

<b>MHR</b>	<p>N. R. ROBLES [2006] MED HYPOTHESES RES 3: 709-725.</p> <p style="text-align: center;"><b>CALCIUM ANTAGONISTS AND RENAL FAILURE: NEW PROPERTIES FOR NEW GENERATIONS</b></p> <p style="text-align: center;">NICOLÁS ROBERTO ROBLES*</p> <p style="text-align: center;">SERVICIO DE NEFROLOGÍA, HOSPITAL INFANTA CRISTINA, BADAJOZ, SPAIN</p>	<b>• MEDICAL HYPOTHESES AND RESEARCH • THE JOURNAL FOR INNOVATIVE IDEAS IN BIOMEDICAL RESEARCH •</b>
<b>REVIEW</b>	<p><b>ABSTRACT.</b> CALCIUM ANTAGONISTS are first-line antihypertensive agents but their effects in patients with chronic renal diseases have not been clearly defined. The available information concerning the renoprotective effects of calcium antagonists is complex in view of the conflicting data coming out of various clinical trials. Based on a critical review of the available literature, some conclusions are drawn here. (i) Use of calcium antagonists in hypertensive patients with renal disease is safe and has no deleterious effects on renal functions. (ii) Calcium antagonists may be better than diuretics and <math>\beta</math>-blockers to protect renal function against hypertension. (iii) Renin-angiotensin axis-blocking agents are more effective than calcium channel blockers to reduce proteinuria and to prevent renal disease progression. (iv) The combination of calcium antagonists and renin-angiotensin axis-blocking agents may be beneficial to improve renal protective effects of ACE inhibitors or angiotensin receptors blockers when administered singly. (v) As suggested in some recent reports, the new-generation calcium antagonists, which have the property of vasodilator action on both afferent and efferent glomerular arterioles, may have interesting renal protective effects. More clinical studies will be needed to confirm this possible beneficial effect.</p> <p>*ADDRESS ALL CORRESPONDENCE TO: DR. NICOLÁS ROBERTO ROBLES, SERVICIO DE NEFROLOGÍA, HOSPITAL INFANTA CRISTINA, CARRETERA DE PORTUGAL S/N. 06070, BADAJOZ, SPAIN. E-MAIL: <a href="mailto:nroblesp@senefro.org">nroblesp@senefro.org</a></p>	

## 1. INTRODUCTION

Following the results of the INSIGHT study [1], the recent publications of the final results of the ALLHAT [2] and the INVEST studies [3] have consolidated the position of long-acting calcium antagonists as first-line antihypertensive agents. With the volume of supportive evidence from other randomized clinical outcome trials, including Syst-Eur [4], STOP-2 [5] and NORDIL [6], and also the Syst-China [7] and STONE [8] trials, there is a consistent message from all of these trials indicating that treatment by calcium channel blockade reduces cardiovascular morbidity and mortality in hypertensive patients, including those with significant coronary artery disease and post-myocardial infarction.

In terms of clinical pharmacology and therapeutic applicability, there are fundamental differences between the dihydropyridine group of calcium antagonists (its prototype, nifedipine) and other commonly-used calcium antagonists, namely, verapamil and diltiazem. Both verapamil and diltiazem have direct effects on cardiac contractility and conduction, and often are described as "rate-limiting" because of their shared tendency to reduce heart rate. This feature alone sets them apart from the dihydropyridine group, to the extent that calcium antagonists should not be discussed as if they constituted a homogeneous group [9].

Of even greater importance (because they are less well-recognized and often ignored) are the significant differences between agents within the dihydropyridine group. The development of new dihydropyridine calcium antagonists (numerically the most important group) has largely been focused upon the synthesis of alternative derivatives (with longer elimination half-lives) and the use of modified release formulations. As a general consequence, the pharmacodynamic profile of these newer dihydropyridine calcium antagonists, particularly the duration of action, has been determined by the following pharmacokinetic characteristics: First, an extended elimination half-life: this is 'intrinsic' in the case of amlodipine with its plasma half-life of approximately 40 h. Second, an 'apparent' increase in elimination half-life in asso-

ciation with modifications in the release characteristics of the drug formulation, e.g., nifedipine GITS (gastrointestinal therapeutic system), felodipine ER (extended release). Third, an increased degree of membrane binding in the case of the 'lipophilic' dihydropyridine calcium antagonists (e.g., lacidipine and lercanidipine), which have relatively short plasma half-lives but longer durations of action, attributed to a high membrane partition coefficient [10].

Since hypertension is a major determinant of progression of renal disease, irrespective of cause, and the relative risk of developing end-stage renal disease in hypertensive patients (compared with that of patients with "optimal" BP) increases 3-fold when diastolic BP increases to 90 mmHg [11], this article seeks to highlight these differences, with particular emphasis on the renal protective effects of calcium channel blockers. Although tighter BP control is considered the main mechanism for preventing from the progression of chronic renal failure [12,13], some antihypertensive agents, such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), seem to have an additional organ protective role and are routinely used in hypertensive patients with renal disease [10]. The effects of calcium antagonists in renal disease are not so clearly defined and will be discussed here.

