Renal and cardiac effects of antihypertensive treatment with ramipril vs metoprolol in autosomal dominant polycystic kidney disease

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Abstract

Background. Hypertension is a common complication in autosomal dominant polycystic kidney disease (ADPKD). This prospective randomized double-blind study was performed to compare the renal and cardiac effects of the ACE inhibitor ramipril and the β-blocker metoprolol as first line therapy in ADPKD patients with hypertension.

Methods. Forty-six hypertensive ADPKD patients were randomized to either ramipril (n = 23) or metoprolol (n = 23). Twenty-four hour (24-h) ambulatory blood pressure (BP), glomerular filtration rate (GFR) as calculated by the Cockcroft and Gault formula, urinary albumin excretion (albumin/creatinine ratio), and left ventricular mass index (LVMI) were established at baseline and at yearly intervals. The total follow-up was 3 years. Baseline characteristics were similar in both groups.

Results. Mean arterial pressure (MAP) decreased significantly in both the ramipril and the metoprolol group (−8 ± 2 and −6 ± 2 mmHg; both P < 0.01). There was a significant decline in renal function during follow-up which was similar in patients treated with ramipril or metoprolol (−2.5 ± 0.7 vs −2.9 ± 0.8 ml/min/year; P = NS). After the 3 years follow-up, no differences in GFR, LVMI and urinary albumin excretion were observed between the ramipril and the metoprolol group (80.7 ± 10.7 vs 78.0 ± 7.6 ml/min, 102.6 ± 6.8 vs 100.3 ± 5.4 g/m²; and 42.6 ± 12.3 vs 70.3 ± 32.5 mg/g, respectively; all P = NS). A post-hoc analysis evaluating the effects of BP control, revealed that LVMI increased in patients with standard BP control while it remained stable in patients with rigorous BP control with a significant difference in LVMI between the groups after 3 years of follow-up (105.3 ± 6.3 vs 90.9 ± 4.7 g/m²; P = 0.017). Also, by the end of the study albuminuria was lower in patients with rigorous vs standard BP control (23.5 ± 6.7 vs 94.8 ± 35.4 mg/g; P = 0.05).

Conclusions. In our study population of hypertensive ADPKD patients, no differences in renal function, urinary albumin excretion and LVMI were detected between those treated with ramipril or metoprolol, respectively, during a 3 years follow-up. Rigorous BP control prevented an increase in LVMI and reduced urinary albumin excretion, suggesting a crucial role of BP control for slowing progression of cardiac and renal organ damage in ADPKD.

Keywords: autosomal dominant polycystic kidney disease; hypertension; left ventricular hypertrophy; progression of renal disease

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disease, accounting for 8–10% of the population requiring renal replacement therapy [1]. Hypertension is a prevalent complication in patients with ADPKD. It occurs early in the course of the disease and is associated with a faster deterioration of renal function [2,3]. In ADPKD patients, cardiovascular morbidity and mortality are increased in the presence of hypertension [4]. Left ventricular hypertrophy (LVH) and proteinuria, both risk factors for a worse renal prognosis in ADPKD, are also associated with elevated blood pressure (BP) [3,5,6].

Although early and effective treatment of hypertension is thought to be very important in order to slow disease progression and prevent cardiovascular complications, there is no consensus about the group of antihypertensive drugs that is most appropriate in patients with ADPKD. Evidence exists for an early and sustained activation of the renin–angiotensin–aldosterone system (RAAS) in ADPKD [7–9]. Also, glomerular hyperfiltration was observed during the initial stages of the disease [10,11]. These findings suggest that the RAAS might be the optimal target for the initial treatment of hypertension in ADPKD. Angiotensin-converting enzyme (ACE) inhibition has proven effective in delaying the loss of renal function in glomerular diseases and nephrosclerosis [12]. However, in patients with ADPKD, previous studies have failed to demonstrate a renoprotective effect of ACE inhibitors [12,13]. Although the ACE inhibitor enalapril has been shown to be more
effective than the calcium antagonist amlodipine in reversing LVH and reducing microalbuninuria (MA), the progression of renal disease over time was similar with either drug [14,15]. Also, hypertensive ADPKD patients treated with enalapril showed an equal decline in renal function as patients treated with the ß-blocker atenolol [13]. Apart from the type of antihypertensive therapy, a BP goal for the optimal preservation of renal function in ADPKD has not been defined. Until now, no randomized long-term trial was able to show a positive influence of rigorous vs standard BP control on the progression of renal disease in ADPKD [14,16]. However, in a 7-year prospective study rigorous BP control was more effective than standard BP control in reversing LVH, a major risk factor for cardiovascular morbidity and mortality [14].

