

## Effects of the N/L-Type Calcium Channel Blocker Cilnidipine on Nephropathy and Uric Acid Metabolism in Hypertensive Patients With Chronic Kidney Disease (J-CIRCLE Study)

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This study assessed the urinary albumin/creatinine ratio (ACR) and uric acid metabolism in 70 hypertensive patients with chronic kidney disease in whom urinary ACR had remained  $\geq 30$  mg/g under the treatment of the L-type calcium channel blocker amlodipine. Three months after switching to the N/L-type calcium channel blocker cilnidipine, blood pressure (BP) did not change; however, urinary ACR significantly decreased with cilnidipine. Serum uric acid levels showed no significant change. In cases where uric acid production had been high (urinary uric acid/creatinine ratio  $\geq 0.5$ ), the urinary uric acid/creatinine ratio decreased

significantly after cilnidipine treatment, suggesting that cilnidipine can suppress excessive uric acid formation. These results suggest that switching from amlodipine to cilnidipine results in a significant reduction in urinary ACR as well as significant reduction in uric acid production. Thus, cilnidipine is more useful than amlodipine in improving albuminuria and uric acid metabolism in hypertensive patients with chronic kidney disease. *J Clin Hypertens (Greenwich)*. 2014;16:746–753. © 2014 The Authors. Journal of Clinical Hypertension Published by Wiley Periodicals, Inc.

Chronic kidney disease (CKD) has been shown to be an independent risk factor for cardiovascular disease and end-stage kidney disease.<sup>1–3</sup> Factors known to be associated with progression of renal disease in patients with CKD include hypertension, diabetes mellitus, and hyperuricemia. Among them, hypertension is a strong risk factor for CKD, and the existing guidelines on CKD management recommend a strict goal for antihypertensive treatment.<sup>4</sup> Renin-angiotensin system (RAS) inhibitors, which are used as first-line drugs for antihypertensive therapy in patients with CKD, have been shown to exert excellent organ-protective effects (eg, reduction of proteinuria and alleviation of heart failure).<sup>5,6</sup> However, it is difficult to achieve the strict goals for antihypertensive treatment with a RAS inhibitor alone, often requiring combined use of other antihypertensive agents.<sup>7</sup> Regarding combined antihypertensive therapy in general, the usefulness of

combining a RAS inhibitor and a calcium channel blocker (CCB) has been reported, eg, in the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) and the Nifedipine and Candesartan Combination (NICE Combi) studies.<sup>8,9</sup> CCBs have potent hypotensive activity, and the 2009 guidelines by the Japanese Society of Hypertension also recommend the combined use of a RAS inhibitor and a CCB.<sup>10</sup> This approach now prevails as a major combined antihypertensive therapy in Japan.

Following the recent increase in complications associated with hypertension, such as the metabolic syndrome, close attention has been paid to the importance of hyperuricemia management when dealing with hypertensive patients with CKD.<sup>11</sup> Patients with CKD are known to have a high incidence of complications associated with hyperuricemia,<sup>12,13</sup> likely caused by reduced uric acid excretion via the tubule in the presence of compromised renal function (called renal hyperuricemia) or excessive production of uric acid as a result of stimulated production of a uric acid precursor hypoxanthine in the skeletal muscles under sympathetic hyperactivity (myogenic hyperuricemia).<sup>14</sup> The guidelines on hyperuricemia/gout treatment attach importance to BP control in drug therapy for hypertension and recommend the use of CCBs as antihypertensives because they have no adverse effects on uric acid metabolism.<sup>15</sup>

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CCBs are a group of antihypertensive agents often used in clinical medicine, and it has been reported that their pharmacologic activity varies depending on the calcium channel that the drug inhibits.<sup>16</sup> An L-type CCB such as amlodipine exerts hypotensive activity through blocking the L-type calcium channel (primarily distributed in vascular smooth muscles), while cilnidipine (N/L-type CCB) can suppress reflexive sympathetic hyperactivity during antihypertensive treatment through blocking the L-type calcium channel as well as the N-type calcium channel located at sympathetic nerve endings.<sup>17</sup> Differences in organ protective effects between cilnidipine and L-type CCB arising from such differences have been demonstrated in the Cilnidipine versus Amlodipine Randomised Trial for Evaluation in Renal Disease (CARTER).<sup>18</sup>

Patients with CKD often have various complications such as hypertension and metabolic disease, and these complications often accelerate the progression of CKD, thus leading to the cycle of these conditions. Therefore, controlling BP and other complications is important when dealing with CKD. In the present study, we first reproduced the albuminuria-lowering effect of cilnidipine in the clinical practice of family physicians and then looked into the changes in uric acid metabolism by this drug as compared with amlodipine. To this end, we evaluated not only BP and urinary albumin/creatinine ratio (ACR) but urinary uric acid/creatinine ratio and fractional excretion of uric acid as well.

