The effects of an ACE inhibitor and a calcium antagonist on the progression of renal disease: the Nephros Study

Hans Herlitz1, Kevin Harris2, Teut Risler3, Geoffrey Boner4, Jacques Bernheim5, Jacques Chanard6 and Mattias Aurell1

1Mattias Aurell and Hans Herlitz, Department of Nephrology, Sahlgrenska Hospital, Göteborg University, Sweden, 2Kevin Harris, Department of Nephrology, Leicester General Hospital, University of Leicester, UK, 3Teut Risler, Sektion Nieren- und Hochdruckkrankheiten, Universitätsklinikum Tübingen, Germany, 4Geoffrey Boner, Institute of Hypertension and Kidney Diseases, Rabin Medical Center, Tel-Aviv University, Israel, 5Jacques Bernheim, Department of Nephrology and Hypertension, Meir General Hospital, Sapir Medical Center, Israel and 6Jacques Chanard, Service de Nephrologie, Dialyse, Hypertension et Transplantation Rénale, Reims, France

Abstract

**Background.** The renoprotective effect of ACE inhibition in chronic renal disease is well established but the studies on effects of calcium antagonists on progression of renal disease and on proteinuria have given varying results.

**Methods.** We conducted an open long-term randomized prospective multi-centre study comparing the combination of ramipril (R) and felodipine ER (F) with either drug alone in non-diabetic renal disease. Included were patients with uncontrolled hypertension (diastolic blood pressure (DBP)) $\geq$ 95 mmHg on treatment with a diuretic and a beta-blocker. Fifty-one patients received the combination of R and F, 54 patients R, and 53 patients F. The treatment goal was a DBP < 90 mmHg and a similar BP reduction in the three groups. Mean doses at the last visit were 5 + 5, 10 and 9 mg, respectively, after a mean treatment time of nearly 2 years. The progression of renal impairment was studied by serial measurements of serum creatinine, iohexol clearance, and albuminuria.

**Results.** The reduction in supine systolic (S) BP and DBP expressed as median values were $-19.0/-14.5$, $-14.3/-15.0$ and $-13.5/-13.3$ mmHg in the R + F, R, and F groups, respectively. There was no significant difference between the groups. When correction for the acute drug effect was performed the R + F group had a slower progression rate of the renal disease (loss of glomerular filtration rate (GFR) ml/min/year) compared with the F group ($P < 0.05$) but not to the R group ($P > 0.20$). There was a rise in albuminuria after 2 years in the F group ($P < 0.05$), but no significant change was found in the other groups.

**Conclusions.** In patients with non-diabetic renal disease the combination of an ACE inhibitor and a calcium antagonist in reduced doses used in addition to baseline therapy with beta-blockers and diuretics, tended to cause a better BP reduction as each drug *per se*. The R + F treatment also caused a slower progression of the renal disease compared with F alone. The combination treatment seems to afford better BP control and appears to be a favourable therapeutic option in patients with renal disease and hypertension.

**Keywords:** ACE inhibitor; albuminuria; calcium antagonist; hypertension; progression; renal disease

Introduction

In chronic renal disease, renal function often continues to deteriorate even if the initiating insult is no longer present. Hypertension is one of the most prominent risk factors for the progression of renal disease and antihypertensive treatment is considered the cornerstone therapy for slowing the progression of chronic renal failure [1,2]. In experimental models of both non-diabetic and diabetic renal disease, antihypertensive treatment with ACE inhibitors caused an improvement in systemic and glomerular hypertension leading to a diminished albumin excretion and to a slower rate of progression of renal disease when compared with conventional antihypertensive treatment [3]. In 1986, it was shown that ACE inhibition had a beneficial effect on the progression of human diabetic nephropathy which was beyond that achieved by the blood pressure (BP) lowering effect *per se* [4]. This finding
was later confirmed in a larger trial by Lewis et al. [5] who demonstrated a reduced risk of developing terminal renal failure after initiation of treatment with an ACE inhibitor in patients with type I diabetes and nephropathy. The mechanism of the renoprotective effect of ACE inhibition is not clear, but reduction in proteinuria via beneficial effects on glomerular haemodynamics and/or on the permeability and size-selective function of the glomerulus may play an important role. This concept was further strengthened by data from the REIN study performed in patients with non-diabetic renal disease [6]. In this study, patients with proteinuria of \( \geq 3 \text{ g/24 h} \) experienced a clear reduction in proteinuria and in the rate of decline in glomerular filtration rate (GFR), which could not be explained by the improved BP control alone.