This prospective, randomized, double-blind, 3-year follow-up study was undertaken to compare the effects of the ACE inhibitor ramipril and the ß-blocker metoprolol on renal function, left ventricular structure and urinary albumin excretion in hypertensive patients with ADPKD. In a post-hoc analysis, the renal and cardiac effects of rigorous vs standard BP control were examined.

**Patients and methods**

*Study population and study design*

Between 1998 and 2000, 46 hypertensive ADPKD patients from our outpatient clinic were randomized to either ramipril or metoprolol in a double-blind fashion. The diagnosis of ADPKD was defined by ultrasonographic criteria as described by Ravine et al. and a positive family history [17]. Inclusion criteria for the trial were: Confirmed diagnosis of ADPKD, age 18–65 years, evidence for hypertension (casual BP ≥140/90 mm Hg and/or presence of an antihypertensive medication), and serum creatinine ≤4.0 mg/dl. Exclusion criteria were as follows: Serum creatinine >4.0 mg/dl, myocardial infarction or cerebrovascular accident in the past 12 months, known intolerance to study medication, pregnancy or females without contraception, evidence for severe hepatic disease, use of immunosuppressants or non-steroidal anti-inflammatory drugs (NSAIDs), congestive heart failure, alcohol abuse or consumption of narcotics, the presence of a malignant disease or non-compliance of the subjects. The Medical Ethics Committee of the University Erlangen-Nuernberg, Erlangen, Germany, approved the protocol of the study and informed written consent was obtained from all study participants.

Antihypertensive therapy was discontinued for at least 2 weeks (in case of ß-blocker use for at least 4 weeks) prior to the beginning of the study. During this washout period, a medication with diuretics was allowed. After the washout period, patients received either 2.5 mg ramipril or 50 mg metoprolol per day. The maximum doses were 5 mg/day for ramipril and 100 mg/day for metoprolol. If the target BP of less than 135/85 mmHg (24-h ambulatory BP) was not achieved with the maximum dose of either drug, felodipin (5–10 mg/day) was given as second-line agent. If this medication was not sufficient, doxazosin and/or furosemide were added to the regimen.

The duration of the study was 3 years. Follow-up visits were scheduled at 3 monthly intervals. The follow-up visits included clinical assessment, measurement of resting BP and routine laboratory tests. All patients underwent 24-h ambulatory BP measurement (ABPM) and 2D guided M-mode echocardiography at baseline, at 1, 2 and 3 years of follow-up. Glomerular filtration rate (GFR) was calculated using the Cockcroft and Gault formula [18]. Primary end points of the trial were a doubling of serum creatinine, a 50% reduction in GFR, or the need for renal replacement therapy. Secondary end-points were changes in serum creatinine concentration, urinary albumin excretion and left ventricular mass index (LVMI).

**Blood pressure measurements**

Casual systolic and diastolic BP were measured with a standard mercury sphygmomanometer at each clinical visit. BP readings were taken with the patient seated after 5 min of rest. Ambulatory BP was measured over a 24-h period by the oscillometric method using an automatic non-invasive recorder (ICR 5200, SpaceLabs 90207, Spacelab Inc., Redmond, WA, USA). The monitor was programmed to measure BP at 15 min intervals between 7:00 a.m. and 10:00 p.m. and at 30 min intervals between 10:00 p.m. and 7:00 a.m. During measurement, patients performed their usual regular daily activities. For a post-hoc analysis, patients were stratified into two different BP control groups according to the mean 24-h ambulatory BP registered at the 3 years follow-up visit. Rigorous BP control was defined as a mean arterial pressure (MAP) of ≤97 mm Hg and standard BP control was defined as a MAP of >97 mm Hg.

**Echocardiography**

Standard two-dimensionally guided M-mode echocardiography was performed under cross-sectional control using a CS 192 PQ system (Picker International GmbH, Hitachi Medical Corporation, 1989) with an 2.5 MHz mechanical transducer. Measurements of the left ventricle were taken at end-diastole and end-systole according to the recommendations of the American Society of Echocardiography [19]. Measurements included interventricular septal thickness at end-diastole (IVSd), left ventricular internal dimension at end-diastole (LVIDD) and posterior wall thickness at end-diastole (PWTd). The left ventricular mass (LVM) was calculated using the Devereux-modified cube formula: 0.8 * 1.04 * {[(IVSd + LVIDD + PWTd) / 2] ^ 3 - LVIDD ^ 3} + 0.6 g [20]. The LVMI was calculated dividing LVM by body surface area (BSA). All echocardiographic measurements were performed by two experienced sonographers independently. Echocardiographic tracings were evaluated by both investigators without knowledge of patient’s clinical data. LVH was defined as LVMI >125 g/m² in men and >110 g/m² in women.