## PATIENTS AND METHODS

### Patients

This study was designed as a multicenter study and registered as the Johoku-Cilnidipine Trial of Renal Function and Blood Pressure for Clinical Evaluation (J-CIRCLE) (UMIN ID: 00003956). This study was conducted with the approval of the Teikyo University Hospital Ethics Committee (#08-091) and all other participating medical facilities and was carried out in compliance with the Declaration of Helsinki. Informed consent was obtained from all patients.

There were 84 patients with a urinary ACR  $\geq 30$  mg/g despite 3 months or longer amlodipine treatment among the patients managed at the 19 participating facilities between September 2009 and February 2011. Of these, eight patients with a serum creatinine level  $>2$  mg/dL, five patients poorly complying with dosing instructions, and one patient not available for follow-up were excluded. The remaining 70 hypertensive patients with CKD (34 women and 36 men, aged  $70.0 \pm 10.1$  years) were enrolled in this study. Other demographic data are shown in Table I. The original kidney diseases consisted of mainly nephrosclerosis ( $n=44$ , 62.9%) and diabetes ( $n=26$ , 37.1%). Patients with chronic glomerulonephritis were not included because hematuria was not evident. Patients with gout or urinary stones were not included. The values of BP were not controlled as

**TABLE I.** Demographic Data

	Mean $\pm$ SD or No. (%)
Age, y	70.0 $\pm$ 10.1
Male	36 (51.4)
Body height, cm	159.0 $\pm$ 10.5
Body weight, kg	64.2 $\pm$ 12.7
Kidney disease	
Nephrosclerosis	44 (62.9)
Diabetes	26 (37.1)
Albuminuria, mg/g creatinine	
30–299	55 (78.6)
$>300$	15 (21.4)
CKD stage	
G1	5 (7.1)
G2	35 (50.0)
G3a	13 (18.6)
G3b	5 (7.1%)
G4	7 (10.0)
ND	5 (7.1)
Abbreviations: CKD, chronic kidney disease; ND, not determined; SD, standard deviation.	

inclusion/exclusion criteria, because the study design was a crossover method.

### Methods

Amlodipine was switched to cilnidipine (equivalent in terms of hypotensive efficacy), and changes in BP, heart rate, urinary ACR, serum uric acid level, urinary uric acid/creatinine ratio, and fractional excretion of uric acid were analyzed at 3 months after switching and compared with the baseline values. The dose level at the time of switching was from 2.5 mg, 5 mg, or 10 mg for amlodipine to 5 mg, 10 mg, or 20 mg for cilnidipine, respectively. Drugs other than cilnidipine were neither changed nor initiated during the study period.

Each patient visited the outpatient clinic at similar times and underwent BP measurement after sitting still using a brachial artery BP device. The mean of three measurements was adopted as the baseline BP at the time of switching. Three months after switching, BP was measured during a visit to the outpatient clinic. Blood was sampled for measurement of serum uric acid and creatinine levels. Random urine samples were obtained for measurement of urinary albumin, uric acid, and creatinine levels, yielding the calculation of urinary ACR, log (urinary ACR), urinary uric acid/creatinine ratio, and fractional excretion of uric acid.

### Analytical Methods

Data are expressed as mean  $\pm$  standard deviation. Data were tested with the Wilcoxon signed rank sum test or Spearman correlation test. Statistical analysis was carried out using JMP 10 (SAS Institute Inc, Cary, NC). A *P* value of  $<.05$  was considered statistically significant.

## RESULTS

The time course of baseline values before and after switching from amlodipine to cilnidipine is shown in Table I. The mean cilnidipine dose was  $10.2 \pm 3.9$  mg. Body weight did not change and edema formation was not observed during the study.

