Heart Vessels (2009) 24:301–307
DOI 10.1007/s00380-008-1125-y

ORIGINAL ARTICLE

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Influence of T-calcium channel blocker treatment on deterioration of renal function in chronic kidney disease

Received: May 21, 2008 / Accepted: October 24, 2008

Abstract Some calcium channel blockers (CCBs) have renoprotective effects. Our aim was to compare the effects of different subclasses of CCBs on the deterioration of renal function in chronic kidney disease (CKD). This is a prospective, observational cohort study in a single center. The subjects were 107 nondiabetic CKD patients. The rate of deterioration of estimated glomerular filtration rate (ΔeGFR) was calculated by [last visit eGFR – baseline eGFR/follow-up duration]. Multivariate analysis was performed using the change in urinary protein (ΔUP) and ΔeGFR during follow-up as response variables. CCB subclasses were L-type in 76 patients, T- and L-type in 28 patients, and nondihydropyridines in 6 patients. Multiregression analysis indicated that higher baseline proteinuria (UP) and the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers were associated with the decrease of UP, while the use of L-type CCBs, prednisolone, and probucol was associated with the increase of UP. The use of T- and L-type CCBs, ACEIs and diuretics was associated with a good outcome in terms of ΔeGFR, whereas chronic glomerulonephritis, polycystic kidney disease, and higher baseline eGFR and UP were associated with a poor outcome. It is suggested that the use of T- and L-type CCB among other subclasses may improve the outcome of patients with nondiabetic CKD in terms of renal function.

Key words Chronic kidney disease · Calcium channel blocker · Angiotensin-converting enzyme inhibitor · Estimated glomerular filtration rate · Proteinuria

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Introduction

There is a report that complication of cardiovascular disorder increases with the progression of disease stage in patients with chronic kidney disease (CKD), resulting in an increased hazard ratio to 2.8 in stage 4 and 3.4 in stage 5.[1] Slowing the progression of CKD appears to be important not only for the prevention of hemodialysis introduction but also for the long-term outcome. The most influential clinical risk factor for the progression of CKD is urinary protein excretion (UP) among others, with a report that 1 g or higher of persistent UP may lead to the progression of CKD.[2] Many other reports suggest blood pressure (BP) as another important prognostic factor,[3–5] including the results of a meta-analysis by Jafer et al. that BP control to less than 130 mmHg systolic BP reduced the incidence of terminal renal failure or doubling of serum creatinine (S-Cr).[5] BP control to 125/75 mmHg or less is recommended in patients with 1 g/day or higher UP, from the results of the Modification of Diet in Renal Disease (MDRD) study.[6] Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and other renin angiotensin system (RAS) inhibitors are antihypertensive drugs concomitant with an effect to reduce UP, which is the reason why they are used as a standard medication for CKD at present. BP control, however, to the recommended level is often difficult with RAS inhibitors alone in a clinical setting,[3,7] so many patients are treated in combination with CCBs.[7]

CCBs are classified into dihydropyridines (DHPs) and non-DHPs by chemical structure, and L-, T-, and N-types by the calcium ion channel they act on. Non-DHP CCBs (nDHPs), T-type CCBs (T/L-CCBs), and N-type CCBs (N/L-CCBs) have been reported to reduce UP.[8–11] The effect of reducing UP of T/L-CCBs and N/L-CCBs has been attributed to the decrease of intraglomerular pressure through the dilatation of efferent arterioles.[10,11] RAS inhibitors with similar activity also reduce the progression of CKD as reported by many authors.[12–14] It has not been reported that these subclasses of CCBs improve the outcome of CKD, and it may be clinically significant to clarify the

association of the use of CCBs in CKD patients with the outcome of the disease. We have, therefore, assessed by multivariate analysis whether the change of UP and the rate of deterioration of renal function are related to the subclass of CCBs used in the CKD patients.

