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ORIGINAL ARTICLE

Effect of N- and T-type calcium channel blocker on proteinuria, blood pressure and kidney function in hypertensive patients: a meta-analysis

This article has been corrected since Advance Online Publication, and a corrigendum is also printed in this issue.

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The combination of a calcium channel blocker (CCB) and a blocker of the renin–angiotensin–aldosterone system (RAAS) is recommended in clinical practice guidelines. L/N- and L/T-type CCBs might provide an additional effect on lowering proteinuria. Therefore, we conducted a meta-analysis to assess the efficacy of L/N- and L/T-type CCBs in hypertensive patients with proteinuria. We searched MEDLINE, Scopus, Cochrane Central Register of Controlled Trials and ClinicalTrials.gov for single-arm studies and randomized controlled trials (RCTs) that examined the effect of L/N- and L/T-type CCBs as add-on therapy compared with standard antihypertensive regimen for proteinuria on hemodynamic and kidney-related parameters in hypertensive patients with proteinuria. Random-effect model meta-analyses were used to compute changes in the outcomes of interest. We identified 17 RCTs, representing 1905 patients. By meta-analysis, L/N- and L/T-type CCB add-on therapy did not yield significant changes in systolic and diastolic blood pressure compared with standard treatment, but there was a significant lowering of the pulse rate. However, L/N- and L/T-type CCBs resulted in a significant standardized net decrease in albuminuria and proteinuria (−1.01; 95% confidence interval (CI), −1.78 to −0.23; $P=0.01$), and a standardized net improvement in the estimated glomerular filtration rate and serum creatinine (0.23; 95% CI, 0.11 to 0.35, $P<0.001$; and −0.25; 95% CI, −0.46 to −0.03; $P=0.02$, respectively). Despite no additional lowering effect on blood pressure, L/N- and L/T-type CCBs combined with a blocker of the RAAS provided a decrease in proteinuria and improvement in kidney function. Further studies are required to establish the long-term kidney benefits of this combination therapy.
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Keywords: calcium channel blocker; kidney function; meta-analysis; proteinuria

INTRODUCTION

Hypertension is a global public health problem that contributes to the burden of heart disease, stroke, kidney failure, disability and premature mortality. Unfortunately, only 30% of hypertensive patients have well-controlled blood pressure.[1] Globally, cardiovascular disease accounts for approximately 17 million deaths per year, almost one-third of all deaths.[2] Complications of hypertension account for 9.4 million deaths worldwide every year.[3] Treating the cardiovascular consequences of hypertension, including coronary artery disease, cerebrovascular disease, peripheral arterial disease and kidney failure, are associated with significant resource consumption and health-care expenditure.[4] The 2013 European Society of Hypertension and European Society of Cardiology guidelines for management of hypertension recommend the use of calcium channel blockers (CCBs) as monotherapy as well as in combination with other agent classes, as they may provide specific benefits beyond blood pressure reduction.[5] Combined blockade of the renin–angiotensin–aldosterone system (RAAS) in patients with chronic kidney disease (CKD) has recently been associated with a decrease in glomerular filtration rate (GFR) and an increased incidence of hyperkalemia and hypotension compared with monotherapy.[6] The 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults recommends avoiding combined blockers of the RAAS.[7]

Proteinuria and albuminuria are generally considered as independent risk factors for cardiovascular morbidity and mortality in the

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general population and in patients with CKD. Moreover, the amount of proteinuria, even non-pathological proteinuria and albuminuria, have been linked to an increased cardiovascular risk.[8,9] Hypertension and proteinuria are also well-known predictors of progression of CKD.[10] The Kidney Disease Improving Global Outcomes guidelines for the management of blood pressure in patients with CKD recommends prescribing an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor type 1 blocker (ARB) as the primary antihypertensive drug for patients with CKD regardless of proteinuria unless there is a contraindication.[11] Although combined RAAS blockade is currently not recommended, there is insufficient evidence regarding the add-on therapy of other renoprotective agents among patients who have already been maximized on an ACEI or ARB. Although CCBs are commonly used antihypertensive medications, their potential beneficial effects on the kidneys remain controversial.[12–16] CCBs such as amlodipine and nifedipine dilate the afferent renal arteriole by acting on the L-type calcium channel while sparing the efferent arteriole, thereby inducing glomerular hyperfiltration and no renoprotective effect. More recently, L/N-type (cilnidipine) and L/T-type (azelnidipine, efonidipine and benidipine) CCBs have been shown to provide kidney protection by decreasing the activity of both the sympathetic nervous system and RAAS, resulting in dilation of both afferent and efferent arterioles.[17] Although these newer agents have been shown to further decrease proteinuria in patients with CKD and persistent proteinuria despite use of blockers of the RAAS,[18] there are no systematic reviews on the potential efficacy of L/N- and L/T-type CCBs as add-on therapy for reducing proteinuria. Therefore, we conducted a meta-analysis on the efficacy and safety of L/N- and L/T-type CCBs as add-on treatment to an ACEI or ARB in hypertensive patients with proteinuria.

METHODS

Data sources and searches

We performed a literature search in MEDLINE (through 30 September 2014), Scopus (through 30 September 2014), Cochrane Central Register of Controlled Trials and ClinicalTrials.gov to identify eligible studies using the Medical Subject Headings database search terms 'N-type calcium channel blocker', 'N-type calcium channel antagonist', 'N-type calcium channel blockade', 'T-type calcium channel blocker', 'T-type calcium channel antagonist', 'T-type calcium channel blockade', 'benidipine', 'cilnidipine', 'azelnidipine' and 'efonidipine'. The search was limited to English language and to clinical trials of adults (age $\geqslant$ 18 years).

Study selection

We included crossover and parallel-arm randomized controlled trials examining the efficacy of L/N- and L/T-type CCBs as add-on treatment to an ACEI or ARB compared with the standard treatment group (ACEI or ARB with or without other type of antihypertensive medications) on proteinuria, blood pressure, pulse rate and kidney function in hypertensive patients with proteinuria. There were no restrictions on sample size or study duration. Two authors (NT and PT) independently screened the titles and abstracts of all electronic citations, and full-text articles were retrieved for comprehensive review and independently re-screened.