**Measurement of urinary albumin excretion**

Albumin excretion was measured in spot urine samples using an autoanalyzer (Nephelometer Behring Analyzer, Germany). The ratio between urinary concentrations of
Systolic BP (mm Hg) 143
Mean arterial BP (mm Hg) 106

This study and were randomized to either ramipril (n = 575) or metoprolol (n = 17). Of these, 37 patients (80.4%) completed the 3 year follow-up. Nine patients, two patients from the metoprolol and seven patients from the ramipril group, were excluded from the study for the following reasons. In the metoprolol group, one patient dropped out after 22 months because he became dialysis-dependent and another patient was excluded after 13 months due to non-adherence to the study medication. In the ramipril group, two patients dropped out because of drug-related cough after 3 and 4 months, respectively. One patient was excluded because of allergic exanthema and one because of gastrointestinal complaints, both within the first month after randomisation. Another patient stopped taking the study medication without consultation after 3 months, after experiencing perioral paresthesia. The five patients from the ramipril group mentioned above were subsequently switched to open label treatment with metoprolol. Of the two remaining patients dropped from the ramipril group, one was excluded after 19 months because of suspected drug-related sexual dysfunction and one after 16 months because of uncontrollable hypertension. During follow-up, two patients (one in each group) suffered an acute myocardial infarction. There were no cases of death.

The analysis was based on the 37 patients who completed the 3 year follow-up. Baseline characteristics of the study population are shown in Table 1. The two treatment groups were comparable with respect to age, body mass index, duration of hypertension, BP, baseline renal function, urinary albumin excretion and LVMI. Although there were more men in the ramipril than in the metoprolol group, gender distribution was not significantly different.

During follow-up, systolic, diastolic and mean arterial BP significantly decreased in both treatment groups (Table 2). The reduction in MAP was similar in the ramipril group and metoprolol group. The reduction in diastolic BP was greater in the metoprolol group, but this difference was not significant. Significant changes in LVMI were also noted, but conclusions about the mechanisms of the changes in LVMI would be speculative.

Table 1. Baseline clinical characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Ramipril (n = 17)</th>
<th>Metoprolol (n = 20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40.7 ± 2.2</td>
<td>40.0 ± 2.2</td>
<td>NS</td>
</tr>
<tr>
<td>Males/Females</td>
<td>10/7</td>
<td>7/13</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.5 ± 3.1</td>
<td>74.2 ± 2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.5 ± 0.6</td>
<td>24.6 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.96 ± 0.05</td>
<td>1.90 ± 0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of hypertension (years)</td>
<td>5.9 ± 1.9</td>
<td>8.1 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)α</td>
<td>143 ± 2</td>
<td>142 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)α</td>
<td>93 ± 2</td>
<td>90 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial BP (mm Hg)α</td>
<td>106 ± 2</td>
<td>104 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.30 ± 0.19</td>
<td>1.16 ± 0.09</td>
<td>NS</td>
</tr>
<tr>
<td>Estimated GFR (ml/min)</td>
<td>88.0 ± 9.5</td>
<td>87.3 ± 6.4</td>
<td>NS</td>
</tr>
<tr>
<td>Albumin/creatinine ratio (mg/g)</td>
<td>64.0 ± 21.6</td>
<td>75.3 ± 22.8</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>97.6 ± 6.1</td>
<td>95.0 ± 4.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

*24-h ambulatory BP.

