988). The high mortality is due to an excess of cardiovascular mortality (Borch-Johnsen 1987) and to end stage renal failure (Knowles 1971; Andersen 1983; Borch-Johnsen 1985; Krolewski 1985). Albuminuric diabetics may be 20 times more likely to die of cardiovascular disease than are non-albuminuric diabetics (Borch-Johnsen et al 1985). On average, death occurs five to 10 years after the start of persistent proteinuria (Knowles 1971; Andersen 1983; Krolewski 1985). Long term angiotensin converting enzyme inhibitor treatment of insulin dependent diabetic patients with nephropathy has been associated with a low rate of decline in kidney function (Lewis 1993; Mulec 1994).
PREDICTION OF NEPHROPATHY
The insulin dependent diabetes mellitus subpopulation at risk of developing nephropathy may be identified fairly accurately by the detection of microalbuminuria (Parving 1993). Microalbuminuria is also a strong predictor of all causes of mortality, particularly cardiovascular ones, in non insulin dependent patients (Parving 1993). Incipient diabetic nephropathy is considered to be present if persistent microalbuminuria is found in two of three urine samples collected consecutively, preferably within six months (Parving 1993).

POSSIBLE EFFECTS OF ANGIOTENSIN CONVERTING ENZYME INHIBITOR ANTIHYPERTENSIVE TREATMENT
Non-insulin dependent diabetic patients with early nephropathy and mild to moderate hypertension demonstrate a progressive increase in urinary protein excretion. Administration of captopril has resulted in prompt control of hypertension and reversal of the increase in urinary protein excretion (Vora 1996).

Antihypertensive treatment prevents overt proteinuria in insulin dependent diabetes mellitus patients with microalbuminuria (Passa 1992). It may be that angiotensin converting enzyme inhibitors contribute to a slowing of progression by contributing an antiproteinuric effect not necessarily related to the effects of systemic blood pressure (Marre 1988; Mathiesen 1991; Valentino 1991; Liou 1995). If so it may be advantageous to use them before the patient has become hypertensive. One meta-analysis, of studies lasting at most one year, showed that the treatment of diabetic patients with angiotensin converting enzyme inhibitors not only effectively reduced high blood pressure but also reduced microalbuminuria/proteinuria and, in addition, exhibited an antihyperglycaemic effect by improving blood sugar levels (Bergemann 1992). Another meta-analysis, of studies lasting four or more weeks, concluded that as angiotensin converting enzyme inhibitors exert a specific antiproteinuric effect even without a change in systemic blood pressure, they are superior to other agents in treating microalbuminuria or overt proteinuria in initially normotensive or mildly hypertensive diabetic patients (Böhlen 1994).

In a study (of both normotensives and hypertensives) designed to determine whether captopril was associated with an effect independent of its role as an antihypertensive agent, Lewis et al concluded that the beneficial effect of captopril was not explained by small differences in the level of blood pressure control between captopril and placebo groups (Lewis 1993). They concluded that captopril slows the progression of diabetic nephropathy by a mechanism that is independent of its antihypertensive properties. In proteinuric diabetic patients with normal blood pressure and normal renal function, captopril acutely lowered albuminuria without lowering blood pressure (Elving 1992).

Parving et al (Parving 1994) concluded, from a meta-analysis based on randomised controlled trials lasting more than one year, that angiotensin converting enzyme inhibition arrests the progressive rise in albuminuria in normotensive insulin dependent diabetic patients with nephropathy (Parving 1989). But mean arterial pressure fell by 3 (SE 2) mmHg in the captopril treated group and rose by 6 (SE 1) mmHg in the controls. Albuminuria declined by 11% in the captopril group and rose by 55% in the controls. The glomerular filtration rate declined by 3.1 (SE 2.8) ml/min/1.73 m2 with captopril and by 6.4 (SE 3.1) ml/min/1.73 m2 in the controls. No severe side effects occurred. They concluded that, the crucial question, requiring longer term follow up, had not been answered - namely can the rate of decline in the glomerular filtration rate be reduced or even prevented in normotensive diabetic nephropathy by captopril or other hypotensive regimens?

SIDE EFFECTS
Known side effects of angiotensin converting enzyme inhibitors are persistent dry cough (EUCLID 1997), in some 5% to 20% of patients (Irsaii 1992; Molyneaux 1996), and exacerbation of inflammation (Vane 1995). Angiotensin converting enzyme inhibitors may affect potassium levels and should not be used in combination with potassium sparing diuretics or potassium supplements (British Nat For 1997).

OBJECTIVES
It may be possible to slow or halt the progression of diabetes to end-stage renal failure by the use of angiotensin converting enzyme inhibition for reasons other than their antihypertensive properties. If so, it may be desirable to treat normotensive diabetics exhibiting microalbuminuria
with angiotensin converting enzyme inhibitors. This has been investigated by examining published randomised controlled trials on initially normotensive patients.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies
Randomised controlled trials of angiotensin converting enzyme inhibitors versus placebo, lasting for at least one year.

Types of participants
Initially normotensive diabetic patients with microalbuminuria or overt albuminuria.

Types of intervention
The angiotensin converting enzyme inhibitors captopril and enalapril were each used in six studies. Lisinopril was used in one study. The meta-analyses exclude one of the captopril studies.

