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Reduction in microalbuminuria by calcium channel blockers in patients with type 2 diabetes mellitus and hypertension—A randomized, open-label, active-controlled, superiority, parallel-group clinical trial

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Summary

Background: It has been suggested that renoprotection with calcium channel blockers (CCBs) may differ. This study aimed to compare the anti-proteinuric effect of different CCBs in patients with type 2 diabetes (T2D).

Methods: A multicentre, randomized, open-label, active-controlled study was performed in seven centres in Korea. A total of 74 patients with T2D and microalbuminuria treated with renin-angiotensin system (RAS) blockers were randomized to a cilnidipine 10 mg treatment (n=38) or amlodipine 5 mg treatment (n=36).

Results: Urine albumin to creatinine ratio (ACR) reduction was similar between the two groups at 12 weeks (−53.0±123.2 mg/g in cilnidipine group and −35.7±83.6 mg/g in amlodipine group, *P*=.29) or 24 weeks (−57.3±106.9 mg/g in cilnidipine group and −20.0±110.4 mg/g in amlodipine group, *P*=.24). In a subgroup analysis, cilnidipine treatment showed a larger ACR reduction than amlodipine treatment at 12 weeks (−84.7±106.8 mg/g in cilnidipine group and −9.5±79.2 mg/g in amlodipine group, *P*=.01) and 24 weeks (−84.0±111.7 mg/g in cilnidipine group and 14.6±119.4 mg/g in amlodipine group, *P*=.008), particularly in patients with a longer duration of diabetes more than 10 years.

Conclusions: Cilnidipine did not show any additional anti-albuminuric effect compared with amlodipine in patients with T2D and microalbuminuria treated with an RAS blocker. However, the anti-albuminuric effect of cilnidipine might differ according to the duration of diabetes.

1 | INTRODUCTION

Microalbuminuria is an early sign of diabetic nephropathy[1] and is associated with incident cardiovascular events.[2,3] It has been well known that tight blood pressure control with antihypertensive medications targeting the renin-angiotensin system (RAS) can delay the deterioration of renal function and protect against cardiovascular events in patients with type 2 diabetes (T2D) and microalbuminuria.[4] However, previous study showed that approximately three to four antihypertensive drugs are necessary to control blood pressure in patients with diabetes.[5] Therefore, although RAS blockers are the first-line option for controlling blood pressure in patients with diabetes, the majority of patients need another class of antihypertensive drugs in addition to RAS blocker. In addition, it was reported that combination of drugs with different mechanism of action reduces blood pressure more effectively with fewer adverse effects.[6] Therefore, combination treatment of two different classes of antihypertensive medications showed a larger blood pressure reduction compared with doubling the dose of a single drug.[7]

For optimal blood pressure control, different classes of antihypertensive drugs can be added to angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors in patients with T2D. Among them, RAS blocker in combination with a calcium channel blocker (CCB) was reported to be better for reducing cardiovascular events than were diuretics.[8] In addition, different voltage-gated calcium channel subtypes, including L-, T-, N- and P-/Q-types, have been suggested to be present within the renal vascular bed and tubules.[9] In clinical practice, although L-type CCBs are the most frequently prescribed CCBs, they mainly dilate afferent arterioles and possibly increase intraglomerular pressure. Therefore, L-type CCBs may not be appropriate for patients with renal impairment.[9] In contrast, N-type calcium channels are present at peripheral sympathetic nerve endings, which innervate both afferent and efferent arterioles. Therefore, inhibiting N-type calcium channels reduces intraglomerular pressure by dilating both afferent and efferent arterioles.[10] Cilnidipine is a dual L-/N-type CCB and a previous study demonstrated that cilnidipine treatment significantly reduces urinary protein excretion compared with amlodipine treatment in patients with chronic kidney disease and hypertension receiving an RAS blocker.[11]

Therefore, this study aimed to compare the anti-albuminuric effect of the L-/N-type CCB cilnidipine with the L-type CCB amlodipine in patients with T2D who were treated with ARB or ACE inhibitor. In addition, we tried to determine whether cilnidipine has more favourable effects on glucose tolerance, lipid parameters and endothelial function compared with amlodipine.

What's known

- Renin-angiotensin system blockers are the first-line drug to control blood pressure in patients with diabetes.
- Renoprotection with calcium channel blockers may differ according to the types of calcium channel.