Table 2. Cardiovascular and renal parameters at baseline and at 3 years follow-up in both treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 years</th>
<th>P-value</th>
<th>Baseline</th>
<th>3 years</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mm Hg)α</td>
<td>143 ± 2</td>
<td>130 ± 2</td>
<td>&lt;0.01</td>
<td>142 ± 2</td>
<td>131 ± 2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)α</td>
<td>93 ± 2</td>
<td>83 ± 1</td>
<td>&lt;0.01</td>
<td>90 ± 2</td>
<td>82 ± 1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean arterial BP (mm Hg)α</td>
<td>106 ± 2</td>
<td>99 ± 1</td>
<td>&lt;0.01</td>
<td>104 ± 2</td>
<td>98 ± 1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.30 ± 0.19</td>
<td>1.88 ± 0.50</td>
<td>&lt;0.01</td>
<td>1.16 ± 0.09</td>
<td>1.70 ± 0.41</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Estimated GFR (ml/min)</td>
<td>88.0 ± 9.5</td>
<td>80.7 ± 10.7</td>
<td>&lt;0.01</td>
<td>87.3 ± 6.4</td>
<td>78.0 ± 7.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Albumin/creatinine ratio (mg/g)</td>
<td>64.0 ± 21.6</td>
<td>42.6 ± 12.3</td>
<td>NS</td>
<td>75.3 ± 22.8</td>
<td>70.3 ± 32.5</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>97.6 ± 6.1</td>
<td>102.6 ± 6.8</td>
<td>NS</td>
<td>95.0 ± 4.2</td>
<td>100.3 ± 5.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

*24-h ambulatory BP.

*Comparison of the 3 years follow-up values between the two treatment groups.

Statistical methods

Statistical calculations were performed using the statistical software SPSS, version 8.0 for Windows (SPSS Inc., Chicago, IL, USA). All variables are expressed as mean ± standard error (SEM). For normally distributed variables, the means were compared using the Student’s t-test or ANOVA. For variables with non-parametric distribution, the Wilcoxon’s analysis was used for comparison. Repeated measures analysis of variance (MANOVA) was used to test for changes of parameters during follow-up. A two-sided P-value of <0.05 was considered significant for all tests.

Results

Forty-six hypertensive ADPKD patients were included in this study and were randomized to either ramipril (n = 23) or metoprolol (n = 23). Of these, 37 patients (80.4%) completed the 3 year follow-up. Nine patients, two patients from the metoprolol and seven patients from the ramipril group, were excluded from the study for the following reasons. In the metoprolol group, one patient dropped out after 22 months because he became dialysis-dependent and another patient was excluded after 13 months due to non-adherence to the study medication. In the ramipril group, two patients dropped out because of drug-related cough after 3 and 4 months, respectively. One patient was excluded because of allergic exanthema and one because of gastrointestinal complaints, both within the first month after randomisation. Another patient stopped taking the study medication without consultation after 3 months, after experiencing perioral paresthesia. The five patients from the ramipril group mentioned above were subsequently switched to open label treatment with metoprolol. Of the two remaining patients dropped from the ramipril group, one was excluded after 19 months because of suspected drug-related sexual dysfunction and one after 16 months because of uncontrollable hypertension. During follow-up, two patients (one in each group) suffered an acute myocardial infarction. There were no cases of death.

The analysis was based on the 37 patients who completed the 3 year follow-up. Baseline characteristics of the study population are shown in Table 1. The two treatment groups were comparable with respect to age, body mass index, duration of hypertension, BP, baseline renal function, urinary albumin excretion and LVMI. Although there were more men in the ramipril than in the metoprolol group, gender distribution was not significantly different.

During follow-up, systolic, diastolic and mean arterial BP significantly decreased in both treatment groups (Table 2). The reduction in MAP was similar in the ramipril group and metoprolol group. The reduction in diastolic BP was greater in the metoprolol group, but this difference was not significant. Significant changes in LVMI were also noted, but conclusions about the mechanisms of the changes in LVMI would be speculative.
and the metoprolol group (−8 ± 2 mm Hg vs −6 ± 2 mm Hg; \( P = NS \)). To achieve BP control, eight patients on ramipril and 10 patients on metoprolol needed additional antihypertensive therapy. The number of drugs applied for the treatment of hypertension was similar in ramipril and metoprolol-treated patients (1.7 ± 0.2 vs 1.8 ± 0.2; \( P = NS \)).

GFR significantly declined by an annual rate of −2.5 ± 0.7 ml/min/year in the ramipril and −2.9 ± 0.8 ml/min/year in the metoprolol group during the 3 years follow-up (both \( P < 0.01 \), Table 2). The drop in GFR was similar in both treatment groups (Figure 1). The combined renal end-point of the study was reached by five patients (14%), two patients in the ramipril and three patients in the metoprolol group. Of these, one patient in the metoprolol group reached end stage renal disease and the other patients experienced a doubling of serum creatinine or a reduction in GFR of at least 50%.

In both groups, no significant change in LVMI was observed during follow-up (Table 2). By the end of the study, there was no difference in LVMI between patients treated with ramipril or metoprolol (102.6 ± 6.8 vs 100.3 ± 5.4 g/m²; \( P = NS \)). LVH was present in eight patients (22%) at baseline (four patients in each group) and in 11 patients (30%) at the end of the observation period (six patients in the ramipril and five patients in the metoprolol group).