Materials and methods

Subjects

This is a prospective, observational cohort study in a single center. Local ethical committee permission was obtained. The subjects of this study were extracted from the outpatients who gave their informed consent to enroll into this study. A total of 107 patients were eligible to participate in this study. Subject diseases for analysis were chronic glomerulonephritis (CGN), focal glomerulosclerosis (FGS), membranous nephropathy (MN), nephrosclerosis, and polycystic kidney disease (PKD). At entry, subject drugs included antihypertensives [CCBs, ACEIs, ARBs, α-blockers (α-Bs), β-blockers (β-Bs), α/β-blockers (α/β-Bs), α2-antagonists], diuretics, prednisolone (PSL), antiplatelets, eicosapentaenoic acid (EPA), anticoagulants, and antihyperlipidemics (statin, probucol). CCBs were further grouped into L-CCBs which act on the L-type calcium ion channel, T/L-type CCBs which act on L- and T-type channels, and nondihydropyridines (nDHPs) to be used as explanatory variables. The patients were followed for a mean period of 37.1 ± 13.0 months.

Methods

Multivariate analysis

Urinary protein excretion (g/gCr) was measured in urine samples taken on hospital visits,[15] and the change of UP (ΔUP) was calculated by deducting a baseline UP from the measurement on their last visit. Renal function (estimated glomerular filtration rate; eGFR) was estimated from age, sex, and S-Cr by the simple MDRD equation, and the rate of deterioration of renal function (ΔeGFR) was calculated by the formula ΔeGFR = last visit eGFR – baseline eGFR/follow-up period (years).[16] Multiregression analysis by the backward estimation method was performed using ΔUP and ΔeGFR as response variables and antihypertensives and other drugs administered, age, sex, underlying disease, baseline eGFR and UP, and last visit BP [systolic BP (SBP) and diastolic BP (DBP)] as explanatory variables. Last visit UP was also used as an additional explanatory variable for the analysis of ΔeGFR.

Survival analysis

A Kaplan–Meier curve was made, depicting progression to stage 5 CKD or –10 ml/min/1.73 m^2 or more ΔeGFR (in patients with stage 5 CKD at baseline) as the survival end point. Patients were grouped by subclasses of CCBs. The survival curve was tested for significance by the log-rank test.

Statistical analysis

The results were analyzed using Dr. SPSS II version 11.0.1 J (SPSS Inc., Chicago, IL, USA) software without exception. The unpaired *t*-test was employed for comparison between two groups and one-way ANOVA for comparison among three groups. A difference with $P < 0.05$ was considered as statistically significant.

Results

Profile of patients

A total of 107 patients (71 men and 36 women) were eligible in this study with an average 56.4 ± 6.8 years of age, 25.3 ± 6.4 ml/min/1.73 m^2 of eGFR, and 1.71 ± 1.01 g/gCr of UP as the mean on the baseline (Table 1). The patients were followed for a mean period of 37.1 ± 13.0 months, and the mean ΔeGFR during follow-up was –2.73 ± 1.24 ml/min/

Table 1. Profile of eligible patients ($n = 107$)

Baseline	
Age (years)	56.4 ± 6.8
Sex (M:F)	71:36
eGFR (ml/min)	25.3 ± 6.4
UP (g/gCr)	1.72 ± 1.01
Last visit	
SBP (mmHg)	133.9 ± 6.7
DBP (mmHg)	81.4 ± 5.1
eGFR (ml/min)	16.8 ± 4.5
UP (g/gCr)	1.46 ± 0.81
Follow-up period (months)	37.1 ± 13.0
ΔGFR (ml/min/year)	–2.73 ± 1.24
Alpha-blocker	15
Beta-blocker	12
Alpha/beta-blocker	18
Alpha2-agonist	11
CCB	
L-CCB	73
T/L-CCBs	28
nDHP	6
ACEI	43
ARB	13
PSL	7
Antiplatelet	55
EPA	18
Anticoagulant	5
Statin	25
Probucol	14
Diuretics	22

Value are means ± SD
eGFR, estimated glomerular filtration rate; UP, urinary protein excretion; SBP, systolic blood pressure; DBP, diastolic blood pressure; CCB, calcium channel blocker; L-CCB, L-type CCB; T/L-CCB, T- and L-type CCB; nDHP, nondihydropyridine CCB; ACEI, angiotensin-converting enzyme inhibitor, ARB, angiotensin receptor blocker, PSL, prednisolone, EPA, eicosapentaenoic acid

