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REVIEW

Dihydropyridine calcium channel blockers and renal disease

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Although blood pressure control is considered the main mechanism for preventing the progression of chronic kidney disease (CKD), angiotensin-converting enzyme inhibitors and angiotensin receptors blockers have an additional organ-protective role. The effects of calcium channel blockers (CCBs) in renal disease are not so clearly defined. CCBs have pleiotropic effects that might contribute to protection of the kidney, such as attenuating the mesangial entrapment of macromolecules, countervailing the mitogenic effect of platelet-derived growth factors and platelet-activating factors and suppressing mesangial cell proliferation. Some evidence has accumulated in recent years demonstrating that the new dihydropyridinic CCBs (such as lercanidipine or efonidipine) may affect both postglomerular and preglomerular vessels, resulting in a decreased filtration fraction and nephroprotective effect. Increasing clinical and experimental evidence supports this view and the use of CCBs in CKD hypertensive patients.
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INTRODUCTION

Hypertension is a major determinant of renal disease progression, irrespective of its cause. The relative risk of 3developing end-stage renal disease in hypertensive patients increases threefold when a patient's diastolic blood pressure (DBP) increases to 90 mm Hg compared with that of patients with 'optimal' BP.[1] Although tighter BP control is considered the main mechanism for slowing the progression of chronic renal failure, some antihypertensive agents, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), have an additional organ-protective role and are routinely used in renal disease.[2] In terms of clinical pharmacology and therapeutic use, there are fundamental differences between the dihydropyridine (DHP) group of CCBs (such as nifedipine) and other commonly used non-DHP calcium channel blockers (CCBs; such as verapamil and diltiazem). This latter group has shown little, if any, effect on albuminuria or renal disease progression; therefore, this article will focus on dihydropyridinic CCBs.[3] Furthermore, this review seeks to highlight the differences within the DHP CCB group, with a particular emphasis on the renoprotective effects of last-generation CCBs.

Although non-DHP CCB (verapamil and diltiazem) effects on renal disease are beyond the scope of this review, diabetes mellitus animal models provide evidence that they can blunt both the rise in proteinuria as well as mesangial glomerular scarring.[4] Diltiazem appears to have an inhibitory effect on mitochondrial sodium–calcium exchange that is unique among CCBs.[5] Moreover, non-DHP CCBs have been shown to attenuate the increase in matrix protein synthesis induced by glycated albumin.[6] In the experimental remnant kidney model, diltiazem reduced glomerulosclerosis progression compared with verapamil and felodipine, although none of them reduced glomerular hypertrophy.[7] From a clinical point of view, several long-term trials with non- DHP drugs have demonstrated reductions in proteinuria intensity and slowed declines in glomerular filtration rates (GFRs),[8–16] although some studies failed to show this effect.[17–19] Specifically, a meta-analysis examining the differential effects of calcium antagonist subclasses on markers of nephropathy progression found similar efficacy between subclasses of calcium antagonists to lower BP but greater reductions in proteinuria non-DHP CCBs compared with classic DHP calcium antagonists.[20] Nevertheless, this review will exclusively focus on the effects of dihydropyridinic CCBs on chronic kidney disease (CKD).

'IN VITRO' RENOPROTECTIVE EFFECTS OF CCBs

Calcium antagonists have pleiotropic effects that might contribute to protecting the kidney against hypertension-induced damage. Calcium antagonists have demonstrated modulation of macromolecular traffic through the mesangium and attenuate mesangial entrapment of macromolecules, which induce inflammatory and proliferative responses.[21,22] It has also been suggested that calcium antagonists may counteract the mitogenic effect of platelet-derived growth factors and platelet-activating factors, which seem to have an important

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role in renal lesions induced by hypertension.[23] Similarly, calcium antagonists suppress mesangial cell proliferation by inhibiting activator protein-1,[24] as well as the cell cycle transition from the G1 to S phase,[25] and have an inhibitory effect on the stimulated transcriptional action of interleukin-1β and granulocyte/monocyte colony-stimulating factors by platelet-derived growth factors in human mesangial cells.[26] In this regard, calcium antagonists have been shown to suppress the phorbol 12-myristate 13-acetate-induced activation of nuclear factor kappa β in cultured human mesangial cells.[27]