Data extraction and quality assessment

The following data were extracted: country of origin, year of publication, study design, sample size, duration of intervention, percentage of men, and mean age of subjects, baseline serum creatinine, GFR, urine albumin or protein excretion, systolic blood pressure, diastolic blood pressure, and pulse rate. For assessment of kidney function, we extracted data on methods of measuring GFR that included measured, estimated or calculated GFR. We extracted data on the urine albumin and protein specimen collection methods used in each study, including the use of random or timed (24-h) samples. In terms of safety end points, we also extracted data on reported adverse effects, serious adverse effects, hypotension, worsening kidney function, edema and death. Disagreements were resolved through consensus and arbitration by a third author (SW). Study quality was assessed with a modified version of the Jadad scale, which assesses randomization adequacy, blinding and attrition, with higher scores reflecting better quality.[19]

Data synthesis and analysis

We used random-effects model meta-analyses to compute standardized net changes for continuous outcomes and risk ratios for binary outcomes. The standardized net change was computed to overcome the use of different units of measurement and allowed us to include trials that reported only net changes among study groups. The standardized effect size is derived by dividing the mean change in the continuous outcome level of a particular variable by the s.d. of the mean change in the variable. The variance of the standardized effect size is estimated through the inverse of the sample size. All pooled estimates are displayed with a 95% confidence interval (CI). Existence of heterogeneity among effect sizes estimated by individual studies was described with the I^2 index and the Q test. An I^2 index $\geqslant$75% was used to indicate medium-to-high heterogeneity.[20] We investigated sources of heterogeneity for the outcomes of interest by performing subgroup analysis based on *a priori* selected study characteristics, including type of CCB, status of blood pressure control at enrollment based on the Japanese Society of Hypertension and Japanese Society of Nephrology (poorly controlled ($>$130/80 mm Hg) *vs.* well-controlled ($\leqslant$130/80 mm Hg)), urine albumin or protein excretion rate (microalbuminuria (30–300 mg day^{-1} or mg g^{-1} of creatinine), macroalbuminuria ($>$300 mg day^{-1} or mg g^{-1} of creatinine) *vs.* overt proteinuria ($>$500 mg day^{-1} or mg g^{-1} of creatinine)), baseline GFR (preserved kidney function (GFR $\geqslant$ 60 ml min^{-1} or ml min^{-1} 1.73 m^{-2}) *vs.* low GFR (GFR $<$ 60 ml min^{-1} or ml min^{-1} 1.73 m^{-2})), duration of follow up ($\leqslant$6 *vs.* $>$6 months) and study quality (fair (quality score 1–3), good (quality score 4–5)). Publication bias was formally assessed (if there was a minimum of three studies) using funnel plots and the Egger test, which assesses asymmetry of the funnel plot, whereby a value of $P<0.05$ indicates publication bias.[21] The meta-analyses were performed with Comprehensive Meta-Analysis version 2.0 (www.meta-analysis.com; Biostat, Englewood, NJ, USA). Figures for the subgroup analyses were generated with the R system software version 2.13.0 (http://cran.rproject.org/bin/windows/base/old/2.13.0).

RESULTS

Characteristics and quality of the studies

A total of 3725 potentially relevant citations were identified and screened; 139 articles were retrieved for detailed evaluation, of which 17, consisting of 3 crossover and 14 parallel-arm randomized controlled trials, fulfilled the eligibility criteria for inclusion in the meta-analysis (Figure 1).[22–38] Blockers of the RAAS were prescribed in both the intervention and control groups in all included studies. Characteristics of the individual trials are displayed in Table 1. The trials spanned over 7 years, varied in sample size (17–365 patients) and enrolled diabetics, non-diabetics or a mixture of the two populations. The mean age of the subjects ranged from 33 to 72 years, and the duration of follow-up ranged from 4 to 24 months. Nine studies enrolled patients with preserved kidney function (GFR $>$ 60 ml min^{-1} 1.73 m^{-2})[22,24,26,28–30,32,33,36] and eight studies enrolled patients with low GFR ($<$60 ml min^{-1} 1.73 m^{-2}).[23,25,27,31,34,35,37,38] At enrollment, hypertension was well controlled in only 3 studies[22,28,34] and poorly controlled in the remaining 14 studies. The GFR was assessed in 15 studies. The GFR was estimated using the Cockcroft–Gault equation in one study[34] and either the modified estimated GFR (eGFR) estimating equation developed for Japanese persons by the Japanese Society of Nephrology[39] in nine studies[26,27,31–33,35–38] or the Modification of Diet in Renal Disease Study equation for Japanese patients[40] in four trials.[24,25,29,30] One study did not specify the calculation method.[22] Thirteen studies used the first void (morning urine) to measure

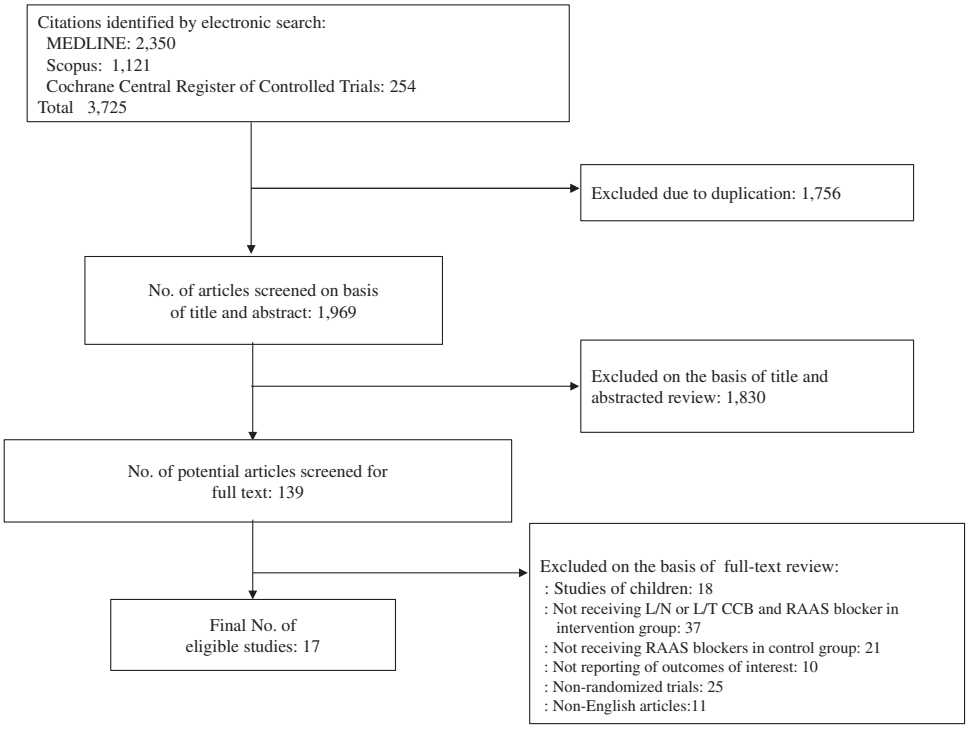

Figure 1 Study selection flow diagram.

albumin or protein urine excretion. Two studies measured 24-h urine protein excretion.[28,30] Two trials did not identify the method of urine protein collection.[24,33] Seven studies enrolled only patients with microalbuminuria (30–300 mg day^{-1}).[22,26,28,29,31,32,36] Three studies enrolled patients with macroalbuminuria (>300 mg day^{-1}).[25,37,38] Proteinuria was reported instead of albuminuria in five studies.[23,27,30,34,35] Two studies did not specify inclusion criteria regarding proteinuria.[24,32] According to the Jadad scale, all of the studies were of fair quality (Table 1).

Effect of L/N- and L/T-type CCBs on blood pressure and pulse rate

As shown in Table 2, by meta-analysis of 17 trials (1806 patients), L/N- and L/T-type CCBs add-on therapy relative to standard therapy yielded no significant effect on the standardized net change in systolic blood pressure (0.09; 95% CI, –0.34 to 0.52; $P=0.68$; $I^2=94\%$) or diastolic blood pressure (0.15: 95% CI, –0.46 to 0.75; $P=0.63$; $I^2=97\%$). However, L/N- and L/T-type CCB add-on therapy resulted in a significant standardized net decrease in the pulse rate relative to standard therapy (−0.42, 95%CI, −0.12 to −0.72, $P=0.006$, $I^2=83\%$).