Also, no significant change in urinary albumin excretion was detected in either treatment group, although a numerical decrease in albumin/creatinine ratio was observed in patients receiving ramipril (Table 2). After 3 years of follow-up, no statistically significant difference in albumin/creatinine ratio was detected between the ramipril and the metoprolol group (42.6 ± 12.3 mg/g vs 70.3 ± 32.5 mg/g; \( P = NS \)).

In a post-hoc analysis, the effects of rigorous vs standard BP control on renal and cardiac outcome parameters were evaluated. For this purpose, patients were stratified into a group with rigorous BP control defined by a MAP of <97 mm Hg and a group with standard BP control defined by a MAP of >97 mm Hg according to the mean 24-h ambulatory BP measured at the 3 years follow-up. At baseline, the rigorous and the standard BP control group did not differ with respect to age (40 ± 2 vs 41 ± 2 years; \( P = NS \)), gender (males/females: 9/10 vs 8/10; \( P = NS \)), duration of hypertension (7.2 ± 2.3 vs 6.0 ± 1.8 years; \( P = NS \)), GFR (83.1 ± 8.6 vs 91.2 ± 6.4 ml/min/m²; \( P = NS \)), LVMI (94.5 ± 4.7 vs 97.0 ± 5.2 g/m²; \( P = NS \)), and urinary albumin/creatinine ratio (56.8 ± 23.2 vs 84.2 ± 19.8 mg/g; \( P = NS \)). Also, the distribution of the study medication was similar in patients with rigorous and standard BP control (ramipril/metoprolol: 8/11 vs 9/9; \( P = NS \)). However, in the standard BP control group body mass index was higher than in the rigorous BP control group (25.7 ± 0.5 vs 24.2 ± 0.3 kg/m²; \( P < 0.05 \)) and patients with subsequent standard BP control already had a higher MAP at baseline than patients with rigorous BP control on follow-up (108 ± 2 vs 102 ± 2 mm Hg; \( P < 0.05 \)). During follow-up, BP significantly decreased in both groups with a trend towards a stronger reduction in MAP in the rigorous compared with the standard BP control group (−9 ± 2 mm Hg vs −5 ± 2 mm Hg; \( P = 0.07 \)). Accordingly, there was a clear separation of the two groups by MAP throughout the observation period (Table 3).

A significant loss of GFR was observed in both groups which tended to be lower in the rigorous than in the standard BP control group (−1.7 ± 0.5 vs −3.5 ± 0.9 ml/min/year; \( P = 0.04 \)).

During follow-up, BP significantly decreased in both groups with a trend towards a stronger reduction in MAP in the rigorous compared with the standard BP control group (−9 ± 2 mm Hg vs −5 ± 2 mm Hg; \( P = 0.07 \)). Accordingly, there was a clear separation of the two groups by MAP throughout the observation period (Table 3).

A significant loss of GFR was observed in both groups which tended to be lower in the rigorous than in the standard BP control group (−1.7 ± 0.5 vs −3.5 ± 0.9 ml/min/year; \( P = 0.04 \)).

**Table 3.** Cardiovascular and renal parameters at baseline and at 3 years follow-up according to the BP control groups

<table>
<thead>
<tr>
<th></th>
<th>Standard BP control (( n = 18 ))</th>
<th></th>
<th>Rigorous BP control (( n = 19 ))</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 years</td>
<td>( P)-value</td>
<td>Baseline</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)(^a)</td>
<td>146 ± 2</td>
<td>136 ± 1</td>
<td>&lt;0.01</td>
<td>138 ± 2</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)(^a)</td>
<td>93 ± 2</td>
<td>86 ± 1</td>
<td>&lt;0.01</td>
<td>88 ± 2</td>
</tr>
<tr>
<td>Mean arterial BP (mm Hg)(^a)</td>
<td>108 ± 2</td>
<td>103 ± 1</td>
<td>&lt;0.01</td>
<td>102 ± 2</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.33 ± 0.14</td>
<td>2.18 ± 0.56</td>
<td>0.052</td>
<td>1.17 ± 0.14</td>
</tr>
<tr>
<td>Estimated GFR (ml/min)</td>
<td>83.1 ± 8.6</td>
<td>72.5 ± 10.3</td>
<td>&lt;0.01</td>
<td>91.2 ± 6.4</td>
</tr>
<tr>
<td>Albumin/creatinine ratio (mg/g)</td>
<td>84.2 ± 19.8</td>
<td>94.8 ± 35.4</td>
<td>0.693</td>
<td>56.8 ± 23.2</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>97.0 ± 5.2</td>
<td>110.5 ± 6.3</td>
<td>&lt;0.01</td>
<td>94.5 ± 4.7</td>
</tr>
</tbody>
</table>

\(^a\)24-h ambulatory BP.