Finally, calcium antagonists might act as free radical scavengers.[28,29] They may reduce the activity of some intracellular free radical sources (that is, they could inhibit the activity of NADPH oxidase, xanthine oxidase and cyclooxygenase, which are the main sources of intracellular reactive oxygen species).[30] Second, CCBs may decrease the intracellular-free radical concentration through its direct antioxidant capacity.[31] Calcium antagonists may protect the redox potential of the free radical targets through their effect on nuclear factor kappa β and hence on the signaling pathways leading to its activation.[32]

Last of all, inhibition of the renal effects of endothelin by CCBs has been demonstrated under experimental conditions.[33] Endothelin-1 is a potent vasoconstrictor that has been implicated in the pathogenesis of kidney disease and animal models of hypertension.[34–36] It is therefore of considerable interest that endothelin appears to preferentially reduce blood flow in the renal cortex, with either small reductions, or even increases, in the medullary blood flow in anesthetized rats[37] and dogs.[38] Furthermore, treatments that reduce renal medullary blood flow cause hypertension, if chronically administered, and attenuate BP-lowering mechanisms in the kidney.[39,40] This phenomenon may have important implications in pathological conditions associated with increased circulating or local intrarenal levels of endothelin, such as acute and chronic renal failure,[17] advanced atherosclerosis[40] and perhaps essential hypertension.[41]

EFFECTS ON RENAL HEMODYNAMICS

The classic molecular target of the CCBs is the voltage-activated L-type Ca^{2+} channel, also referred to in the past as the DHP receptor because of the presence of a high-affinity DHP-binding site. However, in addition to sharing the antihypertensive effect of CCBs, third-generation DHPs also exhibit therapeutic benefits on renal hemodynamics. In contrast to most CCBs, which predominantly dilate afferent glomerular arterioles and potentially cause glomerular hypertension and other undesirable effects, new DHPs have an additional vasodilatory effect on efferent arterioles. Recent advances in basic science have emphasized that new DHPs can inhibit other types of Ca^{2+} channels, including the T-type, the neuronal P/Q type and N-type Ca^{2+} channels.[42] In parallel, these Ca^{2+} channel subtypes have been localized in renal vascular and tubular tissues (T-type, P/Q type) and in sympathetic nerve endings (N-type), which may also impact vascular tone. The lack of functional expression of the L-Type Ca^{2+} channel and DHP insensitivity to most CCBs in renal efferent arterioles strongly further supports the hypothesis of a critical role of the T-type Ca^{2+} channel (and possibly of the N- and P/Q types) in the vascular tone in these arterioles. The effect of mibefradil and of new DHPs on non-L-type Ca^{2+} channels may account for the divergent actions of CCBs on afferent and efferent arterioles and for the beneficial effect on glomerular hemodynamics.[43] Recent results have also opened the provocative perspective that neuronal P/Q type (α 1A) Ca^{2+} channels are also expressed in vascular myocytes (from renal preglomerular resistance vessels and the aorta), as well as in mesangial cells, where they account for Ca^{2+} influx and the depolarization-mediated contraction of renal afferent arterioles.[44]

After the discovery of the T-type and the neuronal N, P/Q, and R-type Ca^{2+} channels, it became clear that DHPs, and often other CCBs as well, could inhibit the various types of Ca^{2+} channels, which stimulated interest for potential clinical applications. For example, nicardipine had a significant effect on the T-type Ca^{2+} channel in sensory neurons, but nifedipine and nitrendipine had only a weak effect.[45] In vascular myocytes, nicardipine and flunarizine could also inhibit the T-type Ca^{2+} channel.[46] Some DHPs, as well as verapamil and diltiazem, could inhibit P-type Ca^{2+} currents at concentrations that are not maximally active for the L-type Ca^{2+} channel inhibition with functional impact on renal afferent arterioles.[47]

In addition to their remarkable effectiveness in inhibiting the activity of the L-type Ca^{2+} channel, the last generation of DHPs has additional protective effects on renal function. These effects seem to occur, at least in part, independently of long-term antiremodeling effects that are observed in the ACEI or the ARBs. To explain the differential effect of third-generation DHPs on glomerular function, a blocking action on T-type Ca^{2+} channels has been proposed, based on the dual effects of these compounds on both L- and T-type Ca^{2+} channels.[48–50] In contrast with the lack of effect of DHPs such as nifedipine, the other DHPs, such as mibefradil, nilvadipine and efonidipine, inhibit both the T-type and the L-type Ca^{2+} channels, reversing the angiotensin (Ang) II-induced afferent and efferent arteriolar constriction.[51] However, the renoprotective effects of T-type CCBs may be based not only on a reduction in systemic BP but also on decreased Rho-kinase activity, tubulointerstitial fibrosis and epithelial–mesenchymal transitions.[52] New DHPs also cause very moderate peripheral edema owing to their equal vasodilatory effects on precapillary and postcapillary vessels, which may reflect the differential expression of T- and L-type Ca^{2+} channels in arterial and venous tissues.[53]