year with 133.9 ± 6.7 mmHg of SBP, 81.4 ± 5.1 mmHg of DBP, 16.8 ± 4.5 ml/min of eGFR, and 1.46 ± 0.81 g/gCr of UP on the last visit (Table 1). The underlying kidney diseases were CGN in 55 patients, nephrosclerosis in 21 patients, PKD in 8 patients, and others in 15 patients (Table 2). ACEIs were used in 43 patients, diuretics in 22 patients, antiplatelets in 55 patients, and statins in 25 patients (Table 1). DHP-CCBs used in the patients included nifedipine, amlodipine, nicardipine, nitrendipine, benidipine, barnidipine, manidipine, nilvadipine, and efonidipine. The first four were classified, as previously reported, as L-CCBs and the others as T/L-CCBs[17–19] (Table 3). Seventy-six patients were treated with L-CCBs, 28 patients with T/LCCBs, and 6 patients with nDHPs according to this classification (Table 3). Five patients in the nDHPs treatment group were treated with diltiazem and one with verapamil (Table 3).

Table 2. Etiology of chronic kidney disease

CGN	55
MN	4
FGS	3
Nephrosclerosis	21
PKD	8
Other/Unknown	15

CGN, chronic glomerulonephritis; MN, membranous nephropathy; FGS, focal glomerulosclerosis, DM, diabetes mellitus; PKD, polycystic kidney disease

Multivariate analysis

Multiregression analysis for ΔUP indicated an significant association of the use of α/β-Bs, ACEIs, ARBs, and antiplatelets with a decrease of UP with correlation coefficients of –0.171, –0.165, –0.166, and –0.161, respectively (Table 4), whereas the use of L-CCBs, PSL, and probucol was significantly associated with an increase of UP with correlation

Table 3. Details of CCB subclass

L-CCBs	
Nifedipine	21
Amlodipine	50
Nicardipine	4
Nitrendipine	1
T/L-CCBs	
Benidipine	13
Barnidipine	6
Manidipine	5
Nilvadipine	2
Efonidipine	2
nDHP	
Diltiazem	5
Verapamil	1

Table 4. Correlation coefficient with ΔUP

	Monovariate regression Correlation coefficient	*P* value	Multivariate regression Correlation coefficient	*P* value
Age	0.087	n.s.		n.s.
Sex (male vs female)	–0.054	n.s.		n.s.
Etiology				
CGN	0.021	n.s.	0.130	0.142
FGS	0.019	n.s.		n.s.
MN	–0.221	**0.022**		n.s.
Nephrosclerosis	–0.034	n.s.	–0.162	0.065
PKD	–0.025	n.s.	–0.127	0.094
Baseline				
eGFR	–0.070	n.s.	0.094	0.215
UP	–0.633	**<0.001**	–0.744	**<0.001**
Last visit				
SBP	–0.092	n.s.		n.s.
DBP	–0.030	n.s.		n.s.
Alpha-blocker	–0.134	n.s.		n.s.
Beta-blocker	0.086	n.s.		
Alpha/beta-blocker	–0.156	n.s.	–0.171	**0.018**
Alpha2-agonist	0.132	n.s.		n.s.
CCB				
L-CCB	0.085	n.s.	0.142	**0.034**
T/L-CCBs	–0.052	n.s.		n.s.
nDHP	–0.074	n.s.		n.s.
ACEI	–0.143	n.s.	–0.165	**0.019**
ARB	–0.056	n.s.	–0.166	**0.022**
PSL	0.115	n.s.	0.162	**0.021**
Antiplatelet	–0.172	n.s.	–0.161	**0.048**
EPA	–0.081	n.s.	0.071	0.358
Anticoagulant	–0.175	n.s.	–0.126	0.063
Statin	–0.165	n.s.		n.s.
Probucol	–0.030	n.s.	0.157	0.029
Diuretics	–0.099	n.s.		n.s.