Effect of L/N- and L/T-type CCBs on proteinuria and albuminuria

Urinary protein reduction as an efficacy end point was reported in 6 trials (494 patients), with 3 studies reporting 24-h urine protein excretion rates and 3 studies reporting random urine protein-to-creatinine ratios. Urinary albumin reduction was reported in 8 trials (947 patients) using random urinary albumin-to-creatinine ratios. By meta-analysis, L/N- and L/T-type CCBs resulted in a significant decrease in albuminuria and proteinuria (standardized net change of −1.01; 95% CI, −1.78 to −0.23; $P=0.01$, $I^2=97\%$; Table 2).

Effect of L/N- and L/T-type CCBs on kidney function

There were 13 studies (1487 patients) reporting on changes in serum creatinine and 10 studies (592 patients) reporting on changes in eGFR. By meta-analysis, L/N- and L/T-type CCBs resulted in a significant trend toward an improvement in the standardized net change in eGFR (0.23; 95% CI, 0.11 to 0.35; $P<0.001$, $I^2=10\%$) and serum creatinine (−0.25; 95% CI −0.46 to −0.03, $P=0.02$, $I^2=72\%$) relative to standard medical therapy (Table 2).

Safety analysis

There was no significant effect of L/N- and L/T-type CCBs on safety end points, including adverse effects, serious adverse effects, hypotension, worsening kidney function, edema and death (Table 2).

Investigations of heterogeneity

Figure 2 displays the results of the subgroup analyses of standardized net changes in pulse rate, stratified by type of CCBs, baseline blood pressure status, baseline level of GFR, baseline level of albuminuria or proteinuria and duration of follow-up. As shown in the figure, larger standardized net decreases in pulse rate were observed in studies of patients who had lower GFR and longer duration of follow-up. In addition, greater effects in standardized net decreases in albuminuria and proteinuria were observed for add-on therapy with L/N- or L/T-type CCBs in studies that had lower baseline GFR, baseline macroalbuminuria (>300 mg day^{-1} or mg g^{-1} of creatinine), baseline overt proteinuria (>500 mg day^{-1} or mg g^{-1} of creatinine) and longer duration of follow-up (Figure 3).

Finally, greater effects on eGFR were observed in studies that used L/T-type CCBs, those with poorly controlled hypertension, higher baseline GFR, baseline microalbuminuria (30–300 mg day^{-1} or mg g^{-1} of creatinine) and those with longer duration of follow-up (Figure 4).

Table 1 Characteristics of the studies included in the meta-analysis

Author	Year	Study design	Treatment group	Comparison group	N	Follow-up (months)	Mean age (years)	Men (%)	Mean systolic blood pressure (mm Hg)	Mean diastolic blood pressure (mm Hg)	Mean serum creatinine (mg dl^{-1})	Mean pulse rate (b.p.m.)	Mean eGFR (ml min^{-1} 1.73 m^{-2})	Mean proteinuria or albuminuria	Diabetes mellitus (%)	Hypertension (%)	Jadad score
Katayama *et al.*[22]	2006	Parallel-arm	Cilnidipine +Valsartan	Valsartan	87	12	66.5	51.7	137.4	76.5	0.75	NA	85	41.766[a]	NA	NA	2
Fujita *et al.*[23]	2007	Parallel-arm	Cilnidipine+RAAS blockade+other antihypertensive drug	Amlodipine+RAAS blockade+other antihypertensive drug	339	12	59.6	63.1	152.4	87.4	1.28	75	NA	1822.36[b]	4 3.66	100	2
Ogawa *et al.*[24]	2008	Parallel-arm	Azelnidipine +RAAS blockade	Nifedipine+RAAS blockade	38	4	60.7	52.6	156.8	78.4	0.77	NA	70	NA	100	100	2
Sasaki *et al.*[25]	2009	Parallel-arm	Efonidipine +Candesartan	Amlodipine +Candesartan	40	12	64.4	NA	158.5	86.0	1.46	NA	46	1353.5[a]	100	100	2
Ishimitsu *et al.*[26]	2009	Crossover	Azelnidipine +Olmesartan	Trichlormethiazide +Olmesartan	29	4	60.0	48.3	149.0	94.0	0.77	72	74	115.72[a]	NA	100	2
Abe *et al.*[27]	2009	Parallel-arm	Benidipine+RAAS blockade+other antihypertensive drugs	Amlodipine+RAAS blockade+other antihypertensive drug	47	6	65.7	NA	153.6	87.0	3.02	NA	22	3362.75[b]	11	100	3
Miwa *et al.*[28]	2010	Parallel-arm	Cilnidipine+RAAS blockade+other antihypertensive drug	Amlodipine+RAAS blockade+other antihypertensive drug	41	12	66.5	51.4	138.3	75.9	0.86	70	NA	0.489[c]	NA	100	2
Miyagawa *et al.*[29]	2010	Crossover	Benidipine+Olmesartan+Diuretics	Amlodipine+Olmesartan+Diuretics	17	6	72.0	64.7	169.7	89.8	0.83	71	63	22.8[a]	18	100	2
Nakamura *et al.*[30]	2010	Parallel-arm	Benidipine+RAAS blockade+other antihypertensive drugs	Amlodipine+RAAS blockade+other antihypertensive drug	40	12	32.6	55.0	153.5	91.5	0.72	NA	92	1.55[c]	0	100	3
Abe *et al.*[31]	2011	Parallel-arm	Benidipine+RAAS blockade+other antihypertensive drugs	Amlodipine+RAAS blockade+other antihypertensive drug	104	6	67.4	57.7	144.5	81.5	1.24	75	45	174.3[a]	46.1	100	3
Matsui *et al.*[32]	2011	Parallel-arm	Azelnidipine +Olmesartan	HCTZ+Olmesartan	207	24	68.5	40.0	147.5	NA	NA	69	73	27.99[a]	16	100	2
Yoshii *et al.*[33]	2011	Crossover	Azelnidipine +Olmesartan	Trichlormethiazide+ Olmesartan	39	24	63.2	66.7	149.8	84.0	0.95	77	71	NA	100	100	2
Hatta *et al.*[34]	2012	Parallel-arm	Cilnidipine+RAAS blockade	Other CCB+RAS blockade	50	12	56.5	72.0	128.9	71.8	1.86	80	36	1580[b]	NA	100	3
Kanaoka *et al.*[35]	2013	Parallel-arm	Cilnidipine+RAAS blockade+other antihypertensive drug	Other CCB+RAAS blockade+other antihypertensive drug	45	6	69.9	64.5	140.6	79.6	1.89	75	35	1190[b]	37.78	100	3
Ando *et al.*[36]	2013	Parallel-arm	Cilnidipine+RAAS blockade+other antihypertensive drug	Amlodipine+RAAS blockade+other antihypertensive drug	365	12	63.8	65.8	146.0	80.8	0.77	75	73	99.67[a]	100	100	2
Abe *et al.*[37]	2013	Parallel-arm	Cilnidipine+RAAS blockade+alpha blocker, diuretics	Amlodipine+RAAS blockade+alpha blocker, diuretics	73	12	66.5	57.1	143.0	81.5	1.15	69	47	323.5[a]	50	100	2
Ando *et al.*[38]	2014	Parallel-arm	Benidipine+RAAS blockade	HCTZ+RAAS blockade	344	12	59.0	68.3	144.1	84.0	0.96	NA	577	907.37[a]	58.14	100	3

Abbreviations: b.p.m., beats per minute; HCTZ, hydrochlorothiazide; NA, not applicable; RAAS, renin–angiotensin–aldosterone system.
[a]Albuminuria reported as urine albumin-to-creatinine ratio (mg g^{-1} of creatinine).
[b]Proteinuria reported as urine protein-to-creatinine ratio (mg g^{-1} of creatinine).
[c]Proteinuria reported as 24-h urine protein excretion (g day^{-1}).