Calcium antagonists, in addition to their pronounced BP reduction, also have favourable effects on renal haemodynamics and renal tubular sodium reabsorption. As this class of drugs also has other properties that could contribute to their ability to protect the kidney [7] they have also been used with the intention to attenuate progression of renal disease. In some experimental studies, calcium antagonists have been shown to retard progression of renal insufficiency [8,9] but in others no beneficial effect has been demonstrated [10,11].

Different types of calcium antagonists could act differently on the kidneys [12]. Studies with calcium antagonists of the non-dihydropyridine type have demonstrated a benefit on slowing progression of renal disease mirrored by reduction in proteinuria. However, calcium antagonists of the dihydropyridine type have had variable effects on renal disease progression and have often shown a lack of effect on proteinuria reduction. The effect of any putative renoprotective drug on proteinuria does, however, appear to be dependent on the BP reduction achieved [13].

As there is evidence that angiotensin II is involved in the progression of renal disease it would make sense to combine ACE inhibitors, which diminish generation of angiotensin II, and calcium antagonists, which interfere with the renal response to angiotensin II on post-receptor level. We, therefore, decided to conduct a randomized prospective multi-centre study to compare the long-term renoprotective effect of the combination of the ACE inhibitor ramipril (R) and the calcium antagonist felodipine (F) and each drug per se in patients with non-diabetic renal disease. The antihypertensive treatment was titrated with the aim of achieving the same BP control in the three study groups during the study period.

### Patients and methods

The protocol for this study was approved by the ethics committee of each of the five countries (UK, Germany, France, Israel, and Sweden) involved. The patients gave written informed consent.

### Study objectives

The primary objective of the study was to compare the progression of renal impairment in patients with hypertension and reduced renal function during treatment with the combination of ramipril + felodipine (R+F) with that seen with either drug alone at the same achieved BP. A secondary objective was to assess the long-term effects of the three types of treatment on the degree of proteinuria in the patients.

### Patients

Twenty-eight centres in Sweden, UK, Germany, France, and Israel took part in the study. Study participants were hypertensive patients of either sex, between 18 and 74 years old, with chronic nephropathy (nephrosclerosis, chronic glomerulonephritis, chronic pyelonephritis, or polycystic kidney disease) who had not received ACE inhibition or calcium antagonist treatment for at least 2 months. To enter the study supine diastolic blood pressure (DBP) (mean of two recordings) had to be \( \geq 95 \text{ mmHg} \) despite ongoing background therapy with a beta-blocker and a diuretic. This group of patients was at higher risk of progression because of uncontrolled BP on treatment with two antihypertensive agents. The beta-blocker and diuretic had to have been initiated at least 4 weeks before entry into the study. Chronic nephropathy was defined as a GFR value (Cr EDTA, inulin, or iothexol clearance) below the age-adjusted normal. Exclusion criteria were treatment with corticosteroids, non-steroidal anti-inflammatory drugs, immunosuppressive drugs, or anti-epileptic drugs; acute myocardial infarction or stroke within 6 months before entry into the study; renal artery stenosis (as judged by investigator), diabetes mellitus; systemic disease; heart failure or angina pectoris requiring treatment other than short-acting glyceryl trinitrate; renal transplantation; nephrectomy; known bladder dysfunction; known intolerance to dihydropyridine calcium antagonists or ACE inhibitors.

### Study design

After screening assessment, all eligible patients entered a 1-month run-in phase during which treatment was only with the background therapy with a beta-blocker and a diuretic (see Figure 1). The patients were asked to return to the hospital every second week for measurement of their BP. After 4 weeks, GFR, 24-h urinary albumin excretion, and routine biochemical tests were measured. Patients who had a supine DBP \( \geq 95 \text{ mmHg} \) and a GFR below the age-adjusted normal then entered the randomized open limb of the study.