## 2. EXPERIMENTAL RENOPROTECTIVE MECHANISM OF CALCIUM ANTAGONISTS

Multiple mechanisms of action of calcium antagonist might contribute to protect the kidney against hypertension. Besides glomerular hemodynamic factors (discussed below), calcium antagonists have been demonstrated to modulate macromolecular traffic through mesangium and attenuate mesangial entrapment of macromolecules which induce inflammatory and proliferative responses [14,15].

It has also been suggested that calcium antagonists may act to counteract the mitogenic effect of platelet-derived growth factor and platelet-activating factor which appear to play an impor-

tant role in renal damage caused by hypertension [12]. Similarly, calcium antagonists suppress mesangial cell proliferation by inhibiting activator protein-1 (AP-1) [16] as well as cell cycle transition from the G<sub>1</sub> to S phase [17], and modulate gene transcription involved in pro-inflammatory changes (interleukin-1 $\beta$  and granulocyte/monocyte colony-stimulating factors) [18]. In this regard, calcium antagonists have been shown to suppress the PMA-induced activation of nuclear factor kappa B in cultured human mesangial cells [19].

Finally, calcium antagonists could act as free radical scavengers [20,21]. Calcium antagonists could affect intracellular reactive oxygen species at least in three different ways. (i) They may reduce the resources of certain intracellular free radicals, such as by inhibiting the activity of NADPH oxidase, xanthine oxidase, and cyclooxygenase which are dominant contributors of the intracellular reactive oxygen species [22]. (ii) Calcium channel blockers may decrease intracellular free radical concentrations through their direct antioxidant activity. By using the crocin bleaching test, vitamin E was only twice as active as lacidipine in scavenging free radicals generated either by reductive decomposition of tert-butyl hydroperoxide or by thermal decomposition of a diazo compound [23]. (iii) Calcium antagonists may protect the targets of free radicals. Lacidipine was found to reduce the expression of ICAM-1, VCAM-1 and eselectin induced by TNF- $\alpha$  and inhibit the synergistic effect of oxidized LDL on TNF- $\alpha$ -induced adhesion molecule expression. This effect on adhesion molecules may be attributed to its effect on nuclear factor kappa  $\beta$  and hence on the signalling pathways leading to its activation [24].

Last, the inhibition of the renal effects of endothelin by calcium channel blockers has been experimentally demonstrated [25]. Endothelin-1 is a potent vasoconstrictor that has been implicated in the pathogenesis of kidney disease [26] and animal models of hypertension [27,28]. It is, therefore, of considerable interest to observe that endothelin preferentially reduced blood flow in the renal cortex, without meaningful reduction in renal medullary blood flow, in anaesthetized rats [29] and dogs [30]. Furthermore, treatments that reduce re-

nal medullary blood flow, such as blockade of renal medullary nitric oxide synthesis and medullary interstitial infusion of a vasopressin V1 agonist, cause hypertension if administered chronically, and attenuate the blood-pressure lowering mechanisms in the kidney [31,32]. This phenomenon may have important implications in the pathological conditions associated with increased circulating or local intrarenal levels of endothelin. These conditions include acute and chronic renal failures [26], advanced atherosclerosis [33], and perhaps also essential hypertension [34].

### 3. CHANGES IN RENAL VASCULATURE

ACE inhibitors and ARBs are reputed to minimize the hypertension-induced renal damage. These agents are reported to preserve or even increase renal blood flow in the face of reduction in systemic blood pressure, suggesting a rather renal selective action of these agents [35]. Several lines of investigations have documented that within the renal vasculature, calcium antagonists could cause a preferential dilation of the afferent arterioles, with only modest action on the efferent arterioles [36-38]. These effects are in contrast to those exerted by ACE inhibitors and ARBs, which are documented to elicit predominant vasodilation of the efferent arterioles, ameliorate glomerular hypertension, and afford renal protection [39,40]. Thus, it is inferred that whereas the depressor action of the calcium antagonists favors an attenuation of glomerular hypertension and the subsequent renal protection [41-44], the predominant activity of these agents on preglomerular vessels might cause glomerular hypertension that could eventually be associated with the progression of renal diseases [45-48].

The action of calcium antagonists varies depending on the agents used. Nifedipine, when administered into anesthetized dogs, caused a greater increase in glomerular filtration rate (GFR) than that in renal plasma flow (RPF), resulting in elevated filtration fraction [49-50]. Furthermore, other calcium antagonists including nicardipine and verapamil are reported to increase filtration fraction, suggesting predominant action on the afferent

arteriole [50-52]. In contrast, nicardipine and diltiazem are reported to have no effect on filtration fraction [53,54]. Kimura et al. suggested that nicardipine elicited preferential reduction in afferent arteriolar resistance in hypertensive patients, using renal function curves. In the *in vivo* settings described above, however, systemic blood pressure was decreased, which may affect glomerular perfusion pressure [55].