n.s., not significant

Table 5. Correlation coefficient with ΔGFR

	Monovariate regression Correlation coefficient	*P* value	Multivariate regression Correlation coefficient	*P* value value
Age	0.205	**0.034**		n.s.
Sex (male vs female)	–0.102	n.s.		n.s.
Etiology				
CGN	–0.286	**0.003**	–0.277	**0.002**
FGS	–0.077	n.s.		n.s.
MN	–0.103	n.s.		n.s.
Nephrosclerosis	0.288	**0.003**		n.s.
PKD	–0.090	n.s.	–0.174	**0.042**
Baseline				
eGFR	–0.311	0.001	–0.218	**0.014**
UP	–0.365	<**0.001**	–0.285	**0.001**
Last visit				
UP	–0.361	0.001		n.s.
SBP	–0.091	n.s.		n.s.
DBP	–0.174	n.s.		n.s.
Alpha-blocker	–0.043	n.s.		n.s.
Beta-blocker	–0.090	n.s.		n.s.
Alpha/beta-blocker	0.104	n.s.		n.s.
Alpha2-agonist	0.004	n.s.		n.s.
CCB				
L-CCB	–0.201	**0.038**		n.s.
T/L-CCBs	0.215	**0.026**	0.233	**0.005**
nDHP	–0.004	n.s.		
ACEI	0.070	n.s.	0.178	**0.033**
ARB	–0.063	n.s.		n.s.
PSL	0.033	n.s.		n.s.
Antiplatelet	–0.192	**0.048**		n.s.
EPA	–0.067	n.s.		n.s.
Anticoagulant	0.059	n.s.		n.s.
Statin	–0.052	n.s.		n.s.
Probucol	–0.177	n.s.		n.s.
Diuretics	0.183	n.s.	0.187	**0.028**

coefficients of 0.142, 0.162, and 0.157, respectively (Table 4). In addition, baseline UP was significantly associated with ΔUP with a correlation coefficient of –0.744 (Table 4). Factors, on the other hand, that correlated with ΔeGFR were the use of T/L-CCBs, ACEIs, and diuretics among drugs used for treatment, CGN and PKD among the underlying diseases, and baseline eGFR and UP (Table 5). The use of T/L-CCBs, ACEIs, and diuretics was associated with the retention of eGFR with correlation coefficients of 0.233, 0.178, and 0.187, respectively. Underlying diseases CGN and PKD were associated with a decrease of eGFR with correlation coefficients of –0.277 and –0.174, respectively (Table 4). Higher baseline eGFR and UP were associated with a decrease in eGFR with correlation coefficients of –0.218 and –0.285, respectively (Table 5).

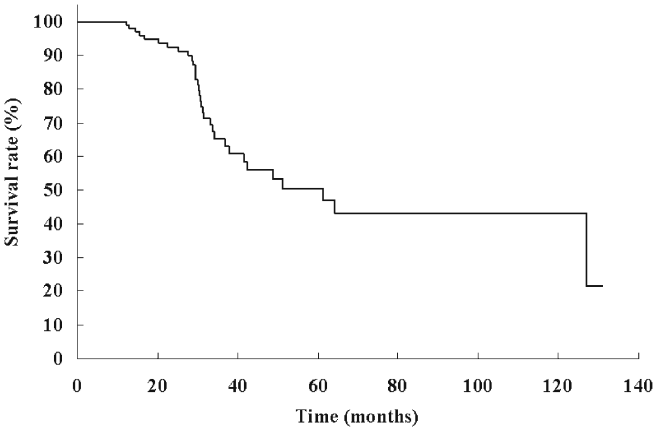

Fig. 1. Survival curve in nondiabetic patients with chronic kidney disease

Survival analysis

A total of 34 patients reached the end point with a 50% renal survival rate after about 50 months of follow-up (Fig. 1). Twenty-six patients (35.6%) in the L-CCBs group, 5 patients (17.9%) in the T/L-CCBs group, and 3 patients (50%) in the nDHPs group reached the end point (Table 6). There was no significant difference in patient profile between groups, but survival analysis indicated that renal outcome was significantly better in the T/L-CCBs group (T vs L $P = 0.023$, T vs nDHP $P = 0.043$) compared to other groups while the L-CCBs and nDHPs groups showed a similar outcome (Fig. 2).