\(^\)Comparison of the 3 years follow-up values between the two BP control groups.
Urinary albumin excretion, were detected. Furthermore, no differential effects of the study medication revealed no difference in the decline of renal function between patients with standard and rigorous BP control. However, LVMI increased in patients with standard BP control during follow-up while it remained stable in those with rigorous BP control. In addition, albuminuria was found to be higher in the standard BP control group by the end of the observation period.

Several limiting factors of this study have to be taken into account. First, the number of included patients is relatively small due to the single-centre design of this trial. Second, the follow-up of 3 years is limited in view of the slowly progressive course of the disease. Thus, the conclusions must be interpreted cautiously since the study is not statistically powered to unequivocally exclude any differences between the treatment groups or definitely prove the effects of the different BP control levels. In addition, we observed an unexpectedly high drop-out rate and a statistically non-significant higher number of male subjects in the ramipril group. Since male ADPKD patients have a worse renal prognosis than female patients, this might have masked a potential renoprotective effect of the ACE inhibitor treatment in the ramipril group [3]. Moreover, the maximum dose of ramipril was limited to 5 mg per day in this study. However, in other studies using higher ACE inhibitor doses no beneficial effect of ACE inhibition on renal function could be observed, arguing against a major dose-dependent effect of the ACE inhibitor treatment on renal disease progression in patients with ADPKD [13–15].

A pathogenetic role for the RAAS has been suggested in the development of hypertension in ADPKD. Activation of the RAAS occurs early in the course of the disease and may result from cyst expansion causing local renal ischemia [7–9]. This mechanism may lead to further impairment of renal perfusion and consequently to tissue ischemia. Thus, treatment of hypertension with ACE inhibitors may be optimal for delaying renal disease progression in ADPKD. However, previous studies have yielded conflicting results regarding the potential renoprotective effect of ACE inhibition in patients with ADPKD. In a non-randomized trial, Ecder et al. reported a slower progression of renal disease in hypertensive ADPKD patients treated with an ACE inhibitor without a diuretic compared with patients treated with a diuretic and no ACE inhibitor [21]. In a prospective study comparing the effects of ACE inhibition vs calcium channel blockade in patients with primary renal disease, the subgroup of patients with ADPKD had better renal outcome under treatment with the ACE inhibitor than with the calcium channel blocker [22]. Other investigators were unable to confirm a beneficial effect of ACE inhibition on renal function in ADPKD. In a study comparing the effect of the ACE inhibitor benazepril with placebo on the decay of renal function in patients with progressive renal insufficiency, patients with ADPKD did not benefit from ACE inhibitor treatment, in contrast to patients with other underlying causes of chronic kidney disease such as diabetic nephropathy [12]. Van Dijk et al. observed a similar decline in renal function comparing the ACE inhibitor enalapril with placebo in normotensive or with the β-blocker atenolol in hypertensive ADPKD patients with well-preserved renal function [13]. Also, no difference in renal disease

\[ P = 0.07 \]. Although GFR was numerically higher in patients with rigorous than in patients with standard BP control at baseline and during follow-up, this difference was not statistically significant (Table 3).

Of interest, LVMI significantly increased in patients with standard BP control while no change in LVMI was observed in patients with rigorous BP control (Table 3, Figure 2). Accordingly, LVMI was significantly higher in the standard than in the rigorous BP control group after the 3 years follow-up (110.5 ± 6.3 \textit{vs} 90.9 ± 4.7 g/m², \( P = 0.017 \)).

Urinary albumin excretion did not change significantly in both BP control groups during follow-up, although in the rigorous BP control group a numerical decrease and in the standard BP control group a slight increase in albumin/creatinine ratio was observed (Table 3). However, by the end of the observation period urinary albumin excretion was found to be significantly higher in patients with standard than in those with rigorous BP control (94.8 ± 35.4 \textit{vs} 23.5 ± 6.7 mg/g, \( P = 0.05 \)).