Using direct visualization of the juxtamedullary nephron circulation, it was shown that verapamil, diltiazem, and nifedipine each potently inhibited the afferent arteriolar vasoconstriction, whereas efferent arterioles were relatively refractory to the vasodilator action of these agents [36,56]. The isolated perfused rat kidney model which allows constant renal perfusion pressure with unaltered myogenic tone of renal microvessels, has produced similar results for nifedipine, nisoldipine, diltiazem, and amlodipine [37,57].

Collectively, these observations support the notion that the calcium antagonists act predominantly on the renal preglomerular vessels. In contrast, when administered in normotensive subjects, calcium antagonists appear to have only modest effect on renal hemodynamics [58,59]. These observations may bear on the issue that calcium antagonists may largely inhibit calcium channels that are activated by vasoconstrictors but they have little effect on unstimulated vessels.

#### 4. EVIDENCE FOR EFFERENT ARTERIOLAR DILATION BY NOVEL CALCIUM ANTAGONISTS

In contrast with this large amount of investigations suggesting that first and second generation of calcium antagonists have predominant action on preglomerular vessels, a growing body of evidence has been accumulated demonstrating that certain types of these agents may affect postglomerular as well as preglomerular vessels. The intravenous administration of manidipine caused a greater increase in RPF than that in GFR in spontaneously hypertensive rats (SHR), resulting in decreased filtration fraction [60]. Furthermore, nilvadipine is reported to increase RPF without any changes in

GFR in humans [61]. Finally, it has been reported that efonidipine potently increased RPF more markedly than GFR, causing a decrease in filtration fraction [62].

Furthermore, the assessment of renal arteriolar resistance with the use of renal function curves indicates an efferent arteriolar dilation by benidipine in human nondiabetic nephropathy [63]. Another calcium antagonist, manidipine, elicits both afferent and efferent arteriolar dilation [64,65]. Furthermore, Zhou et al. showed decreases in both afferent and efferent arteriolar resistance by cilnidipine in nitro-L-arginine methylester-treated SHR [66].

Hayashi et al. have demonstrated that several calcium antagonists, including manidipine, nilvadipine, benidipine and efonidipine, cause substantial dilation of efferent arterioles in isolated, perfused rat hydronephrotic kidney. In contrast, in the same preparation, both dihydropyridine-class (nifedipine, nicardipine, and amlodipine) and nondihydropyridine-class calcium antagonists (diltiazem) cause predominant dilation in afferent arteriolar [67-70]. Sabbatini et al. demonstrated the histological dilatation of efferent as well as afferent arteriolar lumen after 12 weeks of treatment with lercanidipine in spontaneously hypertensive rats [71].

The mechanisms for the efferent arteriolar vasodilation, however, remain undetermined. It has been suggested the role of nitric oxide and vasodilatory prostaglandins in mediating the efonidipine-induced efferent arteriolar dilation but neither nitro-L-arginine methylester nor indomethacin had any effect on efonidipine-induced efferent arteriolar vasodilation [72]. Hansen et al. have demonstrated that T-type calcium channels prevail at juxtamedullary efferent arterioles, as well as afferent arterioles of superficial and juxtamedullary nephrons [73]. It has been found that mibefradil decreased both afferent and efferent arteriolar resistance in SHR kidneys, using the micropuncture technique [74]. Efferent arteriolar dilation by some calcium antagonists which possess the blocking activity on T-type calcium channels has been showed, such as mibefradil, efonidipine, nilvadipine and aranidipine [75,76]. These novel findings therefore suggest a

critical role of T-type calcium channels in mediating the efferent arteriolar tone.

On the other hand, it is established that angiotensin II-induced vasoconstriction is mediated by two main intracellular signaling pathways, protein kinase C (PKC) and inositol-1,4,5-trisphosphate (IP<sub>3</sub>)-induced intracellular calcium release and this pathway constitutes an important target for the action of mibefradil during the angiotensin II-induced arteriolar constriction [77].

It has also been reported that T-type calcium channel activation stimulates renin release and that mibefradil suppresses renin release [78]. This observation raises the possibility that T-type calcium channel blockade inhibits the angiotensin II production, and therefore would be anticipated to contribute in part to the efferent arteriolar vasodilation.

#### 5. RENOPROTECTIVE EFFECT OF CALCIUM ANTAGONISTS IN ANIMALS

The glomerular hemodynamic effects of traditional calcium antagonists suggest that these antagonists fail to correct glomerular hypertension in certain experimental conditions [79,80]. The long-term effect of calcium antagonists on injured kidney is conflicting. Since the net effect of calcium antagonists on glomerular hemodynamics is determined by the balance between the reduction in afferent arteriolar resistance and the fall in systemic blood pressure, and the changes in these two factors may vary depending on the experimental settings, magnitude of depressor activity, or types of calcium antagonists used.

