

Antihypertensive treatment with calcium channel blockers and renal protection: focus on lercanidipine and lercanidipine/enalapril

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Abstract. – OBJECTIVE: The aim of the study was to review the literature on clinical pharmacology of lercanidipine and experimental and clinical evidence and evaluate its ability to reduce proteinuria and preserve renal function when used as monotherapy or in combination with the angiotensin-converting enzyme (ACE) inhibitor enalapril.

MATERIALS AND METHODS: MEDLINE/PubMed was searched for appropriate keywords.

RESULTS: Lercanidipine, a third-generation calcium channel blocker, has been shown to have a unique pharmacological and clinical profile, which translates into favorable renal hemodynamic changes. The fixed-dose combination lercanidipine/enalapril has been proposed to overcome unmet therapeutic needs, often as the initial treatment in the high-risk patient.

CONCLUSIONS: Lercanidipine may be regarded as an ideal antihypertensive drug for patients at renal risk and possibly the preferred choice among calcium channel blocker drugs.

Key Words:

Hypertension, Calcium channel blocker, Angiotensin-converting enzyme inhibitor, Fixed-dose combination, Renal protection, Lercanidipine.

Introduction

Ranging worldwide from 30% in the general population to more than double that in the elderly, hypertension is arguably a major modifiable risk factor for adverse cardiovascular complications, including stroke, acute coronary events, and chronic renal failure¹. On the other hand, pharmacologic treatment for hypertension, with several drug classes currently available for clinical use, has been shown to reduce the incidence of such complications effectively². Despite these

potential benefits, recent surveys indicate that overall blood pressure (BP) rates control are disappointingly low worldwide, thus contributing to a persistently high burden of hypertension-related diseases³.

Inadequate adherence to treatment, often related to the side effect profile of drugs and multiple daily prescriptions, is probably the most influential among the many factors that contribute to this unmet clinical need⁴. In an attempt to improve BP control and, therefore, reduce cardiovascular morbidity and mortality under real-life clinical conditions, European Guidelines currently recommend fixed-dose combination therapy, also as an initial choice, at least in patients at high cardiovascular risk who are unlikely to be controlled with monotherapy⁵.

Combination treatment has several potential advantages, such as improved antihypertensive efficacy due to the synergistic effect of drugs with a different mechanism of action, reduced side effects incidence thanks to lower doses administered, and easier therapeutic schedules. Although several fixed-dose combinations of antihypertensive drugs are available on the market, different associations of first-line drugs, i.e., renin-angiotensin-aldosterone system (RAS) inhibitors, calcium channel blockers (CCBs), and diuretics, are not always interchangeable, as they do not share similar tolerability and safety profile. Among the various combinations available, CCBs and angiotensin-converting enzyme (ACE) inhibitors have been proven effective while also displaying good tolerability².

The kidney is well known for being a major target organ of hypertension⁶. Systemic arterial hypertension is the second most common cause of end-stage kidney disease (ESKD), with dia-

betic nephropathy being the first. Furthermore, increased BP in patients with type 2 diabetes is a major contributor to the development and progression of kidney damage⁷. Pathophysiological studies^{8,9} suggest that the severity of such damage depends on the degree to which renal autoregulatory mechanisms fail to prevent the transmission of BP elevation to renal microvasculature. In fact, under normal physiologic conditions, autoregulatory vasoconstriction of the preglomerular resistance vessels, mainly the afferent arteriole, prevents transmission of systemic hypertension to glomerular microvasculature, thus maintaining constant renal blood flow, intraglomerular hydrostatic pressure, and ultimately preserving GFR (glomerular filtration rate) and avoiding hypertensive renal damage. In patients with chronic hypertension, both upper and lower thresholds of autoregulation are usually shifted to the right as a means of protective adaptation¹⁰. However, intrarenal resistance arteries and arterioles exposed to long-term hemodynamic stress progressively develop atherosclerotic changes leading to benign nephrosclerosis. An impairment of these protective mechanisms associated with a significant reduction in renal mass in patients with diabetic and nondiabetic chronic kidney disease (CKD) is likely to account for their increased susceptibility to progressive glomerulosclerosis even with a moderate increase in systemic BP. In addition, the consequent renal damage causes additional nephron loss and further strengthens the transmission of systemic hemodynamic load to the glomerulus.

Adequate BP reduction, with target values individually tailored to each patient's risk profile, is a prerequisite for adequate cardiovascular and renal protection¹¹. Furthermore, each antihypertensive drug's specific mechanism of action is of paramount importance for renal protection. To provide optimal blood perfusion to the kidney, the ideal drug should be able to lower systemic BP and favorably impact glomerular hemodynamics¹².

The combination of CCB and ACE inhibitors is particularly effective due to their complementary mechanisms, which provide antihypertensive efficacy with a low rate of side effects, such as peripheral edema and improved drug compliance. Findings from the ACCOMPLISH trial have demonstrated a distinct advantage of the CCB-ACE inhibitor combination in managing CV risk in obese and hypertensive patients¹³. These findings have formed the basis for developing drugs combining a CCB and angiotensin-axis

blocker. The fixed-dose combinations (single-pill) of lercanidipine 10 mg and enalapril 10 or 20 mg have been available in some European countries since 2006¹⁴.

Some scholars¹⁵ have compared the renal effects of CCBs with ACE inhibitors or angiotensin receptor blockers (ARBs). Overall, the antiproteinuric effect was higher for ACE inhibitors or ARBs compared with first- or second-generation CCBs, likely because these latter agents cause a preferential dilation of the glomerular afferent arteriole, with only modest action on the efferent arteriole¹⁶. In contrast, a growing body of evidence^{17,18} shows that the third-generation CCB may act on post- and pre-glomerular vessels. Among different third-generation CCBs, lercanidipine has been shown to dilate afferent and efferent renal glomerular arteries and protect smaller renal vessels from hypertensive damage¹⁵.