For example, the DHPs amlodipine, barnidipine, benidipine, efonidipine, manidipine, nicardipine and nilvadipine, with effects on recombinant Ca^{2+} channels of both the L-type and the T-type (a1G), were reported to exhibit blocking actions comparable to that of mibefradil on the T-type Ca^{2+} channel.[54,55] In contrast to the predominant afferent arteriolar action of conventional CCBs (nifedipine, nicardipine, amlodipine and diltiazem), the novel DHP CCBs (for example, manidipine, nilvadipine, benidipine, efonidipine and lercanidipine) potently dilate both afferent and efferent arterioles and have beneficial effects on intrarenal hemodynamics.[56] In addition, efonidipine has also been reported to decrease plasma aldosterone concentration in accordance with reported effects on the key role of T-type Ca^{2+} channels on aldosterone production.[57]

EFFECTS OF CLASSIC CCBs ON THE KIDNEY

There is a large amount of information regarding the effects of calcium antagonists on human renal disease. Most of the reports have evaluated the changes in proteinuria or urinary albumin excretion (UAE). The studies with follow-up for >12 weeks have been taken into account in this review, which excludes most comparisons against placebo (Figure 1).[58,59] Taken altogether, the results demonstrate a clearly unfavorable effect on CCBs compared with the antiproteinuric effect of renin–angiotensin axis-blocking drugs. Table 1 summarizes the effects of classic CCBs on the GFR and renal failure progression.[60–70] The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm, a multicenter randomized controlled trial (RCT), compared the effects on the cardiovascular end points of two pharmacological regimens: the first was based on amlodipine (using perindopril as the second-step drug) and the other on atenolol (using bendroflumethiazide as the second-step drug). There was a

significant reduction in the development of renal impairment associated with the amlodipine-based regimen (15%). Nevertheless, by the end of the trial, as intended by design, most patients (78%) were taking at least two antihypertensive agents, and only 15% were taking amlodipine monotherapy. Therefore, it could be risky to come to any conclusions on the renoprotective effects of amlodipine from this trial.[71]

Some studies have compared the possible beneficial effect of combining calcium antagonists and renin–angiotensin blocking drugs for treating hypertension but, taken altogether, the published results are conflicting and inconclusive. A ramipril and felodipine combination therapy was tested in the NEPHROS trial. The combination group had a slower renal disease progression rate compared with the felodipine group ($P<0.05$) but not to the ramipril group ($P>0.20$). There was a rise in albuminuria after 2 years in the felodipine group ($P<0.05$), but no significant change was found in the other groups. The beneficial effect of the combination of an ACEI and a calcium antagonist could be due to increased BP reduction.[72] Shigihara *et al.*[73] examined the effects of combination therapy using an ACEI plus amlodipine and compared them with the effect of an ACEI alone under intensive BP control (DBP < 80 mm Hg) on UAE in hypertensive, type 2 diabetic patients with microalbuminuria. The UAE decrease attained statistical significance only in the combination group ($P<0.05$).[73] Fogari *et al.*[74] compared the long-term effect of amlodipine and fosinopril in monotherapy or in combination on UAE in hypertensive diabetic patients with microalbuminuria. The combination therapy was more effective in reducing BP than either drug alone at any time of the study. All three treatments provided a significant decrease in UAE during the 48-month study period. However, this effect was more pronounced and became evident earlier with fosinopril than with amlodipine monotherapy (after 3 *vs.* 18 months of therapy). In addition, the combination therapy provided a greater antialbuminuric effect than the use of the drugs singly. This result could be due to the greater antihypertensive effects.[74] The REIN 2 study was a multicenter, RCT of patients with non-diabetic proteinuric nephropathies receiving a background treatment with ramipril. The participants were randomly assigned either conventional (DBP < 90 mm Hg; $n=169$) or intensified (SBP/DBP < 130/80 mm Hg; $n=169$) BP control. To achieve the intensified BP level, patients received add-on therapy with felodipine. The main conclusion was that no additional benefit from further BP reduction with felodipine could be shown in patients with non-diabetic proteinuric nephropathies receiving background ACEI therapy.[75]