Table 2 Summary effects of N- and T-type calcium channel blocker on efficacy and safety end points

					Assessment of heterogeneity		Assessment of publication bias
End points of interest	*No. of studies*	*No. of patients*	*Standadized net change[a] (95% CI)*	P-*value*	I^2 *index*[b]	*Q test* P-*value*	*Egger test* P-*value*
Efficacy end points							
Hemodynamic parameters							
Systolic blood pressure	17	1806	0.09 (–0.34, 0.52)	0.68	94%	<0.001	0.69
Diastolic blood pressure	16	1599	0.15 (–0.46, 0.75)	0.63	97%	<0.001	0.84
Pulse rate	10	1249	–0.42 (–0.12, –0.72)	0.006	83%	<0.001	0.11
Kidney-related parameters							
Serum creatinine	13	1487	–0.25 (–0.46, –0.03)	0.02	72%	<0.001	0.40
eGFR	10	1252	0.23 (0.11, 0.35)	<0.001	10%	0.35	0.43
Albuminuria/proteinuria	14	1441	–1.01 (–1.78, –0.23)	0.01	97%	<0.001	0.20
Safety end points			*Risk ratio (95% CI)[a]*				
Adverse effects	4	1137	0.90 (0.73, 1.12)	0.34	0%	0.65	0.25
Serious adverse effects	2	711	0.59 (0.17, 2.05)	0.40	0%	0.52	—
Hypotension	2	426	0.79 (0.23, 2.77)	0.71	14%	0.28	—
Worsening kidney function	2	704	0.96 (0.18, 5.23)	0.97	0%	0.47	—
Edema	2	704	0.99 (0.15, 6.72)	0.99	0%	0.42	—
Death	2	685	0.52 (0.11, 2.43)	0.40	0%	0.74	—

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate.
[a]By meta-analysis of random-effects model.
[b]An I^2 index ⩾75% indicates medium-to-high heterogeneity.

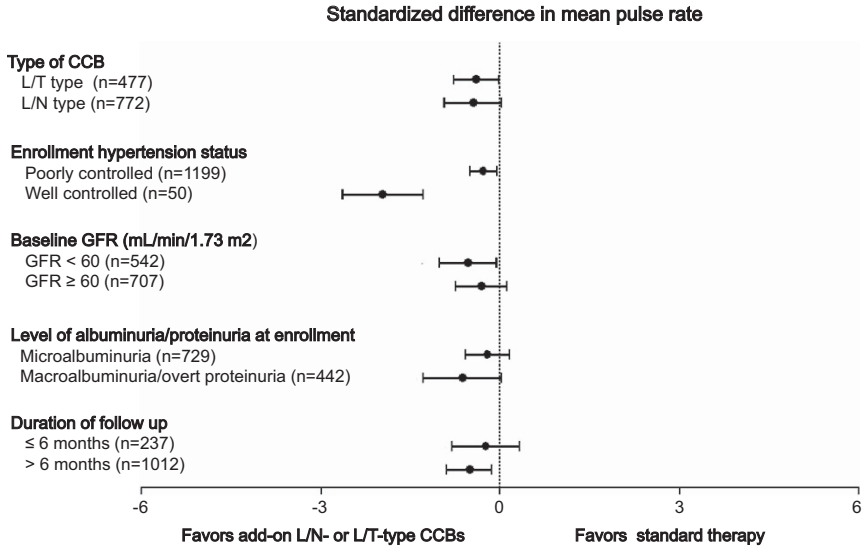

Figure 2 Subgroup analyses displaying the effect of N- and T-type calcium channel blockers (CCBs) on standardized net change in pulse rate. L/N-type, cilnidipine; L/T-type, azelnidipine, efonidipine and benidipine.

DISCUSSION

This is the first meta-analysis of 17 randomized controlled trials (1905 patients) that demonstrates the antiproteinuric effects of L/N- and L/T-type CCBs as add-on therapy to RAAS blockade (ACEI or ARB) relative to RAAS blockade with or without other antihypertensive drugs. We analyzed the effect of L/N- and L/T-type CCBs on blood pressure parameters, pulse rate, proteinuria/albuminuria and kidney function. By meta-analysis, L/N- and L/T-type CCB add-on therapy was associated with a significant net improvement in urine albumin and protein excretion compared with standard therapy, despite comparable changes in both systolic and diastolic blood pressure. Regarding kidney function, the use of L/N- and L/T-type CCBs were associated with an improvement in the serum creatinine and eGFR compared with standard therapy with and without L-type CCB, for example, amlodipine and nifedipine. Moreover, no significant incidences of adverse effects were demonstrated.

Voltage-dependent calcium channels are classified into two subfamilies by their electrophysiological properties. These include a family of high-voltage-activated calcium channels, such as the P-/Q-, L-, N- and R-type calcium channel, and a family of low-voltage-activated calcium channels, such as the T-type calcium channel.[41] The L-,

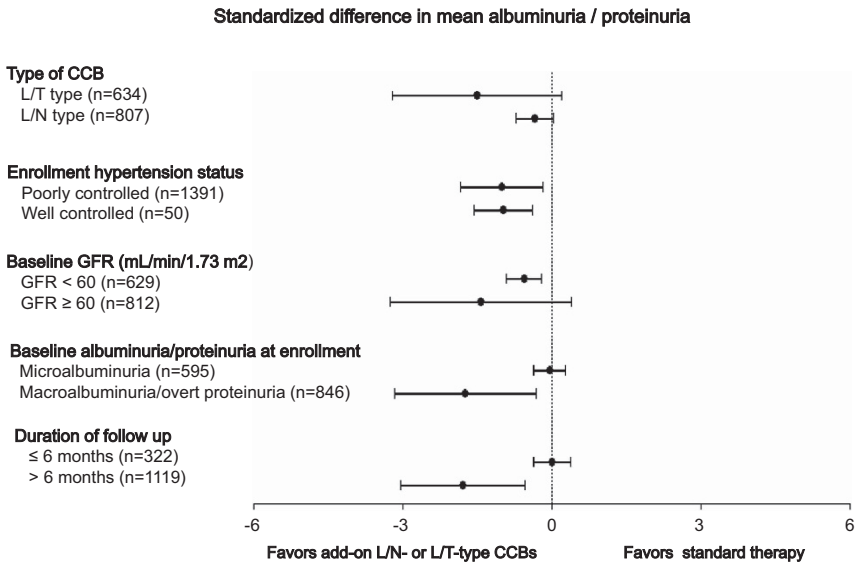

Figure 3 Subgroup analyses displaying the effect of N- and T-type calcium channel blockers (CCBs) on standardized net change in albuminuria and proteinuria. L/N-type, cilnidipine; L/T-type, azelnidipine, efonidipine and benidipine.