Types of outcome measures
Study changes in blood pressure, glycosylated haemoglobin, glomerular filtration rate, and albumin excretion rate. Longer term outcomes were not available.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: Cochrane Metabolic and Endocrine Disorders Group search strategy

MEDLINE was searched for English language reviews and randomised controlled trials using the terms 'diabetes & ACE inhibitors'; 'diabetes & renal failure'; and 'diabetes & microalbuminuria'. Interest was confined to randomised controlled trials in which normotensive diabetic patients received angiotensin converting enzyme inhibitors for at least one year. Reference lists of retrieved papers were checked. Personal reference lists were also used. A draft of the first version of this review was presented to a scientific meeting of the Scottish Study Group for the Care of the Young Diabetic which, inter alia, provided an opportunity to check comprehensiveness of retrieved studies. Readers are invited to suggest studies, particularly in other languages, which should be considered for inclusion when this report is next updated.

METHODS OF THE REVIEW

Where publications included appropriate raw data, means and variances were recalculated. Otherwise a measure of location could be either mean or median or midpoint of a confidence interval or range. Variances were sometimes calculated from standard deviations, standard errors, confidence intervals or ranges. In the latter case this involved a, sometimes questionable, assumption of distribution symmetry. Not all publications specify whether '±' is followed by a standard deviation or standard error. Some papers, or groups of papers contained conflicting figures. For some study variables, published standard errors and standard deviations were reconciled by assuming that not all patients contributed to the given data. Data from Hansen et al (1994) were used to supplement those of Viberti et al (1994), but only when there was no risk of double counting. Generally, meta-analyses were carried out using inverse variance weighted, rather than standardised, means but the latter were employed to reduce heterogeneity and logarithmic transformation to counteract skewness. In order to assess changes, an 'effect' is defined as the difference between study duration increment for the angiotensin converting enzyme inhibition and control groups. Unless raw data were available, the standard deviation of change has been
calculated assuming (questionably) that start and end measures of location are independent. This was necessitated by the summary nature of the data examined and leads to a conservative estimate of standardised average change. Since data may be a mixture of arithmetic mean, geometric mean and median using two units of measurement, caution is advisable.

**DESCRIPTION OF STUDIES**

Twelve studies were found to satisfy the criteria for inclusion in a meta-analysis. Data and descriptions may have been extracted from more than one publication but without multiple counting. The Ahmad 1997 and Laffel 1995 studies were not included in the previous review and that of Sano 1995 now includes extended data. Ravid 1994 has also been extended but only the first five years met our criteria for inclusion.

Usual diabetic diets were specified with only Bakris 1994 mentioning salt restriction. The control group for Hallab 1993 was given a diuretic, otherwise controls received no treatment or an inert placebo unless there was more than one control group, in which case only the placebo control group has been included here. If patients became hypertensive, antihypertensive therapy was sometimes added.

Definitions of normotensive varied for the studies included in this report, although none had blood pressure exceeding 160/95 mmHg, which is the World Health Organisation definition in the absence of multiple risk factors. Most studies explicitly excluded co-morbidities but the presence of diabetes could make the lower WHO guideline blood pressure of 140/90 mmHg inappropriate. See table 1 for the definitions of ‘normotensive’ used in the different trials.

Both insulin dependent and non-insulin-dependent diabetes mellitus patients are included in randomised controlled trials usually of captopril (25 to 100 mg/day) or enalapril (5 to 20 mg/day). Lisinopril was used in one study, the dosage being chosen to reduce glomerular filtration rate to at most 140 mL/min. Sample sizes in individual studies were often small. The numbers on angiotensin converting enzyme inhibition and placebo who completed their respective courses were 237 and 234 out of a total of 538 patients admitted to studies in the meta-analyses and 304 and 304 out of 681 patients overall. Most patients initially had microalbuminuria but some had overt albuminuria. When the age of onset of diabetes was specified, it was always less than 41 years.

**METHODOLOGICAL QUALITY**

The 12 studies had a variety of inclusion/exclusion criteria but all were randomised control studies in which normotensive diabetics received an angiotensin converting enzyme inhibitor for at least one year. Randomisation was reported to have been concealed in only two of these trials. Blinded outcome was mentioned for most but the use of intention-to-treat analyses were less in evidence. Six studies reported steps taken to establish compliance. No study continued until patients experienced end-stage renal failure. Reasons for withdrawal were generally given but in three studies it was not possible to identify the treatment group of patients withdrawing prior to the end of the study. The reported reasons for dropouts show little difference between treated and control patients.

The quality of studies was assessed using a score with seven components, based on Kleijnen 1991. This allocates 30 of the available 100 points for the numbers of patients in the groups compared. Only the study excluded from the meta-analyses and one other were large enough to obtain more than ten of these and most scored zero. Maximum scores available for other aspects were patient characteristics (10), randomisation (20), intervention descriptions (5), double blinding (20), relevance and description of outcomes (10), and checkability of analysis (5). The average score of meta-analyses studies was 55 (range 34-78).