What's new

- Anti-albuminuric effect of cilnidipine is similar to that of amlodipine.
- Anti-albuminuric effect of cilnidipine differs according to duration of diabetes.
- Anti-albuminuric effect of cilnidipine is superior to that of amlodipine in patients with long duration of diabetes.

2 | MATERIALS AND METHODS

2.1 | Study subjects

Patients with T2D (age ≥18 years) with an HbA1c level ≤8.0% who had not used insulin for at least 12 weeks before screening were eligible to participate. Study participants had hypertension with microalbuminuria and were being treated with an ARB or ACE inhibitor for at least 12 weeks and had systolic and diastolic blood pressure controlled in the range of 100 to 140 mm Hg and ≤90 mm Hg at entry, respectively. Study participants were eligible for the study if the urine albumin to creatinine ratio (ACR) ranged from 30 to 300 mg/g creatinine on two of three morning urine collections. Exclusion criteria were treatment with an antihypertensive drug other than RAS blocker within 2 weeks before randomization, serum creatinine level higher than normal, abnormal liver function test (AST/ALT ≥ 3 × upper normal limit), severe hepatic dysfunction, severe aortic stenosis, use of drugs possibly affecting glucose metabolism (eg, glucocorticoid), and women who were pregnant or lactating. Lipid-lowering drugs, antiplatelet agents, anti-thrombotics, and vasodilators were prohibited but could be used if the patients were prescribed the drugs before screening and did not change the dosage.

Considering 20% drop out rate, the required sample size was estimated as 74 that significant difference could be detected when the difference in the mean ACR change between both groups was 15 mg/g creatinine (statistical power: 80%, two-sided level of significance: 5%) considering the previous report.[12] Of the 157 screened patients with T2D, 83 were excluded, and 74 were enrolled in this study (intention-to-treat population). Among these 74 patients, 17 did not complete the study (withdrew informed consent, one patient; adverse effect, four patients; and violation of study protocol, 12 patients), and the remaining 57 patients were eligible for the per-protocol analysis.

This study was conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained from all participants, and the study was approved by the Internal Review Board of each participating centre.

2.2 | Study design

This was a 24-week randomized, open-label, active-controlled, superiority, parallel-group clinical trial conducted at seven centres in Korea. The study included a 2- to 4-week run-in period. If the systolic and diastolic blood pressure was maintained at 100-150 mm Hg and <90 mm Hg, respectively, during the run-in period, the patient was eligible for the study and began a 24-week active treatment

period. Eligible patients were randomly assigned to cilnidipine treatment (10 mg daily) or amlodipine treatment (5 mg daily) in combination with an ARB or ACE inhibitor. If blood pressure was low after randomization and caused a safety concern, the RAS blocker dosage could be titrated according to the investigator's decision. Clinic visits were scheduled 4, 12 and 24 weeks after randomization. Adherence to medication was assessed at each visit by pill counting, and non-adherent patients (<70%) were eliminated from the study.

The primary end-point was change in urine ACR from the pre-treatment period to 12 and 24 weeks. The secondary end-points included metabolic parameters and endothelial function test at 12 and 24 weeks and change in blood pressure at 24 weeks.

2.3 | Clinical and laboratory examination

Comprehensive physical examination was performed at baseline, and personal medical history including smoking status, alcohol drinking, and physical activity were assessed by a questionnaire. Body mass index was calculated as the weight divided by the square of height (kg/m^2). Waist circumference was measured at the midline between the iliac crest and the rib edge in a standing position. After resting at least 5 minutes, blood pressure was measured with an automatic sphygmomanometer in a seated position. Blood pressure was measured twice at 2-min intervals, and the mean value of two stable measurements (difference of <5 mm Hg) was used.

All blood tests were determined after an overnight fast more than 8 hours. Using an autoanalyzer, plasma glucose was measured by the hexokinase method. Plasma insulin was measured by radioimmunoassay. To estimate insulin sensitivity and insulin secretory capacity, the homoeostasis model assessment of insulin resistance (HOMA-IR) and HOMA-B% was calculated, respectively, based on fasting serum insulin and FPG levels.[13] The standard enzymatic method was used to measure total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol. HbA1c level was measured by high-performance liquid chromatography. The Cockcroft-Gault formula was used to estimate glomerular filtration rate (GFR).[14] Urinary albumin concentration (μg) was measured using a turbidimetric immunoassay. Urinary creatinine concentration (mg) was measured with a colorimetric method, and ACR (mg/g) was calculated by dividing the urinary albumin concentration by the urinary creatinine concentration.[15] Serum total adiponectin, plasminogen activator inhibitor-1 (PAI-1), and 8-isoprostane levels were measured with commercial enzyme linked-immunosorbent assay (ELISA) kits. Serum cystatin C level was measured by the immuno-nephelometry method.