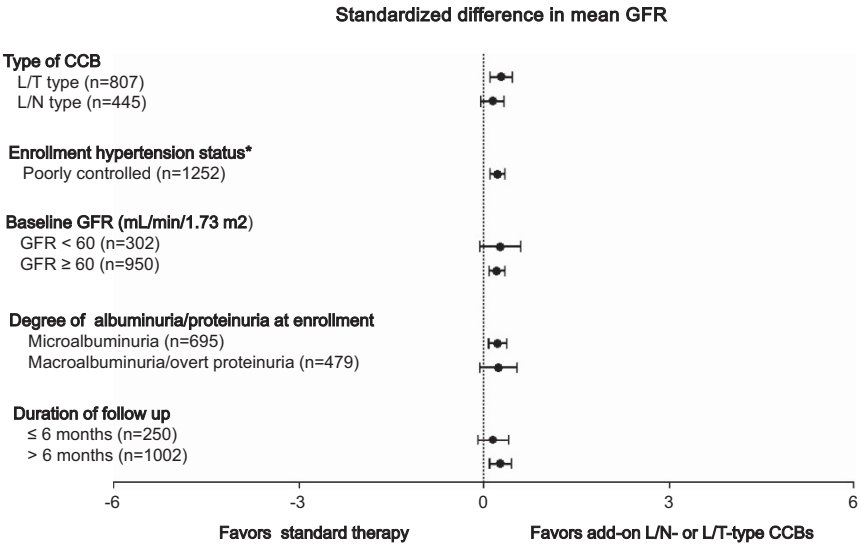

Figure 4 Subgroup analyses displaying the effect of N- and T-type calcium channel blockers (CCBs) on standardized net change in eGFR. L/N-type, cilnidipine; L/T-type, azelnidipine, efonidipine and benidipine. *All included studies enrolled patients with poorly controlled hypertension.

T-, N- and P/Q-type calcium channels are expressed in the kidney but the localization of these calcium channel subtypes varies considerably.[42,43] As L-type calcium channels prevail predominantly in the afferent arteriole but are sparsely expressed in the efferent arteriole, L-type CCBs such as amlodipine and nifedipine tend to dilate the afferent arteriole preferentially and thus might accelerate glomerular hypertension and proteinuria.[42,43] By contrast, N-type calcium channels are expressed in nerve terminals innervating both afferent and efferent arterioles as well as glomerular podocytes. L/N-type CCBs has been shown to provide renal protection by decreasing the activity of the sympathetic nervous system and the RAAS, resulting in vasodilation of both arterioles, inhibition of podocyte injury and decrease in proteinuria.[44–48] With respect to L/T-type CCBs, T-type channels have an important role in the kidney, mediating efferent arteriole tone, and combined T- and L-type CCBs might have a therapeutic advantage over selective L-type CCBs by providing renoprotection via a lower glomerular pressure and filtration fraction.[49]

Hypertension and proteinuria are well-recognized risk factors for predicting progression of CKD[10] and cardiovascular morbidity and mortality.[50,51] Several clinical practice guidelines recommend the use of RAAS blockade therapy for hypertension in patients with CKD especially those with proteinuria. However, the combination of ACEI and ARB should be cautiously used, as there is a higher incidence of hyperkalemia, hypotension and a decline in GFR.[6] In several clinical practice guidelines, CCBs are recommended as monotherapy for the treatment of hypertension and in combination with other agent classes.[5,7,52–54] Their use may provide specific benefits beyond their

blood pressure-lowering effect, particularly the L/N- and L/T-type CCBs. In our analysis, as the blood pressure between the two groups was comparable, the reduced proteinuria and preserved kidney function, including eGFR and serum creatinine, might be the result of the non-hemodynamic effects of the L/N- and L/T-type CCBs, including antioxidant effects.[24,30,55] On the other hand, the antiproteinuric effects of L/N- and L/T-type CCBs could also be explained by their ability to decrease nocturnal and morning blood pressure, especially in patients with CKD who lack the circadian blood pressure rhythm, so called non-dipper-type hypertension.[56] The use of RAAS blockers and diuretics in patients with CKD has previously been shown to lower nocturnal blood pressure in the subset of non-dipper hypertensives, hence reducing in proteinuria.[57] L/T- and L/N-type CCBs, azelnidipine and cilnidipine in particular,[58–60] have been shown to lower nocturnal and morning blood pressure, which might result in antiproteinuric effect through a similar speculated mechanism. Although reflex tachycardia is a known side effect of CCB, and increased heart rate may be related to cardiovascular events, the decreased pulse rate observed with L/N- and L/T-type CCBs in our meta-analysis argues for a salutary benefit on the sympathetic nervous system activity. Based on our subgroup analyses, L/T-type CCBs (mainly azelnidipine) affected the pulse rate more significantly than other CCB types, consistent with the known direct sympathetic inhibitory effect of L/T-type CCBs.[61] However, the potential long-term benefit on cardiovascular morbidity and mortality as the end point requires further study.

In our subgroup analyses, the greater effects on albuminuria and proteinuria were observed in studies that included patients with lower GFR, macroalbuminuria and overt proteinuria at enrollment and those that had longer follow-up periods. In addition, the greater effects on eGFR were observed in studies that used L/T-type CCBs, studies that included patients with poorly controlled hypertension, higher GFR, microalbuminuria at enrollment and those that had longer follow-up periods. These potential benefits of L/N- and L/T-type CCBs on proteinuria and kidney function should be considered preliminary and need to be confirmed in large studies.

Strengths of our synthesis include the large number of trials. There are several limitations that should be emphasized. L/N- and L/T-type CCBs are currently in use only in East Asian countries (that is, Japan and China). As the studied populations were mostly Japanese, our findings are not generalizable to other ethnicities. The trials included in our analysis had a small sample size and were of relative short duration. We observed a benefit of the L/N- and L/T-type CCBs on albuminuria and proteinuria especially in the studies that included patients with lower GFR, macroalbuminuria and overt proteinuria at enrollment and longer follow-up. We can only speculate as to whether patients with earlier stages of kidney disease with features of microalbuminuria and preserved GFR might not benefit from the use L/N- and L/T-type CCBs.