The patients were randomly allocated to receive either the combination of R+F or either drug alone. The randomization code was prepared by Astra Hässele and the tablets were packed in blisters and supplied with a label showing the patients number. Each patient was given only the study medication carrying his or her number. The sequence of patients numbers was randomly assigned to each of the 28 study centres and the study medication randomly assigned to patient numbers in advance. Each centre received a set of randomization envelopes, one for each patient number.

R and F were available as 1.25, 2.5, 5 and 10 mg tablets. The tablets were packed in blisters labelled with dose
The NEPHROS Study

A progression study in renal disease.

level (low, medium-low, medium-high, high) in addition to the study code. The group randomized to receive the combination of R + F initially received 1.25 mg F + 1.25 mg R and the dose could be increased up to a maximum of 10 + 10 mg of each drug. The starting dose in the R and F groups was 2.5 mg once daily and the dose could be increased up to a maximum of 20 mg daily, respectively.

Each patient was examined by a physician at randomization and every 6 months thereafter. Six times during the first year and thereafter, four times a year the following measurements were made: BP and heart rate in the supine and standing positions, serum creatinine and electrolyte concentrations, liver enzymes, lipids, and uric acid.

Assessment of GFR and 24-h urinary excretion of albumin, sodium, and potassium were performed at months 3, 6, and 12 after randomization and every 12 months thereafter.

The study drug dose was increased every 2 weeks until DBP was reduced to below 90 mmHg. The doses of the background therapy (beta-blocker + diuretic) could be increased if necessary to control the BP once the maximal tolerated dose level of study drugs had been achieved. Addition of antihypertensive therapies other than those of the defined background therapy and the study drugs was not allowed. All tablets should be taken once daily in the morning before visit to the clinic for study assessments.

Other than the choice of antihypertensive therapy, the routine care of the patients was determined by their responsible physician according to local practice. The responsible physician, however, was asked not to modify any aspect of the patient’s care unless there was a clear clinical indication. Dietary intake with respect to protein content should remain as stable as possible throughout the entire study period. Patients were advised to adhere to modest sodium restriction and compliance was assessed by measurement of 24-h urinary sodium excretion.

Patients were withdrawn from the study if GFR fell below 10 ml/min, if goal BP DBP < 90 mmHg could not be attained despite treatment with maximal beta-blocker, diuretic, and study drug doses or if unacceptable adverse events could not be relieved by dose reduction of antihypertensive treatment. The analysis of the study was performed according to the intention to treat principle.

Measurements of BP and renal function

BP and heart rate were measured after 5 min in the supine position and after 1 min in the standing position at every visit. The recordings were made in duplicate, with at least 1 min between the recordings. BP was recorded using a mercury sphygmomanometer and measured to the nearest 2 mmHg. Systolic blood pressure (SBP) was recorded as Korotkoff phase I and DBP as phase V. Heart rate was recorded by pulse palpations for 30 s immediately after the recording of the BP. The measurements were taken at the same time of the day for every visit.

GFR was assessed by measuring the clearance of iohexol, inulin, or of chromium-51 EDTA using the single injection clearance technique with blood sampling after 150, 195, and 240 min [14]. Each individual centre employed the same method to determine the GFR consistently in all patients throughout the duration of the study. All clearance measurements were corrected to 1.73 m² body surface area.

Statistics

Differences between baseline and last value were compared using the non-parametric Fisher’s test for pair comparison. For two variables, GFR and serum creatinine the regression coefficient, i.e. the slope of a line that fits with all observed values in each patient, was calculated. Only patients with a follow-up time of at least 6 months were included in this analysis. In the analysis, GFR and serum creatinine were the dependent variables and the time from baseline the independent variable. In the statistical evaluation, the mean of all regression coefficients in each treatment group were compared. Differences between the groups with respect to regression coefficients were tested by means of Fisher’s permutation test. Adjustment for multiple comparisons was
performed by Bonferroni’s inequality within the set of comparisons between groups.