Table 6. Profile of each group

	L-CCB (n = 73)	T/L-CCB (n = 28)	nDHP (n = 6)	P value
Age (years)	55.6 ± 7.2	58.2 ± 6.6	57.9 ± 3.9	0.691
Sex (M:F)	50:23	18:10	3:3	0.638
Etiology				
CGN	37	15	3	0.965
FGS	2	1	0	0.892
MN	3	1	0	0.879
Nephrosclerosis	14	5	2	0.684
PKD	6	2	0	0.766
Baseline				
eGFR (ml/min)	26.1 ± 6.8	24.5 ± 5.9	19.3 ± 3.3	0.431
UP (g/gCr)	1.76 ± 1.11	1.64 ± 0.85	1.56 ± 0.33	0.668
Last visit				
SBP (mmHg)	133.2 ± 7.2	136.8 ± 5.6	129.7 ± 5.5	0.367
DBP (mmHg)	81.2 ± 4.9	82.6 ± 5.0	77.5 ± 7.6	0.536
eGFR (ml/min)	16.9 ± 4.4	17.5 ± 4.9	12.1 ± 2.5	0.401
UP (g/gCr)	1.59 ± 0.91	1.23 ± 0.53	0.79 ± 0.38	0.579
Follow up period (months)	35.3 ± 12.3	42.5 ± 14.9	34.1 ± 12.6	0.449
ΔGFR (ml/min/year)	–3.07 ± 1.28	–1.85 ± 0.89	–2.77 ± 1.74	0.083
Reached the end point (n)	26	5	3	0.144
Medication				
Alpha-blocker	11	3	1	0.841
Beta-blocker	8	2	2	0.185
Alpha/beta-blocker	19	7	3	0.986
Alpha2-agonist	9	2	0	0.525
ACEI	32	10	1	0.372
ARB	11	2	0	0.362
PSL	5	2	0	0.804
Antiplatelet	38	14	3	0.981
EPA	10	6	2	0.356
Anticoagulant	3	1	1	0.363
Statin	16	9	0	0.215
Probucol	10	4	0	0.625
Diuretics	15	4	3	0.148

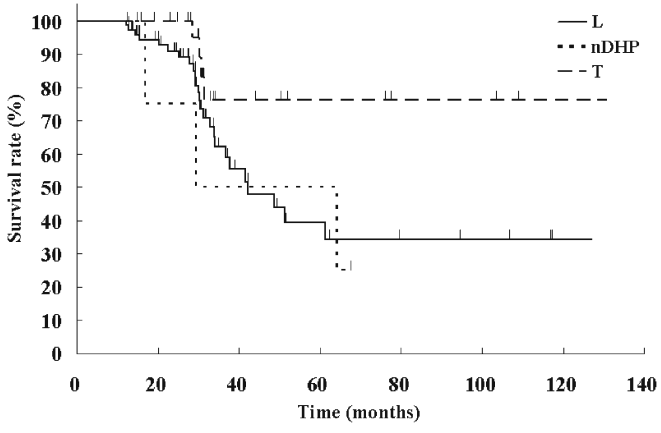

Fig. 2. Survival curve in each calcium channel blocker (CCB) treatment group. *L*, L-type CCB; *T*, T-type CCB; *nDHP*, nondihydropyridine CCB

Discussion

We studied CKD patients, prospectively, who were undergoing treatment with CCBs at entry to see if there was an association between subclasses of CCBs and a decrease of UP or the rate of deterioration of renal function. Treatment with L-CCBs compared to other subclasses was associated with an increase of UP and treatment with T/L-CCBs with the retention of eGFR. Renal survival rate was significantly higher in the patient group treated with T/L-CCBs than in the other two groups.

CCBs have been described to exhibit a renoprotective effect in the treatment of patients with nephropathy by lowering BP,[20] and an AASK (African American Study of Kidney Diseases) subanalysis in a recent large-scale study has shown that the nonrecovery of renal function occurred less in a patient group with lower mean BP (92 mmHg) among patients treated with amlodipine.[21] Decreases of UP by nDHP-CCBs, N/L-CCBs, and T/L-CCBs have been reported as a subclass-specific renoprotective effect.[8–11] There has not, however, been any report until now to show that these subclasses of CCBs have an effect in reducing the progression of renal failure. It has been reported instead that renal function deteriorated faster in the diabetic patients treated with the L-CCB nifedipine than in those treated with placebo.[22]

Multiregression analysis with regard to renal function indicated an association of T/L-CCBs with the retention of eGFR in the present study, and this subclass of CCBs showed a significantly higher renal survival rate than other subclasses when assessed by survival analysis. T/L-CCBs have been reported to have pleiotropic effects includ-

ing an aldosterone secretion reducing effect,[23] an anti-inflammatory effect,[24] and a nitric oxide-increasing effect.[24,25] No difference in renal function has been previously reported between patients treated with T/L-CCB and those treated with a placebo, but a decrease in renal survival rate was found in L-CCB-treated patients after the third year of follow-up in the present study where the overall follow-up period was as long as 130 months. The length of follow-up period may have affected the study results in consideration of the fact that the period was no longer than 1 year in the previous study.