This narrative review will focus on the pharmacological and clinical profiles of lercanidipine and lercanidipine/enalapril combination and their renal effects on arterial hypertension.

Materials and Methods

The aim of the study to address the objective of this article, a review of the literature has been carried out. MEDLINE/PubMed was searched for appropriate keywords: lercanidipine, calcium channel blocker, angiotensin receptor blocker, and angiotensin-converting enzyme inhibitor. *In vitro* and *in vivo* preclinical studies, clinical studies, as well as reviews and meta-analyses, were retrieved; only articles in English or with English abstracts were considered. All retrieved articles were read and examined by authors. They were selected when relevant to the aim of the review; this selection was carried out based on the clinical and scientific expertise of the authors. A narrative review article was written, reporting published evidence and the expert opinion of the authors.

Clinical Pharmacology of Lercanidipine

Chemistry

Lercanidipine is a third-generation dihydropyridine calcium channel blocker (DHP-CCB) used in the form of hydrochloride. It is readily insoluble in water with elevated lipophilicity having a value of repartition coefficient (LogP) positive and higher than other CCBs (LogP = 6.42, Table I

Table I. Lipophilicity of dihydropyridine CCBs.

Drug	logP
Lercanidipine	6.42
Lacidipine	5.18
Amlodipine	2.22
Nitrendipine	3.21
Isradipine	3.00
Nimodipine	3.41

logP: octanol-water partition coefficient. Elaborated from ALOGPS39.

Lipophilicity of dihydropyridine CCBs). The lercanidipine has one chiral carbon atom. The S-enantiomer is more effective than the R-enantiomer, and marketed formulations contain a 1:1 mixture of both (i.e., the racemate). Thus, similarly to other asymmetric DHP, the antihypertensive action of lercanidipine mainly derives from its (S)-enantiomer (Figure 1).

Mechanism of Action

Like other dihydropyridine class CCBs, lercanidipine blocks L-type calcium channels in the smooth muscle cells of blood vessels, relaxing them and thus lowering BP. The high lipophilicity (LogP: 6.42) of lercanidipine compared to older DHPs (Table I) determines its binding to lipid membranes, prolonged interaction with the L-type calcium channel and a longer duration of action compared to other DHPs^{19,20}. Lercanidipine had the lowest negative inotropic efficacy compared to amlodipine and nifedipine²⁰. Moreover, lercanidipine acts differently from other DHP-CCBs by directly dilating both the afferent and the efferent glomerular arteries, with no changes in intraglomerular capillary pressure^{21,22}. This effect is likely due to the inhibition of the L-type and T-type calcium chan-

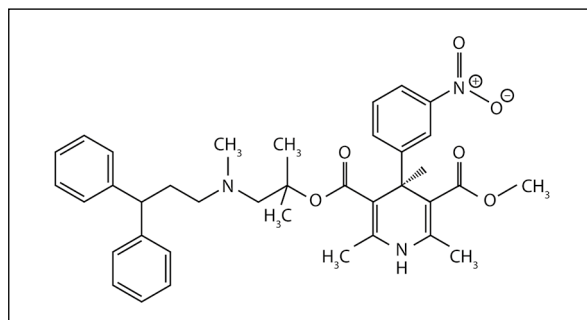


Figure 1. Chemical structure of (S)-lercanidipine. Source: https://pubchem.ncbi.nlm.nih.gov/compound/S_-Lercanidipine#section=2D-Structure⁴⁰.

nels at preglomerular and postglomerular renal levels, respectively. The third-generation DHP amlodipine has been proved to inhibit T-type calcium channels in postglomerular vessels^{23,24}. Among tested dihydropyridines, lercanidipine showed a very similar inhibitory potency on T and L-type calcium channels, while lacidipine is more selective on L-type and mibefradil (not more available for clinical use) is a specific T-type blocker (Figure 2)²⁵.

Pharmacokinetic Properties

Absorption

After oral administration lercanidipine is slowly but completely absorbed by the gastrointestinal tract. The drug undergoes extensive first-pass metabolism in the liver, and thus, its absolute bioavailability under fed conditions is around 10%. This value is further reduced to 1/3 when administered in fasting conditions. Since oral bioavailability of lercanidipine increases in the presence of high-fat meals, it should be taken before meals.

After oral administration of 10-20 mg of lercanidipine, the peak of plasma concentration is reached after 1.5-3 hours (T_{max} , Table II). A similar pharmacokinetic profile has been shown for the two enantiomers of lercanidipine, although the peak plasma concentration and AUC (area under the curve) are, on average, 1.2-fold higher for the (S) enantiomer.

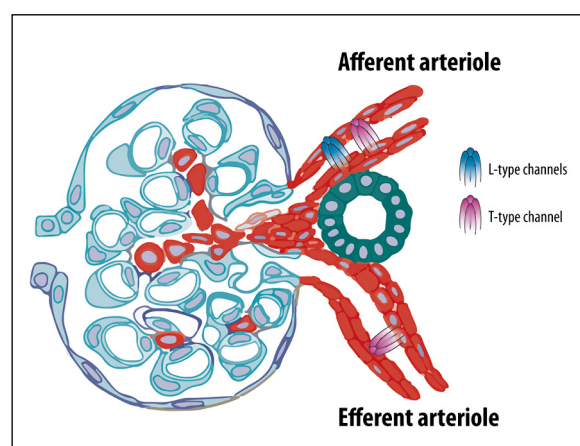


Figure 2. Ca T-type channels vs. Ca L-type channels selectivity ratio. LAC, lacidipine, AML, amlodipine; MIB, mibefradil; LER, lercanidipine; * $p < 0.05$, ** $p < 0.01$ vs. LAC (low concentrations); † $p < 0.01$ LAC vs. all other CCBs (high concentrations). Source: Cerbai et al²⁵ Reproduced from European Review for Medical and Pharmacological Sciences under a Creative Commons (CC BY-ND 4.0) license.