### Change in BP and Heart Rate Measured at Outpatient Clinics

Systolic BP and diastolic BP (SBP/DBP) measured in the outpatient clinics were  $138.1 \pm 18.8/75.2 \pm 12.8$  mm Hg to  $135.8 \pm 17.7/74.8 \pm 11.4$  mm Hg. Thus, neither SBP nor DBP showed a significant change. In addition, no significant change was seen in heart rate ( $72.2 \pm 9.9$  beats per minute [bpm] to  $71.5 \pm 11.1$  bpm).

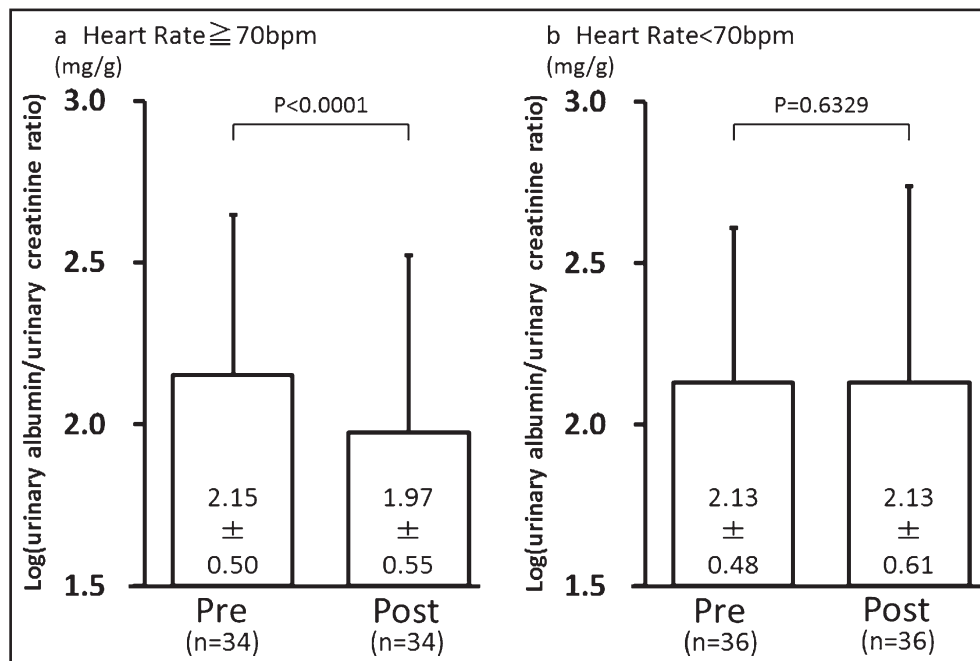
### Change in Renal Function and Urinary ACR

Serum creatinine level increased significantly from  $0.89 \pm 0.41$  mg/dL to  $0.94 \pm 0.42$  mg/dL ( $P < .001$ , Table II). Estimated glomerular filtration rate (eGFR) also decreased significantly from  $64.6 \pm 22.9$  mL/min/ $1.73$  m<sup>2</sup> to  $60.7 \pm 21.7$  mL/min/ $1.73$  m<sup>2</sup> ( $P = .003$ , Table II). On the other hand, the log (urinary ACR) decreased significantly from  $2.14 \pm 0.49$  mg/g creatinine to  $2.06 \pm 0.58$  mg/g creatinine ( $P = .0282$ , Table II). When the log (urinary ACR) was analyzed in relation to the baseline pulse rate or change in eGFR, it decreased significantly after switching ( $2.15 \pm 0.50$  mg/g to  $1.97 \pm 0.55$  mg/g [ $P < .001$ ];  $2.15 \pm 0.50$  mg/g to  $2.04 \pm 0.58$  mg/g [ $P = .0191$ ], respectively; Figure 1 and Figure 2) in cases with a high pulse rate (pulse rate at