In conclusion, in the present meta-analysis, we demonstrate that L/N- and L/T-type CCBs as add-on therapy to an ACEI or an ARB reduce albuminuria and proteinuria and improve kidney function compared with the use of an ACEI or ARB alone or in combination with other antihypertensive agents. These benefits were observed irrespective of blood pressure-lowering effect, suggestive of a non-hemodynamic-mediated mechanism. The potential long-term hemodynamic and non-hemodynamic effects of L/N- and L/T-type CCBs on the kidneys in patients with hypertension need to be further examined.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

1 Yokokawa H, Goto A, Sanada H, Watanabe T, Felder RA, Jose PA, Yasumura S. Association between control to target blood pressures and healthy lifestyle factors among Japanese hypertensive patients: Longitudinal data analysis from Fukushima Research of Hypertension (FRESH). *Obes Res Clin Pract* 2014; **8**: e364–e373.

2 Electronic Material. Department of Health Statistics and Informatics, World Health Organization. Causes of death 2008: data sources and methods. http://www.who.int/healthinfo/global_burden_disease/cod_2008_sources_methods.pdf (accessed 14 October 2014).

3 Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, Atkinson C, Bacchus LJ, Bahalim AN, Balakrishnan K, Balmes J, Barker-Collo S, Baxter A, Bell ML, Blore JD, Blyth F, Bonner C, Borges G, Bourne R, Boussinesq M, Brauer M, Brooks P, Bruce NG, Brunekreef B, Bryan-Hancock C, Bucello C, Buchbinder R, Bull F, Burnett RT, Byers TE, Calabria B, Carapetis J, Carnahan E, Chafe Z, Charlson F, Chen H, Chen JS, Cheng AT, Child JC, Cohen A, Colson KE, Cowie BC, Darby S, Darling S, Davis A, Degenhardt L, Dentener F, Des Jarlais DC, Devries K, Dherani M, Ding EL, Dorsey ER, Driscoll T, Edmond K, Ali SE, Engell RE, Erwin PJ, Fahimi S, Falder G, Farzadfar F, Ferrari A, Finucane MM, Flaxman S, Fowkes FG, Freedman G, Freeman MK, Gakidou E, Ghosh S, Giovannucci E, Gmel G, Graham K, Grainger R, Grant B, Gunnell D, Gutierrez HR, Hall W, Hoek HW, Hogan A, Hosgood HD 3rd, Hoy D, Hu H, Hubbell BJ, Hutchings SJ, Ibeanusi SE, Jacklyn GL, Jasrasaria R, Jonas JB, Kan H, Kanis JA, Kassebaum N, Kawakami N, Khang YH, Khatibzadeh S, Khoo JP, Kok C, Laden F, Lalloo R, Lan Q, Lathlean T, Leasher JL, Leigh J, Li Y, Lin JK, Lipshultz SE, London S, Lozano R, Lu Y, Mak J, Malekzadeh R, Mallinger L, Marcenes W, March L, Marks R, Martin R, McGale P, McGrath J, Mehta S, Mensah GA, Merriman TR, Micha R, Michaud C, Mishra V, Mohd Hanafiah K, Mokdad AA, Morawska L, Mozaffarian D, Murphy T, Naghavi M, Neal B, Nelson PK, Nolla JM, Norman R, Olives C, Omer SB, Orchard J, Osborne R, Ostro B, Page A, Pandey KD, Parry CD, Passmore E, Patra J, Pearce N, Pelizzari PM, Petzold M, Phillips MR, Pope D, Pope CA 3rd, Powles J, Rao M, Razavi H, Rehfuess EA, Rehm JT, Ritz B, Rivara FP, Roberts T, Robinson C, Rodriguez-Portales JA, Romieu I, Room R, Rosenfeld LC, Roy A, Rushton L, Salomon JA, Sampson U, Sanchez-Riera L, Sanman E, Sapkota A, Seedat S, Shi P, Shield K, Shivakoti R, Singh GM, Sleet DA, Smith E, Smith KR, Stapelberg NJ, Steenland K, Stöckl H, Stovner LJ, Straif K, Straney L, Thurston GD, Tran JH, Van Dingenen R, van Donkelaar A, Veerman JL, Vijayakumar L, Weintraub R, Weissman MM, White RA, Whiteford H, Wiersma ST, Wilkinson JD, Williams HC, Williams W, Wilson N, Woolf AD, Yip P, Zielinski JM, Lopez AD, Murray CJ, Ezzati M, AlMazroa MA, Memish ZA. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2224–2260.

4 Collins AJ, Foley RN, Herzog C, Chavers B, Gilbertson D, Ishani A, Kasiske B, Liu J, Mau LW, McBean M, Murray A St, Peter W, Guo H, Gustafson S, Li Q, Li S, Li S, Peng Y, Qiu Y, Roberts T, Skeans M, Snyder J, Solid C, Wang C, Weinhandl E, Zaun D, Arko C, Chen SC, Dalleska F, Daniels F, Dunning S, Ebben J, Frazier E, Hanzlik C, Johnson R, Sheets D, Wang X, Forrest B, Constantini E, Everson S, Eggers P, Agodoa LUS. Renal Data System 2010 Annual Data Report. *Am J Kidney Dis Jan* 2011; **57**: A8, e1–526.

5 Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Redon J, Dominiczak A, Narkiewicz K, Nilsson PM, Burnier M, Viigimaa M, Ambrosioni E, Caufield M, Coca A, Olsen MH, Schmieder RE, Tsioufis C, van de Borne P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Clement DL, Coca A, Gillebert TC, Tendera M, Rosei EA, Ambrosioni E, Anker SD, Bauersachs J, Hitij JB, Caulfield M, De Buyzere M, De Geest S, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano G, Gielen S, Haller H, Hoes AW, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Olsen MH, Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Rydén L, Sirenko Y, Stanton A, Struijker-Boudier H, Tsioufis C, van de Borne P, Vlachopoulos C, Volpe M, Wood DA. 2013 ESH/ESC guidelines for the management ofarterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013; **34**: 2159–2219.

6 Susantitaphong P, Sewaralthahab K, Balk EM, Eiam-ong S, Madias NE, Jaber B. 'Efficacy and safety of combined vs. single renin-angiotensin-aldosterone system blockade in chronic kidney disease: a meta-analysis'. *Am J Hypertens* 2013; **26**: 424–441.