After 5 minutes rest in the supine position, brachial-ankle pulse wave velocity (baPWV) and Ankle Brachial Index (ABI) were determined using an automatic device (VP-2000; Colin, Komaki, Japan). Briefly, blood pressures were measured in the both arms and legs and simultaneously recorded pulse waves using an oscillometric cuff technique.

2.4 | Statistical analysis

Data are expressed as mean±SD for continuous variables and as proportion for categorical variables. To compare differences between groups, independent *t*-test or Wilcoxon's rank-sum test and χ^2 test or Fisher's exact test were used for continuous variables and for categorical variables, respectively. Paired t-test was used to compare differences within groups before and after treatment. All statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). A P <.05 was considered significant.

3 | RESULTS

Table 1 shows the baseline characteristics of study participants. The mean age was 61.0 years and 59.8 years in cilnidipine and amlodipine

TABLE 1 Baseline characteristics of study subjects (intention-to-treat analysis)

	Cilnidipine (n=38)	Amlodipine (n=36)	*P*
Age (y)	61.0 (8.5)	59.8 (10.4)	.59
Male (%)	28 (73.7)	23 (63.9)	.36
Current smoking (%)	5 (13.2)	10 (27.8)	.29
Alcohol consumption (%)	17 (44.7)	13 (36.1)	.45
Body mass index (kg/m^2)	24.4 (2.7)	24.6 (2.8)	.78
Waist circumference (cm)	85.6 (9.6)	87.1 (6.7)	.45
Hip circumference (cm)	95.8 (6.6)	97.2 (6.2)	.34
Systolic blood pressure (mm Hg)	125.3 (10.8)	125.6 (11.0)	.89
Diastolic blood pressure (mm Hg)	74.0 (7.5)	76.2 (8.6)	.25
Heart rate (beat/min)	75.0 (7.4)	75.2 (9.4)	.93
White blood cells (10^9/L)	6.4 (1.6)	6.5 (1.8)	.77
Haemoglobin (g/L)	139.2 (12.1)	140.3 (15.3)	.71
Platelets (10^9/L)	234.8 (63.0)	231.7 (54.2)	.91
Total bilirubin (μmol/L)	14.5 (6.5)	12.8 (5.3)	.17
Protein (g/L)	72.0 (3.7)	72.0 (4.4)	.96
Albumin (g/L)	45.0 (2.7)	45.0 (3.0)	.91
Aspartate aminotransferase (U/L)	26.1 (13.7)	21.5 (6.4)	.11
Alanine transaminase (U/L)	24.5 (13.5)	24.8 (15.7)	.73
Alkaline phosphatase (U/L)	66.9 (19.0)	66.8 (20.0)	.82
Blood urea nitrogen (mmol/L)	5.74 (1.45)	5.98 (1.78)	.72
Creatinine (μmol/L)	84.9 (15.0)	80.4 (14.1)	.18
Estimated GFR (mL/min)	75.5 (21.2)	78.0 (23.6)	.78
Na (mmol/L)	140.6 (2.1)	140.9 (2.1)	.42
K (mmol/L)	4.6 (0.4)	4.6 (0.4)	.76
Cl (mmol/L)	102.3 (2.8)	103.1 (2.9)	.23
Fasting plasma glucose (mmol/L)	7.07 (1.18)	6.92 (1.32)	.80
HbA1c (%)	6.7 (0.6)	6.8 (0.6)	.46

Data are expressed as mean (SD) or proportion (%).
Independent *t*-test or Wilcoxon's rank-sum test were used.
GFR, glomerular filtration rate.

groups, respectively, and 68.9% of subjects were male. Blood pressure and glucose were well controlled in both groups, and no differences were noted between the two groups. In addition, renal function as estimated by GFR was slightly impaired (stage 2) and did not differ between groups (75.5±21.2 mL/min in the cilnidipine group and 78.0±23.6 mL/min in the amlodipine group, *P*=.78).

