

## Calcium Channel Blocker versus Angiotensin II Receptor Blocker in Autosomal Dominant Polycystic Kidney Disease

Kikuo Nutahara<sup>a</sup> Eiji Higashihara<sup>a</sup> Shigeo Horie<sup>b</sup> Kouichi Kamura<sup>c</sup>  
 Ken Tsuchiya<sup>d</sup> Toshio Mochizuki<sup>e</sup> Tatsuo Hosoya<sup>f</sup> Tomohiro Nakayama<sup>g</sup>  
 Norio Yamamoto<sup>h</sup> Yoshio Higaki<sup>i</sup> Toshiko Shimizu<sup>j</sup>

<sup>a</sup>Department of Urology, Kyorin University School of Medicine, Tokyo; <sup>b</sup>Department of Urology, Teikyo University School of Medicine, Tokyo; <sup>c</sup>Department of Urology, Sakura National Hospital, Sakura; <sup>d</sup>Department of Medicine, Kidney Center, Tokyo Women's Medical University, Tokyo; <sup>e</sup>Department of Internal Medicine, Hokkaido University Graduate School of Medicine, Sapporo; <sup>f</sup>Department of Kidney and Hypertension, Jikei University School of Medicine, Tokyo; <sup>g</sup>Department of Internal Medicine, Nihon University School of Medicine, Tokyo; <sup>h</sup>Department of Urology, Hikari City General Hospital, Hikari; <sup>i</sup>Department of Urology, National Hospital, Tokyo Disaster Medical Center, Tokyo, and <sup>j</sup>Department of Clinical Genetics, Kyorin University School of Health Sciences, Tokyo, Japan

### Key Words

Autosomal dominant polycystic kidney disease · Hypertension · Angiotensin II receptor blocker

### Abstract

**Background:** Although hypertension is commonly found in patients with autosomal dominant polycystic kidney disease (ADPKD), there is no consensus about which antihypertensive agents are most appropriate. The effects of calcium channel blockers (CCB) and angiotensin II receptor blockers (ARB) on blood pressure and renal protection were compared in hypertensive patients with ADPKD. **Methods:** We randomly assigned 49 participants to CCB amlodipine-based (2.5–10 mg/day) or ARB candesartan-based (2–8 mg/day) regimens. Twenty-five patients (13 males and 12 females) received amlodipine, and 24 patients (13 males and 11 females) received candesartan. This was followed up for 36 months. **Results:** Baseline characteristics were similar, and blood pressure was well controlled in both groups throughout the study

period. Six out of 25 (24.0%) amlodipine and 1 out of 24 (4.2%) candesartan patients were terminated from the protocol due to a twofold increase in serum creatinine and/or decrease in creatinine clearance (Ccr) to half of the baseline. The renal event-free survival rate was significant ( $p < 0.05$ , Breslow-Gehan-Wilcoxon test). Serum creatinine was higher in the amlodipine group than in the candesartan group at 24 and 36 months ( $p < 0.05$ ). The decrease in Ccr at 36 months was larger in the amlodipine group than in the candesartan group ( $\Delta\text{Ccr}$ :  $-20.9 \pm 13.1$  vs.  $-4.8 \pm 13.8$  ml/min,  $p < 0.01$ ). Urinary protein excretion was significantly lower in the candesartan group than in the amlodipine group at 36 months. Urinary albumin excretion was significantly lower in the candesartan group than in the amlodipine group at 12, 24 and 36 months. **Conclusions:** The renoprotective effect of candesartan is considered more favorable than amlodipine in the treatment of ADPKD. This is independent of the antihypertensive effect per se.

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Kikuo Nutahara  
 Department of Urology, Kyorin University School of Medicine  
 6-20-2 Shinkawa, Mitaka-shi, Tokyo 181-8611 (Japan)  
 Tel. +81 422 47 5511/ext 5717, Fax +81 422 428431  
 E-Mail [kinuta@kyorin-u.ac.jp](mailto:kinuta@kyorin-u.ac.jp)

## Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common hereditary disorders that cause end-stage renal disease [1, 2]. In Japan, the rate of end-stage renal disease increases with the progression of the patients' age, reaching about 50% at the age of 65–69 years and declining thereafter [3]. Hypertension is a common finding in patients with ADPKD and often occurs before the onset of detectable evidence of renal impairment [1, 2, 4, 5]. Hypertension associated with ADPKD accelerates the rate of renal function deterioration and is an important risk factor for cardiovascular death, one of the most common causes of mortality in ADPKD patients [2].