**RESULTS**
Except where otherwise stated, these results refer to studies included in the meta-analyses.

BASELINE DATA
The proportions of males were not significantly heterogeneous and overall, at 54% and 58% did not differ substantially for the treatment and control groups. Duration of diabetes was not significantly heterogeneous or different for the 11 studies with estimates, the treatment and control means being 12.3 and 12.7 years, respectively. Age on admission to the 12 combined studies varied because of patient selection criteria used but, if it were considered reasonable to perform a test, overall the studies would not be found to be significantly heterogeneous. Less surprisingly, because of de facto within study matching, the average ages of all those receiving and those not receiving angiotensin converting enzyme inhibition were the same, at 41 years. Body mass index was available for eight of the studies, some of which stated an upper limit for trial acceptance. Most studies had a (baseline) lower average body mass index in their treatment group; pooled mean body mass indices being 23.8 and 23.2 for patients on placebo and angiotensin converting enzyme inhibition, respectively. The difference has a 95% confidence interval from 0.4 to 0.9 and is highly significant. Those studies that provided data on baseline insulin dose exhibited no significant heterogeneity or difference between treated and untreated groups.

The studies do not exhibit significant heterogeneity in initial mean systolic, diastolic or arterial blood pressures even though the latter may have been the subject of varying definitions. The pooled mean initial blood pressures were non-significantly higher for those treated with angiotensin converting enzyme inhibitors (130/78 mmHg) than for those on placebo (128/78 mmHg). But the five mean arterial pressures of those assigned to angiotensin converting enzyme inhibitors had a significantly higher average (96.7 compared to 95.4 mmHg), the excess having 95% confidence interval 0.8 to 2.9 mmHg.

The ten studies for which adequate estimates were available did not have significantly heterogeneous or different initial glycosylated haemoglobin, means being 8.9% and 8.7% for the angiotensin converting enzyme inhibition and control groups, respectively. Glomerular filtration rates could be compared for patients entering seven studies. Again there was no significant heterogeneity between the studies and the pooled means were not significantly different for angiotensin converting enzyme inhibitor and control groups, at 125 and 128 ml/min/1.73m², respectively.

Baseline albumin excretion rates that had been measured in mg per day were not significantly heterogeneous or different, averaging 134 and 129 for treatment and control. But those measured in microg per minute (treatment mean 96; control mean 115) were significantly heterogeneous. After logarithmic transformation, to counteract distributional skewness, neither heterogeneity or difference between treated and untreated groups remained significant.

END OF STUDY DATA
The seven studies with estimates for systolic and diastolic blood pressure were very highly significantly heterogeneous, as were the five with end of study arterial pressures (p<0.001). This reflects different policies on blood pressure targets and the addition of other antihypertensive treatments. Pooled mean blood pressures for the treated group were lower than for the untreated group for all three types of pressure (127/76 and 97 mmHg for treated; 129/79 and 101 mmHg for control), but mean blood pressures for individual studies did not all follow the same pattern and the heterogeneity renders the differences nonsignificant.

End of study glycosylated haemoglobin showed significant heterogeneity between ten studies (Hansen et al (1994) being used vice Viberti et al (1994)). (Chisquared was 20 with nine degrees of freedom; p<0.025). Values for the angiotensin converting enzyme inhibitor (8.8%) and placebo (8.7%) groups were, however, very close. End of study glomerular filtration rate was homogeneous for five studies compared, also with no significant difference between the two groups of patients (treatment 121; control 119 ml/min/1.73m²).

End-of-study albumin excretion rates measured in microg per minute were very significantly heterogeneous but this was entirely removed by (skewness and variance reducing) logarithmic transformation. The overall treatment mean (98 mg per day; 71 microg per minute) was significantly lower than the corresponding control group mean (285 mg per day; 187 microg per minute).

STUDY CHANGES IN BLOOD PRESSURE
The studies for which initial and final systolic and diastolic blood pressure were available did not
have homogeneous data (p<0.001) although, curiously, those with mean arterial blood pressure were not so different (p>0.1) despite not having the same definition in all studies. Estimated mean changes in systolic and diastolic pressures during the course of trials were downward for those on angiotensin converting enzyme inhibition (130/78 to 127/76 mmHg) and upwards for controls (128/78 to 129/79 mmHg) despite the use of other antihypertensives in some cases. Mean arterial pressure rose little for the angiotensin converting enzyme inhibitor group (96.7 to 97.0 mmHg) and not as much as for the controls (95 to 101 mmHg). Thus overall a significantly greater antihypertensive effect was experienced by initially normotensive patients in the angiotensin converting enzyme inhibitor than in the placebo group. The relatively large study excluded from meta-analysis (Laffel 1995) had results consistent with the above.

STUDY CHANGES IN GLYCOSYLATED HAEMOGLOBIN
Where beginning and end of study data were available, the differential effect on glycosylated haemoglobin was not significantly heterogeneous. The pooled mean effect was just significant with an average fall from 8.89% to 8.85% for the treated groups and a rise from 8.71% to 8.74% in the control groups. Glycaemic control did not differ between treatment and control groups in Laffel 1995.

STUDY CHANGES IN GLOMERULAR FILTRATION RATE
Where beginning and end of study data were available, the differential effects were not significantly heterogeneous and pooled mean effects were not significantly different for glomerular filtration rate.