At baseline, subjects in both groups had similar urinary albumin excretion (138.2±109.9 mg/g in the cilnidipine group and 97.1±66.3 mg/g in the amlodipine group, *P*=.11). After 12 weeks, subjects in the cilnidipine group showed a significant decrease in ACR from baseline both in the intention-to-treat (−53.0±123.2 mg/g, *P*=.003) and per-protocol analyses (−59.6±135.1 mg/g, *P*=.007). In addition, the anti-albuminuric effect of cilnidipine persisted for up to 24 weeks in the cilnidipine group (−57.3±106.9 mg/g in intention-to-treat, *P*=.004 and −65.5±112.3 mg/g in per-protocol, *P*=.006). The amlodipine treatment could not decrease in ACR at 12 or 24 weeks. The decrease in ACR did not differ between groups at 12 and 24 weeks (Table 2).

We next divided study participants according to duration of diabetes. ACR reduction was similar between the two groups in patients with diabetes duration shorter than 10 years. However, in patients with diabetes longer than 10 years, the cilnidipine group showed a greater decrease in ACR than did the amlodipine group at 12 weeks (−84.7±106.8 mg/g in the cilnidipine group and −9.5±79.2 mg/g in the amlodipine group, *P*=.010) and 24 weeks (−84.0±111.7 mg/g in the cilnidipine group and 14.6±119.4 mg/g in the amlodipine group, *P*=.008) (Table 3).

In terms of metabolic parameters, fasting glucose and glycated haemoglobin level, lipid measurements, and insulin sensitivity and resistance measures determined by HOMA-IR did not differ between the two groups at 12 or 24 weeks. In addition, adiponectin, high-sensitivity C-reactive protein (hsCRP), 8-isoprostane, and cystatin C levels were similar between the two groups. The cilnidipine group showed a greater decrease in PAI-1 level than did the amlodipine group at 12 weeks (−2.8±10.1 ng/mL in the cilnidipine group and 2.2±16.1 ng/mL in the amlodipine group, *P*=.011). However, at 24 weeks, the amlodipine group had a greater decrease in diastolic blood pressure (2.0±7.4 mm Hg in the cilnidipine group and −1.9±8.0 mm Hg in the amlodipine group, *P*=.035) and brachial artery pulse wave velocity (right: 55.0±193.5 cm/s in the cilnidipine group and −40.6±213.1 cm/s in the amlodipine group, *P*=.05; left: 29.0±179.4 cm/s in the cilnidipine group and −63.7±207.9 cm/s in the amlodipine group, *P*=.046) than did the cilnidipine group (Table 4).

4 | DISCUSSION

In the current randomized control study in 74 Korean patients with T2D and hypertension treated with RAS blocker, cilnidipine treatment significantly reduced urine albumin excretion after 12 and 24 weeks but, not with amlodipine treatment. Although cilnidipine treatment did not decrease urinary ACR in the total study population, the cilnidipine

TABLE 2 Changes in urine albumin creatinine ratio

Intention-to-treat analysis	Cilnidipine (n=38)	P^a	Amlodipine (n=36)	P^a	P^b
Baseline	138.2 (109.9)		97.1 (66.3)		.11
Difference from baseline (12 wk)	−53.0 (123.2)	.003	−35.7 (83.6)	.07	.29
Difference from baseline (24 wk)	−57.3 (106.9)	.004	−20.0 (110.4)	.31	.24
Per-protocol analysis	**Cilnidipine (n=27)**	P^a	**Amlodipine (n=30)**	P^a	P^b
Baseline	141.0 (99.5)		99.5 (68.0)		.09
Difference from baseline (12 wk)	−59.6 (135.1)	.007	−39.1 (90.2)	.12	.22
Difference from baseline (24 wk)	−65.5 (112.3)	.006	−25.2 (118.2)	.20	.33

[a]vs baseline within group.
[b]Between groups.

