Calcium Channel Blockers and Renal Protection: Insights from the Latest Clinical Trials

Julián Segura, José A. García-Donaire, and Luis M. Ruilope
Hypertension Unit, Hospital 12 de Octubre, Madrid, Spain

Calcium channel blockers have been widely used in clinical practice because of their antihypertensive capacity. Prevention of renal damage is a very important aim of antihypertensive therapy. This is particularly so taking into account the high prevalence of chronic kidney disease (CKD) in the general population. Recent data have shown that CKD is related to the absence of adequate BP control and also to the clustering of other cardiovascular risk factors seen in the metabolic syndrome. The knowledge of the capacities of the different antihypertensive drugs or their combinations to simultaneously control BP while protecting the kidney and avoiding the facilitation of metabolic alterations is warranted. Recent data from the Intervention as a Goal in Hypertension Treatment trial, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, and African American Study of Kidney Disease and Hypertension (AASK) allow the conclusion that in hypertensive patients with preserved renal function or with CKD, calcium channel blockers are effective antihypertensive drugs to be considered alone or in combination with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker.

Calcium channel blockers (CCB) are widely used for the treatment of cardiovascular disease, particularly angina pectoris, arrhythmias, and arterial hypertension. Their beneficial effects are related to systemic vasodilation caused by the inhibition of the inward flow of calcium ions through the L-type calcium channels in the cell membrane. Three main classes of CCB are in current use: The benzo thiazepines (diltiazem), phenylalkylamines (verapamil), and dihydropyridines (nifedipine, amlodipine, and others).

A growing interest in the investigation of renal function in big trials that deal with different aspects of cardiovascular disease has developed in recent years. This is justified by different reasons, including the high prevalence of nephrosclerosis as a cause of ESRD (1) and the capacity of minor alterations of renal function to predict a poor outcome for the patients (2). The finding of a small increase in serum creatinine values, a diminished estimated GFR (<60 ml/min per 1.73 m²), microalbuminuria, and/or proteinuria heralds a significant elevation in cardiovascular events and death as well as in total mortality (2,3). These alterations are frequent in the hypertensive population and are related to an inadequate BP control and also to the clustering of other associated risk factors, particularly those seen in the metabolic syndrome (2–4).

The elevated prevalence of albuminuria and/or a diminished renal function in the general population in United States (5) and in the hypertensive population, in particular in patients who present with high BP and metabolic syndrome. This necessity is related to the potential capacity of these drugs to worsen the metabolic profile of the hypertensive patient, leading to an increase in the development of diabetes during the chronic administration of certain antihypertensive agents, thus facilitating further renal damage and cardiovascular risk (6).

CCB and Renal Protection in Recent Trials in Hypertensive Patients

Two recently published trials in which different antihypertensive agents were compared have shown that CCB could be particularly positive for the long-term maintenance of GFR levels when compared with a diuretic and with an angiotensin-converting enzyme (ACE) inhibitor. These were the Intervention as a Goal in Hypertension Treatment trial (INSIGHT) and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (7,8).

The INSIGHT study randomized 6321 hypertensive patients who had one or more associated risk factors to the dihydropyridine CCB, nifedipine gastrointestinal therapeutic system (GITS), or the diuretic combination hydrochlorothiazide/amilozide for the treatment of hypertension. BP control throughout the study was similar in both groups, with no statistically significant difference in the primary combined endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure. However, there was a small but significant decrease in estimated creatinine clearance during follow-up in the diuretic-treated patients compared with the one observed in those who received nifedipine GITS (7), suggesting that antihypertensive treatment that is based on a long-acting dihydropyridine may offer better renoprotection than therapy that is based on the diuretic combination co-amilozide.

The recent publication of the main results of the ALLHAT study also included the analysis of the changes observed in serum creatinine, slope of the reciprocal of serum creatinine,
and also estimated creatinine clearance (8). The results show that a 448 of 33,357 patients developed ESRD without significant differences among the three arms of the study. The slopes of the reciprocal of serum creatinine over time were virtually identical in the chlorthalidone and lisinopril groups, whereas the decline in the amlodipine slope was significantly less than that of the chlorthalidone arm. Finally, the estimated creatinine clearance exhibited a significantly better preservation in the amlodipine arm that had a final mean value of 75.1 ml/min, than compared with 70.0 and 70.7 ml/min in the chlorthalidone and lisinopril groups, respectively.

These results seem to differ from the available evidence indicating that the administration of an ACE inhibitor or an angiotensin receptor blocker (ARB) is required to protect renal function beyond the benefit obtained by BP control (9). The better evolution observed in both the slope of the reciprocal of serum creatinine and the estimated creatinine clearance with a CCB argues against recently published comparative studies in which an ACE inhibitor or an ARB were shown to be better than a CCB in primary renal disease, in type 2 diabetic nephropathy, and in black patients with nephrosclerosis (10–12).