7 James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS, Ortiz E. 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.
8 Hillege HL, Janssen WM, Bak AA, Diercks GF, Grobbee DE, Crijns HJ, Van Gilst WH, De Zeeuw D, De Jong PE, Prevend Study Group. Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. *J Intern Med* 2001; **249**: 519–526.
9 Wachtell K, Ibsen H, Olsen MH, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlöf B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristianson K, Lederballe-Pedersen O, Nieminen MS, Okin PM, Omvik P, Oparil S, Wedel H, Snapinn SM, Aurup P. Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: the LIFE study. *Ann Intern Med* 2003; **139**: 901–906.
10 Hunsicker LG, Adler S, Caggiula A, England BK, Greene T, Kusek JW, Rogers NL, Teschan PE. Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study. *Kidney Int* 1997; **51**: 1908–1919.
11 Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int Suppl* 2012; **2**: 337–414.
12 Kaneshiro Y, Ichihara A, Sakoda M, Kurauchi-Mito A, Kinouchi K, Itoh H. Add-on benefits of amlodipine and thiazide in nondiabetic chronic kidney disease stage 1/2 patients treated with valsartan. *Kidney Blood Press Res* 2009; **32**: 51–58.
13 Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V, Hester A, Gupte J, Gatlin M, Velazquez EJ, ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008; **359**: 2417–2428.
14 Bakris GL, Toto RD, McCullough PA, Rocha R, Purkayastha D, Davis P, GUARD (Gauging Albuminuria Reduction With Lotrel in Diabetic Patients With Hypertension) Study Investigators. Effects of different ACE inhibitor combinations on albuminuria: results of the GUARD study. *Kidney Int* 2008; **73**: 1303–1309.
15 Takai S, Jin D, Aritomi S, Niinuma K, Miyazaki M. Powerful vascular protection by combining cilnidipine with valsartan in stroke-prone, spontaneously hypertensive rats. *Hypertens Res* 2013; **36**: 342–348.
16 Rakugi H, Ogihara T, Umemoto S, Matsuzaki M, Matsuoka H, Shimada K, Higaki J, Ito S, Kamiya A, Suzuki H, Ohashi Y, Shimamoto K, Saruta T, Combination Therapy of Hypertension to Prevent Cardiovascular Events Trial Group. Combination therapy for hypertension in patients with CKD: a subanalysis of the Combination Therapy of Hypertension to Prevent Cardiovascular Events trial. *Hypertens Res* 2013; **36**: 947–958.
17 Homma K, Hayashi K, Yamaguchi S, Fujishima S, Hori S, Itoh H. Renal microcirculation and calcium channel subtypes'. *Curr Hypertens Rev* 2013; **9**: 182–186.
18 Abe M, Okada K, Soma M. T-type Ca channel blockers in patients with chronic kidney disease in clinical practice'. *Curr Hypertens Rev* 2013; **9**: 202–209.
19 Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1–12.
20 Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychol Methods* 2006; **11**: 193–206.
21 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629–634.
22 Katayama K, Nomura S, Ishikawa H, Murata T, Koyabu S, Nakano T. Comparison between valsartan and valsartan plus cilnidipine in type II diabetics with normo- and microalbuminuria. *Kidney Int* 2006; **70**: 151–156.
23 Fujita T, Ando K, Nishimura H, Ideura T, Yasuda G, Isshiki M, Takahashi K, Cilnidipine versus Amlodipine Randomised Trial for Evaluation in Renal Desease (CARTER) Study Investigators. 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.
24 Ogawa S, Mori T, Nako K, Ito S. Combination therapy with renin-angiotensin system inhibitors and the calcium channel blocker azelnidipine decreases plasma inflammatory markers and urinary oxidative stress markers in patients with diabetic nephropathy. *Hypertens Res* 2008; **31**: 1147–1155.
25 Sasaki H, Saiki A, Endo K, Ban N, Yamaguchi T, Kawana H, Nagayama D, Ohhira M, Oyama T, Miyashita Y, Shirai K. Protective effects of efonidipine, a T- and L-type calcium channel blocker, on renal function and arterial stiffness in type 2 diabetic patients with hypertension and nephropathy. *J Atheroscler Thromb* 2009; **16**: 568–575.
26 Ishimitsu T, Numabe A, Masuda T, Akabane T, Okamura A, Minami J, Matsuoka H. Angiotensin-II receptor antagonist combined with calcium channel blocker or diuretic for essential hypertension. *Hypertens Res* 2009; **32**: 962–968.
27 Abe M, Okada K, Maruyama T, Maruyama N, Matsumoto K. Comparison of the antiproteinuric effects of the calcium channel blockers benidipine and amlodipine administered in combination with angiotensin receptor blockers to hypertensive patients with stage 3-5 chronic kidney disease. *Hypertension Res* 2009; **32**: 270–275.
28 Miwa Y, Tsuchihashi T, Ohta Y, Tominaga M, Kawano Y, Sasaguri T, Ueno M, Matsuoka H. Antiproteinuric effect of cilnidipine in hypertensive Japanese treated with renin-angiotensin-system inhibitors-A multicenter, open, randomized trial using 24-hour urine collection. *Clin Exp Hypertens* 2010; **32**: 400–405.
29 Miyagawa K, Dohi Y, Nakazawa A, Sugiura T, Yamashita S, Sato K, Kimura G. Renoprotective effect of calcium channel blockers in combination with an angiotensin receptor blocker in elderly patients with hypertension. A randomized crossover trial between benidipine and amlodipine. *Clin Exp Hypertens* 2010; **32**: 1–7.
30 Nakamura T, Sato E, Fujiwara N, Kawagoe Y, Ueda Y, Sugaya T, Yamagishi S, Yamada S, Koide H. Comparative effects of benidipine and amlodipine on proteinuria, urinary 8-OHdG, urinary L-FABP, and inflammatory and atherosclerosis markers in early-stage chronic kidney disease. *Am J Med Sci* 2010; **339**: 157–163.
31 Abe M, Okada K, Maruyama N, Matsumoto S, Maruyama T, Fujita T, Matsumoto K, Soma M. Benidipine reduces albuminuria and plasma aldosterone in mild-to-moderate stage chronic kidney disease with albuminuria. *Hypertens Res* 2011; **34**: 268–273.
32 Matsui Y, Eguchi K, Ishikawa J, Shimada K, Kario K. Urinary albumin excretion during angiotensin II receptor blockade: comparison of combination treatment with a diuretic or a calcium-channel blocker. *Am J Hypertens* 2011; **24**: 466–473.
33 Yoshii H, Mita T, Sato J, Kodama Y, Choi JB, Komiya K, Matsumoto K, Kanno R, Kawasumi M, Koyano H, Hirose T, Onuma T, Kawamori R, Watada H. Comparison of effects of azelnidipine and trichlormethiazide in combination with olmesartan on blood pressure and metabolic parameters in hypertensive type 2 diabetic patients. *J Diabetes Investig* 2011; **2**: 490–496.
34 Hatta T, Takeda K, Shiotsu Y, Sugishita C, Adachi T, Kimura T, Sonomura K, Kusaba T, Kishimioto N, Narumiya H, Tanda S, Tamagaki K, Yamada K, Kameyama H, Kido H, Harada S, Bito Y, Moriguchi J, Morimoto S, Okigaki M, Itoh H, Mori Y, Nakata T, Maki K, Sasaki S, Sawada K, Matsubara H. Switching to an L/N-type calcium channel blocker shows renoprotective effects in patients with chronic kidney disease: the Kyoto Cilnidipine Study. *J Int Med Res* 2012; **40**: 1417–1428.
35 Kanaoka T, Tamura K, Wakui H, Ohsawa M, Azushima K, Uneda K, Kobayashi R, Fujikawa T, Tsurumi-Ikeya Y, Maeda A, Yanagi M, Toya Y, Umemura S. L/N-type calcium channel blocker cilnidipine added to renin-angiotensin inhibition improves ambulatory blood pressure profile and suppresses cardiac hypertrophy in hypertension with chronic kidney disease. *Int J Mol Sci* 2013; **14**: 16866–16881.
36 Ando K, Ueshima K, Tanaka S, Kosugi S, Sato T, Matsuoka H, Nakao K, Fujita T. Comparison of the antialbuminuric effects between 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 microalbuminin randomized (Sakura) trial. *Int J Med Sci* 2013; **10**: 1209–1216.
37 Abe M, Maruyama N, Suzuki H, Inoshita A, Yoshida Y, Okada K, Soma M. L/N-type calcium channel blocker cilnidipine reduces plasma aldosterone, albuminuria, and urinary liver-type fatty acid binding protein in patients with chronic kidney disease. *Heart Vessels* 2013; **28**: 480–489.
38 Ando K, Nitta K, Rakugi H, Nishizawa Y, Yokoyama H, Nakanishi T, Kashihara N, Tomita K, Nangaku M, Takahashi K, Isshiki M, Shimosawa T, Fujita T. Comparison of the antialbuminuric effects of benidipine and hydrochlorothia-zide in Renin-Angiotensin System (RAS) inhibitor-treated hypertensive patients with albuminuria: the COSMO-CKD (COmbination Strategy on Renal Function of Benidipine or Diuretics TreatMent with RAS inhibitOrs in a Chronic Kidney Disease Hypertensive Population) study. *Int J Med Sci* 2014; **11**: 897–904.
39 Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; **53**: 982–992.
40 Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Hara S, Ura N, Kiyohara Y, Hirakata H, Watanabe T, Moriyama T, Ando Y, Inaguma D, Narita I, Iso H, Wakai K, Yasuda Y, Tsukamoto Y, Ito S, Makino H, Hishida A, Matsuo S. Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. *Clin Exp Nephrol* 2007; **11**: 41–50.
41 Catterall WA. Structure and regulation of voltage-gated Ca2+ channels. *Annu Rev Cell Dev Biol* 2000; **16**: 521–555.
42 Hansen PB, Jensen BL, Andreasen D, Friis UG, Skott O. Vascular smooth muscle cells express the alpha(1A) subunit of a P-/Q-type voltage-dependent Ca(2+) channel, and it is functionally important in renal afferent arterioles. *Circ Res* 2000; **87**: 896–02.
43 Hansen PB, Jensen BL, Andreasen D, Skøtt O. Differential expression of T- and L-type voltage-dependent calcium channels in renal resistance vessels. *Circ Res* 2001; **89**: 630–638.
44 Fan YY, Kohno M, Nakano D, Ohsaki H, Kobori H, Suwarni D, Ohashi N, Hitomi H, Asanuma K, Noma T, Tomino Y, Fujita T, Nishiyama A. Cilnidipine suppresses podocyte injury and proteinuria in metabolic syndrome rats: possible involvement of N-type calcium channel in podocyte. *J Hypertens* 2010; **28**: 1034–1043.
45 Lei B, Nakano D, Fujisawa Y, Liu Y, Hitomi H, Kobori H, Mori H, Masaki T, Asanuma K, Tomino Y, Nishiyama A. N-type calcium channel inhibition with cilnidipine elicits glomerular podocyte protection independent of sympathetic nerve inhibition. *J Pharmacol Sci* 2012; **119**: 359–367.
46 Sugano N, Hayashi K, Hosoya T, Yokoo T. Mechanistic view of renal protective action of calcium channel blockade. *Curr Hypertens Rev* 2013; **9**: 187–192.
47 Ando K. L-/N-type calcium channel blockers and proteinuria. *Curr Hypertens Rev* 2013; **9**: 210–218.
48 Homma K, Hayashi K, Yamaguchi S, Fujishima S, Hori S, Itoh H. Renal microcirculation and calcium channel subtypes. *Curr Hypertens Rev* 2013; **9**: 182–186.
49 Hansen PBL. Functional and pharmacological consequences of the distribution of voltage-gated calcium channels in the renal blood vessels. *Acta Physiol* 2013; **207**: 690–699.
50 De Nicola L, Minutolo R, Chiodini P, Zoccali C, Castellino P, Donadio C, Strippoli M, Casino F, Giannattasio M, Petrarulo F, Virgilio M, Laraia E, Di Iorio BR, Savica V, Conte G. Global approach to cardiovascular risk in chronic kidney disease: reality and opportunities for intervention. *Kidney Int* 2006; **69**: 538–545.