Although the early detection and treatment of hypertension may retard the rate of renal function deterioration and decrease cardiovascular events in patients with ADPKD, there is no consensus on which antihypertensive agents are the most appropriate. The cause of hypertension in patients with ADPKD is controversial. The renin-angiotensin-aldosterone system (RAAS) may play a central role in the development of hypertension in ADPKD, and is related to the level of renal structural involvement where cyst expansion results in activation of the RAAS. In this regard, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) may be considered the drugs of choice [6]. Ecker et al. [7] examined the effects of a calcium channel blocker (CCB) and an ACE inhibitor as first-line therapy on blood pressure, renal function, and urinary albumin excretion in hypertensive patients with ADPKD. They concluded that blood pressure was similar in both groups but only the ACE inhibitor had the significant effect of sustaining a decrease in urinary albumin excretion during a 5-year follow-up.

In Han:SPRD rats that were autosomal dominant models of polycystic kidneys, Keith et al. [8] reported that the Han:SPRD rats receiving ARB losartan had lower plasma creatinine than those in the control that did not receive any medication as well as hydralazine treatment groups. However, there was no published report of clinical study using ARB.

The present prospective and randomized study was performed to compare the effects of the CCB amlodipine and the ARB candesartan, specifically their therapeutic benefits in regard to renal function, urinary protein and albumin excretion in hypertensive patients with ADPKD.

## Patients and Methods

The present study was a multicenter, prospective and randomized clinical trial. Patients were randomly allocated to two groups using the dynamic balancing method to ensure equal distributions of the subject's gender, age, serum creatinine levels and blood pressure levels between two groups. We included patients with ADPKD aged 20–70 years with previously treated or untreated hypertension. Exclusion criteria were pregnant women or those who desired to raise a child and patients whose serum creatinine was  $>2$  mg/dl. Forty-nine participants with hypertension (blood pressure: systolic  $>140$  and/or diastolic  $>90$  mm Hg in sitting position) were randomly assigned to CCB amlodipine-based (2.5–10 mg/day) or angiotensin II receptor blocker candesartan-based (2–8 mg/day) regimens. Twenty-five patients (13 males and 12 females; mean age 48.4 years) were allocated to amlodipine, and 24 patients (13 males and 11 females; mean age 47.3 years) were allocated to candesartan. Treatment target of systolic pressure was  $<130$  mm Hg and diastolic pressure was  $<85$  mm Hg. If targeted blood pressure was not achieved with maximum doses of the drugs, propranolol and/or carvedilol were used additionally. In the amlodipine group, 1 patient received propranolol, 6 patients received carvedilol, and 2 patients received both drugs simultaneously. In the candesartan group, 1 patient received propranolol, 1 patient received carvedilol, and the other patient received both drugs simultaneously. After a 2-week washout phase during withdrawal of the antihypertensive drugs, baseline measurements of blood pressure, serum creatinine and 24-hour urine data were performed. Blood pressure was measured once every 1 or 2 months. Creatinine clearance (Ccr), urinary protein excretion and urinary albumin excretion were measured every 12 months by collecting 24-hour urine. The primary outcome measure of this study was a composite endpoint of patient's serum creatinine levels increased twofold over baseline or Ccr decreased to half of the baseline. This study was terminated in patients who reached an endpoint. An independent, blinded endpoint committee adjudicated all clinical endpoints according to predefined guidelines.

All local ethics committees approved the trial protocol and all participants gave informed written consent.

Analysis was done by intent to treat. Renal event-free survival rate was evaluated by survival analysis, using Kaplan-Meier methods. Statistical significance was determined using a paired and unpaired Student's *t* test and repeated measures ANOVA appropriately. The terms significant or significantly different were used to describe a *p* value difference of  $<0.05$ . Variables were reported as mean  $\pm$  SD.

## Results

One candesartan patient was excluded because she wanted to become pregnant. No side effect necessitating withdrawal of the drugs was observed in any patient throughout the study. Mean follow-ups were  $33.6 \pm 5.4$  months (median 36) in the amlodipine group and  $34.9 \pm 3.5$  months (median 36) in the candesartan group. There was no significant difference in follow-up periods between the two groups. As 3 amlodipine and 2 candesartan

**Table 1.** Changes in serum creatinine levels, values of creatinine clearance, urinary protein and albumin excretion; mean  $\pm$  SD values; patients (n) in parentheses