**Discussion**

In this prospective, randomized, double-blind trial no difference in the decline of renal function was observed between hypertensive ADPKD patients treated with the ACE-inhibitor ramipril \textit{vs} the β-blocker metoprolol during a 3 year follow-up. In both treatment groups, an effective and sustained reduction in arterial BP could be achieved. During follow-up, GFR decreased at an overall annual rate of −2.7 ± 0.5 ml/min/year with no difference between the treatment groups. Also, the number of primary renal end points was not significantly different between both groups. Furthermore, no differential effects of the study medication on cardiovascular and renal risk factors, i.e. LVMI and urinary albumin excretion, were detected. A \textit{post-hoc} analysis evaluating the effects of BP control irrespective of the study medication revealed no difference in the decline of renal function between patients with standard and rigorous BP control. However, LVMI increased in patients with standard BP control during follow-up while it remained stable in those with rigorous BP control. In addition, albuminuria was found to be higher in the standard BP control group by the end of the observation period.

Several limiting factors of this study have to be taken into account. First, the number of included patients is relatively small due to the single-centre design of this trial. Second, the follow-up of 3 years is limited in view of the slowly progressive course of the disease. Thus, the conclusions must be interpreted cautiously since the study is not statistically powered to unequivocally exclude any differences between the treatment groups or definitely prove the effects of the different BP control levels. In addition, we observed an unexpectedly high drop-out rate and a statistically non-significant higher number of male subjects in the ramipril group. Since male ADPKD patients have a worse renal prognosis than female patients, this might have masked a potential renoprotective effect of the ACE inhibitor treatment in the ramipril group [3]. Moreover, the maximum dose of ramipril was limited to 5 mg per day in this study. However, in other studies using higher ACE inhibitor doses no beneficial effect of ACE inhibition on renal function could be observed, arguing against a major dose-dependent effect of the ACE inhibitor treatment on renal disease progression in patients with ADPKD [13–15].

A pathogenetic role for the RAAS has been suggested in the development of hypertension in ADPKD. Activation of the RAAS occurs early in the course of the disease and may result from cyst expansion causing local renal ischemia [7–9]. This mechanism may lead to further impairment of renal perfusion and consequently to tissue ischemia. Thus, treatment of hypertension with ACE inhibitors may be optimal for delaying renal disease progression in ADPKD. However, previous studies have yielded conflicting results regarding the potential renoprotective effect of ACE inhibition in patients with ADPKD. In a non-randomized trial, Ecder et al. reported a slower progression of renal disease in hypertensive ADPKD patients treated with an ACE inhibitor without a diuretic compared with patients treated with a diuretic and no ACE inhibitor [21]. In a prospective study comparing the effects of ACE inhibition vs calcium channel blockade in patients with primary renal disease, the subgroup of patients with ADPKD had better renal outcome under treatment with the ACE inhibitor than with the calcium channel blocker [22]. Other investigators were unable to confirm a beneficial effect of ACE inhibition on renal function in ADPKD. In a study comparing the effect of the ACE inhibitor benazepril with placebo on the decay of renal function in patients with progressive renal insufficiency, patients with ADPKD did not benefit from ACE inhibitor treatment, in contrast to patients with other underlying causes of chronic kidney disease such as diabetic nephropathy [12]. Van Dijk et al. observed a similar decline in renal function comparing the ACE inhibitor enalapril with placebo in normotensive or with the β-blocker atenolol in hypertensive ADPKD patients with well-preserved renal function [13]. Also, no difference in renal disease
progression was found between ADPKD patients treated with the ACE inhibitor enalapril and the calcium channel blocker amlodipine in two further studies [14,15].

The data presented here correspond to the latter observations which failed to detect a beneficial effect of ACE inhibitors compared with other antihypertensive drugs in delaying the deterioration of renal function in patients with ADPKD. The natural progression of renal disease in ADPKD is characterised by an early phase in which GFR can remain relatively stable for many decades. However, in patients with chronic kidney disease stage 3–4 renal disease progression is typically accelerated with a annual drop in GFR of approximately -5 ml/min/year [23]. The subjects in this study had relatively well-preserved renal function and few patients displayed a rapid loss of GFR reaching the primary renal end-point of the study. This indicates that most participants were in a more or less stable phase of their disease. Thus, although early intervention seems to be crucial for delaying the loss of renal function in patients with ADPKD, the comparatively slow decline in GFR of -2.7 ± 0.5 ml/min/year observed in this study might have prevented the detection of a difference in renal disease progression between the treatment groups within the limited follow-up time of 3 years.