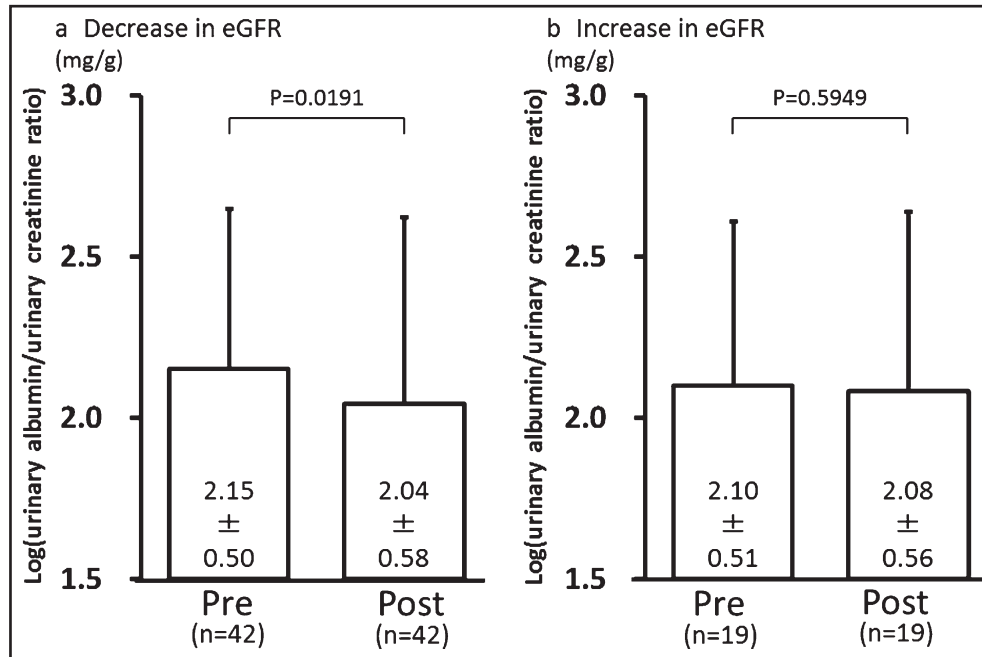
**TABLE II.** Time Course of Baseline Values Before and After Switching From Amlodipine to Cilnidipine

Parameters	No.	Pretreatment	Post-Treatment	P Value
Systolic blood pressure, mm Hg	70	$138.1 \pm 18.8$	$135.8 \pm 17.7$	.3276
Diastolic blood pressure, mm Hg	70	$75.2 \pm 12.8$	$74.8 \pm 11.4$	.7398
Heart rate, beats per min	61	$72.2 \pm 9.9$	$71.5 \pm 11.1$	.6877
Log (urinary albumin/urinary creatinine), mg/g creatinine	70	$2.14 \pm 0.49$	$2.06 \pm 0.58$	.0282
Serum creatinine, mg/dL	65	$0.89 \pm 0.41$	$0.94 \pm 0.42$	.0009
Estimated glomerular filtration rate, mL/min/ $1.73$ m <sup>2</sup>	65	$64.6 \pm 22.9$	$60.7 \pm 21.7$	.0003
Serum uric acid, mg/dL	65	$6.0 \pm 1.4$	$6.1 \pm 1.4$	.1744
Urinary uric acid/urinary creatinine ratio, g/g creatinine	67	$0.48 \pm 0.19$	$0.46 \pm 0.22$	.7062
Fraction excretion of uric acid, %	55	$7.27 \pm 3.42$	$7.01 \pm 3.35$	.6611

Data are expressed as mean  $\pm$  standard deviation. Statistical analysis was performed by Wilcoxon signed rank test.



**FIGURE 1.** Changes in the ratio of urinary albumin/creatinine in hypertensive patients. (a) Heart rate  $\geq 70$  beats per minute (bpm), (b) heart rate  $< 70$  bpm. Data are expressed as mean  $\pm$  standard deviation. Statistical analysis was performed by Wilcoxon signed rank sum test.



**FIGURE 2.** Changes in the ratio of urinary albumin/creatinine in hypertensive patients. (a) Decrease in estimated glomerular filtration rate (eGFR) and (b) increase in eGFR. Data are expressed as mean  $\pm$  standard deviation. Statistical analysis was performed by Wilcoxon signed rank sum test.

baseline,  $\geq 70$  bpm) or with decrease in eGFR after switching.

