A comparative study of lisinopril and atenolol on low degree urinary albumin excretion, renal function and haemodynamics in uncomplicated, primary hypertension

O. Samuelsson, T. Hedner, S. Ljungman, H. Herlitz, B. Widgren, and K. Pennert

Departments of Nephrology, Clinical Pharmacology, and Internal Medicine, Sahlgrenska Hospital, University of Göteborg, Sweden

ICI-Pharma Göteborg, Sweden

Summary. The presence of slightly increased urinary albumin excretion (UAE), even at levels well below levels detectable by an ordinary dipstick, has been suggested as a predictor of cardiovascular morbidity and as a reflection of the degree of overall vascular permeability.

The aim of the present investigation was to study the effects of two different antihypertensive drug regimens, an ACE inhibitor and a β-adrenoceptor antagonist, on the low UAE rate observed in subjects with uncomplicated, mild to moderate primary hypertension.

After a 4-week placebo run-in period, 49 patients (mean age 54 y) were randomly assigned in a double blind manner either to further 4 weeks on placebo (P, n = 15), 8 weeks on lisinopril (L, n = 17; 20 mg/40 mg o.d.) or 8 weeks on atenolol (A, n = 17; 50 mg/100 mg o.d.). The 24-h UAE was measured every second week. At entry and after 4 weeks the glomerular filtration rate and the renal plasma flow were measured.

Both drugs lowered blood pressure (BP) to a similar extent after 4 and 8 weeks of treatment; the blood pressures were 160/106 (P), 159/104 (L) and 154/103 (A) at entry, and 133/83 (L) and 134/87 (A) at the end of the study after 8 weeks. On entry the 24-h UAE in all patients ranged from 4 to 49 mg (mean 14.1 mg), and it did not differ significantly between groups. After 4 weeks the UAE during 24 h was reduced by approximately one third in the lisinopril-treated group, and by 10% in the atenolol treated group (A, n = 17; 50 mg/100 mg o.d.). The 24-h UAE was measured every second week. At entry and after 4 weeks the glomerular filtration rate and the renal plasma flow were measured.

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It is concluded that in patients with uncomplicated, mild to moderate hypertension both an ACE-inhibitor, such as lisinopril, as well as a β1-selective adrenoceptor blocking agent, such as atenolol, may be used without particular preference with regard to the short-term effects on renal function and haemodynamics, and to the low level of UAE normally observed in such patients.

Key words: Hypertension, ACE-inhibition, Atenolol; urinary albumin excretion, renal haemodynamics, lisinopril, GFR, renal function, adverse events

The risk of a future cardiovascular complication varies substantially in individual untreated and treated hypertensive subjects [Kannel 1985; Samuelsson 1988]. Clinically apparent proteinuria, i.e. urinary albumin excretion (UAE) detectable by dip-slide test (sometimes referred to as macroalbuminuria), has been shown to be an important, independent prognostic factor for death and cardiovascular morbidity both in untreated and treated hypertensive populations [Kannel 1984; Samuelsson 1988]. In addition, a smaller elevation in UAE, often termed microalbuminuria, independently predicts cardiovascular complications in the diabetic population [Mogensen 1984; Mattock 1988]. Microalbuminuria has also been suggested to be of prognostic importance in non-diabetic hypertensive patients [Yudkin 1988; Ljungman 1990; Damsgaard 1990].

It has been suggested that increased UAE is one manifestation of a general increase in vascular permeability, and so it could be regarded as a sign of general vascular dysfunction [Deckert 1989; Shearman 1988]. Consequently, it is tempting to speculate that both macro- as well as microalbuminuria may be used as sensitive prognostic tools in the clinical management of hypertensive patients. It may also be hypothesised that any therapeutic intervention resulting in a reduction in the UAE may be associated with an improved cardiovascular prognosis. However, this hypothesis still remains to be tested in clinical studies.

Treatment with an ACE-inhibitor has been shown to reduce the UAE to a greater extent than treatment with other classes of antihypertensive agents in patients with renal disease and proteinuria in the nephrotic range [Rui-
Serum creatinine (μmol/l) 100.7 (14.0) 94.7 (13.8) 95.1 (12.2)
UAE during 24 h (mg/24 h) 14.3 (8.9) 15.9 (15.9) 12.4 (6.9)

Due to a few missing day samples the UAE during 24 h is based on 44 patients. (Placebo n = 13; Lisinopril n = 15; Atenolol n = 16)

### Patients and methods

After approval by the Ethics Committee of the Medical Faculty, 67 middle-aged patients with uncomplicated, mild to moderate primary hypertension were included in the run-in period of the study. All patients were previously treated and had their antihypertensive therapy withdrawn at least two weeks prior to the run-in period. The experimental design was a double-blind, randomised, parallel study group (Fig 1) comparing the effects of lisinopril and atenolol.