In this study, LVM and urinary albumin excretion as factors associated with a faster progression towards end stage renal disease in patients with ADPKD were evaluated. LVH is a common finding in patients with ADPKD and is a known prognostic factor for cardiovascular morbidity and mortality, especially in patients with renal failure [5,24,25]. Increased LVM even occurs in young normotensive patients, suggesting non-haemodynamic factors are important in the development of LVH in ADPKD [26,27]. In a previous study, Ecder et al. reported that treatment with the ACE inhibitor enalapril was capable of reversing LVH in hypertensive ADPKD patients [28]. Furthermore, Schrier et al. demonstrated that enalapril was more effective than amlodipine in decreasing LVM in hypertensive ADPKD patients [14]. In the present study, we did not observe a significant change in LVM during treatment with either ramipril or metoprolol. However, in our study population LVH was less frequent (22%) and LVM and BP levels at baseline were overall lower than in the patients included in the aforementioned studies, who all had LVH at study entry. Furthermore, the follow-up in our trial was shorter than in the studies mentioned above (3 vs 7 years).

MA is a prognostic factor for renal and patient outcome in patients with essential hypertension [29]. It is also associated with progression of renal failure and elevated BP levels in patients with ADPKD [6]. At present, data on the antiproteinuric effect of ACE inhibition in ADPKD remain inconclusive. While Ecder et al. demonstrated a decrease in urinary albumin excretion in patients treated with enalapril, but not in patients treated with amlodipine [15], in another study no beneficial effect of the treatment with enalapril on MA was found when compared with placebo in normotensive or with atenolol in hypertensive ADPKD patients [13]. In the current study, urinary albumin excretion did not change significantly during follow-up and no difference in the albumin/creatinine ratio was detected between the treatment groups. However, the numerical decrease in MA observed in the ramipril group raises the possibility that statistical power might not have been sufficient to detect a potential antiproteinuric effect of ACE inhibition in this study.

In a post-hoc analysis, the effects of BP control on renal function, LVM, and urinary albumin excretion were evaluated irrespective of the study medication. No statistically significant difference in renal function was observed between the rigorous and the standard BP control group, although there was a trend towards a faster decline in GFR in patients with standard BP control. In contrast, LVM markedly increased in patients with standard BP control while it remained stable in patients with rigorous BP control during follow-up. In a previous study, LVM decreased with both rigorous and standard BP control, but rigorous BP control was more effective in reducing LVM in patients with ADPKD and hypertension [14]. All patients included in the latter trial had LVH at study entry compared with only 22% of the patients in the present trial. Furthermore, in the aforementioned study lower BP levels than in our trial were achieved in both the standard and the rigorous BP control group. This might explain why rigorous BP control was capable of preventing an increase in LVM in our study population but did not induce a reduction in LVM as observed in the above-mentioned trial. However, our data confirm that rigorous BP control is associated with lower LVM compared with standard BP control. Moreover, after the 3 years follow-up albumin/creatinine ratio was found to be lower in the rigorous compared with the standard BP control group. Thus, rigorous BP control seems to be capable of ameliorating renal organ damage irrespective of the type of antihypertensive drug, i.e. ACE inhibitor or β-blocker. Although it is unclear whether MA is a pathogenetic factor for renal disease progression in ADPKD, this observation suggests a role of rigorous BP control in improving the renal prognosis in patients with ADPKD. However, it must be emphasised that it was not a primary goal of this study to achieve different target BP levels. Thus, post-hoc stratification for BP control might have resulted in the separation of patients at slightly different stages of disease progression. Indeed, patients with subsequent standard BP control were at higher BP levels throughout the study and had numerically lower renal function from the beginning, although the difference in GFR between the two BP control groups was not significant. Despite these limitations, the data reported here stress the importance of a tight BP control for improving risk factors associated with renal disease progression and cardiovascular complications in patients with ADPKD and hypertension.

In conclusion, no beneficial effect of the ACE inhibitor ramipril compared with the β-blocker metoprolol with respect to renal disease progression, cardiac structure as assessed by LVM or urinary albumin excretion was detected in hypertensive ADPKD patients. Rigorous BP control seems to be a key determinant to slow the progression of cardiac and renal organ damage in ADPKD. Further large randomized prospective trials are warranted to define the role of ACE inhibitors and angiotensin receptor blockers as well as the optimal target BP in the treatment of ADPKD patients with hypertension.
Acknowledgements. This research was supported by Astra-Zeneca who provided the study medication. We thank Claudia Donhauser for excellent technical assistance.

Conflict of interest statement. No conflict of interest is declared by any of the authors.


References


Received for publication: 22.8.06
Accepted in revised form: 18.9.07