#### Change in Serum Uric Acid Level, Urinary Uric Acid/Creatinine Ratio, and Fractional Excretion of Uric Acid

The serum uric acid level as a whole showed no significant change ( $6.0 \pm 1.4$  mg/dL to  $6.1 \pm 1.4$  mg/dL,  $P = .1744$ ). A change in urinary uric acid/creatinine can reflect a change in uric acid excretion in addition to uric acid production. This indicator showed no significant change ( $0.48 \pm 0.19$  g/g to  $0.46 \pm 0.22$  g/g,  $P = .7062$ ) and the fractional excretion of uric acid also showed no significant change ( $7.17 \pm 3.42\%$  to  $7.01 \pm 3.35\%$ ,  $P = .6611$ ). However, when these parameters were analyzed in relation to the magnitude of urinary uric acid excretion, the urinary uric acid/creatinine ratio decreased significantly ( $0.66 \pm 0.14$  g/g to  $0.56 \pm 0.25$  g/g,  $P = .0437$ ; Figure 3) and the fractional excretion of uric acid also decreased significantly after switching ( $8.60\% \pm 3.33\%$  to  $6.84\%$  [ $P = .0114$ ]; Figure 4) in cases with enhanced uric acid excretion (urinary uric acid/creatinine ratio at baseline,  $\geq 0.50$  g/g). In contrast, the urinary uric acid/creatinine ratio showed no significant change ( $0.36 \pm 0.10$  g/g to  $0.40 \pm 0.17$  g/g [ $P = .1228$ ]; Figure 3) and the fractional excretion of uric acid did not change either ( $6.31\% \pm 3.20\%$  to  $7.14\% \pm 3.46\%$  [ $P = .0784$ ]; Figure 4) in cases with reduced uric acid excretion (urinary uric acid/creatinine ratio at baseline,  $< 0.5$  g/g). The change in urinary uric acid/creatinine ratio was positively and significantly correlated with the

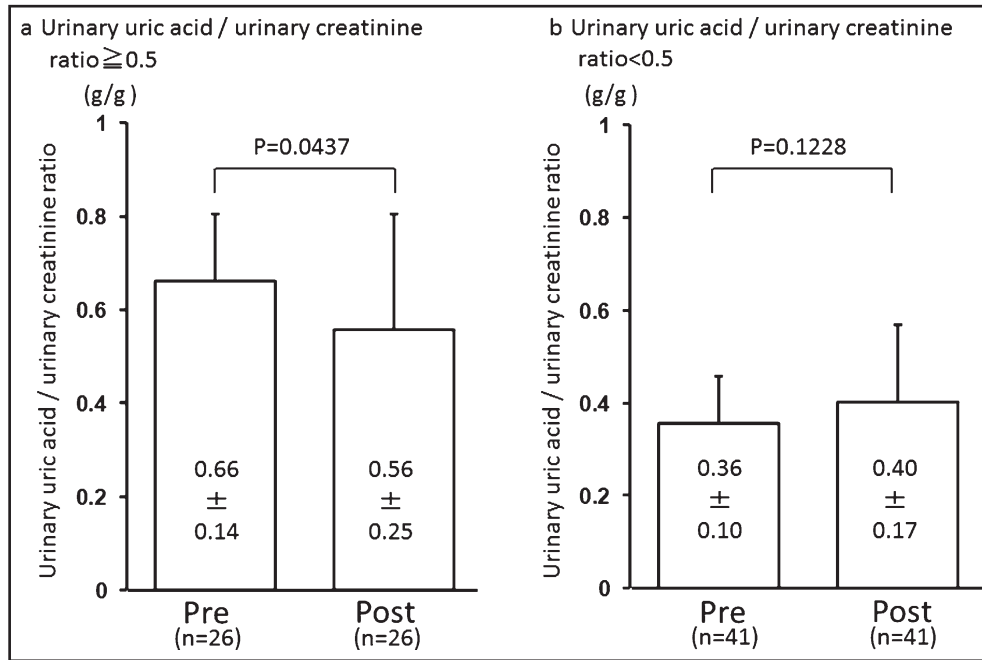
change in eGFR (Spearman  $\rho = 0.4131$ ,  $P = .009$ ; Figure 5) after switching from amlodipine to cilnidipine.