	Baseline	12 months	24 months	36 months
Serum creatinine, mg/dl				
Amlodipine group	1.22 $\pm$ 0.34 (25)	1.37 $\pm$ 0.48 (25)	1.63 $\pm$ 0.77 (24)	1.71 $\pm$ 0.89 (19)
Candesartan group	1.12 $\pm$ 0.30 (24)	1.18 $\pm$ 0.33 (23)	1.22 $\pm$ 0.34 (24)	1.26 $\pm$ 0.46 (21)
CCB vs. ARB, p value	0.277	0.114	0.023	0.046
Creatinine clearance, ml/min				
Amlodipine group	71.9 $\pm$ 20.5 (19)	66.4 $\pm$ 18.5 (17)	63.3 $\pm$ 23.5 (14)	58.5 $\pm$ 14.2 (11)
Candesartan group	69.8 $\pm$ 24.6 (22)	68.2 $\pm$ 25.5 (20)	64.0 $\pm$ 25.8 (20)	64.8 $\pm$ 27.8 (20)
CCB vs. ARB, p value	0.770	0.812	0.930	0.491
Urinary protein excretion, mg/day				
Amlodipine group	148 $\pm$ 187 (16)	363 $\pm$ 543 (15)	332 $\pm$ 376 (11)	458 $\pm$ 419 (10)
Candesartan group	116 $\pm$ 102 (20)	111 $\pm$ 127 (17)	142 $\pm$ 187 (17)	154 $\pm$ 176 (15)
CCB vs. ARB, p value	0.554	0.073	0.087	0.019
Urinary albumin excretion, mg/day				
Amlodipine group	91 $\pm$ 67 (10)	191 $\pm$ 181 (9)	273 $\pm$ 295 (9)	287 $\pm$ 238 (9)
Candesartan group	66 $\pm$ 63 (17)	74 $\pm$ 69 (15)	60 $\pm$ 65 (13)	49 $\pm$ 37 (15)
CCB vs. ARB, p value	0.375	0.034	0.020	0.001

patients had moved out, their clinical follow-ups ended within 24 months.

Baseline characteristics were similar in the amlodipine and candesartan randomization group (table 1). Systolic and diastolic blood pressure decreased significantly in both hypertensive groups after administration of any anti-hypertensive agents and remained in the normal range throughout the period (fig. 1, 2). The values of systolic and diastolic blood pressure were not different between the two groups and changes with time in the values of systolic and diastolic blood pressure were significant ( $p < 0.01$ ) using the repeated measures ANOVA methods.

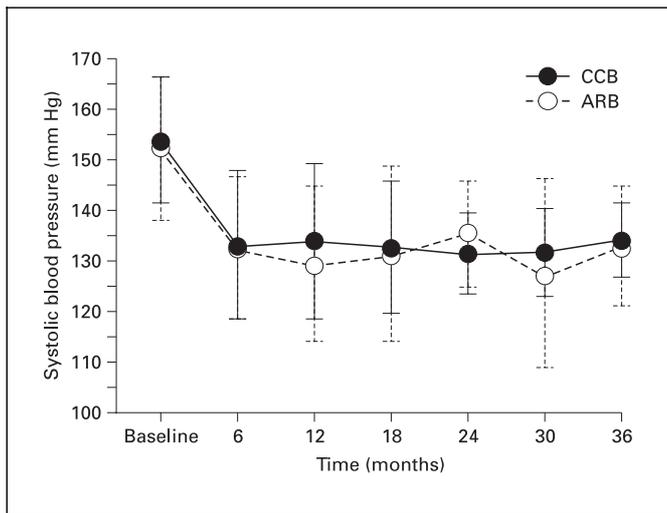
Six out of 25 (24.0%) amlodipine and 1 out of 24 (4.2%) candesartan patients were deleted from the protocol due to deteriorated renal function (fig. 3). There was a significant difference between the two groups ( $p < 0.05$ , Breslow-Gehan-Wilcoxon test) in the renal event-free survival rate.

Changes in serum creatinine and 24-hour urine-related data are shown in table 1. Serum creatinine was higher in the amlodipine group than in the candesartan group at 24 and 36 months ( $p < 0.05$ ). Although changes with time in the serum concentration of creatinine were significant ( $p < 0.01$ ), there were no significant differences between the two groups using the repeated measures ANOVA methods. Ccr was not different between the two groups throughout the study (table 1), however patients treated