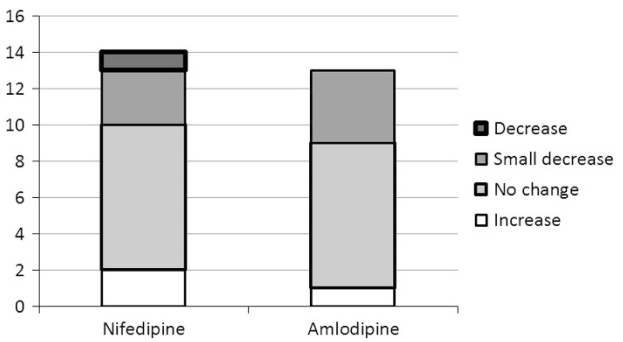

Figure 1 Results of the reported trials describing the effects of classic CCBs on albuminuria/proteinuria. Most of the trials cannot show a protective effect on proteinuria and/or albuminuria.[59,60,77,78,103–124]

The GUARD study (Gauging Albuminuria Reduction With Lotrel in Diabetic Patients With Hypertension) tested the hypothesis that combining an ACEI with either a thiazide diuretic or a CCB will cause similar reductions in BP and albuminuria in hypertensive type 2 diabetics. It was a double-blind RCT on 332 hypertensive, albuminuric type 2 diabetic patients treated with benazepril and either amlodipine or hydrochlorothiazide for 1 year. Both combinations significantly reduced the urinary albumin-to-creatinine ratio and the sitting BP of the entire cohort. The percentage of patients progressing to overt proteinuria was similar between groups. In patients who had only microalbuminuria and hypertension, a larger percentage of the diuretic and ACEI normalized their albuminuria.[76]

The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial showed that initial antihypertensive therapy with benazepril plus amlodipine was superior to benazepril plus hydrochlorothiazide in reducing cardiovascular morbidity and mortality.[77] More recently, a second report has assessed the effects of these drug combinations on the progression of CKD. ACCOMPLISH was a double-blind, randomized trial that recruited 11 506 patients with hypertension who were at high risk for cardiovascular events. They were randomly assigned to receive benazepril (20 mg) plus amlodipine (5 mg; $n=5744$) or benazepril (20 mg) plus hydrochlorothiazide (12.5 mg; $n=5762$), orally once daily. Drug doses were force-titrated for patients to attain the recommended BP goals. Progression of CKD, a prespecified end point, was defined as the doubling of the serum creatinine concentration or end-stage renal disease (estimated GFR < 15 ml min^{-1} 1·73 m^{-2} or need for dialysis). The trial was terminated early (mean follow-up 2.9 years) because of the superior

Table 1 Effects of classic CCBs on renal disease progression

Reference number	*Name*	N	*CCB*	*Comparator*	*Result*
61	Schnack	15	Nifedipine		Decrease GFR
62	SYST-EUR	4406	Nitrendipine	Diuretic	Prevent GFR↓
63	NCSEH	414	Nicardipine	Diuretic	Less Cr increase
64	INSIGHT	6321	Nifedipine	Diuretic	Prevent GFR↓
65	ALLHAT	33 357	Amlodipine	Diuretic/ACEI	Prevent GFR↓
66	AASK	1094	Amlodipine	β-Blocker/ACEI	No GFR difference[a]
67	ESPIRAL	341	Nifedipine	ACEI	Better renal survival with ACEI
68	AVER	263	Amlodipine	ACEI/ARB	No differences
69	Ziakka	62	CCBs	ACEI	Better renal survival with ACEI
70	Nakamura	30	Amlodipine	ARB	Better Cr clearance with ARB
71	INDT		Amlodipine	ARB	Better renal survival with ARB

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; Cr, serum creatinine; GFR, glomerular filtration rate.
[a]Better renal survival with an ACEI.