TABLE 3 Changes in urine albumin creatinine ratio by duration of diabetes

Diabetes duration <10 y	Cilnidipine (n=18)	P^a	Amlodipine (n=18)	P^a	P^b
Baseline	127.1 (83.8)		99.2 (68.8)		.30
Difference from baseline (12 wk)	−17.7 (133.4)	.53	−61.9 (81.7)	.007	.21
Difference from baseline (24 wk)	27.8 (95.8)	.71	−54.5 (91.1)	.054	.35
Diabetes duration ≥10 y	**Cilnidipine (n=20)**	P^a	**Amlodipine (n=18)**	P^a	P^b
Baseline	148.1 (130.5)		94.9 (65.5)		.19
Difference from baseline (12 wk)	−84.7 (106.8)	<.001	−9.5 (79.2)	.78	.010
Difference from baseline (24 wk)	−84.0 (111.7)	.003	14.6 (119.4)	.54	.008

[a]vs baseline within group.
[b]Between groups.

TABLE 4 Changes in cardiometabolic parameters (intention-to-treat analysis)

	Baseline	Difference from baseline after 12 wk	Difference from baseline after 24 wk	P^a	P^b	P^c	P^d
Systolic blood pressure (mm Hg)							
Cilnidipine	125.3 (10.8)	1.5 (9.5)	2.3 (10.2)	.35	.17	.06	.09
Amlodipine	125.7 (11.0)	−4.4 (11.0)	−2.9 (15.4)	.028	.27		
Diastolic blood pressure (mm Hg)							
Cilnidipine	74.0 (7.5)	0.7 (7.8)	2.0 (7.4)	.59	.11	0.30	.035
Amlodipine	76.2 (8.6)	−1.2 (7.4)	−1.9 (8.0)	.36	0.17		
Heart rate (beat/min)							
Cilnidipine	75.0 (7.4)	−2.8 (5.0)	−1.5 (7.9)	.001	0.24	0.43	.63
Amlodipine	75.2 (9.4)	−1.6 (7.3)	−2.0 (7.6)	.19	0.032		
Fasting plasma glucose (mmol/L)							
Cilnidipine	7.07 (1.18)	0.12 (1.29)	0.38 (0.98)	.58	0.06	0.90	.57
Amlodipine	6.92 (1.32)	0.16 (1.45)	0.29 (1.17)	.53	0.41		
HbA1c (%)							
Cilnidipine	6.7 (0.6)	0.2 (0.5)	0.2 (0.5)	.08	0.005	0.29	1.00
Amlodipine	6.9 (0.6)	0.1 (0.5)	0.1 (0.5)	.10	0.45		
HOMA-IR							
Cilnidipine	2.61 (1.91)	−0.11 (1.02)	0.33 (1.74)	.28	0.56	0.08	.18
Amlodipine	2.25 (1.78)	0.41 (1.43)	0.43 (1.18)	.12	0.013		
HOMA-B%							
Cilnidipine	48.2 (35.0)	−1.6 (23.7)	0.5 (26.7)	.29	0.80	0.34	.68
Amlodipine	56.0 (76.5)	3.5 (64.1)	−5.7 (38.5)	.66	0.71		
Total cholesterol (mmol/L)							
Cilnidipine	4.09 (0.85)	0.03 (0.61)	0.02 (0.67)	.29	0.80	0.64	.99
Amlodipine	4.15 (0.72)	0.03 (0.71)	0.01 (0.69)	.83	0.75		
LDL cholesterol (mmol/L)							
Cilnidipine	2.21 (0.68)	0.04 (0.44)	0.05 (0.51)	.53	0.93	0.67	1.00
Amlodipine	2.30 (0.67)	0.00 (0.45)	0.02 (0.57)	1.00	0.81		
HDL cholesterol (mmol/L)							
Cilnidipine	1.13 (0.23)	0.04 (0.18)	0.06 (0.19)	.21	0.051	0.64	.98
Amlodipine	1.26 (0.28)	0.04 (0.20)	0.05 (0.20)	.21	0.14		
Triglycerides (mmol/L)							
Cilnidipine	1.69 (1.59)	−0.02 (0.85)	−0.27 (1.50)	.52	0.59	0.45	.97
Amlodipine	1.31 (0.71)	−0.06 (0.66)	−0.10 (0.58)	.57	0.40		
Adiponectin (μg/mL)							
Cilnidipine	8.3 (6.1)	−0.7 (4.1)	−0.5 (2.8)	.26	0.37	0.52	.99
Amlodipine	9.3 (8.0)	−1.8 (4.4)	−1.2 (4.7)	.049	0.20		
hsCRP (mg/dL)							
Cilnidipine	0.13 (0.21)	0.04 (0.30)	−0.02 (0.19)	.59	0.99	0.49	.90
Amlodipine	0.15 (0.21)	−0.02 (0.28)	0.03 (0.35)	.47	0.97		
PAI-1 (μg/L)							
Cilnidipine	29.1 (18.5)	−2.8 (10.1)	−1.8 (12.8)	.10	0.40	0.011	.16
Amlodipine	27.7 (19.4)	2.2 (16.1)	2.6 (27.1)	.11	0.29		
8-isoprostane (ng/mL)							
Cilnidipine	10.7 (8.2)	1.5 (8.3)	−1.0 (11.6)	.35	0.67	0.37	.33
Amlodipine	8.1 (7.5)	3.8 (10.4)	2.4 (13.0)	.07	0.33		