Thus, verapamil has been reported to reduce proteinuria and protect against renal injury in remnant kidney models [81]. Although Dworkin et al. demonstrated that nifedipine reduced both urinary protein excretion and glomerular injury in several "in vitro" models [80,82], there have been several reports suggesting a deleterious effect of dihydropyridine-class calcium antagonists in renal diseases [80,83]. It has been demonstrated that nitrendipine did actually increase proteinuria and glomerulosclerosis in two kidney one clip model of hyperten-

sion [84]. Furthermore, in another report, amlodipine did not exhibit renal protective action in DOCA-salt hypertensive rats [85]. Finally, felodipine impaired renal auto-regulation more markedly than verapamil or diltiazem, which tended to parallel the degree of glomerulosclerosis [86].

In contrast, the novel calcium antagonists, acting on both afferent and efferent arterioles, may correct glomerular hypertension, and could therefore exert salutary actions on the progression of renal injury as it has been shown with nilvadipine, efonidipine and manidipine in SHR rats [87-89]. An 8-week-treatment with calcium antagonists, including nicardipine, amlodipine, efonidipine, pranidipine, lercanidipine and aranidipine reduced BP and prevented the progression of renal injury in subtotal nephrectomized SHR. Furthermore, the histopathological changes and serum creatinine levels were also ameliorated, but the effects of these agents on proteinuria differed. Thus, nifedipine tended to decrease urinary protein excretion, but lercanidipine, pranidipine and efonidipine significantly reduced proteinuria [57].

#### 6. EFFECTS ON THE PROGRESSION OF RENAL INJURY IN HUMANS

There is a large amount of information concerning the effects of calcium antagonists on human renal disease. Most of the reports have evaluated the changes on proteinuria or microalbuminuria. Those with a follow-up time longer than 12 weeks have been taken into account in this review, and this condition also excluded most of the comparisons against placebo. There is only one report on the renal effects of long-term treatment with nifedipine (N = 8; dosage 30 mg/day) in normotensive Type 1 diabetic patients with microalbuminuria (AER) compared with placebo (N = 7). In a randomized, double-blind clinical trial, nifedipine treatment caused a significant reduction of AER after 6 and 12 months. GFR was significantly decreased by nifedipine whereas RPF remained constant. Nifedipine treatment did not influence SBP or DBP, and no significant alterations of AER, GFR, RPF and arterial blood pressure were observed [90]. Also, the data from the SYST-EUR

TABLE 1. EFFECTS OF CALCIUM ANTAGONIST ON AER OR PROTEINURIA.

N	CALCIUM ANTAGONISTS	EFFECTS	ACE INHIBITORS / ARBS	EFFECTS	OBJECTIVES	LENGTH OF FOLLOW-UP	REFERENCES
453	Amlodipine	Small	Fosinopril	Decrease	AER	48 months	107
36	Amlodipine	No	Lisinopril	Decrease	AER	12 weeks	115
117	Amlodipine	No	Losartan	Decrease	Proteinuria	12 months	116
17	Amlodipine	Small	Temocapril	Decrease	Proteinuria	12 weeks	117
24	Amlodipine	No	Enalapril	Decrease	AER	60 months	118
48	Amlodipine	No	Losartan	Decrease	AER	12 weeks	119
332	Amlodipine	No	Valsartan	Decrease	AER	24 weeks	120
391	Amlodipine	No	Irbesartan	Decrease	AER	24 months	121
97	Amlodipine	No	Losartan	Decrease	Proteinuria	20 weeks	122
92	Nifedipine	No	Lisinopril	Decrease	Proteinuria	36 months	123
162	Nifedipine	Decrease	Lisinopril	Decrease	AER	24 weeks	124
30	Nifedipine	Decrease	Captopril	Decrease	Proteinuria	12 weeks	125
28	Nifedipine	No	Lisinopril	Decrease	AER	19 weeks	126
43	Nifedipine	Decrease	Perindopril	Decrease	AER	12 months	127
32	Nifedipine	No	Lisinopril	Decrease	AER	24 months	128
77	Nifedipine	No	Perindopril	Decrease	AER	12 months	129*
30	Nifedipine	No	Enalapril	Decrease	Proteinuria	12 months	130
102	Nifedipine	No	Enalapril	Decrease	AER	12 months	131
18	Nifedipine	Raise	Captopril	No	AER	12 months	132
335	Nifedipine	Small	Lisinopril	Decrease	AER	12 months	133
54	Nifedipine	No	Enalapril	No	AER	36 months	134
436	Nifedipine	No	Enalapril	No	AER	24 months	102
51	Nitrendipine	Decrease	Ramipril	Decrease**	AER	24 months	135
480	Nisoldipine	Decrease	Enalapril	Decrease	AER	64 months	136
158	Felodipine	Increase	Ramipril	Decrease	AER	24 months	105

\* Nevertheless, macroalbuminuria incidence was similar in both groups and rather less frequent than placebo at 72 months of follow-up.