efficacy of benazepril plus amlodipine compared with benazepril plus hydrochlorothiazide. Additionally, in patients with CKD, the progression of CKD was slower in the benazepril plus amlodipine group. In 446 of those patients with baseline microalbuminuria, there was a deeper reduction in UAE from baseline in the benazepril plus hydrochlorothiazide group compared with the benazepril plus amlodipine group.[78]

Nevertheless, the end point in ACCOMPLISH was a composite of the doubling of serum creatinine (this increment approximately reflects a sustained loss of 50% of a patient's starting GFR) and end-stage renal disease. Although it is assumed that these changes are related to the structural decline in renal function, GFR might be affected by different ways over time: initially a drug might induce a change in GFR via a hemodynamic effect, whereas it might induce long-term GFR changes via renal structural effects. Thus the end point could reflect a reversible hemodynamic GFR change or a structural worsening of kidney function. In ACCOMPLISH, the end point was driven by the doubling of serum creatinine with no difference in end-stage renal disease, which did not occur often. This finding could be interpreted as a hemodynamic change rather than a structural renal function loss. It has been reported that the diuretic plus the ACEI induced a distinct fall in GFR within 12 weeks, whereas the addition of the CCB to the diuretic increased GFR slightly. After this acute hemodynamic change in GFR, the subsequent long-term slope was similar between the two treatment groups.[79] Taking these data into consideration, it can be argued that the benefit of CCBs is mainly based on the hemodynamic effect and thus GFR would return to similar levels after stopping the treatments. However, this hypothesis remains untested. There is no reason to reject the concept that hemodynamic changes induced by a diuretic become structural after long-term treatment. The long-term effects of CCBs are produced by non-hemodynamic mechanisms. At worst, the long-term structural effects will cause a slightly higher renal function (if a calcium antagonist is used) or a diuretic-induced decreased renal function, and this situation will be dangerous for the patient.

In a recently published substudy of the ACCOMPLISH trial, 573 subjects underwent 24-h ambulatory BP monitoring. Subjects were recruited from the US cohort and did not differ in baseline clinical characteristics from the overall study population. The study groups did not differ significantly in mean 24-h, daytime or nighttime systolic BP (SBP) levels. The finding that 24-h BP levels did not significantly differ between the two groups supports the original interpretation of the investigators that the difference in the primary composite cardiovascular end point that favored the amlodipine-based regimen could not be explained by between-group differences in BP levels.[80]

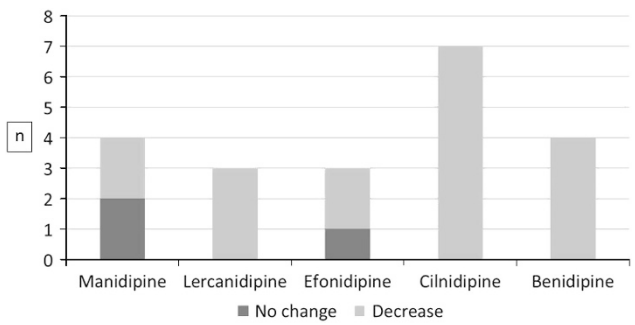

Figure 2 Results of the reports describing the effects of new CCBs on albuminuria/proteinuria. Most of the trials found a decrease in proteinuria/albuminuria after treatment.[63–83]

New calcium antagonists

There is an increasing number of reports on the clinical renal effects of new CCBs, which have rendered promising results (Figure 2, Table 2). Bellinghieri *et al.*[81] compared the effects of manidipine and nifedipine on BP and renal function. Significant reductions in SBP and DBP were reached in both treatments. Creatinine blood levels and creatinine clearance were significantly increased in the manidipine group. Proteinuria did not significantly change in the manidipine group, but it increased in the nifedipine group.[81] Del Vecchio *et al.*[82] evaluated the efficacy and tolerability of manidipine in comparison with enalapril in patients with chronic renal disease. Proteinuria remained unchanged with manidipine and significantly decreased with enalapril. No significant difference was observed in the rate of renal function decline in the two groups.[82] Fogari *et al.*[83] compared the effect of long-term monotherapy with manidipine or lisinopril on UAE and left ventricular mass index in hypertensive patients with type 2 diabetes and microalbuminuria. Manidipine and lisinopril both significantly reduced SBP and DBP levels. Both drugs provided a significant decrease in UAE, but it was significantly more pronounced with lisinopril than with manidipine and became evident earlier in the lisinopril group.[83] The aim of the AMANDHA study (Adición de MANidipino al tratamiento de Diabéticos tipo 2 Hipertensos con microAlbuminuria) was to compare the efficacy and safety of adding manidipine *vs.* amlodipine to the treatment of diabetic patients with uncontrolled hypertension and microalbuminuria despite a full-dose treatment with a renin–angiotensin system blocker for at least 6 months. Manidipine and amlodipine decreased BP values to a similar extent; urinary albumin excretion was reduced by 62.7% *vs.* 16.6%, respectively, at the end of the extension phase.[84]