Subjects with a diastolic blood pressure (DBP), measured after 1 min of supine rest (Korotkoff Phase V), between 95 and 110 mm Hg after 4 weeks of single-blind, placebo treatment were eligible for the study. Patients with secondary hypertension, coronary heart disease, renal impairment, haematuria, bacteruria, albuminuria of more than 250 mg during 12 h (i.e. overnight), or any known contraindication to treatment with ACE-inhibitors, β-adrenoceptor blocking agents or thiazide diuretics were excluded. Patients with overt diabetes mellitus were also excluded, but the patients were not screened for any other abnormality in the carbohydrate metabolism (i.e. glucose tolerance tests were not done).

After the single-blind placebo run-in period 49 patients met the inclusion criteria. They were randomised into three groups to receive placebo for 4 weeks, or active treatment with lisinopril or atenolol for 8 weeks. The starting doses were lisinopril 20 mg o.d. or atenolol 50 mg o.d. If the blood pressure (BP) goal, a DBP below 90 mm Hg and a reduction of at least 10 mm Hg, was not achieved after 2 (or 4) weeks, the initial dose levels were doubled, and, if necessary, 25 mg hydrochlorothiazide was added after further 2 weeks.

BP was measured to the nearest 2 mm Hg with a mercury sphygmomanometer, with the patient supine, after 5 min rest, and after 1 min of standing. The patients attended the outpatient clinic every other week. Routine haematology and biochemistry variables were measured every 4 weeks. The UAE during day (07.00-19.00 h) and overnight (19.00-07.00 h) was measured every other week. The patients were advised to avoid any heavy physical exercise or training during the day as well as during the evening of the urinary collection period. The urinary albumin concentration was determined by radioimmunoassay (ALBUMIN RIA Kabi Pharmacia, Sweden), which had a detection limit of 0.4 mg/l. The urinary excretion of creatinine was not measured during the collection periods. On three occasions unexpected high levels of individual UAE were observed in direct temporal association with viral infections. Those values were excluded from the analyses. Renal function and renal haemodynamics were determined at the start and after 4 weeks of double-blind treatment. The glomerular filtration rate (GFR) was determined as the renal clearance of 51Cr-EDTA (Brechner-Mortensen and Rødbo 1976) and renal plasma flow (RPF) was measured as PAH-clearance using the continuous infusion technique [Ljungman 1980]. Clearance values were expressed as ml/min·1.73 m² body surface area (BSA). The renal extraction of PAH was not measured. Renal blood flow (RBF) was calculated as the ratio of the RPF and (1-the haematocrit value), renal vascular resistance (RVR) as the ratio of mean arterial pressure and RBF, and the filtration fraction (FF) as the ratio between GFR and RPF.

### Statistical methods and considerations

Standard statistical techniques were used to summarise and illustrate the features of interest of the data. The primary end points of the study were UAE by day, overnight and for 24 h after 4 and 8 weeks of treatment. Since this was an early explorative study of antihypertensive treatment effects on low degree UAE in uncomplicated hypertension, there were no relevant data in the literature for calculation and estimation of appropriate patient numbers. It was considered that a study size of 15 patients per group would permit meaningful exploration of the primary and the secondary objectives. The secondary objectives were GFR, RBF, FF and supine BP. The primary and the secondary objectives were analysed using analysis of variance. The assumption underlying the models, i.e. normality of residuals, was checked using various plotting techniques and was found to be satisfactory. In addition, the data subjected to analysis were tested for normality and the hypothesis of a normal distribution could not be rejected. Only two-tailed tests were performed and \( P < 0.05 \) was considered significant.

### Table 1. Entry characteristics of 49 patients with uncomplicated, mild to moderate hypertension. (Mean with (SD))

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Placebo n = 17</th>
<th>Lisinopril n = 17</th>
<th>Atenolol n = 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>14/1</td>
<td>15/2</td>
<td>14/3</td>
</tr>
<tr>
<td>Age (y)</td>
<td>52.4 (9.4)</td>
<td>56.2 (7.7)</td>
<td>52.5 (8.1)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>86.4 (10.1)</td>
<td>83.6 (13.9)</td>
<td>80.3 (9.2)</td>
</tr>
<tr>
<td>Supine SBP/DBP (mm Hg)</td>
<td>161/100 (21/6)</td>
<td>160/96 (15/5)</td>
<td>162/100 (5/7)</td>
</tr>
<tr>
<td>Supine heart rate (beats·min⁻¹)</td>
<td>70 (9)</td>
<td>71 (10)</td>
<td>71 (12)</td>
</tr>
<tr>
<td>Standing SBP/DBP (mm Hg)</td>
<td>159/109 (22/8)</td>
<td>159/106 (16/8)</td>
<td>158/108 (15/6)</td>
</tr>
<tr>
<td>Standing heart rate (beats·min⁻¹)</td>
<td>78 (10)</td>
<td>80 (12)</td>
<td>79 (15)</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
<td>100.7 (14.0)</td>
<td>94.7 (13.8)</td>
<td>95.1 (12.2)</td>
</tr>
<tr>
<td>UAE during 24 h (mg/24 h)</td>
<td>14.3 (8.9)</td>
<td>15.9 (15.9)</td>
<td>12.4 (6.9)</td>
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