\*\* Earlier effect.

study demonstrated a renal protective effect of calcium channel blockers compared with placebo in hypertensive patients. This study compared the changes in renal function in 2258 treated and 2148 untreated patients with isolated systolic hypertension, of whom 455 had diabetes mellitus and 390 had proteinuria. Active treatment was initiated with nitrendipine with the possible addition of enalapril, hydrochlorothiazide, or both. Serum creatinine and the creatinine clearance were not influenced by active treatment. However, in the patients assigned randomly to receive active treatment, the incidence of mild renal dysfunction (serum creatinine at least

176.8 mmol/L) decreased by 64% ( $P = 0.04$ ) and that of proteinuria by 33% ( $P = 0.03$ ) [91].

There are several reports on the protective effect of calcium antagonists when compared with diuretics. In the National Intervention Cooperative Study in Elderly Hypertensives, older hypertensive patients ( $\geq 60$  years of age) were assigned randomly to receive double-blind treatment with nicardipine ( $N = 204$ ) or trichlormethiazide ( $N = 210$ ). Over 4.3 years of follow-up, the blood urea nitrogen (BUN) increased by 0.35 mmol/L in the nicardipine group, and by 1.14 mmol/L in diuretic group ( $P = 0.07$ ). Fewer patients in the nicardipine group had the ab-

normally increased BUN concentrations (2.6% compared with 7.6%;  $P = 0.03$ ) [92]. Furthermore, in the SYST-EUR study, the serum creatinine concentration did not change in patients that continued to receive monotherapy with nitrendipine, whereas it was increased by 6.73 mmol/L ( $P < 0.001$ ) in patients that received hydrochlorothiazide alone or in combination with other study medication ( $P < 0.001$  for difference in trends) [91].

The results of the INSIGHT study suggest that antihypertensive treatment with nifedipine GITS also offers higher renal protective effect than thiazides [35]. It was a prospective, randomized, double-blind clinical trial in hypertensive patients aged 55–80. Patients were randomly assigned nifedipine GITS formulation ( $N = 3157$ ), or hydrochlorothiazide 25 g plus amiloride 2.5 mg ( $N = 3164$ ). The incidence of renal failure was higher in combination treatment group (4.6% vs 1.8%,  $P < 0.0001$ ) in spite of a similar BP levels through all the follow-up [93].

Amlodipine has been demonstrated to confer more substantial renal protective action than diuretics or ACE inhibitors when the systemic blood pressure is reduced to an optimal level [94]. The ALLHAT, a randomized, double-blind, active-controlled clinical trial, included a total of 33,357 participants randomly assigned to receive chlorthalidone ( $N = 15,255$ ), amlodipine ( $N = 9,048$ ), or lisinopril ( $N = 9,054$ ). The primary outcome was combined fatal CHD or nonfatal myocardial infarction, analyzed by intent-to-treat. Secondary outcomes did not include renal function but the final report contained substantial information about this item. Mean follow-up was 4.9 years. Five-year SBP was significantly higher in the amlodipine (0.8 mm Hg,  $P = 0.03$ ) and lisinopril (2 mm Hg,  $P < 0.001$ ) groups compared with chlorthalidone, and 5-year DBP was significantly lower with amlodipine (0.8 mmHg,  $P < 0.001$ ). For amlodipine vs chlorthalidone, GFR was similar at baseline (78.0 vs 77.6 mL/min), after the follow-up it was higher in amlodipine treated patients (75.1 vs 70.0 mL/min,  $P < 0.001$ ). For lisinopril vs amlodipine, lisinopril group also had a lower GFR (70.7 mL/min). Although lisinopril significantly differed from amlodipine in slowing the decay of renal function, the

better BP control in amlodipine-treated group may explain the better outcome when a calcium antagonist was used.

There is only one randomized study which compared the effects of verapamil with those of atenolol on the progression of diabetic renal disease. The primary end point of the study was a change in creatinine clearance slope. Thirty-four African Americans were randomized to one of the two groups. After a mean follow-up of  $54 \pm 6$  months, the calcium channel blocker group demonstrated both a slower rate of decline in creatinine clearance ( $-1.7 \pm 0.9$  vs  $-3.7 \pm 1.4$  mL/min per year,  $P < 0.01$ ) and a greater reduction in proteinuria. Additionally, a greater proportion of the atenolol group had a 50% or more increase in serum creatinine compared with the verapamil group ( $32 \pm 9\%$  vs  $16 \pm 7\%$ ,  $P < 0.05$ ). These between-group differences could not be explained by differences in blood pressure control [95].

## 7. CALCIUM ANTAGONISTS VS RENIN-ANGIOTENSIN AXIS-BLOCKING AGENTS

NONDIHYDROPIRIDINIC CALCIUM ANTAGONISTS. A randomized, open label, parallel group designed study tests the hypothesis that, at similar levels of blood pressure, the combination oftrandolapril with verapamil produces a greater reduction in proteinuria over either agent alone at one year. Thirty seven participants with Type 2 diabetes nephropathy completed the study. Proteinuria reduction was significantly greater in the combination group ( $-62 \pm 10\%$ ), compared to eithertrandolapril alone ( $-33 \pm 8\%$ ,  $P < 0.001$ ) or verapamil alone ( $-27 \pm 8\%$ ,  $P < 0.001$ ) in spite of that the mean daily dose of the combination was significantly lower than the dose of eithertrandolapril or verapamil alone [96].