The DIAL (Diabetes Ipertensione Albuminuria Lercanidipina) study evaluated the effectiveness of lercanidipine in comparison with ramipril on the reduction in UAE in patients with type 2 diabetes and persistent microalbuminuria. After 9–12 months of follow-up, a significant reduction in UAE was observed, without differences between the groups.[85] More recently, the ZAFRA study has shown a positive effect on proteinuria of the combination of the new CCB lercanidipine (10 mg) and renin–angiotensin axis-blocking drugs. The plasma creatinine concentration did not change, but creatinine clearance measured by a 24 h urine collection increased at the final visit. Proteinuria significantly decreased at the end of the follow-up.[86] In a second trial, a higher dose of lercanidipine (20 mg) was associated with renin–angiotensin axis-blocking drugs in a group of patients with proteinuric renal disease. Proteinuria significantly decreased at the end of the follow-up period.[87]

A plethora of new calcium antagonists have been introduced in the Far East, but they are not authorized in Europe or the United States of America. One of them is efonidipine. A randomized crossover study compared the chronic effects of efonidipine and amlodipine on proteinuria in patients with chronic glomerulonephritis. Urinary protein excretion was significantly less in the efonidipine period than in the amlodipine period. Serum albumin was significantly higher in the efonidipine period than in the amlodipine period.[88] In diabetic patients, significant increases in serum creatinine and urinary albumin and a significant decrease in the estimated GFR were observed in the amlodipine group but not in the efonidipine group.[89] A study evaluated the effect of efonidipine and ACEIs on BP and proteinuria in hypertensive patients with renal impairment or chronic renal parenchymal disease. Proteinuria tended to decrease in both groups, with a significant reduction observed in proteinuric patients (>1 g per day). Of interest, efonidipine decreased proteinuria in

Table 2 Effects of new CCBs on albuminuria/proteinuria

n	*CCB*	*Effect*	*Other drug*	*Effect*	*Objective*	*Follow-up*	*Reference*
101	Manidipine	No	Nifedipine	Increase	UAE	3 months	81
136	Manidipine	No	Enalapril	Decrease	Proteinura	48 weeks	82
99	Manidipine	Decrease	Lisinopril	Decrease[a]	UAE	24 months	83
91	Manidipine	Decrease	Amlodipine	Small	UAE	6 months	84
180	Lercanidipine	Decrease	Ramipril	Decrease	UAE	12 months	85
203	Lercanidipine	Decrease			Proteinuria	6 months	86
68	Lercanidipine	Decrease			Proteinuria	6 months	87
21	Efonidipine	Decrease	Amlodipine	Small	Proteinuria	4 months	88
40	Efonidipine	No change	Amlodipine	Increase	UAE	12 months	89
43	Efonidipine	Decrease	ACEIs	Decrease	Proteinuria	11 months	90
43	Cilnidipine	Decrease	Placebo	No change	UAE	6 months	91
20	Cilnidipine	Decrease	Benazepril	Decrease	UAE	12 months	92
28	Cilnidipine	Decrease	Amlodipine	Increase	Proteinuria	12 months	93
87	Cilnidipine	Decrease			UAE	12 months	94
339	Cilnidipine	Decrease	Amlodipine	Small	Proteinuria	12 months	95
365	Cilnidipine	Decrease	Amlodipine	Decrease	UAE	12 months	96
35	Cilnidipine	Decrease	Amlodipine	No change	Proteinuria	11 months	97
104	Benidipine	Decrease			UAE	6 months	98
47	Benidipine	Decrease[a]	Amlodipine	No change	Proteinuria	6 months	99
233	Benidipine	Decrease	Cilinidipine	Decrease	Proteinuria	12 months	100
65	Benidipine	Decrease			Proteinuria	12 months	101