Table II. Pharmacokinetic parameters of lercanidipine.

Parameters	Assessment
Bioavailability	10% (due to first-pass effect)
Oral absorption	100%
T _{max}	1.5-3 hours
Protein binding	> 98%
Volume distribution	> 2 L/kg
Metabolism	Mainly CYP3A4
Elimination half-life	8-10 hours
Duration of action	> 24 hours
Excretion	In the urine, 50%

Source: Barchielli et al²⁶.

Distribution

Lercanidipine is rapidly and extensively distributed from plasma to peripheral tissues, although it is highly bound to serum proteins (>98%). Thus, the free fraction of the drug may increase in patients with severe renal or hepatic dysfunction due to lower plasma protein concentration.

Biotransformation

Lercanidipine is metabolized by CYP3A4, and no parent drug is found in the urine or the feces. It is mainly converted to inactive metabolites, and approximately 50% of the dose is excreted in the urine.

Elimination

Lercanidipine has a biphasic elimination profile with the first phase with an elimination half-life of 3-5 hours and the second of 10.5 hours. Elimination occurs essentially by biotransformation, and the mean terminal elimination half-life has been calculated to be 8-10 hours. Differently, the therapeutic activity lasts for 24 hours due to its binding to the lipid membrane. No accumulation has been seen upon repeated administration²⁶. The elimination half-lives are superimposable, and no *in vivo* interconversion of enantiomers has been observed.

Linearity/Nonlinearity

After oral administration, the plasma levels of lercanidipine are not directly proportional to the dose (non-linear kinetics). The ratio of peak plasma concentration was 1:3:8 after the dose of 10, 20, or 40 mg, respectively. Even more pronounced saturation of first-pass metabolism was observed with AUC with ratios of 1, 4 and 18 for 10, 20 and 40 mg of lercanidipine. Accordingly, the bioavailability increases with dosage (Table II)²⁶.

Drug-Drug Interactions

Lercanidipine shows an inhibitory action on CYP3A4 and CYP2D6 in experimental *in vitro* models with human liver microsomes. However, the reduction of enzymatic activity was observed at concentrations more than 40-fold higher than those reached at the peak in the plasma after the oral dosing of 20 mg.

In accordance, pharmacokinetic studies in humans demonstrated that lercanidipine did not modify the plasma levels of midazolam, a typical substrate of CYP3A4, or metoprolol, a typical substrate of CYP2D6. Thus, lercanidipine is not predicted to alter the pharmacokinetics of drugs metabolized by CYP3A4 and CYP2D6.

On the other hand, a strong CYP3A4 inhibitor, such as ketoconazole, increased the C_{max} of lercanidipine by eight folds and the AUC by 15 folds. Concomitantly, ciclosporin, a strong CYP3A4 inhibitor, increased lercanidipine plasma levels threefold when given simultaneously. Thus, other inhibitors of this enzyme, such as itraconazole, erythromycin, and grapefruit juice, are expected to increase plasma concentrations of lercanidipine and thus amplify the antihypertensive effect. Conversely, CYP3A4 inducers, such as carbamazepine, rifampicin, and St John's wort, are expected to lower the exposure and the effectiveness of lercanidipine. According to this evidence, lercanidipine should be avoided with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir, erythromycin, troleandomycin, clarithromycin) and should not be taken with grapefruit juice, a natural occurring CYP3A4 inhibitor.

Importantly, metoprolol, a β -blocker mainly eliminated by the liver, reduced the bioavailability of lercanidipine by 50%. This effect may be due to reducing the hepatic blood flow caused by

β -blockers. Consequently, lercanidipine may be safely administered with β -adrenoceptor blocking drugs, but dose adjustment may be required. On the other hand, lercanidipine does not interact with diuretics and ACE inhibitors; thus, its concomitant use is possible.

Differently from other DHP-CCBs, lercanidipine increased the plasma concentration of simvastatin. Indeed, when a dose of 20 mg of lercanidipine was repeatedly co-administered with 40 mg of simvastatin, the AUC of simvastatin and its active metabolite β -hydroxyacid increased by 56% and 28%, respectively. However, these changes are considered not clinically relevant.

Special Populations

In elderly patients and patients with mild to moderate renal dysfunction or mild to moderate hepatic impairment, the pharmacokinetic behavior of lercanidipine was similar to that observed in the general patient population. In patients with moderate to severe hepatic impairment, the systemic bioavailability of lercanidipine is likely to be increased since the drug is normally metabolized extensively in the liver²⁷.

Patients with severe renal dysfunction or dialysis-dependent patients showed higher levels (about 70%) of the drug, and the dosage should be reduced to avoid high plasma concentrations.

Recently, the carvedilol-lercanidipine drug interaction and the influence of CKD (in hypertensive patients with estimated glomerular filtration rate [eGFR] categories G3b to G5 ranging from 12 to 38 mL/min/1.73 m² (mean 26.5) on both drugs have been investigated²⁸. Lercanidipine pharmacokinetics was not enan-

tioselective and unaffected by carvedilol and CKD, thus supporting the rationale for its renal protection use.

Pharmacodynamic Properties

As previously described, despite its short pharmacokinetic plasma half-life, lercanidipine has a prolonged antihypertensive activity and is devoid of negative inotropic effects due to its high vascular selectivity. The high lipophilicity of lercanidipine provides a slow onset of action, long-lasting smooth muscle relaxation, and peripheral vasodilation. These findings show that lercanidipine is a long-acting CCB allowing for once-daily administration.

Due to the gradual vasodilatation induced by lercanidipine, acute hypotension with reflex tachycardia has rarely been observed in hypertensive patients. In addition, differently from CCBs verapamil and diltiazem, lercanidipine does not act on calcium channels in the atrioventricular node, and therefore, does not decrease heart rate²⁹.