(Continues)

TABLE 4 (Continued)

	Baseline	Difference from baseline after 12 wk	Difference from baseline after 24 wk	P^a	P^b	P^c	P^d
Estimated GFR (mL/min)							
Cilnidipine	75.5 (21.2)	ND	−2.2 (6.1)	ND	.048	ND	.89
Amlodipine	78.0 (23.6)	ND	0.7 (11.6)	ND	.42		
Cystatin C (μg/L)							
Cilnidipine	0.79 (0.11)	−0.01 (0.05)	0.01 (0.08)	.35	.99	0.85	.59
Amlodipine	0.76 (0.16)	−0.03 (0.11)	0.00 (0.11)	.52	.67		
baPWV, Right (cm/s)							
Cilnidipine	1594.7 (333.8)		55.0 (193.5)		.09		.05
Amlodipine	1593.3 (318.1)		−40.6 (213.1)		.27		
baPWV, Left (cm/s)							
Cilnidipine	1606.9 (305.8)		29.0 (179.4)		.39		.046
Amlodipine	1644.4 (330.3)		−63.7 (207.9)		.08		
ABI, Right							
Cilnidipine	1.09 (0.13)		0.04 (0.09)		.040		.59
Amlodipine	1.09 (0.09)		0.01 (0.08)		.34		
ABI, Left							
Cilnidipine	1.09 (0.15)		0.03 (0.09)		.06		.49
Amlodipine	1.11 (0.08)		0.01 (0.09)		.60		

[a]Baseline vs 12 wk within group.
[b]Baseline vs 24 wk within group.
[c]12 wk between groups.
[d]24 wk between groups.

group showed a larger ACR reduction compared with the amlodipine group in patients with longer duration of diabetes more than 10 years.

There have been conflicting results regarding whether an L-/N-type CCB such as cilnidipine has additional renoprotective effects over an L-type CCB such as amlodipine. In a study performed in patients with hypertension and kidney disease receiving RAS blocker, a 1-year treatment with cilnidipine significantly decreased the urine protein excretion compared with amlodipine.[11] In addition, urine albumin excretion decreased significantly in patients with T2D after changing from L-type CCB to cilnidipine but not after changing from cilnidipine to an L-type CCB.[16] However, in this study, cilnidipine treatment did not show significant reduction in urinary ACR compared with amlodipine treatment, although cilnidipine decreased urinary ACR from baseline. We cannot clearly explain why the anti-albuminuric effect of cilnidipine was not evident in our study, but we offer the following possibilities. First, contrary to previous studies,[11,16] blood pressure was already well controlled in our study and was less than 130/80 mm Hg at enrolment (mean of approximately 125/75 mm Hg in both groups).[17,18] Tight blood pressure control is essential for the prevention of progression of kidney disease[19]; thus, the addition of another antihypertensive drug in our study may have had limited value in reducing ACR through blood pressure reduction. Systolic and diastolic blood pressure did not change after adding cilnidipine (Table 4). Second, in our analysis, amlodipine treatment showed a greater reduction in blood pressure than cilnidipine treatment after 24 weeks, especially diastolic blood pressure (P=.03, Table 4). Thus, a greater decrease in ACR could be anticipated with the addition of amlodipine than with cilnidipine. Third, we uniformly enrolled subjects treated with RAS blocker. However, only 28%-62% of subjects with T2D in a previous study were treated with an RAS blocker.[16] Thus, whether cilnidipine has an anti-albuminuric effect in patients already receiving an RAS blocker remains uncertain. In accordance with our results, Ando et al. reported that a 1-year treatment with cilnidipine did not show a greater anti-albuminuric effect than did amlodipine in patients with T2D and hypertension treated with an RAS blocker.[20] The authors speculated that the sympatholytic action of cilnidipine is mild and thus, it can delay kidney injury only in patients without diabetes but, may be too weak to counteract the severe afferent arteriolar vasodilation caused by diabetes. Thus, cilnidipine could be more appropriate for patients with early-stage diabetic nephropathy or hyperfiltrated kidney.[20]