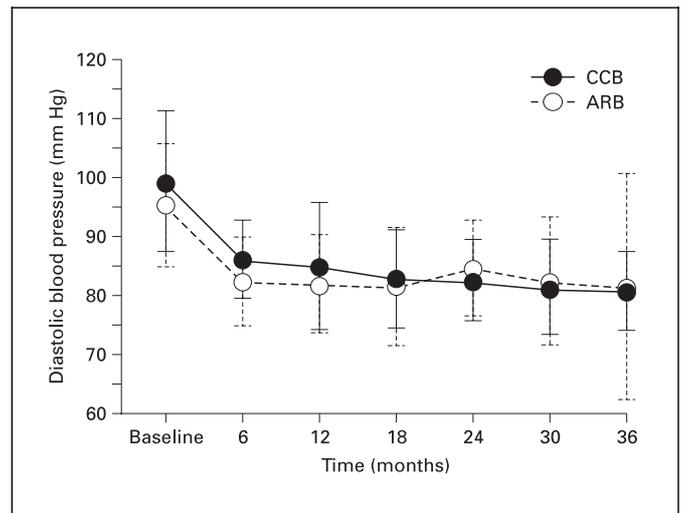
with amlodipine exhibited a larger decrease in Ccr ( $-20.9 \pm 13.1$  vs.  $-4.8 \pm 13.8$  ml/min,  $p < 0.01$ ; fig. 4) than those in the candesartan group at 36 months. Urinary protein and albumin excretion were significantly lower in the candesartan group than in the amlodipine group at 36 months and at 12, 24 and 36 months, respectively. These changes were also significantly different using the repeated measures ANOVA methods (table 1).

## Discussion

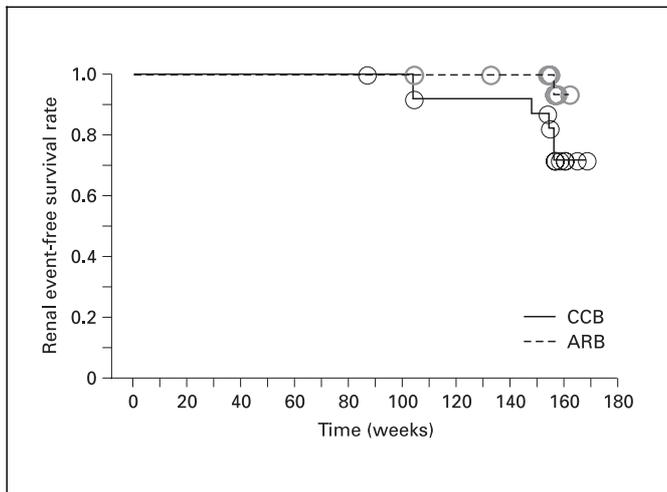
Because an activation of the RAAS caused by cyst expansion and local renal parenchymal ischemia is believed to have an important role in raising blood pressure and increasing renal vascular resistance in patients with ADPKD [6], ACE inhibitors and ARBs appear to be logical agents for the treatment of hypertension in patients with ADPKD and normal renal function. However, a rapid deterioration of renal function has been reported in patients with advanced renal impairment [9] and they were not suitable candidates for the present study in which we examined the renoprotective effect of two drugs. Therefore, in this study we excluded patients with moderately impaired renal function (serum creatinine  $>2$  mg/dl).



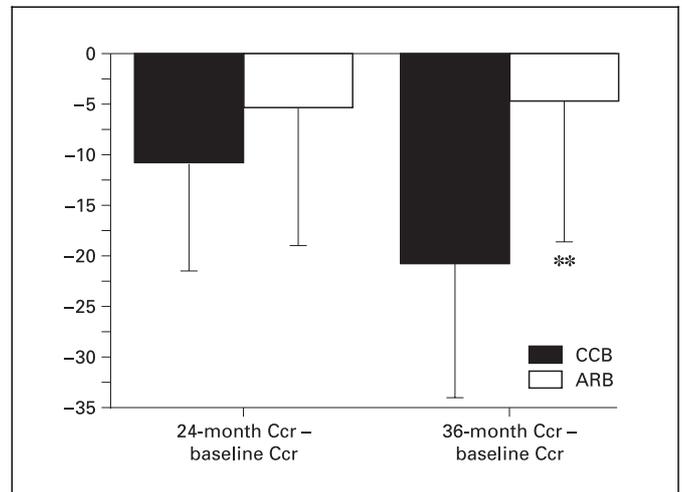
**Fig. 1.** Changes in systolic blood pressure.



**Fig. 2.** Changes in diastolic blood pressure.



**Fig. 3.** Renal event-free survival rate of hypertensive patients treated by CCB and ARB. Renal event-free survival is defined in the text.  $p < 0.05$  CCB vs. ARB.