More recently, the BENEDICT study failed to demonstrate any significant effect of verapamil to prevent from overt microalbuminuria. This was a multicenter double-blind, randomized trial designed to assess whether ACE inhibitors and verapamil, alone or in combination, prevent microalbuminuria in subjects with hypertension, Type 2

diabetes mellitus, and normal AER. One thousand two hundred and four subjects were randomly assigned to receive at least three years of treatment with trandolapril plus verapamil, trandolapril alone, verapamil alone or placebo. The primary end point (development of persistent microalbuminuria) was reached in 5.7% of the subjects receiving the combination, 6.0% of the subjects receiving trandolapril, 11.9% of the subjects receiving verapamil, and 10.0% of control subjects receiving placebo [97].

Again the PROCOPA study compared proteinuria reduction when BP was lowered at the same level with calcium antagonists and ACE inhibitors. It was a prospective, randomized, double-blind, controlled trial which includes 119 patients with primary renal disease. Patients were randomized to atenolol, trandolapril, verapamil, or verapamil + trandolapril combination. Treatment duration was 6 months. BP was significantly reduced with the four treatments without differences between them. A significant fall in proteinuria was seen in the trandolapril (40.2%) and verapamil + trandolapril groups (48.5%) meanwhile atenolol and verapamil alone could not get any reduction in this variable ( $P < 0.04$ ) [98].

The TRAVEND study compare, at equal BP reduction, the effect of two different combinations on metabolic control and albuminuria in Type 2 diabetic hypertensive patients with albuminuria (93 of the patients completed the study). Patients were randomized to receive verapamil + trandolapril or to enalapril + hydrochlorothiazide. Treatment duration was 6 months. Overall BP was significantly reduced ( $P < 0.001$ ), and albuminuria was significantly decreased from  $508.6 \pm 693.8$  mg/24 h to  $253.4 \pm 517.2$  mg/24 h ( $P < 0.001$ ) in both treatment groups, which were not significantly different from each other [99]. Thus, verapamil did not enhance antiproteinuric effect of the ACE inhibitor.

Furthermore, it has been reported that verapamil may improve renal function in hypertensive patients that the renal function was impaired by the previous use of ACE inhibitors [100-101].

In spite of the promising initial results, verapamil has not shown any unique ability to reduce proteinuria per se when compared with renin-

angiotensin axis-blocking drugs.

**DIHYDROPIRIDINIC CALCIUM ANTAGONISTS.** There are large numbers of reports on the antiproteinuric or antimicroalbuminuric effects of dihydropyridinic calcium antagonists in comparison with ACE inhibitors or angiotensin receptor blockers. The trials that followed up longer than 12 weeks are listed in TABLE 1. Taken altogether, the conclusion is clearly unfavourable to calcium channel blockers, with renin-angiotensin axis-blocking drugs having higher antiproteinuric effect.

There were fewer trials about the long-term protective effect of calcium antagonists on renal function and the results seem to be discouraging. The African American Study of Kidney Disease (AASK) showed striking results. This trial compared the effects of 2 levels of BP control and 3 classes of antihypertensive drugs on GFR decline in hypertensive patients. A total of 1094 African Americans aged 18 to 70 with hypertensive renal disease were recruited and followed up for 3 to 6.4 years. None of the drug groups that were compared showed consistent significant differences in the GFR slope. However, when compared with the metoprolol and amlodipine groups, the ramipril group manifested risk reductions in the clinical composite outcome by 22% ( $P = 0.04$ ) and 38% ( $P = 0.004$ ), respectively. Amlodipine significantly increased proteinuria compared with metoprolol and ramipril. Although AASK is the largest and longest clinical trial of dihydropyridinic calcium antagonists for their renoprotective actions, the results should be viewed with caution. First, African American people are a special population highly prone to renal failure with a distinct response to cardiovascular drugs as shown in the ALLHAT study. Second, other shorter trials have not demonstrated such deleterious effects on proteinuria [102].

The ESPIRAL study investigated the capacity of fosinopril ( $N = 127$ ) and of nifedipine GITS ( $N = 112$ ) to modify the decay in renal functions in hypertensive patients with primary renal disease and exhibiting a progressive increase in serum creatinine levels. It was designed as a randomized, open-label, multicenter study. The primary end-point of the study was the appearance of a doubling

of the serum creatinine levels and/or the need to enter a dialysis programme. After 3 years of follow-up, 27 patients treated with fosinopril, and 40 of those receiving nifedipine GITS presented a primary end-point ( $P < 0.01$ ). Renal survival was significantly better when fosinopril was the first step therapy ( $P = 0.002$ ). Proteinuria was decreased at the end of the study by a mean of 57% in the fosinopril group and increased by 7% in the group receiving dihydropyridine. DBP control did not differ among groups. However, the patients receiving an ACE inhibitor showed a decrease of SBP values by  $4 \pm 6$  mmHg. Although fosinopril significantly differed from nifedipine GITS with regard to its capacity to slow down the progressive decay in renal functions, the better BP control in the fosinopril group could have to a better clinical outcome [103].