Although cilnidipine treatment did not reduce urinary ACR in the total study population, adding cilnidipine to a RAS blocker had a greater effect on microalbuminuria than did amlodipine in patients with a long duration of T2D. We do not know why the anti-albuminuric effect of cilnidipine was more evident compared with amlodipine in patients with a long duration of diabetes (≥10 years) compared with patients with a short duration of diabetes (<10 years). However, this result may be partly because of cilnidipine being a dual L-/N-type CCB; thus, the anti-albuminuric effect of cilnidipine could have the greatest benefited in patients with sympathetic overactivity or autonomic

dysfunction compared with amlodipine. Sympathetic nerve activity was reported to be enhanced in patients with diabetes,[21] and the prevalence of diabetic cardiac autonomic neuropathy increases with duration of diabetes.[22] Therefore, cilnidipine likely showed an anti-albuminuric effect only in patients with a long duration of diabetes (≥10 years) who possibly have autonomic dysfunction.

In addition to its anti-proteinuric effect, cilnidipine has been reported to have diverse favourable cardiometabolic effects.[23,24] Cilnidipine was reported to improve insulin sensitivity determined by the euglycemic clamp technique.[25] In addition, cilnidipine was reported to improve insulin sensitivity and glucose tolerance, possibly by increasing high-molecular weight adiponectin level in diet-induced obese mice.[26] However, in our analysis, fasting plasma glucose, HOMA-IR, lipid profile, hsCRP, and adiponectin levels were similar between the two groups. The anti-proteinuric effect of cilnidipine might be at least partly independent of its blood pressure-lowering effect. Cilnidipine dilates both afferent and efferent arterioles and consequently reduces intraglomerular pressure, which is associated with its anti-proteinuric properties.[10] Cilnidipine reduced urine albumin excretion and 8-hydroxy-deoxyguanosine, a marker of oxidative stress, compared with amlodipine treatment.[27] Therefore, the anti-oxidative properties of cilnidipine have been suggested to be associated with its anti-proteinuric effect. However, our results did not show any differences in levels of 8-isoprostane, a marker of oxidative stress; estimated GFR; or cystatin C, a maker of GFR,[28] between the two groups. The lack of effect on oxidative stress and renal function may be partly associated with the inability of cilnidipine to reduce proteinuria.

This study has some limitations. The sample size was relatively small, and it was difficult to perform subgroup analyses. Although we recruited study participants based on two of three morning urine collections, urine was only collected once to determine the efficacy of treatment. We did not determine sympathetic activity of study participants; thus, it is unclear whether the anti-albuminuric effect of cilnidipine differed from sympathetic activity in association with diabetes duration.

In conclusion, cilnidipine treatment did not decrease urine albumin excretion compared with amlodipine treatment in hypertensive patients with T2D and microalbuminuria who were treated with RAS blocker. However, the anti-albuminuric effect of cilnidipine appeared to differ according to duration of diabetes and was greater than that of amlodipine in patients with a duration of diabetes longer than 10 years.

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DISCLOSURES

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

YCH analysed and interpreted the data, contributed to discussion, and wrote the manuscript. MKL designed the study, analysed and interpreted the data, and reviewed/edited the manuscript. KHY, BSC, KWL, HCJ, KWM, CHC and MKL collected the data, contributed to discussion and reviewed the manuscript.