**Fig. 4.** Changes in Ccr from baseline.  $p$  values show comparisons between CCB and ARB. \*\*  $p < 0.01$ .

Prospective and randomized studies suggest that ACE inhibitors and ARB are more effective than conventional antihypertensive agents in preserving the renal function of non-diabetic and diabetic renal diseases [10, 11]. Maschio et al. [10] reported that ACE inhibitor benazepril was ineffective for patients with ADPKD in terms of protecting renal deterioration. Kanno et al. [12] reported that the decreases in Ccr were smaller in the group treated with

CCB than that with the ACE inhibitor. These two reports could not demonstrate nephroprotective effects of ACE inhibitor on hypertensive ADPKD patients. The difference between these findings and those of the present study may be partly due to the inclusion of patients with mild renal insufficiency in these two studies. For example, in Maschio's study, patients with chronic renal insufficiency (creatinine concentration of 1.5–4.0 mg/dl) were included

and in the latter study, patient's serum creatinine values were  $2.0 \pm 0.5$  (SE) mg/dl, which suggests the inclusion of patients with moderate renal insufficiency.

Marin et al. [13] reported on a random multicenter study comparing renoprotective effects with an ACE inhibitor fosinopril versus a long-acting CCB nifedipine GITS in 241 patients with chronic renal failure (serum creatinine values between 1.5 and 5 mg/dl) and hypertension due to primary renal disease. Twenty-nine patients with ADPKD received fosinopril and 16 patients with ADPKD received nifedipine GITS. Renal survival was significantly better when fosinopril constituted the first-step therapy. These results did not seem to be influenced by the type of primary renal disease. They concluded that ACE inhibitor fosinopril significantly differed from CCB nifedipine GITS in its capacity to protect renal function in patients with primary renal disease including ADPKD.

In a non-randomized study comparing antihypertensive treatment with diuretics versus ACE inhibitors in hypertensive ADPKD patients, Ccr decreased significantly in both groups after an average follow-up period of 5.2 years. The decrement in Ccr was significantly larger in the diuretic group than in the ACE inhibitor group. A significant increase in urinary protein excretion occurred in the diuretic but not in the ACE inhibitor group. This paper concluded that hypertensive ADPKD patients treated with diuretics had a faster loss of renal function compared to patients treated with ACE inhibitors, despite similar blood pressure control [14].

Recently, Ecker et al. [7] reported on a prospective and randomized study comparing initial antihypertensive therapy with a CCB, amlodipine, versus an ACE inhibitor, enalapril, in ADPKD patients with Ccrs  $>50$  ml/min/ $1.73$  m<sup>2</sup>. Ccrs remained stable after a 1-year follow-up and decreased significantly at year 3 in both groups. No change was observed in urinary albumin excretion in the amlodipine group, whereas it decreased significantly in the enalapril group at year 1 and remained stable until year 5. In contrast, our study revealed that candesartan had sustained effects on lower urinary protein and albumin in patients with hypertensive ADPKD. The difference of those two results is not clear.

Yamaguchi et al. [15] reported that a cyclic adenosine monophosphate (cyclic AMP)-mediated signal transduction cascade switched from an antimitogenic state to a cellular proliferative state in ADPKD cells. The switch may be induced due to cytosolic calcium depletion caused by polycystin (PKD-protein) mutation. Polycystins 1 and 2 are postulated to act as calcium channels allowing calcium

inflow [16]. CCB may accelerate the cytosolic calcium depletion and hence activate the cellular proliferative effect of cyclic AMP signal transduction cascade in polycystic kidney cells.

There was a significant difference between the two groups ( $p < 0.05$ , Breslow-Gehan-Wilcoxon test) in the renal event-free survival rate. Serum creatinine concentrations in the candesartan group were lower than those in the amlodipine group at 24 and 36 months. Changes in Ccr (36-month Ccr – baseline Ccr) of the candesartan group were much lower than those of the amlodipine group. Ccr was not different between the two groups. This may be due to the deletion of 3 amlodipine patients from the protocol due to a Ccr half that of the baseline. In addition to the antialbuminuric effect of candesartan, the present study showed its protective effect on renal function. These results suggested that candesartan preserved renal function better than amlodipine, which was unrelated to the direct antihypertensive effect.

It has been reported that angiotensin II selectively constricted efferent arterioles [17], and blockade of angiotensin II receptor resulted in dilation of efferent arterioles, which further reduced intraglomerular pressure [18]. Delles et al. [19] reported that the ratio of resistances of the efferent and afferent arterioles was more increased in the CCB amlodipine group than in the ARB valsartan group. Glomerular filtration rate and hydrostatic pressure increased in the amlodipine group whereas they were maintained in the valsartan group. These findings may be related to the difference of renoprotective effect between the candesartan group and the amlodipine group in our study.

In conclusion, the renoprotective effect of candesartan is considered more favorable than amlodipine in treatment of ADPKD, and this effect may be unrelated to the direct antihypertensive effect.

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