Renal Protection with Lercanidipine: Experimental Studies

Lercanidipine vasodilates both the afferent and the efferent arterioles of the renal microvessels in a preclinical model of hypertensive rats (Table III)²¹. Lercanidipine administration prevented wall thickening and luminal narrowing in small-sized arteries and glomerular arterioles of Cohen-Rosenthal diabetic hypertensive rats (Figure 3)³⁰. Although through an indirect comparison, these results could have relevant clinical implications. It is well established that traditional DHP-

Table III. Measures of afferent and efferent arterioles in Wistar-Kyoto normotensive and spontaneously hypertensive rats upon different treatments.

Arteriole	WKY untreated	SHR untreated	SHR lercanidipine	SHR manidipine	SHR nifedipine	SHR hydralazine
Afferent arteriole						
Lumen area, μm^2	79.2 \pm 5.7	63.6 \pm 2.3*	79.1 \pm 3.4 [†]	78.8 \pm 2.4 [†]	79.2 \pm 5.7 [†]	64.7 \pm 2.5* ^{‡§}
Wall area, μm^2	91.6 \pm 4.5	96.6 \pm 5.1	91.1 \pm 5.2	91.6 \pm 4.8	91.9 \pm 7.6	95.7 \pm 4.1
Wall/lumen ratio	1.18 \pm 0.04	1.51 \pm 0.03*	1.16 \pm 0.07 [†]	1.16 \pm 0.03 [†]	1.18 \pm 0.10 [†]	1.48 \pm 0.03* ^{‡§}
Efferent arteriole						
Lumen area, μm^2	60.2 \pm 2.8	50.5 \pm 3.1*	60.0 \pm 3.3 [†]	59.7 \pm 1.1 [†]	50.2 \pm 2.0* ^{‡§}	49.7 \pm 1.7* ^{‡§}
Wall area, μm^2	121.4 \pm 5.1	146.2 \pm 6.7*	140.2 \pm 5.3*	141.4 \pm 2.0*	146.1 \pm 10.8*	146.7 \pm 4.3*
Wall/lumen ratio	2.03 \pm 0.06	2.93 \pm 0.08*	2.37 \pm 0.12* [†]	2.37 \pm 0.02* [†]	2.90 \pm 0.15* ^{‡§}	2.99 \pm 0.18* ^{‡§}

Lumen and wall areas in afferent and efferent glomerular arterioles of Wistar-Kyoto normotensive (WKY) and spontaneously hypertensive (SHR) rats, measured by quantitative image analysis, either exposed to antihypertensive drugs or not exposed. * $p < 0.05$ vs. WKY, [†] $p < 0.05$ vs. SHR, [‡] $p < 0.05$ vs. SHR treated with lercanidipine, [§] $p < 0.05$ vs. SHR treated with manidipine, [\] $p < 0.05$ vs. SHR treated with nifedipine. Source: Sabbatini et al²¹.

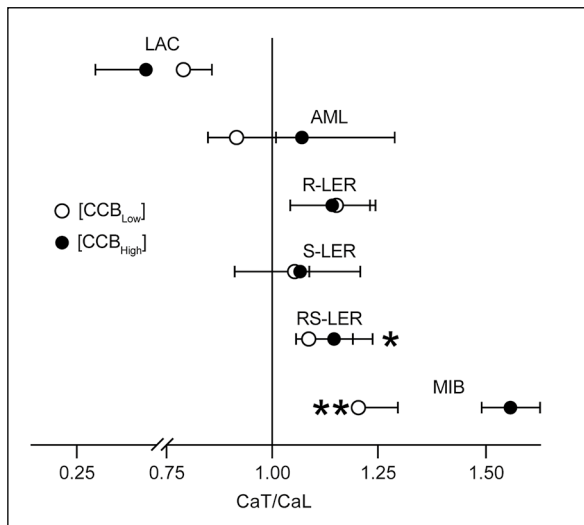


Figure 3. Image analysis of glomerular arterioles in Cohen-Rosenthal diabetic-hypertensive rats (CRDH) with and without lercanidipine. Reproduced from Rosenthal et al³⁰ under a Creative Commons license.

CCBs, including amlodipine, act predominantly on L-type calcium channels. The vasodilator response to L-type CCBs is observed only in afferent preglomerular microvessels with no effect on efferent arterioles in the renal vasculature. This determines an increase in glomerular capillary and intraglomerular pressure, proteinuria, and renal damage.

Conversely, lercanidipine, by vasodilating both the afferent and the efferent arterioles of the renal microvessels¹⁵, may correct glomerular hypertension and could therefore exert protective actions on the progression of renal injury. In nephrectomized spontaneously hypertensive rats (SHR), lercanidipine has been shown to reduce BP, prevent renal injury progression, and ameliorate histopathological changes and serum creatinine levels with a significantly reduced significantly proteinuria²⁴. A similar renal protection effect by lercanidipine was observed in a double-transgenic rat model overexpressing human renin and angiotensinogen genes³¹. Lercanidipine treatment prevented renal damage and mortality induced by angiotensin II. Compared to untreated rats, proteinuria decreased, and plasma creatinine levels were maintained in the normal range. Moreover, an anti-inflammatory and antifibrotic effect in renal vessels has been observed with reduced monocyte infiltration, extracellular matrix formation, and fibrosis, associated with improving nitric oxide (NO) bioavailability.

Indeed, lercanidipine was shown to inhibit protein kinase C and decrease asymmetric di-

methylarginine (ADMA) plasma concentration, an inhibitor of NO synthase, in rats overexpressing human renin and angiotensinogen genes with a concomitant higher availability of intracellular NO. These intracellular effects seem to be related to reducing intracellular calcium concentration²².