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REFERENCES

1. de Zeeuw D, Ramjit D, Zhang Z, et al. Renal risk and renoprotection among ethnic groups with type 2 diabetic nephropathy: a post hoc analysis of RENAAL. *Kidney Int*. 2006;69:1675-1682.
2. Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA*. 2001;286:421-426.
3. de Zeeuw D, Remuzzi G, Parving HH, et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. *Circulation*. 2004;110:921-927.
4. Vejakama P, Thakkinstian A, Lertrattananon D, Ingsathit A, Ngarmukos C, Attia J. Reno-protective effects of renin-angiotensin system blockade in type 2 diabetic patients: a systematic review and network meta-analysis. *Diabetologia*. 2012;55:566-578.
5. Bakris GL. A practical approach to achieving recommended blood pressure goals in diabetic patients. *Arch Intern Med*. 2001;161:2661-2667.
6. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ*. 2003;326:1427-1431.
7. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11000 participants from 42 trials. *Am J Med*. 2009;122:290-300.
8. Weber MA, Bakris GL, Jamerson K, et al. Cardiovascular events during differing hypertension therapies in patients with diabetes. *J Am Coll Cardiol*. 2010;56:77-85.
9. Hayashi K, Wakino S, Sugano N, Ozawa Y, Homma K, Saruta T. Ca^{2+} channel subtypes and pharmacology in the kidney. *Circ Res*. 2007;100:342-353.
10. Konnno Y, Kimura K. Vasodilatory effect of cilnidipine, an L-type and N-type calcium channel blocker, on rat kidney glomerular arteries. *Int Heart J*. 2008;49:723-732.
11. Fujita T, Ando K, Nishimura H, et al. Antiproteinuric effect of the calcium channel blocker cilnidipine added to renin-angiotensin inhibition in hypertensive patients with chronic renal disease. *Kidney Int*. 2007;72:1543-1549.
12. Kojima S, Shida M, Yokoyama H. Comparison between cilnidipine and amlodipine besilate with respect to proteinuria in hypertensive patients with renal diseases. *Hypertens Res*. 2004;27:379-385.
13. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28:412-419.
14. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.
15. Bakker AJ. Detection of microalbuminuria. Receiver operating characteristic curve analysis favors albumin-to-creatinine ratio over albumin concentration. *Diabetes Care*. 1999;22:307-313.
16. Fukumoto S, Ishimura E, Motoyama K, et al. Antialbuminuric advantage of cilnidipine compared with L-type calcium channel blockers in

type 2 diabetic patients with normoalbuminuria and microalbuminuria. *Diabetes Res Clin Pract*. 2012;97:91-98.
17. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2015;313:603-615.
18. ACCORD Study Group, Cushman WC, Evans GW, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1575-1585.
19. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507-520.
20. Ando K, Ueshima K, Tanaka S, et al. Comparison of the antialbuminuric effects of L-/N-type and L-type calcium channel blockers in hypertensive patients with diabetes and microalbuminuria: the study of assessment for kidney function by urinary microalbumin in randomized (SAKURA) trial. *Int J Med Sci*. 2013;10:1209-1216.
21. Huggett RJ, Scott EM, Gilbey SG, Stoker JB, Mackintosh AF, Mary DA. Impact of type 2 diabetes mellitus on sympathetic neural mechanisms in hypertension. *Circulation*. 2003;108:3097-3101.
22. Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. *Circulation*. 2007;115:387-397.
23. Takahara A. Cilnidipine: a new generation Ca channel blocker with inhibitory action on sympathetic neurotransmitter release. *Cardiovasc Ther*. 2009;27:124-139.
24. Kuwahara K, Kimura T. The organ-protective effect of N-type Ca(2+) channel blockade. *Pharmacol Ther*. 2015;151:1-7.
25. Yagi S, Goto S, Yamamoto T, Kurihara S, Katayama S. Effect of cilnidipine on insulin sensitivity in patients with essential hypertension. *Hypertens Res*. 2003;26:383-387.
26. Ueno D, Masaki T, Gotoh K, Chiba S, Kakuma T, Yoshimatsu H. Cilnidipine regulates glucose metabolism and levels of high-molecular adiponectin in diet-induced obese mice. *Hypertens Res*. 2013;36:196-201.
27. Soeki T, Kitani M, Kusunose K, et al. Renoprotective and antioxidant effects of cilnidipine in hypertensive patients. *Hypertens Res*. 2012;35:1058-1062.
28. Filler G, Bökenkamp A, Hofmann W, Le Bricon T, Martínez-Brú C, Grubb A. Cystatin C as a marker of GFR–history, indications, and future research. *Clin Biochem*. 2005;38:1-8.

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