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; UAE, urinary albumin excretion.
[a]The antiproteinuric effect was bigger than amlodipine in diabetics.

proteinuric patients who failed to manifest decreases in systemic BP.[90]

In clinical studies, cilnidipine significantly decreased urinary albumin excretion without affecting serum creatinine concentration in hypertensive patients,[91] which is comparable to the action of the ACEI, benazepril.[92] Other studies have shown that the renoprotective effect of cilnidipine was greater than that of pure L-type Ca^{2+} channel blockers.[93] Furthermore, the combination of cilnidipine and valsartan was shown to decrease the albumin/creatinine ratio more markedly than valsartan alone.[94] Recently, the multicenter, open-labeled and randomized trial, Cilnidipine *vs.* Amlodipine Randomized Trial for Evaluation in Renal disease (CARTER), has shown that cilnidipine is superior to amlodipine in preventing the progression of proteinuria in patients with hypertension and chronic renal disease when coupled with a renin–angiotensin system inhibitor.[95] However, the CARTER study found that the antiproteinuric effect of cilnidipine did not significantly differ from that of amlodipine in the diabetic subgroup of patients with macroproteinuria. In the same way, the SAKURA study did not find that cilnidipine was superior to amlodipine for the treatment of albuminuria in hypertensive patients with early-stage diabetic nephropathy.[96] Nevertheless, in another trial, cilnidipine was again shown to be superior to amlodipine in preventing the progression of proteinuria in hypertensive patients, even after undergoing treatment with renin–angiotensin system inhibitors.[97]

Compared with amlodipine, benidipine enhanced the maximum recommended dose of ARBs (80 mg telmisartan daily and 40 mg olmesartan daily) while reducing albuminuria and plasma aldosterone levels over a 6-month study period, independent of its BP-lowering effect.[98,99] An open-labeled randomized trial compared the effects of benidipine with cilnidipine in hypertensive patients with CKD. The patients who were already being treated with ARBs received benidipine or cilnidipine. After 12 months of treatment, a significant and comparable reduction in SBP and DBP in both groups was observed. The urinary protein:creatinine ratio was significantly decreased in both groups after 3 months of treatment and thereafter; however, the difference between groups was not significant after 12 months of treatment. Benidipine exerted an antiproteinuric effect to a greater extent than cilnidipine in patients with diabetes.[100] In another trial, benidipine treatment reduced the proteinuria in hypertensive patients with CKD, with the most significant percentage decrease of proteinuria observed in elderly patients.[101]

Thamcharoen *et al.*[102] performed a meta-analysis on the effect of N- and T-type CCBs on proteinuria, BP and kidney function in hypertensive patients. They searched for single-arm studies and RCTs that examined the effect of L/N- and L/T-type CCBs as an add-on therapy, compared with a 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 outcomes of interest. Seventeen RCTs were found, representing 1905 patients treated with benidipine, azelnidipine or cilnidipine. By meta-analysis, L/N- and L/T-type CCB add-on therapy did not yield significant changes in SBP or DBP compared with standard treatment, but there was a significant decrease in the pulse rate. However, L/N- and L/T-type CCBs resulted in a significant standardized net decrease in albuminuria and proteinuria, along with a standardized net improvement in the estimated GFR and serum creatinine. The conclusion was that despite no additional lowering effect on BP, L/N- and L/T-type CCBs combined with a renin–angiotensin–aldosterone system blocker provided a decrease in proteinuria and improvement in kidney function.

ENDING REMARKS

The enormous amount of information regarding the renoprotective effects of calcium antagonists is complex, and there are conflicting data coming from the reported trials. Nevertheless, the following conclusions can be drawn:

1. The use of CCBs in hypertensive patients with renal disease is safe and has no deleterious effects on renal function.

2. CCBs may be better than diuretics and beta-blockers at protecting renal function against hypertension.
3. Renin–angiotensin axis-blocking drugs are more effective than CCBs at reducing proteinuria.
4. The combination of CCBs and renin–angiotensin axis-blocking drugs may be beneficial in improving the renoprotective effects of ACEI and ARBs administered alone.
5. Combining renin–angiotensin axis drugs with CCBs is better than a combination with diuretics for preserving renal function and reducing cardiovascular morbidity.
6. New-generation CCBs, with vasodilator action on both afferent and efferent glomerular arterioles, may have interesting renoprotective effects, as suggested by some recent reports.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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