The third generation of CCB decreased glomerular pressure, the filtration fraction and proteinuria, with a nephroprotective effect similar to that exerted by inhibitors of the RAS¹⁶. The combination of these agents should provide complementary effects since CCBs and RAS inhibitors do not share the same mode of action as RAS inhibitors.

Indeed, an additional benefit has been observed in two studies^{18,32} when lercanidipine was combined with RAS inhibitors¹⁵. Thus, lercanidipine in fixed combination with enalapril has a strong rationale for controlling hypertension and hypertension-associated renal damage. Indeed, CCBs are potent vasodilators that induce reflex activation of the sympathetic system and the RAS system. As a result, ACE inhibitors may buffer this excessive activation. In addition, CCBs promote a negative sodium balance and an increase in angiotensin II levels, and for this reason, the inhibition of ACE may reinforce the antihypertensive effect. On the other hand, the concomitance of both treatments may reduce the incidence of adverse events, particularly peripheral edema, due to an increase in intracapillary pressure as a consequence of the selective reduction of precapillary arteriolar tone during calcium entry blockade. ACE inhibitors reduce the lower extremity edema caused by CCBs, likely because of their ability to dilate both the arterial vascular bed and the venous capacitance vessels³². Altogether, there is a strong rationale for combining lercanidipine with enalapril.

Renal Protection with Lercanidipine and Lercanidipine/Enalapril Combination: Clinical Studies

Several clinical studies have investigated the renal protective effect of lercanidipine or lercanidipine/enalapril (Table IV). In the Diabete Ipertensione Albuminuria Lercanidipina (DIAL) study, 277 patients with type 2 diabetes, mild to moderate hypertension, and persistent microalbuminuria were enrolled, and 180 of them were randomized to receive either lercanidipine (10-20 mg/day) or ramipril (5-10 mg/day). After a 9-12-month follow-up, lercanidipine reduced

Table IV. Clinical studies on the renal effects of lercanidipine as monotherapy or as an add-on on ACE-i/ARBs.

Author (Ref)	Study	Patients (n)	Treatments	Follow-up	Outcome
Dalla Vestra (2004) ³³	DIAL	277	Lercanidipine 10/20 mg vs. ramipril 5/10 mg	9-12 months	AER: -17.4 vs. -19.7 µg/min
Robles (2005) ³⁴	ZAFRA	203	Lercanidipine 10 mg + ACE-i or ARB	6 months	SBP/DBP: -30.4/-15 mmHg Prot: -0.7 g/die (-20%)
Robles (2010) ³⁵		68	Lercanidipine 20 mg + ACE-i or ARB	6 months	SBP/DBP: -17/-9 mmHg Prot: -0.54 g/day (-33%)
Robles (2016) ³⁶	RED LEVELS	35	Lercanidipine 10-20 mg + ACE-i vs. Amlodipine 5 mg + ACE-i	12 months	Greater albuminuria reduction -329.0 mg/24 h at 12 months follow-up with Lercanidipine/enalapril vs. amlodipine/enalapril combo ($p = 0.0011$)

Prot = changes in proteinuria (g/24h); AER = changes in albumin excretion rate (µg/min). ACE-I, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin II receptor blocker; AT-II, angiotensin-II. SBP, systolic blood pressure; DBP, diastolic blood pressure (mm/Hg).

urine albumin excretion rate to the same extent as ramipril (-17.4±65 µg/min, $p < 0.05$ and -19.7±52.5 µg/min, $p < 0.05$) in the lercanidipine and ramipril group, respectively³³. A few other studies have considered the effect of lercanidipine as monotherapy or in combination with RAS blocking drugs in patients with chronic kidney disease and/or albuminuria³⁴⁻³⁶. Robles et al³⁴ investigated the protective effect of the addition of lercanidipine (10 mg/day) on renal function in patients with chronic renal failure and uncontrolled BP levels despite treatment with either ACE-i or ARB. Overall, 203 patients with chronic kidney disease and higher than recommended BP were enrolled (63% on ACE-i and 37% on ARB), and 175 were evaluated. Over a 6-month follow-up period, lercanidipine proved safe and effective, further reducing BP (systolic BP from 162 to 132 mm Hg, diastolic BP from 93 to 78 mm Hg) alongside proteinuria (from 3.5 to 2.8 g/day). Plasmatic creatinine did not change, but creatinine clearance increased (41.8±16 at baseline vs. 45.8±18 mL/min after 6 months, $p = 0.019$)³⁴. The same group reported a similar study in 68 hypertensive patients with chronic renal failure in an open-label fashion³⁵. Patients already receiving an ARB or an ACE-I without attaining target BP levels were further treated with lercanidipine (20 mg/day) as add-on therapy and followed-up for 6 months. Interestingly, although systolic and diastolic BP were reduced (from 152/86 mmHg at baseline to 135/77 mmHg after 6 months, with a mean re-

duction -16.8/-9.3 mmHg) to a lesser extent than in the ZAFRA study, proteinuria was reduced by lercanidipine almost twofold in this study, with a dose-response effect, which seems to be independent of BP changes, at least in part³⁶. This renoprotective, anti albuminuric could be due to the activity of lercanidipine on glomerular hemodynamics and to other effects, such as inhibition of mesangial cell proliferation and effects mediated by endothelin, antioxidant effects linked to increased nitric oxide synthase activity. Basal proteinuria was 1.63 ±1.34 g/day, and it was reduced by 23% in the first month, 37% at 3 months, and 33% at 6 months ($p < 0.001$ at all time points) (Figure 4)³⁵.