Results

One hundred and sixty-five patients were randomized into the study and 158 had complete BP data at baseline and at follow-up. Demographic and clinical data at baseline are shown in Tables 1 and 2 and there was no significant difference between the three groups in any variable. The number of patients with glomerulonephritis, nephrosclerosis, polycystic kidney disease, and tubulo-interstitial nephritis are shown in Table 3. Mean follow-up times and ranges were 1.83 (0.1–3.7), 1.52 (0.1–3.6), and 1.83 (0.3–3.8) years for the R+F, R, and F groups, respectively. The number of patients followed for 1 year were 44 in the R+F group, 37 in the R group, and 44 in the F group. Mean doses of medication at last visit were 5 mg for the combination of R+F, 10 mg for R alone, and 9 mg for F alone. The achieved sodium intake measured as urinary sodium excretion was 140 (113–230), 190 (138–220), and 170 (118–214) in the R+F, R, and F groups, respectively. They did not differ significantly from each other.

The reduction in SBP and DBP (baseline mean of last three values) is shown in Table 4. There was a significant decrease in SBP and DBP in all three groups (P < 0.001). The reduction in SBP and DBP tended to be more pronounced in the R+F group compared with the group treated with R alone but the difference did not reach statistical significance (P < 0.10 for SBP).

The attained BP (mean of the three last values) in the three groups are also shown in Table 3. The attained SBP was significantly lower in the R+F group compared with the R group (P < 0.05). The number of non-responders with respect to the BP goal (DBP < 90 mmHg) were in the R+F, R, and F groups 14%, 40%, and 17%, respectively. There was a combination of R+F, 10 mg for R alone, and 9 mg for F alone. The achieved sodium intake measured as urinary sodium excretion was 140 (113–230), 190 (138–220), and 170 (118–214) in the R+F, R, and F groups, respectively. They did not differ significantly from each other.

The reduction in SBP and DBP (baseline mean of last three values) is shown in Table 4. There was a significant decrease in SBP and DBP in all three groups (P < 0.001). The reduction in SBP and DBP tended to be more pronounced in the R+F group compared with the group treated with R alone but the difference did not reach statistical significance (P = 0.10 for SBP).

The attained BP (mean of the three last values) in the three groups are also shown in Table 3. The attained SBP was significantly lower in the R+F group compared with the R group (P < 0.05). The number of non-responders with respect to the BP goal (DBP < 90 mmHg) were in the R+F, R, and F groups 14%, 40%, and 17%, respectively. There was a

Table 1. Demographic data at randomization in patients treated with the combination of ramipril and felodipine ER and each drug alone

<table>
<thead>
<tr>
<th></th>
<th>Ramipril + felodipine</th>
<th>Ramipril</th>
<th>Felodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52 (45–60)</td>
<td>53 (43–61)</td>
<td>54 (49–62)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172 (164–181)</td>
<td>175 (169–180)</td>
<td>171 (163–176)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80 (70–92)</td>
<td>83 (73–92)</td>
<td>77 (65–91)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.7 (24.1–29.8)</td>
<td>27.2 (25.9–29.3)</td>
<td>26.6 (23.6–29.7)</td>
</tr>
<tr>
<td>Sex male (%)</td>
<td>65</td>
<td>65</td>
<td>84</td>
</tr>
</tbody>
</table>

Values are median and 25th and 75th percentiles.

Table 2. Clinical data at baseline in patients treated with the combination of ramipril and felodipine ER and each drug alone