STUDY CHANGES IN ALBUMIN EXCRETION RATE

   The 12 studies were extremely heterogeneous with regard to the differing effects of placebo and angiotensin converting enzyme inhibition on albumin excretion rate (chisquared with 11 degrees of freedom = 120; p < 0.001), more so for those measured in microg/min (chisquared with 4 degrees of freedom = 104; p < 0.001) than for those in mg/day (chisquared with 6 degrees of freedom = 15; p < 0.025). This is partly because albumin excretion rate has a very skewed distribution. Logarithmic transformation reduces but does not eliminate the heterogeneity overall (chisquared with 11 degrees of freedom = 30; p < 0.005), or separately for those measured as mg/day (chisquared with six degrees of freedom = 15; p < 0.025), or microg/min (chisquared with four degrees of freedom = 15; p < 0.005). Albumin excretion rate fell for patients on angiotensin converting enzyme inhibition in 11 of the 12 studies but did so for only two of the 12 groups on placebo. The estimated effect of angiotensin converting enzyme inhibition was highly significant (p < 0.001) whether fixed, random, weighted or standardised models were used. The pattern of effects is the same and significant in both measurement subgroups.

   In seven studies the patients were exclusively described as type 1 or insulin dependent and in four as solely type 2 or non-insulin-dependent. Angiotensin converting enzyme inhibition provided a significant reduction in albumin excretion rate in both groups as well as in the remaining study, which included both types of diabetic patient.

   Captopril, enalapril and lisinopril were used in five, six and one of the combined studies, respectively. All three angiotensin converting enzyme inhibiting drugs significantly reduced albumin excretion rate in comparison with controls.

   Captopril was prescribed for insulin dependent subjects in Laffel 1995, where albumin excretion rate increased at an annual rate of 11.8% (95% confidence interval -3.3% to 29.1%) in the placebo group while it declined by 17.9% (95% confidence interval -29.6% to -4.3%) in the captopril group (p=0.004); results consistent with those of the meta-analyses.

DISCUSSION

There appears to be a rise in blood pressure associated with the change from normoalbuminuria through microalbuminuria (Mathiesen 1991) to macroalbuminuria. Patients may start and some remain normotensive, although with higher pressures than normoalbuminurics (Viberti 1984) and an increased proportion of hypertensives (Parving 1993). This is true of both insulin dependent and non insulin dependent diabetes mellitus patients (Parving et al 1993). Eventually diabetic patients become hypertensive and hypertensive diabetic patients benefit from the use of antihypertensive drugs, including angiotensin
converting enzyme inhibitors, since reduction of blood pressure slows the progression to end-stage renal failure (Mogensen 1982; Parving 1983; Parving 1987; Mathiesen 1989). When systemic blood pressure can be lowered by 20%, as is desirable and achievable in more severely hypertensive patients, angiotensin converting enzyme inhibitors, conventional therapy, and several calcium antagonists all have a reported antiproteinuric action (Böhlen 1994).

Intraglomerular hypertension may exist whether or not systemic hypertension is present (Anderson 1988). Assuming that intraglomerular hypertension is an independent contributor to progressive renal injury, drugs that specifically lower intraglomerular pressures independent of their effect on systemic blood pressure might prove especially beneficial in reducing the rate of progression of renal insufficiency. The angiotensin converting enzyme inhibitors are such a group of drugs. The proposed beneficial effect in renal disease is predicated on their ability to predominate alter efferent arteriolar tone and consequently decrease intraglomerular pressure independent of their effect on systemic blood pressure (Sirmon 1991).

The EUCLID study (EUCLID 1997) found that lisinopril had scarcely any effect on the albumin excretion rate of those starting with normoalbuminuria but considerable effect on the albumin excretion rate of those with microalbuminuria. The purpose of treating microalbuminuric diabetic patients with angiotensin converting enzyme inhibitors is not to reduce albumin excretion rate or to prevent its progression per se, but to prevent a future decline in glomerular filtration rate which otherwise would be expected in the majority of these patients (Mogensen 1995) and lead to end-stage renal failure and cardiovascular death (Passa 1992). In the natural history of diabetes the decline in glomerular filtration rate usually occurs with the development of overt proteinuria. At the stage of normo- or micro-albuminuria, glomerular filtration rate is generally well preserved and may even be at the supranormal level (Mogensen et al 1992). A meta-analysis of controlled and noncontrolled studies, lasting at least 6 months, on diabetics and non-diabetics found that, in addition to the long-term beneficial effects of antihypertensive agents, angiotensin converting enzyme inhibitors have beneficial effects on proteinuria and glomerular filtration rate that are independent of blood pressure reductions (Maki 1995).

Definitions of normotensive varied for the studies included in this report (see description of studies), but reduction of albumin excretion rate associated with lowered blood pressure appears to be no respecter of thresholds.