Finally, in the RED LEVEL study (REnal Disease: Lercanidipine Valuable Effect on urine protein Losses), the effects of lercanidipine/enalapril and amlodipine/enalapril combinations were directly compared in a 12-month, prospective, multi-center, randomized, open-label, blinded-endpoint (PROBE) study conducted on hypertensive patients with albuminuria^{36,37}. Over time, albuminuria was significantly reduced, compared with baseline values, only in the lercanidipine/enalapril treated arm [changes from baseline were: -162.5 ($p = 0.04$), -425.8 ($p = 0.001$), -329.0 ($p = 0.001$) mg/24 h, at months 3, 6 and 12, respectively]. However, it was not significantly changed in patients treated with an amlodipine/enalapril combination. Changes in blood hypertension values were significant for both therapy regimens, without differences³⁶.

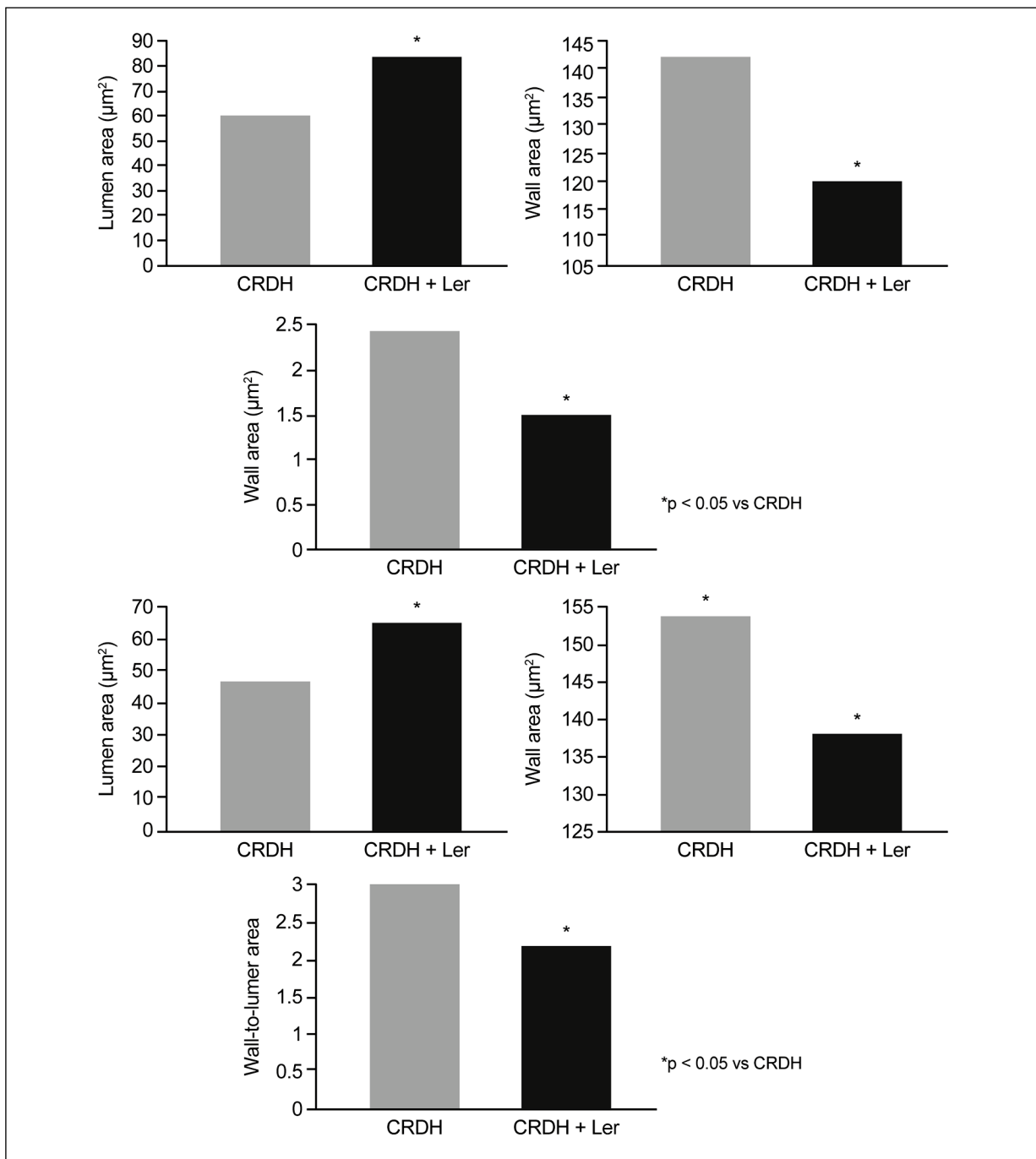


Figure 4. Percentage reduction in proteinuria after 1, 3 and 6 months of treatment with lercanidipine 20 mg/day, in addition to ACE-i or ARB, in previously uncontrolled hypertensive patients with chronic kidney disease. Data from Robles et al³⁵.

Expert Opinion

While effective blood lowering is mandatory for successful cardiovascular and renal protection, different classes of antihypertensive drugs have shown different end-organ protective properties beyond BP reduction. CCBs have tradition-

ally been regarded as powerful antihypertensive agents but less effective than RAS inhibitors in long-term kidney function preservation.

Lercanidipine is a third-generation CCB with an established role in antihypertensive therapy. It has been shown to have a unique pharmacologi-

cal profile, different from first- and second-generation CCBs, as it dilates both the afferent and the efferent glomerular arteries while preserving the intraglomerular pressure. This activity translates into favorable renal hemodynamic changes and provides a clinical benefit compared to class characteristics. While other CCBs provide renal protection if administered in combination with an ACE-I or an ARB, lercanidipine protects renal function as a single-drug regimen. Alone or in combination with ACE-I, lercanidipine has been shown to provide renal vascular protective effects in the experimental setting and reduce proteinuria in clinical studies^{35,36}.