<table>
<thead>
<tr>
<th></th>
<th>Ramipril + felodipine</th>
<th>Ramipril</th>
<th>Felodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>154 (145–166)</td>
<td>159 (145–170)</td>
<td>160 (145–169)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>99 (96–102)</td>
<td>100 (98–106)</td>
<td>98.5 (96–102)</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>115 (114–124)</td>
<td>120 (114–127)</td>
<td>120 (113–105)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>62 (58–72)</td>
<td>64 (58–72)</td>
<td>64 (60–72)</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>147 (123–208)</td>
<td>149 (139–204)</td>
<td>159 (123–204)</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m²)</td>
<td>43 (32–55)</td>
<td>44 (32–53)</td>
<td>41 (31–51)</td>
</tr>
<tr>
<td>Urinary albumin (mg/24 h)</td>
<td>530 (57–1584)</td>
<td>506 (33–2220)</td>
<td>365 (48–1351)</td>
</tr>
<tr>
<td>Urinary sodium (mmol/24 h)</td>
<td>166 (112–223)</td>
<td>172 (130–200)</td>
<td>160 (99–215)</td>
</tr>
</tbody>
</table>

Values are median and 25th and 75th percentiles.

Table 3. Underlying renal disease in 158 hypertensive patients treated with the combination of ramipril + felodipine ER or each drug alone; the number of patients is given

<table>
<thead>
<tr>
<th></th>
<th>Ramipril + felodipine</th>
<th>Ramipril</th>
<th>Felodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulonephritis</td>
<td>14</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Nephrosclerosis</td>
<td>12</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>10</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Tubulo-interstitial nephritis</td>
<td>6</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>
significant difference between the R + F group and the group that received R alone (P < 0.05). Heart rate did not change during treatment in any of the groups.

The urinary albumin excretion did not differ between the three groups at baseline (Table 2). As there was a large standard deviation of urine albumin relative to the mean, urine albumin was transformed to a normally distributed variable. In the statistical analysis of the transformed values, the urinary albumin excretion increased significantly during the treatment period in the F-group, median 25th and 75th percentile (0.137, −0.195 to 0.363, P < 0.05) while it tended to decrease in the R + F (−0.03, −0.362 to 0.318) and R (−0.103, −0.336 to 0.150) groups. There was no significant difference between the groups in this respect.

The change from baseline to last visit is determined by only two observed values rather than the complete data set. Therefore, an analysis was performed which took account of all the measured values in each patient. To do this a regression coefficient, i.e. the slope of a line that fits with the observed values in each patient, was calculated for each treatment group. Only patients with a follow-up time of at least 6 months were included in this analysis. The statistical evaluation was based on the mean of all regression coefficients in each treatment group.

Table 5 shows the median regression coefficients for GFR and 1/serum creatinine in each treatment group. It demonstrates that the R + F group had a 40% slower rate of progression compared with each drug alone but the differences did not reach statistical significance (P > 0.20 for both). It also shows that the R + F group had a tendency to a slower rate of progression of renal disease as measured by 1/creatinine compared with the F group (P = 0.06) but not to the R group during the study period. A differentiation between the acute effects of the interventions on GFR and 1/creatinine in the first few months vs the longer-term effects, was also performed. The acute effect was the difference between GFR or 1/creatinine at baseline and the first post-randomization measurement (at 3 months). A significant acute reduction in GFR was seen in the R group (−3.2 ± 7.0 ml/min, P < 0.01) while no significant change was found in the F (+0.4 ± 8.0 ml/min) and R + F (−0.7 ± 6 ml/min) groups, respectively. No significant difference between the groups was found in this respect. The long-term effect was estimated by calculating the regression coefficient from 3 months to the end of the study. In Table 5 it is shown that with respect to this long-term effect the R + F group had a significantly slower rate of progression compared with the F group (P < 0.05) but not to the R group (P > 0.20).

There was no significant correlation between either changes in or attained SBP or DBP and the rate of progression of renal disease (P > 0.10). Neither was there any significant correlation between changes in urinary albumin excretion and the rate of progression of renal disease (P > 0.20).