**CCB, BP Control, and Renal Protection in the Presence of Preserved Renal Function**

The capacity of a CCB to protect the kidney in hypertensive patients seems to depend mainly on the capacity of these drugs to lower BP as shown by the analysis of renal data in the Systolic Hypertension in Europe study (13), which demonstrated that lowering BP with nitrendipine caused a significant reduction in proteinuria and renal insufficiency events in patients who were actively treated with nitrendipine compared with those who took placebo (13).

The maintenance of a strict BP control represents the most relevant means to maintain a preserved renal function in hypertensive patients. In fact, a recent publication indicated that a very strict BP control attained a similar degree of renal protection in patients with type 2 diabetes, matching the control attained with enalapril or with the CCB nisoldipine (14). A good control of systemic BP counteracts the risk for afferent arteriolar vasodilation induced by the CCB by impeding the transmission of a still elevated systemic BP (15). A CCB then can be renoprotective in the presence of a preserved GFR provided that micro- or macroalbuminuria is not present. If albumin excretion is elevated, then an ACE inhibitor or an ARB is required to obtain full protection of the kidney (16,17).

The ALLHAT study demonstrated a very good control of BP with final mean values for systolic/diastolic BP of 133.9/75.4, 134.7/74.6, and 135.9/75.4 mmHg for chlorthalidone, amlodipine, and lisinopril, respectively, and with 66% of patients achieving BP values <140/90 mmHg (8). Small but significant differences in the control of systolic BP were seen in favor of the chlorthalidone arm, which further favor the concept of a protective effect of amlodipine. It will be interesting to see how many cases of crossover to an ACE inhibitor performed in patients who received the diuretic or the CCB were due to the presence of a diminished renal function and whether this could have contributed to create some biases in the final results.

However, follow-ups longer than 5 yr are required to prove which is the most adequate antihypertensive therapy to maintain a preserved renal function.

**CCB, BP Control, and Nephroprotection in Patients with Established Chronic Kidney Disease**

According to recently published guidelines (16,17), the two main strategies to prevent progression of renal damage and to reduce cardiovascular risk in hypertensive patients with chronic kidney disease (CKD) are a strict BP control and the inhibition of the renin-angiotensin system. A strict BP control can be accompanied by reduction of proteinuria, but usually the fall in mean BP required to see a significant fall in proteinuria with practically any antihypertensive medication is >20 mmHg (18). However, recent data from the African American Study of Kidney Disease and Hypertension (AASK) study have shown that, in black patients, attained mean BP values of 128/78 mmHg did not differ from 141/85 mmHg in affording additional benefit of slowing the progressive fall in GFR values in hypertensive nephrosclerosis (12). This study suggests that in patients with nondiabetic renal disease, blockade of the renin-angiotensin system with either ACE inhibitor or ARB is superior to CCB in the progression of nephropathy in proteinuric patients. Amlodipine did seem to be equally effective as the ACE inhibitor when proteinuria was absent (12).

Data in proteinuric patients with type 2 diabetes obtained in the Irbesartan Diabetic Nephropathy Trial study (11) also showed that at equal BP levels, patients who received irbesartan showed a 20% risk reduction when compared with those who received placebo and a 23% risk reduction when compared with those who were treated with amlodipine. There was no difference between the amlodipine and placebo groups (11). The Reduction of Endpoints in Noninsulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan trial included a patient population similar to that investigated in Irbesartan Diabetic Nephropathy Trial, who were randomized to receive losartan or placebo. It is interesting that >80% of patients in both groups were treated adjunctively with CCB to achieve the goal of BP control (19). The positive effect of the ARB to halt the progression of renal failure was not jeopardized by the simultaneous administration of a CCB. Furthermore, the antiproteinuric effect of losartan was not abrogated by the presence of a CCB. Nondihydropiridined CCB have been shown to lead to a reduction in albuminuria or proteinuria, in particular when associated to an ACE inhibitor (20,21).

The data of the AASK (12) point to a positive effect on renal function of amlodipine in patients with nephrosclerosis without proteinuria. Such an effect must be attributed to the presence of a CCB. Nondihydropiridined CCB have been shown to achieve the goal of BP control (19). The positive effect of the ARB to halt the progression of renal failure was not jeopardized by the simultaneous administration of a CCB. Furthermore, the antiproteinuric effect of losartan was not abrogated by the presence of a CCB. Nondihydropiridined CCB have been shown to lead to a reduction in albuminuria or proteinuria, in particular when associated to an ACE inhibitor (20,21).

**Conclusions**

In hypertensive patients with or without CKD, CCB are excellent antihypertensive drugs. The presence of microalbu-
References