With regard to UP, multiregression analysis indicated that treatment with L-CCBs was associated with an increase of UP, whereas the use of T/L-CCBs was not an independent ΔUP-related factor. T/L-CCBs and N/L-CCBs supposedly dilate glomerular afferent and efferent arterioles without causing an increase in intraglomerular pressure[10,11] compared with L-CCBs that have a strong efferent arteriole-dilating effect causing intraglomerular pressure to increase.[26] Experiments with animal models of nephropathy have demonstrated an increase of UP in animals treated with L-CCBs and a decrease in animals treated with T/L-CCBs and N/L-CCBs, suggesting that the effect of CCBs on UP depends on their influence on intraglomerular pressure,[27,28] and sympathetic activity.[29] Clinical studies also have indicated that T/L-CCBs benidipine, manidipine, and efonidipine, and the N/L-CCB cilnidipine showed a UP-decreasing effect.[8–11] Furthermore, a recent randomized clinical study in Japan has also shown that UP increased in patients treated with the L-CCB amlodipine and decreased in those treated with cilnidipine.[30]

T/L-CCBs did not contribute to a significant decrease of UP in the present study, contrary to the previous reports. Urinary protein excretion decreased in 11 out of 28 patients in the T/L-CCBs group and increased in the remaining 17 patients. These 17 patients had a lower baseline UP compared to those who showed a decrease of UP after follow-up (0.87 vs 2.82 g/gCr, $P = 0.0014$). Ohishi et al. have reported that BP as well as UP decreased in the ABC (Amlodipine-to-Benidipine Changeover) study where amlodipine 5 mg was switched to benidipine 8 mg in hypertensive patients, and that the decrease in UP was associated with higher UP before the drug changeover.[10] The results of the present study may have been influenced by the baseline UP level. The effect of UP fluctuations as a result of prolonged treatment was another possibility for the difference in consideration that many of the previous reports were from short-term studies with follow-up periods of less than 1 year, including the ABC study. Patients treated with cilnidipine were excluded in the analysis of the present study because of paucity of the patients (4 patients).

Many authors have reported that ACEIs and ARBs are useful as standard therapy for CKD.[12–14] These RAS inhibitors have been described to reduce UP through decreasing intraglomerular pressure and to prevent the fibrosis of renal tissues through inhibiting angiotensin II.[12,14] In the present study, ACEIs among the RAS inhibitors were associated with a decrease of UP and retention of eGFR, whereas ARBs did not show any correlation with ΔeGFR. ARBs were used in only 13 of the 107 patients, in combination with ACEIs in six of them. ACEIs were very likely administered in combination to the patients with severe CGN, and the benefit of ARBs may not have been reflected in the outcome accordingly.

Other factors found related to ΔUP or ΔeGFR in the present study were underlying disease, and baseline UP and eGFR. CGN and PKD among the other underlying diseases were related factors for the decrease of eGFR. CGN is a representative disease presenting persistent UP, and the disease is more likely to be progressive in patients with increased UP and deterioration of renal function. PKD is a progressive disease although there is a vast difference in the rate of deterioration of renal function between patients. This may explain why an association with ΔeGFR was indicated for the patients with these diseases. On the other hand only a few patients had FGS or MN; these diseases became nonprogressive in some of the patients who responded well to PSL and, in addition, nephrosclerosis could also be maintained as nonprogressive in some patients by controlling BP.[31] These results may explain why there was no association with ΔeGFR in the patients with these diseases in our study.

Limitations of the study

The present study had a limitation in that the effect of NaCl and protein intake of the patients on the deterioration of renal function was unknown, with no such data available. Another limitation was that the study was a small cohort study indicating only relative relations for the effect of individual drugs at present. A 3-year or longer prospective study based on the results of the present study seems to be necessary.

Conclusions

We prospectively studied patients with CKD to see if there was an association between the subclass of CCBs used and a decrease in UP or the rate of deterioration of renal function. A multiregression analysis demonstrated relations between L-CCBs and UP increase and between T/L-CCBs and the retention of eGFR. Survival analysis indicated a significantly better renal survival in the patients treated with T/L-CCBs compared to the other two groups of patients. The effect of different subclasses of CCBs on renal function remains to be assessed by a long-term prospective study.

Acknowledgments This work was supported by grants from the Japan Research Promotion Society for Cardiovascular Diseases and the International Research and Educational Institute for Integrated Medical Sciences (IREIIMS).

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