#### DISCUSSION

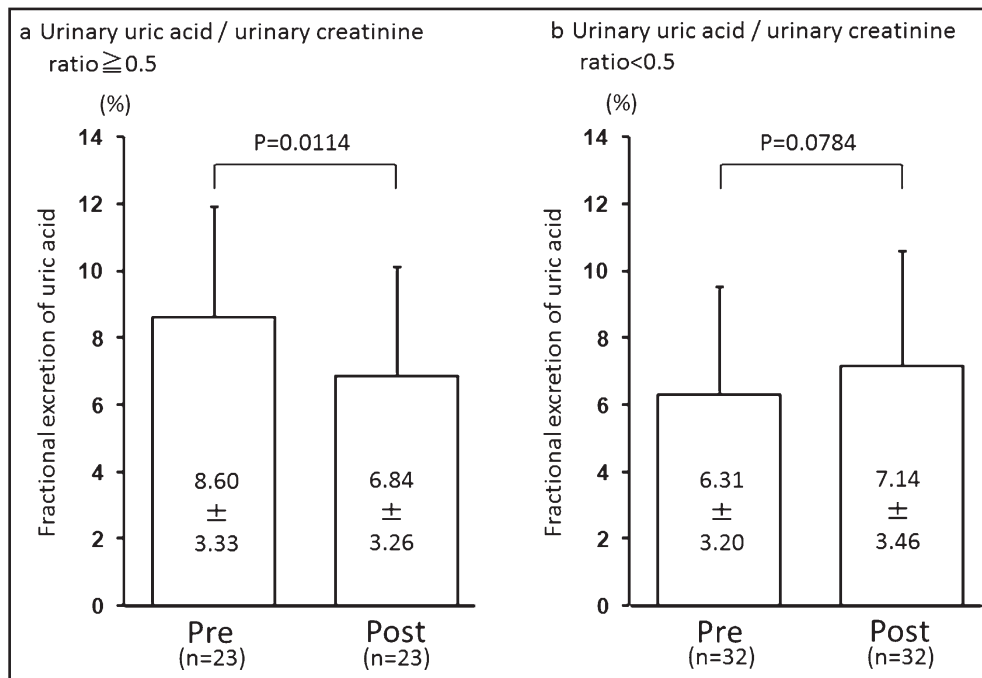
It has long been known that hypertension is closely related to CKD and that both conditions serve as risk factors for cardiovascular diseases. Recently, hyperuricemia was reported to be involved in hypertension and cardiovascular disease, which are major risk factors for progression of CKD in addition to proteinuria.<sup>19,20</sup> Therefore, when treating hypertensive patients with CKD, it is desirable to use antihypertensives that exert potent hypotensive activity and proteinuria-lowering activity without adversely affecting the uric acid metabolism.

In the present study, we analyzed the effects of switching from amlodipine (L-type CCB) to cilnidipine (N/L-type CCB) on BP, renal function, serum uric acid level, and uric acid metabolism in hypertensive patients with CKD. Similar to amlodipine, cilnidipine was shown to control BP and heart rate but also significantly reduce urinary ACR, unlike amlodipine. Cilnidipine additionally reduced uric acid production without adversely affecting the serum uric acid level. In a detailed analysis of the effects on uric acid metabolism, patients with enhanced urinary uric acid excretion (baseline urinary uric acid/creatinine  $\geq 0.50$  g/g) showed a marked decrease (by about 0.1 g/g) in urinary uric acid/creatinine ratio following switching to cilnidipine.

It is known that hypertensive patients show sympathetic hyperactivity and reduced nitric oxide production