Albuminuria, like hypertension, is defined with reference to an underlying continuous variable. Microalbuminuria was defined either as 30 to 300 mg/day or as 20 to 200 microg/min, usually found in at least two out of three determinations. Albumin excretion rates were obtained by differing techniques, recorded sometimes as mg/24h and sometimes as microg/min, and reported as arithmetic or geometric means or medians, perhaps after transformation. But the beneficial effect of angiotensin converting enzyme inhibition in limiting its rise is clear. None of the studies lasted long enough to establish a relationship with end-stage renal failure, but after an open follow-up extension of their study Ravid et al (Ravid 1996) concluded that treatment with enalapril resulted in an absolute risk reduction of 42% for nephropathy to develop during seven years (95% confidence interval 15% to 69%; p<0.001).

The early use of angiotensin converting enzyme inhibition on normotensive microalbuminuric diabetics appears to produce intermediate benefits on both blood pressure and albumin excretion rate. It has been suggested that treatment at the onset of microalbuminuria is an extremely cost-effective therapy (Rodby 1996).

**REVIEWERS' CONCLUSIONS**

**Implications for practice**

Inhibition of angiotensin converting enzyme can arrest and even reduce the albumin excretion rate in microalbuminuric normotensive diabetics. This is accompanied by some reduction or prevention of increase in systemic blood pressure and it is not possible to be certain that reduction of albumin excretion rate is due to a separate renal effect. There appear to be no
substantial side effects. A direct link with postponement of end-stage renal failure has not been demonstrated.

**Implications for research**

Studies which are sufficiently longterm to examine directly the relationship between early use of angiotensin converting enzyme inhibitors and end stage renal failure are still desirable. Ideally these should be carried out in representative groups of patients with both insulin dependent diabetes mellitus and non insulin dependent diabetes mellitus.

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**ACKNOWLEDGEMENTS**

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**POTENTIAL CONFLICT OF INTEREST**

None known.

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**NOTES**

This update was done quite a while before the establishment of the Metabolic and Endocrine Disorders Group, but never published. As two new studies are included in the review we feel that it is appropriate to include the new version. Readers should realise, however, that a new update is due now and that further work will be necessary on this review in the near future.

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**TABLES**

**Characteristics of included studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Ahmad 1997</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Five year prospective randomised single-blind placebo controlled trial.</td>
</tr>
<tr>
<td>Participants</td>
<td>Type 2 nonobese diabetics (120 recruited; 103 analysed). Persistent AER 20-200 microg/min on two consecutive visits, and normal renal function. Age 43-55 years and known duration of diabetes &lt; 15 years. No evidence of non-diabetic renal, systemic, cardiac, hepatic or urinary tract diseases. BMI &lt; 27 kg/m2. GF &lt;= 90 ml/min.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Three months pretreatment then randomised to enalapril 10 mg/day or placebo (similar but not identical tablets). Diet plus oral hypoglycemic agents (60), diet alone (26), or insulin (17). If systolic BP 145 mmHg or more or diastolic BP 95 mmHg or more treatment with long-acting nifedipine was initiated.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Albumin excretion rate, blood pressure, fasting plasma glucose, glycosylated haemoglobin, glomerular filtration rate, renal plasma flow, urinary urea, diabetic retinopathy.</td>
</tr>
<tr>
<td>Notes</td>
<td></td>
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<tr>
<td>Study</td>
<td>Methods</td>
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<tr>
<td>Bakris 1994</td>
<td>Parallel design lasting 18 months. Seven dropouts; four non compliant, one with dizziness and orthostasis, two because of schedule conflicts with their jobs. All subjects were placed on a 120 mEq sodium, 1.0 g per kg protein diet.</td>
</tr>
<tr>
<td>Bilo 1993</td>
<td>Duration one year. Patients were randomised in double blinded order.</td>
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<tr>
<td>Chase 1993</td>
<td>Double blind placebo controlled trial lasting two years. Diabetic nephropathy (albumin excretion rate of 20 to 200microg/min on at least three of four initial overnight urine collections). Seen every three months.</td>
</tr>
<tr>
<td>Hallab 1993</td>
<td>Randomised, double blind, double dummy parallel study for one year after a three month, single blind placebo period</td>
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<tr>
<td>Study</td>
<td>Interventions</td>
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<td>----------------------------------------------------</td>
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<tr>
<td>Laffel 1995</td>
<td>Enalapril 20mg or hydrochlorothiazide 25 mg. Patients were instructed to follow a constant isocaloric diet.</td>
</tr>
<tr>
<td>Marre 1988</td>
<td>Captopril 50 mg or placebo BID. Diet and insulin management were not altered unless diet exceeded the 50-60% carbohydrate, 30% fat, 20% protein guideline or HbA1c exceeded 11.5%. If blood pressure was 140/90 mmHg or more at two consecutive visits, prazosin or clonidine was prescribed.</td>
</tr>
<tr>
<td>Mathiesen 1991</td>
<td>Initially 25 mg captopril; increased to 100 mg; then thiazide added versus placebo.</td>
</tr>
</tbody>
</table>
### Outcomes
- Albuminuria; kidney function; systolic, diastolic and arterial blood pressure.