51 Irie F, Iso H, Sairenchi T, Fukasawa N, Yamagishi K, Ikehara S, Kanashiki M, Saito Y, Ota H, Nose T. The relationships of proteinuria, serum creatinine, glomerular filtration rate with cardiovascular disease mortality in Japanese general population. *Kidney Int* 2006; **69**: 1264–1271.
52 Hypertension Canada. *Canadian Hypertension Education Program (CHEP) 2013 Recommendations*. Hypertension Canada: 2013. http://www.hypertension.ca/chep (accessed 9 August 2013).
53 Liu LS. 2010 Chinese guidelines for the management of hypertension. *Zhonghua Xin Xue Guan Bing ZaZhi* 2011; **39**: 579–615.
54 National Institute for Health and Care Excellence *Hypertension: Clinical Management of Primary Hypertension in Adults (CG127)*. NICE UK: 2013. http://publications.nice.org.uk/hypertension-cg127 (accessed 9 August 2013).
55 Soeki T, Kitani M, Kusunose K, Yagi S, Taketani Y, Koshiba K, Wakatsuki T, Orino S, Kawano K, Sata M. Renoprotective and antioxidant effects of cilnidipine in hypertensive patients. *Hypertens Res* 2012; **35**: 1058–1062.
56 Farmer CK, Goldsmith DJ, Cox J, Dallyn P, Kingswood JC, Sharpstone P. An investigation of the effect of advancing uraemia, renal replacement therapy and renal transplantation on blood. *Nephrol Dial Transplant* 1997; **12**: 2301–2307.
57 Uzu T, Harada T, Namba T, Yamamoto R, Takahara K, Yamauchi A, Kimura G. Thiazide diuretics enhance nocturnal blood pressure fall and reduce proteinuria in immunoglobulin A nephropathy treated with angiotensin II modulators. *J Hypertens* 2005; **23**: 861–865.
58 Kario K, Uehara Y, Shirayama M, Takahashi M, Shiosakai K, Hiramatsu K, Komiya M, Shimada K. Study of sustained blood pressure-lowering effect of azelnidipine guided by self-measured morning and evening home blood pressure: subgroup analysis of the At-HOME study. *Drugs R D* 2013; **13**: 75–85.
59 Yamagishi T. Efficacy of azelnidipine on home blood pressure and pulse rate in patients with essential hypertension: comparison with amlodipine. *Hypertens Res* 2006; **29**: 767–773.
60 Kario K, Nariyama J, Kido H, Ando S, Takiuchi S, Eguchi K, Niijima Y, Ando T, Noda M. Effect of a novel calcium channel blocker on abnormal nocturnal blood pressure in hypertensive patients. *J Clin Hypertens (Greenwich)* 2013; **15**: 465–472.
61 Konno S, Hirooka Y, Araki S, Koga Y, Kishi T, Sunagawa K. Azelnidipine decreases sympathetic nerve activity via antioxidant effect in the rostral ventrolateral medulla of stroke-prone spontaneously hypertensive rats. *J Cardiovasc Pharmacol* 2008; **52**: 555–560.