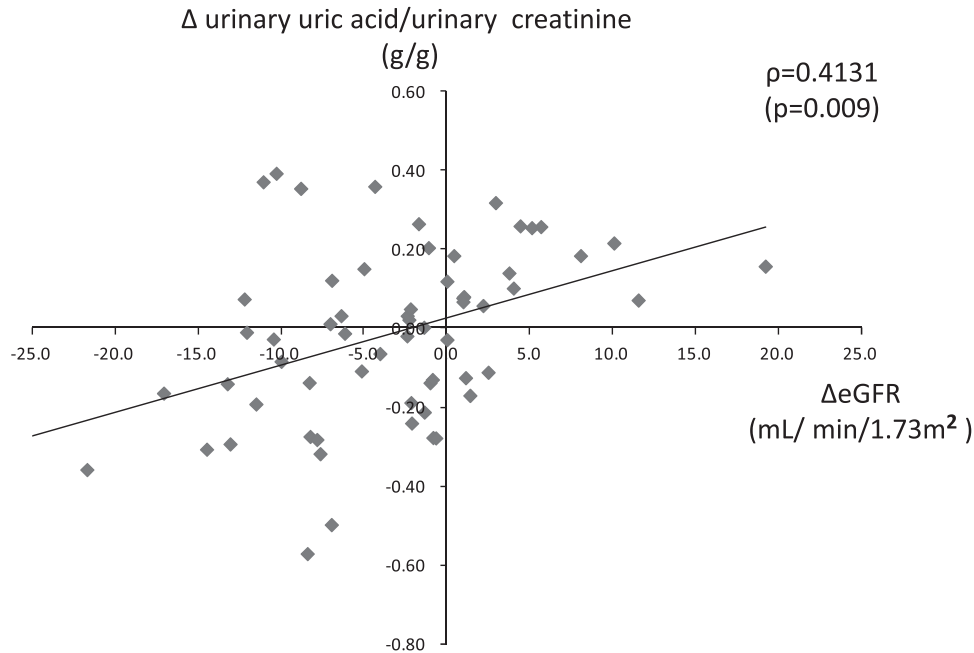
**FIGURE 3.** Changes in urinary uric acid/urinary creatinine ratio in hypertensive patients. (a) Urinary uric acid/urinary creatinine excretion  $\geq 0.5$  g/g and (b) urinary uric acid/urinary creatinine excretion  $< 0.5$  g/g. Data are expressed as mean  $\pm$  standard deviation. Statistical analysis was performed by Wilcoxon signed rank sum test.



**FIGURE 4.** Changes in fractional excretion of uric acid in hypertensive patients. (a) Urinary uric acid/urinary creatinine excretion  $\geq 0.5$  g/g and (b) urinary uric acid/urinary creatinine excretion  $< 0.5$  g/g. Data are expressed as mean  $\pm$  standard deviation. Statistical analysis was performed by Wilcoxon signed rank sum test.

in the vascular endothelium caused by insulin resistance and that these changes can lead to excessive production of uric acid precursors such as hypoxanthine in the

skeletal muscle, resulting in so-called myogenic hyperuricemia. In the present study, switching from amlodipine to cilnidipine reduced the urinary excretion



**FIGURE 5.** Positive correlation between the change in ratio of urinary uric acid to urinary creatinine and the change in estimated glomerular filtration rate ( $\Delta$ eGFR). Statistical analysis was performed by Spearman correlation test.

of uric acid that had been produced excessively before switching. This is a very interesting finding when discussing the relationship between myogenic hyperuricemia and sympathetic hyperactivity, although comparison of cilnidipine with other CCBs is difficult because only a few reports have been published concerning an improvement of uric acid metabolism following CCB treatment. The fractional excretion of uric acid also decreased significantly in cases with a baseline urinary uric acid/creatinine ratio  $\geq 0.50$  g/g, probably reflecting suppressed uric acid production.

A previous report demonstrated that cilnidipine, which suppresses the N-type calcium channel, causes suppression of excessive hyperactivity of renal sympathetic nerves, leading to intense dilatation of both afferent and efferent arterioles of the kidney and reduction in glomerular pressure.<sup>21</sup> In the present study, the log (urinary ACR) was decreased in patients with declined eGFR. Heart rate is reported to be the marker of sympathetic nerve activity,<sup>22</sup> in cases with elevated heart rate ( $\geq 70$  bpm, cutoff of 70 bpm was selected as the median heart rate; cilnidipine greatly reduced SBP in hypertensive patients with  $\geq 70$  bpm,<sup>23</sup> and published evidence has suggested that the risk associated with heart rate rises above this value<sup>24</sup>), the log (urinary ACR) was decreased. In addition, cilnidipine has been shown to suppress the secretion of renin, angiotensin, and aldosterone.<sup>25,26</sup> Furthermore, cilnidipine suppressed renin-angiotensin-aldosterone system (RAAS) activation and podocyte disorder in an experimental study using spontaneously hypertensive rats.<sup>27</sup> Clinically, the CARTER study and a trial involving switching

from amlodipine to cilnidipine in patients with type 2 diabetes mellitus demonstrated better proteinuria-lowering effects with cilnidipine than with amlodipine.<sup>18,28</sup> Cilnidipine reduced RAAS activation and suppressed the rise in microalbuminuria as compared with L-type CCB.<sup>29</sup>

In the present study, serum creatinine level increased significantly following switching to cilnidipine. This result seems to reflect alleviation of nephropathy through reduction of the glomerular pressure, considering that the study covered only a short period (3 months) and that urinary ACR decreased significantly.