### Notes
- Some raw data given.

### Allocation concealment
- B

#### Study
- **Parving 1989**

#### Methods
- Open randomised study for one year.

#### Participants
- Thirtytwo normotensive insulin dependent diabetics with nephropathy.

#### Interventions
- Captopril 25-100 mg/day or no treatment. Usual diabetic diet without sodium or protein restriction.

#### Outcomes
- Albuminuria; mean arterial blood pressure; glomerular filtration rate; glycosylated haemoglobin A1c.

### Notes
- Allocation concealment: B

#### Study
- **Ravid 1994**

#### Methods
- Randomised, double blind, placebo controlled trial lasting five years.

#### Participants
- Ninetyfour normotensive aged under 50 type II diabetics with microalbuminuria (30-300 mg/h) and normal renal function.

#### Interventions
- For five years, enalapril maleate 10mg/day or placebo. Long acting nifedipine added if blood pressure rose above 140/90 mmHg. After five years, patients could choose, and some received additional antihypertensive treatment.

#### Outcomes
- Albumin excretion rate; blood pressure; serum creatinine; fasting blood glucose; glycosylated haemoglobin; retinopathy; total cholesterol, HDL, LDL, and triglyceride.

### Notes
- A two year follow-up of the original five year trial was no longer double blind.

#### Study
- **Sano 1995**

#### Methods
- A four year randomised prospective study.

#### Participants
- Sixtytwo normotensive non insulin dependent diabetics aged 45-70 years, with normal renal function, persistent microalbuminuria (AER 20-300 mg/day on 3-4 separate occasions), serum creatinine < 106.1 mumol/l, HbA1c < 10%, and supine blood pressure < 150/90 mmHg.

#### Interventions
- Enalapril 5 mg/day or no treatment.

#### Outcomes
- Blood pressure; 24h urinary albumin excretion; N-acetyl-beta-glucosaminidase, beta2-microglobulin; Creatinine clearance; serum glycosylated haemoglobin A1c; total cholesterol; and triglycerides.

### Notes
- Data from Sano 1995 replace those from Sano 1994 used in the first edition of this review. Twentysix hypertensives, well controlled with nifedipine, were reported in Sano 1994 but excluded from the review.

#### Study
- **Stornello 1989**

#### Methods
- Double blind randomised design lasting one year.

#### Participants
- Sixteen normotensive, age 40-55, type II diabetics with persistent proteinuria.
Interventions | Enalapril 5 mg or placebo.
---|---
Outcomes | Blood pressure; heart rate; urinary albumin excretion; plasma renin activity and aldosterone; blood glucose; serum fructosamine; urine urea; body weight.
Notes | 161x758
Allocation concealment | B

**Study** Viberti 1994

**Methods** Multicentre randomised (in blocks of two), double blind, placebo controlled trial of two years duration. Albumin excretion rate in range 20-200 microg/min at screening and at least two of three consecutive determinations.

**Participants** Ninetytwo normotensive insulin dependent diabetics, aged 18-55 onset before 39, with persistent microalbuminuria. None had been treated with antihypertensives.

**Interventions** Captopril 50 mg or placebo twice per day. No change in diet. If hypertension later diagnosed, stepped treatment included a betablocker, a diuretic and a vasodilator.

**Outcomes** Albumin excretion rate; blood pressure; glycosylated haemoglobin; urinary urea nitrogen excretion; glomerular filtration rate.

**Notes** Compliance monitored. A subset used for some comparisons.

**Allocation concealment** B

---

### Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anonymous 1996</td>
<td>To avoid double counting. This is a reanalysis of the Laffel and Viberti studies which have been included.</td>
</tr>
<tr>
<td>EUCLID 1997</td>
<td>This study included some patients with normoalbuminuria. Also results were in diagrams rather than useable tables and correspondence did not elicit further data.</td>
</tr>
<tr>
<td>Heinemann 1996</td>
<td>The study lasted less than a year.</td>
</tr>
<tr>
<td>Melbourne 1991</td>
<td>This study used both hypertensive and normotensive patients. It was excluded because the numbers of normotensive patients randomised to perindopril and nifedipine are not given and so data for the normotensives could not be separately identified.</td>
</tr>
<tr>
<td>Mogensen 1992a</td>
<td>Only an abstract was available and this provided insufficient information.</td>
</tr>
<tr>
<td>Molyneaux 1996</td>
<td>treatment lasted less than a year and not all patients were normotensive.</td>
</tr>
<tr>
<td>Trevisan 1995</td>
<td>This study lasted less than a year and included some mildly hypertensive patients.</td>
</tr>
</tbody>
</table>
Table 01 Definition of 'normotensive' used in trial