The reno-protective and anti-albuminuric effect of lercanidipine could be due to its specific action on glomerular hemodynamics and others, such as the inhibition of mesangial cell proliferation, inhibition of endothelin-mediated renal effects, and increased nitric oxide synthase activity, which has been shown to lead to antioxidant effects^{35,36}. The reduction of oxidative stress obtained by administration of lercanidipine was associated with clinically relevant events, such as inhibition of vascular neointimal and smooth muscle cell proliferation and cholesterol accumulation³⁸⁻⁴⁰.

The effect of lercanidipine on proteinuria seemed to be dose-dependent and was not correlated with the antihypertensive activity^{32,33}. Renal protection with a significant decrease of microalbuminuria and improvement of creatinine clearance was demonstrated in patients with diabetes and renal impairment, representing a population at high risk of organ damage.

As lercanidipine is well tolerated and is associated with a low risk of ankle edema, it may be considered a friendly tool for hypertension control in subjects with a high risk of kidney damage.

Conclusions

Lercanidipine is an effective and safe antihypertensive treatment and can be used in patients at renal damage risk. Studies in hypertensive patients with diabetes or chronic renal disease demonstrated protective effects on the kidneys because lercanidipine dilates the afferent and efferent glomerular arteries, preserving the intraglomerular pressure. Notably, lercanidipine has been shown to reduce proteinuria, a peculiar effect in the CCBs class and a recognized risk factor for CV events in hypertensive patients. This

peculiarity was confirmed by a direct comparison trial where proteinuria was reduced by the combination lercanidipine/enalapril but not by amlodipine/enalapril³⁶. However, RED LEVEL represents the only head-to-head comparison study among different CCBs in terms of renal protection. Thus, one should exert great caution when drawing conclusions on long-term renal safety with different CCBs. Nonetheless, based on data discussed in the present manuscript, lercanidipine because of its peculiar intrarenal mechanisms of action, as well as its proven ability to reduce albuminuria, could be the ideal CCB to be used in hypertensive patients at renal risk.

Conflict of Interest

The authors have received a honorarium from Recordati Ireland LTD; A.C. received honoraria from AstraZeneca, AMGEN, Sanofi, Novartis, MSD, Mediolanum, DOC, Mylan and Pfizer. N.F received honoraria from Pfizer, Amgen, Relmada Therapeutics, and Pharmanutra. R.P. received speaker fees and/or advisory boards from AstraZeneca, Boehringer-Ingelheim, Menarini, Eli-Lilly, MSD, Novo-Nordisk, and Alfasigma.

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Authors' Contribution

All authors equally contributed to the selection of articles and to the preparation of the review. All authors approved the final version.

References

- 1) NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet* 2021; 398: 957-980.
- 2) Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, De-

- sormais I; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018; 39: 3021-3104.
- 3) Tocci G, Muiesan ML, Parati G, Agabiti Rosei E, Ferri C, Virdis A, Pontremoli R, Mancia G, Borghi C, Volpe M; Working Group of the Italian Society of Hypertension (SIIA) and SIIA Foundation. Trends in Prevalence, awareness, treatment, and control of blood pressure recorded from 2004 to 2014 during world hypertension day in Italy. *J Clin Hypertens (Greenwich)* 2016; 18: 551-556.
 - 4) Rea F, Savaré L, Franchi M, Corrao G, Mancia G. Adherence to treatment by initial antihypertensive mono and combination therapies. *Am J Hypertens* 2021; 34: 1083-1091.
 - 5) Rea F, Corrao G, Merlino L, Mancia G. Initial antihypertensive treatment strategies and therapeutic inertia. *Hypertension* 2018; 72: 846-853.
 - 6) Leoncini G, Viazzi F, Pontremoli R. Chronic kidney disease and albuminuria in arterial hypertension. *Curr Hypertens Rep* 2010; 12: 335-341.
 - 7) Pontremoli R, Leoncini G, Ravera M, Viazzi F, Vettoretti S, Ratto E, Parodi D, Tomolillo C, Deferrari G. Microalbuminuria, cardiovascular, and renal risk in primary hypertension. *J Am Soc Nephrol* 2002; 13: S169-S172.
 - 8) Carlström M, Wilcox CS, Arendshorst WJ. Renal autoregulation in health and disease. *Physiol Rev.* 2015; 2: 405-511.
 - 9) Mennuni S, Rubattu S, Pierelli G, Tocci G, Fofi C, Volpe M. Hypertension and kidneys: unravelling complex molecular mechanisms underlying hypertensive renal damage. *J Hum Hypertens.* 2014; 28: 74-79.
 - 10) Neuringer JR, Brenner BM. Hemodynamic theory of progressive renal disease: a 10-year update in brief review. *Am J Kidney Dis* 1993; 22: 98-104.
 - 11) Viazzi F, Leoncini G, Grassi G, Pontremoli R. Antihypertensive treatment and renal protection: Is there a J-curve relationship? *J Clin Hypertens (Greenwich)* 2018; 20: 1560-1574.
 - 12) Bakris G. Are there effects of renin-angiotensin system antagonists beyond blood pressure control? *Am J Cardiol* 2010; 105: 21A-29A.
 - 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) Barrios V, Escobar C, Echarri R. Fixed combinations in the management of hypertension: perspectives on lercanidipine-enalapril. *Vasc Health Risk Manage* 2008; 4: 847-853.
 - 15) Burnier M. Renal protection with calcium antagonists: the role of lercanidipine. *Curr Med Res Opin* 2013; 29: 1727-1735.
 - 16) Sabbatini M, Leonardi A, Testa R, Tomassoni D, Vitaioli L, Amenta F. Effects of dihydropyridine-type Ca²⁺ antagonists on the renal arterial tree in spontaneously hypertensive rats. *J Cardiovasc Pharmacol* 2002; 39: 39-48.
 - 17) Tocci G, Palano F, Pagannone E, Chin D, Ferrucci A, Volpe M. Fixed-combination therapies in hypertension management: focus on enalapril/lercanidipine. *Expert Rev Cardiovasc Ther.* 2009; 7: 115-123.
 - 18) Borghi C, Cicero AF. Rationale for the use of a fixed-dose combination in the management of hypertension: efficacy and tolerability of lercanidipine/enalapril. *Clin Drug Investig* 2010; 30: 843-854.
 - 19) Gasser R, Klein W, Köppel H. Lercanidipine, a new third generation Ca-antagonist in the treatment of hypertension. *J Clin Basic Cardiol* 1999; 2: 169-174.
 - 20) Brixius K, Gross T, Tossios P, Geissler HJ, Mehlhorn U, Schwinger RH, Hekmat K. Increased vascular selectivity and prolonged pharmacological efficacy of the L-type Ca²⁺ channel antagonist lercanidipine in human cardiovascular tissue. *Clin Exp Pharmacol Physiol* 2005; 32: 708-713.
 - 21) Sabbatini M, Leonardi A, Testa R, Vitaioli L, Amenta F. Effect of calcium antagonists on glomerular arterioles in spontaneously hypertensive rats. *Hypertension* 2000; 35: 775-779.
 - 22) Grassi G, Robles NR, Seravalle G, Fici F. Lercanidipine in the management of hypertension: an update. *J Pharmacol Pharmacother* 2017; 8: 155-165.
 - 23) Hayashi K, Homma K, Wakino S, Tokuyama H, Sugano N, Saruta T, Itoh H. T-type Ca channel blockade as a determinant of kidney protection. *Keio J Med* 2010; 59: 84-95.
 - 24) Hayashi K, Ozawa Y, Fujiwara K, Wakino S, Kumagai H, Saruta T. Role of actions of calcium antagonists on efferent arterioles--with special references to glomerular hypertension. *Am J Nephrol* 2003; 23: 229-244.
 - 25) Cerbai E, Mugelli A. Lercanidipine and T-type calcium current. *Eur Rev Med Pharmacol Sci* 2018; 22: 4025-4031.
 - 26) Barchielli M. Lercanidipine pharmacokinetics. *J Cardiovasc Pharmacol* 1997; 29: S1-S15.
 - 27) Lercanidipine Smpc. Available at: <https://www.medicines.org.uk/emc/product/5802/smpc#graf>.
 - 28) Hanauer Schaab E, Lanchote VL, Balthazar Nardotto GH, Marques Pereira MP, Dantas M, Pava CE, Barbosa Coelho E. Effect of lercanidipine on the pharmacokinetics-pharmacodynamics of carvedilol enantiomers in patients with chronic kidney disease. *J Clin Pharmacol* 2020; 60: 75-85.
 - 29) Dinnendahl V, Fricke U. *Arzneistoff-Profil* (in German). Eschborn, Germany: Govi Pharmazeutischer Verlag. *Arzneistoff-Profil* (in German), 2015.
 - 30) Rosenthal T, Rosenmann E, Tomassoni D, Amenta F. Effect of lercanidipine on kidney microanatomy in Cohen-Rosenthal diabetic hypertensive rats. *J Cardiovasc Pharmacol Ther* 2007; 12: 145-152.