The J-MIND study was conducted to evaluate the effect of nifedipine retard or enalapril on nephropathy in hypertensive patients with Type 2 diabetes. A total of 436 patients with normoalbuminuria or microalbuminuria were randomized to receive nifedipine retard or enalapril and were followed for 24 months. Intent-to-treat analysis showed no significant difference in microalbuminuria after 2 years, although the mean AER rate increased to 64 and 74 mg/day in the nifedipine retard and enalapril groups, respectively. There were no differences between the two groups with respect to progression from normoalbuminuria to microalbuminuria, progression from microalbuminuria to overt proteinuria, and regression from microalbuminuria to normoalbuminuria. The incidence of cardiovascular events was also similar in both groups. In conclusion, nifedipine retard and enalapril had a similar effect on nephropathy in hypertensive Type 2 diabetic patients without overt proteinuria [104].

Some studies have compared the possible beneficial effects of combining calcium antagonists and renin-angiotensin axis-blocking drugs for treating hypertension but the published results are, nevertheless, conflicting and inconclusive. Combination therapy of ramipril and felodipine was tested in the NEPHROS trial. It was an open-label, long-term randomized prospective multicenter study designed to compare the combination of ramipril and

felodipine with either drug alone in non-diabetic renal disease. Included in this study were patients with uncontrolled hypertension following treatment with a diuretic and a  $\beta$ -blocker. Fifty-one patients received the combination, 54 patients ramipril, and 53 patients felodipine. The reduction in BP was 19.0/14.5, 14.3/15.0 and 13.5/13.3 mmHg, respectively, in the combination, ramipril, and felodipine groups. The combination group had a slower progression rate of the renal disease compared with the felodipine group ( $P < 0.05$ ), but not with 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 combination of an ACE inhibitor and a calcium antagonist could be due to a better BP reduction [105].

Shigihara et al. examined the effects of a combination therapy using an ACE inhibitor plus amlodipine, and compared their effects with an ACE inhibitor alone under intensive BP control (DBP  $< 80$  mmHg) in hypertensive, Type II diabetic patients with positive microalbuminuria. Thirty hypertensive patients were treated with either an ACE inhibitor alone ( $N = 17$ ) or an ACE inhibitor plus amlodipine ( $N = 13$ ) for 32 weeks. BP in both groups was significantly reduced, and DBP was lowered to a much greater extent in combination group ( $P < 0.05$ ). The AER decrease attained statistical significance only in combination group ( $P < 0.05$ ). In conclusion, this study showed that in hypertensive microalbuminuric Type II diabetic patients, the combination of an ACE inhibitor plus amlodipine resulted in a more pronounced decrease in BP and a greater reduction in AER than the use of an ACE inhibitor alone [106].

Fogari et al. compared the long-term effect of amlodipine and fosinopril in monotherapy or in combination on AER in hypertensive diabetic patients. They selected hypertensive patients with Type 2 diabetes and microalbuminuria, and they were randomized into groups receiving amlodipine, fosinopril, or amlodipine plus fosinopril for a 3-month titration period. Three hundred and nine patients were enrolled in the trial and treated with the same therapy for 4 years. 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 AER 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 single drugs. This could be due to the greater antihypertensive effects of the drugs [107].

The REIN 2 study was a multicenter, randomized controlled trial of patients with non-diabetic proteinuric nephropathies receiving background treatment with ramipril. Participants were randomly assigned either conventional (diastolic <90 mmHg; N = 169) or intensified (systolic/diastolic <130/80 mmHg; N = 169) blood-pressure control. To achieve the intensified blood-pressure control, patients received add-on therapy with felodipine. The primary outcome measure was time to end-stage renal disease over 36 months of follow-up. Over a median follow-up of 19 months, 23% of patients assigned to intensified blood-pressure control and 20% of those allocated to conventional control progressed to end-stage renal disease ( $P = 0.99$ ). Throughout the study, the urinary protein excretion was similar in both groups. The main conclusion was that no additional benefit from further blood pressure reduction by felodipine was shown in patients with non-diabetic proteinuric nephropathies that received background ACE-inhibitor therapy [108].

**COMPARISON BETWEEN CALCIUM ANTAGONISTS.** Boero et al. tested whether the combination of verapamil or amlodipine with trandolapril affected proteinuria differently from trandolapril alone in patients with nondiabetic nephropathies in a double-blind fashion. Patients were followed up for 8 months. Proteinuria diminished significantly after trandolapril treatment. In the randomized phase, there was a slight reduction in proteinuria in both groups without significant differences within and between treatments [109].