<table>
<thead>
<tr>
<th>Trial</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmad 1997</td>
<td>&lt;=140/90 mmHg sitting, after 15 minutes rest on two consecutive examinations</td>
</tr>
<tr>
<td>Bakris 1994</td>
<td>&lt;140/90 mmHg implied; &gt; 110/60 mmHg stated</td>
</tr>
<tr>
<td>Bilo 1993</td>
<td>&lt;145/90 mmHg on two separate occasions; no antihypertensives</td>
</tr>
<tr>
<td>Chase 1993</td>
<td>&lt;=141/90 mmHg; no antihypertensive treatment</td>
</tr>
<tr>
<td>Hallab 1993</td>
<td>&lt;160/95 mmHg (supine); no antihypertensive treatment</td>
</tr>
<tr>
<td>Laffel 1995</td>
<td>&lt;140/90 mmHg in the absence of antihypertensive therapy</td>
</tr>
<tr>
<td>Marre 1988</td>
<td>&lt;160/95 mmHg (supine) for 3 months; no antihypertensives</td>
</tr>
<tr>
<td>Mathiesen 1991</td>
<td>diastolic &lt; 95 mmHg; but all subjects were &lt; 160/90 mmHg</td>
</tr>
<tr>
<td>Parving 1989</td>
<td>mean of at least 3 &lt;= 150/90 mmHg; no antihypertensives</td>
</tr>
<tr>
<td>Ravid 1994</td>
<td>&lt;=140/90 mmHg and mean BP &lt;107 mmHg twice, consecutively</td>
</tr>
<tr>
<td>Sano 1995</td>
<td>&lt;150/90 (supine) over a long period; no antihypertensives</td>
</tr>
<tr>
<td>Stornello 1989</td>
<td>&lt;140/90 (supine) on 3 consecutive visits; no antihypertensives</td>
</tr>
<tr>
<td>Viberti 1994</td>
<td>&lt;160/95 (35+ years), &lt;145/90 (&lt;35 years); no antihypertensives</td>
</tr>
</tbody>
</table>

REFERENCES

References to studies included in this review

Ahmad 1997 {published data only}

Bakris 1994 {published data only}

Bilo 1993 {published data only}

Chase 1993 {published data only}

Hallab 1993 {published data only}

Laffel 1995 {published data only}


Marre 1988 {published data only}


**Mathiesen 1991** (published data only)

**Parving 1989** (published data only)

**Ravid 1994** (published data only)


**Sano 1995** (published data only)


**Stornello 1989** (published data only)

**Viberti 1994** (published data only)


**References to studies excluded from this review**

**Anonymous 1996**

**EUCLID 1997**

**Heinemann 1996**

**Melbourne 1991**

**Mogensen 1992a**

Molyneaux 1996

Trevisan 1995

Additional references

Andersen 1983

Anderson 1988

Bergemann 1992

Bilous 1995

Borch-Johnsen 1985

Borch-Johnsen 1987

British Nat For 1997

Böhlen 1994

Elving 1992

Israili 1992

Kleijnjen 1991

Knowles 1971

Krolewski 1985

Lewis 1993

Liou 1995

Maki 1995

Mathiesen 1989

Mogensen 1982

Mogensen 1992b

Mogensen 1995

Mulec 1994

Parving 1983

Parving 1987

Parving 1988

Parving 1993

Parving 1994

Passa 1992

Rodby 1996

Sirmon 1991

Valentino 1991

Vane 1995
Vane J. Trumping the ACE. Lancet 1995;346:916.

Viberti 1984

Vora 1996

**GRAPHS**

To view a graph or table, click on the outcome title of the summary table below.

To view graphs using MetaView, click on the “Show metaview” link at the top of the graph.