- 31) Menne J, Park JK, Agrawal R, Lindschau C, Kielstein JT, Kirsch T, Marx A, Muller D, Bahlmann FH, Meier M, Bode-Böger SM, Haller H, Fliser D. Cellular and molecular mechanisms of tissue protection by lipophilic calcium channel blockers. *FASEB J* 2006; 20: 994-996.
- 32) Borghi C, Santi F. Fixed combination of lercanidipine and enalapril in the management of hypertension: focus on patient preference and adherence. *Patient Prefer Adherence* 2012; 6: 449-455.
- 33) Dalla Vestra M, Pozza G, Mosca A, Grazioli V, Lapolla A, Fioretto P, Crepaldi G. Effect of lercanidipine compared with ramipril on albumin excretion rate in hypertensive type 2 diabetic patients with microalbuminuria: DIAL study (diabete, ipertensione, albuminuria, lercanidipina). *Diabetes Nutr Metab* 2004; 17: 259-266.
- 34) Robles NR, Ocon J, Gomez CF, Manjon M, Pastor L, Herrera J, Villatoro J, Calls J, Torrijos J, Rodríguez VI, Rodríguez MM, Mendez ML, Morrey A, Martínez FI, Marco J, Liebana A, Rincon B, Tornero F. Lercanidipine in patients with chronic renal failure: the ZAFRA study. *Ren Fail* 2005; 27: 73-80.
- 35) Robles NR, Romero B, de Vinuesa EG, Sánchez-Casado E, Cubero JJ. Treatment of proteinuria with lercanidipine associated with renin-angiotensin axis-blocking drugs. *Ren Fail* 2010; 32: 192-197.
- 36) Robles NR, Calvo C, Sobrino J, Espinel E, Esteban R, Mateos L, Macias JF. Lercanidipine valuable effect on urine protein losses: the RED LEVEL study. *Curr Med Res Opin* 2016; 32: 29-34.
- 37) Hansson L, Hedner T, Dahlöf B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. *Prospective Randomized Open Blinded End-Point*. *Blood Press* 1992; 1: 113-119.
- 38) Wu JR, Liou SF, Lin SW, Chai CY, Dai ZK, Liang JC, Chen IJ, Yeh JL. Lercanidipine inhibits vascular smooth muscle cell proliferation and neointimal formation via reducing intracellular reactive oxygen species and inactivating Ras-ERK1/2 signaling. *Pharmacol Res* 2009; 59: 48-56.
- 39) ALOGPS Available at: <http://www.vcclab.org/lab/alogps>.
- 40) Lercanidipine S Available at: https://pubchem.ncbi.nlm.nih.gov/compound/S_Lercanidipine#section=2D-Structure.