Table 6 shows the reasons for withdrawal from the study. Of note seven patients had to be withdrawn from the R group during the study because of uncontrolled hypertension, whereas no patient was

**Table 4. The effect of the combination of ramipril and felodipine ER and each drug alone on SBP and DBP**

<table>
<thead>
<tr>
<th></th>
<th>Ramipril + felodipine n = 51</th>
<th>Ramipril n = 53</th>
<th>Felodipine n = 54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in SBP (mmHg)</td>
<td>−19.0 (−34.7 to 10.8)***</td>
<td>−14.3 (−24.2 to 4.8)***</td>
<td>−13.5 (−29 to −7.5)***</td>
</tr>
<tr>
<td>Change in DBP (mmHg)</td>
<td>−14.5 (−21.7 to 9.7)***</td>
<td>−15.0 (−20.7 to 9.7)***</td>
<td>−13.3 (−19.3 to −10.9)***</td>
</tr>
<tr>
<td>Attained SBP (mmHg)</td>
<td>134 (127 to 144)*</td>
<td>139 (130 to 153)</td>
<td>139 (129 to 152)</td>
</tr>
<tr>
<td>Attained DBP (mmHg)</td>
<td>85.2 (79.9 to 88.3)</td>
<td>87.7 (79.3 to 94.3)</td>
<td>85.7 (82.3 to 88.3)</td>
</tr>
</tbody>
</table>

Both reductions (baseline–mean of the three last values) and absolute values (mean of the three last values) are given. Values are median and 25th and 75th percentiles. Adjustment for multiple comparisons has been performed. ***P < 0.001 compared with 0; #P < 0.05 R + F vs R.

**Table 5. Regression coefficient (change per year) for GFR and 1/serum creatinine in patients treated with the combination of ramipril-felodipine ER or each drug alone**

<table>
<thead>
<tr>
<th></th>
<th>Ramipril + felodipine n = 45</th>
<th>Ramipril n = 41</th>
<th>Felodipine n = 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall effect calculated from baseline GFR (ml/min/year) 1/creatinine (l/μmol/year) × 10⁻³</td>
<td>−3.2 (−6.8 to −0.4)***</td>
<td>−4.7 (−8.8 to −1.5)***</td>
<td>−4.8 (−8.1 to 0.8)***</td>
</tr>
<tr>
<td></td>
<td>0 (−1 to 0)*</td>
<td>0 (−1 to 0)***</td>
<td>0 (−1 to 0)***</td>
</tr>
<tr>
<td></td>
<td>−2.4 ± 7.3</td>
<td>−3.8 ± 6.9</td>
<td>−7.4 ± 13</td>
</tr>
<tr>
<td>Long-term effect calculated from 3 months GFR (ml/min/year) 1/creatinine (l/μmol/year) × 10⁻³</td>
<td>−3.8 (−6.8 to 0.9)***</td>
<td>−5.8 (−8.7 to 0.3)***</td>
<td>−6.0 (−11.0 to 2.3)***</td>
</tr>
<tr>
<td></td>
<td>0 (−1 to 0)</td>
<td>0 (−1 to 0)***</td>
<td>0 (−1 to 0)***</td>
</tr>
<tr>
<td></td>
<td>−2.8 ± 9.6</td>
<td>−2.1 ± 10.0</td>
<td>−9.0 ± 22</td>
</tr>
</tbody>
</table>

Values are median and the 25th to 75th percentile. For 1/creatinine mean ± SD is also given. Adjustment for multiple comparisons has been performed. *P < 0.05. **P < 0.01 compared with baseline. ***P < 0.001 compared with baseline. #P < 0.05 compared with F.
withdrawn from treatment from the R + F group for this reason.

Discussion

The present study is the first to demonstrate a potential benefit for combination therapy with a long-acting ACE inhibitor, R and a calcium antagonist of the dihydropyridine type, such as F when used in addition to baseline therapy with beta-blockers and diuretics, in non-diabetic patients with progressive renal disease and hypertension. It was possible to use lower doses of each drug and still achieve a favourable result as regards reduction in BP, effect on proteinuria and progression. The combination therapy tended to lower the rate of progression of renal disease and no increase in albuminuria occurred.

As calcium antagonists have been found to produce acute increases in GFR and ACE inhibitors cause acute drops in GFR we also calculated a progression rate from 3 months onwards. Long-term progression rate calculated in this way was significantly slower in the group with combined treatment as compared with the F group. This beneficial effect of the calcium antagonist in combination with an ACE inhibitor is probably a result of improved BP control but specific effects of the drug could not be excluded. However, the small number of patients included in each study arm and the variable follow-up time of the patients limit the possibility to draw firm conclusions from the present study in this respect.