In a small prospective randomized study, 14 patients with Type II diabetes mellitus, hypertension, proteinuria, and renal insufficiency were given either isradipine (N = 7) or nifedipine XL (N = 7) for

6 months. After a 2-week washout period, patients were crossed over to the other drug and observed for additional 6 months. At the end of the initial and crossover treatment periods, there were no significant reductions in the level of albuminuria from baseline with either drug [110].

**NEW CALCIUM ANTAGONISTS.** Although there are only few reports concerning the clinical renal effects of new calcium antagonists, these studies have projected promise. Bellinghieri et al. compared the effects of manidipine and nifedipine on blood pressure and renal functions. One hundred and one hypertensive patients with chronic renal failure were randomly assigned to receive either manidipine 20 mg daily or nifedipine 60 mg daily, respectively. Significant reduction in SBP ( $P < 0.001$ ) and DBP ( $P < 0.001$ ), compared to the baseline values, was reached in both treatment groups. Creatinine blood levels ( $P < 0.05$ ) and creatinine clearance ( $P < 0.01$ ) were significantly increased in the manidipine group. Proteinuria was not significantly changed in the manidipine group but was increased in the nifedipine group ( $P < 0.05$ ) [111].

Del Vecchio et al. [112] conducted a multicenter, prospective, randomized, double-blind, parallel group study to evaluate the efficacy and tolerability of manidipine in comparison with enalapril in the treatment of hypertension in 136 patients with chronic renal disease secondary to primary renoparenchymal disease. During a 48-week follow-up, mean BP was decreased from 155/100 to 139/86 mmHg in manidipine group and from 157/100 to 134/85 mmHg in enalapril group. Proteinuria remained unchanged with manidipine (from  $1.6 \pm 1.59$  to  $1.62 \pm 1.79$  g/24 h), but it was significantly decreased with enalapril (from  $1.37 \pm 1.45$  g/24 h to  $1 \pm 1.55$  g/24 h). No significant difference was observed in the rate of renal function decline in the two groups.

The DIAL (Diabetes Ipertensione Albuminuria Lercanidipina) evaluated the effectiveness of lercanidipine (10-20 mg/day), in comparison with ramipril (5-10 mg), on the reduction in AER and BP in mild-to-moderate hypertensive patients with Type 2 diabetes and persistent microalbuminuria. One hundred and eighty patients were enrolled in a multicentric, randomized, double-blind, active-

controlled, parallel-group trial and randomized to receive of lercanidipine or ramipril. After 9-12 months of follow-up, a reduction in AER of  $17.4 \pm 65 \mu\text{g}/\text{min}$  ( $P < 0.05$ ) and  $19.7 \pm 52.5$  ( $P < 0.05$ ) in the lercanidipine and ramipril group, respectively, was observed, without difference between the groups [113].

More recently, the ZAFRA study has shown a positive effect on proteinuria of the combination of the new calcium channel blocker lercanidipine and renin-angiotensin axis-blocking drugs. The study recruited 203 chronic renal failure patients. All patients received an ACE inhibitor (63.4%) or an angiotensin II receptor antagonist (36.6%) but they had blood pressure higher than 130/85 mmHg. BP was significantly decreased from  $162 \pm 17 / 93 \pm 8.3$  mmHg to  $132 \pm 12 / 78 \pm 6$  mmHg. Plasmatic creatinin did not change ( $1.9 \pm 0.5$  baseline vs  $1.9 \pm 0.6$  mg/dL) but creatinine clearance measured by 24 h urine collection increased ( $41.8 \pm 16.0$  mL/min baseline vs  $45.8 \pm 18.0$  mL/min,  $P = 0.019$ ). Proteinuria diminished significantly at the end of the follow-up ( $2.8 \pm 2.8$  vs baseline,  $3.5 \pm 3.2$  g/day,  $P = 0.0155$ ). This was the only report on antiproteinuric effects of new calcium antagonists and suggested interesting properties compared with previously published results with classic calcium channel blockers [114].

Therefore, the new-generation calcium antagonists appear to have experimental and clinical renoprotective effects although there is only small amount of information available on this subject.

## 8. CONCLUSION

The available information concerning the renoprotective effects of calcium antagonists is enormous and complex in view of the conflicting data coming out of many clinical trials. Nevertheless, some conclusions can be drawn. First, use of calcium antagonists in renal disease hypertensive patients is safe and has no deleterious effects on renal function. Second, calcium antagonists may be better than diuretics and  $\beta$ -blockers to protect renal function against hypertension. Third, renin-angiotensin axis-blocking agents are more effective

than calcium channel blockers to reduce proteinuria and to prevent from renal disease progression. Fourth, the combination of calcium antagonists and renin-angiotensin axis-blocking drugs may be beneficial to improve renal protective effects of ACE inhibitors and ARBs administered alone. Fifth, new generation calcium antagonists, with the property of vasodilator action on both afferent and efferent glomerular arterioles, may have interesting renoprotective effects, as suggested by some recent reports. More clinical trials will be needed to confirm this possible effect.

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