There are several possible mechanisms explaining the effect of cilnidipine on reducing uric acid production. Firstly, the drug is known to suppress hyperactivity of sympathetic nerves<sup>17</sup> and, thus, may suppress hypoxanthine formation. Indeed, it is reported that  $\alpha_1$ -blockers, inhibitors of sympathetic hyperactivity, reduce production of hypoxanthine (a uric acid precursor) in the skeletal muscle, thus leading to improvement of myogenic hyperuricemia.<sup>14</sup> Secondly, this drug restores blood flow in the skeletal muscle and, thus, inhibits muscular AMP deaminase activity involved in ATP metabolism, leading to suppressed degradation of AMP to hypoxanthine. Thirdly, the drug improves renal blood flow likely because of the dilatation of afferent arteriole,<sup>30</sup> possibly leading to the enhanced excretion of uric acid. Moreover, a concordant change of decreases in filtration fraction (defined as glomerular filtration rate divided by renal plasma flow) eventually leads to uric acid excretion in the proximal tubules.



Lastly, the intestinal excretion of uric acid should be considered in the present study. It is hypothesized that the intestinal excretion of uric acid mediated by ABCG2 transporters may play a pivotal role in the occurrence of hyperuricemia and gout because the presence of SNP of the ABCG2 transporters are found in a substantial proportion of patients with gout.<sup>31</sup> Moreover, the expression of ABCG2 transporters are increased in the face of reduced kidney function in animal models, explaining the compensatory function of the intestine in uric acid metabolism.<sup>32</sup> Therefore, if cilnidipine activates on the ABCG2 transporter in the intestine, the results obtained in the present study corroborates well with the hypothesis. Further investigation is necessary on this issue.

Other CCBs in general have no influence on uric acid metabolism. However, the results from this study suggest that cilnidipine significantly suppresses uric acid production associated with myogenic hyperuricemia through its dual-blocking actions on L and N types of calcium channels. Many of the patients enrolled in this study had a normal uric acid level at baseline, and the serum uric acid level showed no significant reduction following switching to cilnidipine. More clinical study needs to be done using hypertensive CKD patients with overt hyperuricemia.

## STUDY LIMITATIONS

This study, however, has several limitations. Firstly, urinary albuminuria and urinary uric acid excretion were measured using random urine samples (corrected for the urinary creatinine level), rather than 24-hour pooled urine. Although using 24-hour pooled urine may be adequate for the analysis of the data of interest, we utilized random urine samples of clinical convenience: (1) the study primarily involved outpatients of family physicians, and (2) there is a previous study reporting that urinary ACR and urinary uric acid/creatinine ratio in spot urine samples correlated with the daily excretion of each substance.<sup>15,33</sup>

In addition, the study lasted only 3 months. However, since significant albuminuria-reducing effects have been shown in previous studies of the same time course of albuminuria in patients with type 2 diabetes mellitus,<sup>28,34</sup> we chose the study period of 3 months. Therefore, the number of the participants was small, making us unable to subanalyze the results by sectioning according to the covariates. Finally, the present study was designed as a single-group study rather than as a study for comparison among multiple groups. In this regard, an interventional clinical trial should be conducted in the future.

## CONCLUSIONS

Taken together, the results from this study allow us to conclude that cilnidipine (N/L-type CCB) exerts hypotensive activity, similar to the L-type CCB amlodipine, and that it can also improve albuminuria and uric acid metabolism. Considering these features,

cilnidipine is a promising drug of choice for targeting CKD patients with hypertension and hyperuricemia, since both disorders often coexist in clinical medicine.<sup>35</sup>

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*Conflict of interest:* None.

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