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 baseline systolic blood pressure</td>
<td>9</td>
<td>382</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>0.80 [-0.48, 2.09]</td>
</tr>
<tr>
<td>02 baseline diastolic blood pressure</td>
<td>9</td>
<td>382</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>-0.39 [-1.45, 0.66]</td>
</tr>
<tr>
<td>03 baseline mean arterial blood pressure</td>
<td>5</td>
<td>222</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>1.87 [0.84, 2.89]</td>
</tr>
<tr>
<td>04 baseline glycosylated haemoglobin</td>
<td>10</td>
<td>441</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>0.02 [-0.16, 0.20]</td>
</tr>
<tr>
<td>05 baseline glomerular filtration rate</td>
<td>7</td>
<td>307</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>-1.81 [-5.93, 2.31]</td>
</tr>
<tr>
<td>06 baseline albumin excretion rate</td>
<td>12</td>
<td>519</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>-7.92 [-15.10, -0.74]</td>
</tr>
<tr>
<td>07 sex (proportion of males)</td>
<td>11</td>
<td>464</td>
<td>Peto Odds Ratio 95% CI</td>
<td>0.87 [0.60, 1.26]</td>
</tr>
<tr>
<td>08 years of diabetes</td>
<td>11</td>
<td>508</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>-0.19 [-0.66, 0.28]</td>
</tr>
<tr>
<td>09 age at start of study</td>
<td>12</td>
<td>524</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>-0.52 [-1.26, 0.22]</td>
</tr>
<tr>
<td>10 body mass index</td>
<td>8</td>
<td>451</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>-0.68 [-0.92, -0.45]</td>
</tr>
<tr>
<td>11 baseline insulin dose</td>
<td>4</td>
<td>119</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>0.04 [-0.03, 0.11]</td>
</tr>
<tr>
<td>12 end of study systolic</td>
<td>7</td>
<td>294</td>
<td>Weighted Mean 95% CI</td>
<td>-3.74 [-5.51, -1.96]</td>
</tr>
<tr>
<td>Measure</td>
<td>Study</td>
<td>N</td>
<td>Type</td>
<td>Weighted Mean Difference (Fixed)</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
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<td>------</td>
<td>-------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>13 End of study diastolic blood pressure</td>
<td>7</td>
<td>294</td>
<td>Weighted Mean Difference (Fixed)</td>
<td>-5.67 [-7.04, -4.30]</td>
</tr>
<tr>
<td>14 End of study mean arterial pressure</td>
<td>5</td>
<td>161</td>
<td>Weighted Mean Difference (Fixed)</td>
<td>-2.78 [-4.03, -1.53]</td>
</tr>
<tr>
<td>15 End of study mean glycosylated haemoglobin</td>
<td>10</td>
<td>389</td>
<td>Weighted Mean Difference (Fixed)</td>
<td>-0.09 [-0.23, 0.06]</td>
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<tr>
<td>16 End of study glomerular filtration rate</td>
<td>6</td>
<td>209</td>
<td>Weighted Mean Difference (Fixed)</td>
<td>0.91 [-4.02, 5.84]</td>
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<tr>
<td>17 End of study albumin excretion rate</td>
<td>12</td>
<td>503</td>
<td>Weighted Mean Difference (Fixed)</td>
<td>-153.89 [-168.90, -138.89]</td>
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<tr>
<td>18 Change in systolic blood pressure</td>
<td>7</td>
<td>294</td>
<td>Weighted Mean Difference (Fixed)</td>
<td>-3.49 [-5.77, -1.22]</td>
</tr>
<tr>
<td>19 Change in diastolic blood pressure</td>
<td>7</td>
<td>294</td>
<td>Weighted Mean Difference (Fixed)</td>
<td>-5.89 [-7.55, -4.22]</td>
</tr>
<tr>
<td>20 Change in mean arterial blood pressure</td>
<td>4</td>
<td>146</td>
<td>Weighted Mean Difference (Fixed)</td>
<td>-3.98 [-5.67, -2.30]</td>
</tr>
<tr>
<td>21 Change in glycosylated haemoglobin</td>
<td>9</td>
<td>374</td>
<td>Weighted Mean Difference (Fixed)</td>
<td>-0.36 [-0.60, -0.12]</td>
</tr>
<tr>
<td>22 Change in glomerular filtration rate</td>
<td>5</td>
<td>177</td>
<td>Weighted Mean Difference (Fixed)</td>
<td>0.71 [-6.10, 7.52]</td>
</tr>
<tr>
<td>23 Change in albumin excretion rate</td>
<td>12</td>
<td>503</td>
<td>Weighted Mean Difference (Fixed)</td>
<td>-136.95 [-154.20, -119.69]</td>
</tr>
<tr>
<td>25 Change in albumin excretion rate</td>
<td>12</td>
<td>503</td>
<td>Weighted Mean Difference (Fixed)</td>
<td>-6.53 [-7.35, -5.70]</td>
</tr>
<tr>
<td>26 Ln change in AER by type of diabetes</td>
<td>12</td>
<td>503</td>
<td>Weighted Mean Difference (Fixed)</td>
<td>-6.53 [-7.35, -5.70]</td>
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<tr>
<td>27 Ln change in AER by drug used</td>
<td>12</td>
<td>503</td>
<td>Weighted Mean Difference (Fixed)</td>
<td>-6.33 [-7.16, -5.51]</td>
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<tr>
<td>29 Ln end of study AER</td>
<td>12</td>
<td>503</td>
<td>Weighted Mean Difference (Fixed)</td>
<td>-1.09 [-1.88, -0.30]</td>
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<tr>
<td>Study</td>
<td>Weighted Mean Difference (Fixed)</td>
<td>95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>---------------------------------</td>
<td>-----------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 In baseline albumin excretion rate</td>
<td>Weighted Mean Difference (Fixed)</td>
<td>95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31 change in systolic BP by duration of study</td>
<td>Weighted Mean Difference (Fixed)</td>
<td>95% CI</td>
<td></td>
<td></td>
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<tr>
<td>32 change in diastolic BP by duration of study</td>
<td>Weighted Mean Difference (Fixed)</td>
<td>95% CI</td>
<td></td>
<td></td>
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<tr>
<td>33 ln change in AER by duration of study</td>
<td>Weighted Mean Difference (Fixed)</td>
<td>95% CI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**COVER SHEET**

**Title**
Angiotensin converting enzyme inhibitors in normotensive diabetic patients with microalbuminuria

**Reviewer(s)**
Lovell HG

**Contribution of reviewer(s)**
Information not supplied by reviewer

**Issue protocol first published**
Information not available

**Issue review first published**
Information not available

**Date of most recent amendment**
Information not available

**Date of most recent SUBSTANTIVE amendment**
01 April 1999

**Most recent changes**
Information not supplied by reviewer

**Date new studies sought but none found**
Information not supplied by reviewer

**Date new studies found but not yet included/excluded**
Information not supplied by reviewer

**Date new studies found and included/excluded**
Information not supplied by reviewer

**Date reviewers’ conclusions section amended**
Information not supplied by reviewer
External sources of support

- No sources of support supplied

Internal sources of support

- Scottish Health Purchasing Information Centre UK

Index Terms

Medical Subject Headings (MeSH)
Albuminuria [complications] [drug therapy]; Angiotensin-Converting Enzyme Inhibitors [therapeutic use]; Diabetes Mellitus [complications] [drug therapy]; Diabetic Nephropathies [prevention & control]; Kidney Failure, Chronic [prevention & control]; Randomized Controlled Trials
Mesh check words: Human

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