ACE inhibition has been shown to decrease proteinuria and the rate of progression in both diabetic and non-diabetic renal disease [5,6]. In 1997, a meta-analysis of patients with non-diabetic renal disease showed that ACE inhibitors were more effective than other antihypertensive agents in reducing the development of end-stage renal disease [14]. However, it was not possible to determine whether this beneficial effect was a result of the greater decline in BP seen with ACE inhibition or to some other effects of ACE inhibition. A more recent meta-analysis [15] concluded that the renal protective effect of antihypertensive regimens containing ACE inhibitors were better than those without ACE inhibitors even after accounting for their greater BP lowering effect. This effect was greatest in patients with proteinuria.

Administration of ACE inhibitors prevents the generation of angiotensin II, which normally acts on the renal microvasculature, especially the efferent arteriole causing vasoconstriction. ACE inhibition would, therefore, decrease glomerular capillary pressure and thereby reduce the glomerular permeability to proteins, which are then filtered in lower amounts [16]. The ACE inhibitors may also confer their beneficial effects on the progression of renal disease by modulation of other processes independent of their ability to diminish glomerular hypertension [17].

Calcium antagonists have also been reported to possess renoprotective effects in chronic renal disease [18]. This class of drug preferentially dilate the afferent arteriole causing if anything an increase in glomerular capillary pressure, suggesting their renoprotective effect is independent of changes in glomerular capillary pressure. Calcium antagonists, however, have other beneficial effects that may contribute to their ability to protect the kidney under various circumstances. For example, they may diminish injury by retarding renal growth [19], improve glomerular size selectivity [20], attenuate mesangial entrapment of macro-molecules [21], and counteract or attenuate the mitogenic effects of various cytokines and growth factors [22].

Experimental data on the effects of calcium antagonists has shown variable results. In one experimental model, nifedipine was as good as enalapril in retarding the progression of renal disease [7] although in other models dihydropyridines had no effect [9]. The balance between the loss of intrarenal autoregulation, which occurs with calcium antagonists, and the magnitude of the BP reduction achieved may be important in determining the renal outcome following treatment with these drugs. As long as the BP is well controlled any increase in intraglomerular pressure caused by the decreased afferent arteriolar tone may be offset [23].

There are only a few human studies comparing the renoprotective effects of calcium antagonists and ACE inhibitors. Zuchelli et al. [24] in a prospective randomized controlled trial in non-diabetic renal disease compared the effects of captopril and nifedipine on hypertension and the progression of renal insufficiency. The rate of progression of renal disease assessed as 1/creatinine vs time, creatinine clearance vs

Table 6. Reasons for withdrawal from treatment in patients treated with the combination of ramipril and felodipine ER and each drug alone

<table>
<thead>
<tr>
<th>Reason for withdrawal</th>
<th>Ramipril + felodipine (n = 51)</th>
<th>Ramipril (n = 53)</th>
<th>Felodipine (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Major cardiovascular surgery</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adverse event</td>
<td>6</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Renal function deterioration (GFR &lt; 10 ml/min)</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Uncontrolled BP</td>
<td>0</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Lack of cooperation</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Violation of protocol</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
time and DTPA clearance vs time was retarded to a similar degree in both groups suggesting each drug was equally renoprotective. Concern has, however, been raised regarding this study as very few patients completed the 3-year study period. The data from the present study, having a mean observation time close to 2 years, do support the study by Zuchelli et al. [24]. In our study there was no difference in the rate of progression of renal disease between the ACE inhibitor and the calcium antagonist groups despite the fact that the latter significantly increased albuminuria.

A similar pattern of response was demonstrated by Rossing et al. [25] in patients with diabetic nephropathy. They compared the ACE inhibitor lisinopril with the long-acting dihydropyridine calcium antagonist nisoldipine with respect to proteinuria and decline in GFR. After 1 year there was a clear dissociation between the antiproteinuric effect and the effect on GFR. Albuminuria decreased in the lisinopril but not in the nisoldipine group, while the GFR decrease was less pronounced in the nisoldipine group. Recently the 4-year data from this study has been published demonstrating persistence of the previously reported pattern [26].

Most patients with renal insufficiency and hypertension need more than one antihypertensive drug to achieve BP control [27]. The data from the present study argue in favour of the combination of an ACE inhibitor and a long-acting dihydropyridine calcium antagonist as a promising renoprotective treatment in this group of patients. The combination therapy allowed the use of lower doses of each drug and still there was a high proportion of responders with respect to the target BP, no increase in proteinuria, and a tendency to a slower progression of the renal disease. In addition, no patient from the group receiving the combination treatment was withdrawn from treatment for failure to control the BP compared with seven patients in the group with R alone. There was no significant difference in the reduction of SBP and DBP between the three treatment groups in our study, but we, however, achieved a significantly lower SBP in the group with combination treatment as compared with the group treated with R alone. This difference may have contributed to the effects observed.

Only one clinical study using this combination therapy has been published previously [28]. This demonstrated that in patients with type II diabetes and nephropathy, BP could be lowered to a similar extent with verapamil or lisinopril in monotherapy or the combination of the two in reduced doses during 4 years. However, combination therapy lowered proteinuria to a greater extent than either drug alone.

In conclusion, the combination of the ACE inhibitor R and the calcium antagonist F in reduced doses used in addition to baseline therapy with beta-blockers and diuretics tended to cause better BP lowering response as either drug alone in patients with non-diabetic renal disease. In addition, the group with the combination therapy showed a tendency to a slower progression of the renal disease and a similar urinary albumin excretion as the R group alone. These data suggest that such combination therapy may be an efficient therapeutic strategy for achieving good BP control, and retarding the progression of non-diabetic chronic renal failure.

Investigators and institutions

Sweden. M. Aurell, H. Herlitz, and A. Alfredsson (Department of Nephrology, University of Göteborg), I. Odar-Cederlöf (Department of Nephrology, University of Stockholm), R. Larsson and Å. Lindell (Department of Nephrology, University of Linköping), P. Sjöström and R. Olander, (Regionsjukhuset, Örebro), L. Weiss and G. Welander (Karlstads lasarett), O. Mathillas and S. Cegdå (Skaraborgs sjukhus Falköping), E. Hilme (Kungälvs sjukhus), and Jan Carlström (Norra Alvsborgs läns sjukhus).

UK. K. Harris (Department of Nephrology, Leicester University), G. McInnes and R. S. C. Rodger (Western Infirmary, Glasgow), G. D. Johnston (Queens University, Belfast), D. Wheeler (Queen Elisabeth Hospital, Birmingham), and J. M. Main (University of Middlesexborough).

Germany. T. Risler (Eberhard-Karls-Universität, Tübingen), R. Fünfstück (Klinikum der Friedrich-Schiller-Universität Jena), R. Schäfer (Med. Klinik und Poliklinik, Universität Münster), G. Schütterle (Klinikum der Justus-Liebig-Universität, Giessen), C. Wanner (Mediziniche Universitätsklinik, Würzburg), and G. Kraatz (Ernst-Moritz-Arndt-Universität, Greifswald).

France. J. Chanard (Centre Hospitalier Universitaire dr Reims, Reims), F. Mignon (Hôpital Bichat, Paris), and P. Simon (Centre Hospitalier La Bauchée, Saint Brieuc).

Israel. G. Boner, J. Zabludowski, U. Gafter, and A. Chagnac (Rabin Medical Center, Beilinson and Golda Campus, Petah Tikva), J. Bernheim and E. Podjarny (Sapir Medical Center, Kfar Saba), C. Chaimovitz, and D. Tovbin (Soroka Medical Center, Beer Sheva).

Acknowledgements. The authors are grateful for the assistance of Clinical Data Care (CDC), Lund and the statisticians Anders Odén and Helena Johansson. This study was supported by a grant from Astra-Hässlé, Mölndal, Sweden.

References

Treatment with a calcium antagonist and an ACE inhibitor in renal disease


Received for publication: 19.2.01
Accepted in revised form: 7.7.01