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Antihypertensive and renal protection effects of lercanidipine and lercanidipine/enalapril

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Hypertension; Calcium channel blocker; lercanidipine; renal protection; combination therapy; angiotensin-converting enzyme inhibitor

ABSTRACT

Systemic arterial hypertension is the second most common cause of end-stage kidney disease (ESKD). Renal protection activity has been demonstrated for angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), gliflozins (dapagliflozin ed empagliflozin) and by the third-generation calcium channel blockers (CCB). 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. Here we summarized the pharmacological properties of lercanidipine 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. The fixed-dose combination lercanidipine/enalapril showed an excellent pharmacological profile with demonstrated clinical efficacy and tolerability in high-risk patients. Lercanidipine can be considered the preferred choice among calcium channel blocker drugs for the treatment of hypertensive patients at risk of renal impairment.

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Introduction

Hypertension is a modifiable risk factor for cardiovascular diseases, including stroke, coronary artery disease, and chronic renal failure [1]. Pharmacologic treatment with several classes of antihypertensive drugs has shown to efficiently reduce the incidence of cardiovascular complications [1]. Despite a clear benefit of treating hypertension, the recent WHO Global report indicated that only 54% of adults with hypertension are diagnosed, 42% receive treatment, and a mere 21% have their hypertension controlled [2]. Low treatment adherence, due to safety profile of drugs and multiple daily prescriptions, certainly contribute to this unmet clinical need [1]. Accordingly, the use of fixed-dose combination therapy has been recommended by the European Society of Hypertension (ESH) Guidelines, also as starting treatment for patients at high cardiovascular risk who are unlikely to be controlled with monotherapy [1].

Combination treatment has at least three potential advantages:

1) additive antihypertensive efficacy due to complementary mechanism of action;
2) lower incidence of side effects thanks to the lower doses of drugs administered;
3) higher adherence because of easier therapeutic schedules. Among the various combinations available, CCBs and angiotensin-converting enzyme (ACE) inhibitors have proven effective and good tolerability [1].

The heart, kidney, brain, and arterial blood vessels are prime targets of uncontrolled hypertension that may result in eventual organ failure and cardiovascular death and disability [3]. Systemic arterial hypertension is the second most common cause of end-stage kidney disease (ESKD) after diabetic nephropathy, and in patients with type 2 diabetes is a major contributor of the progression of kidney damage [4]. Pathophysiological studies suggest that kidney damage results from uncontrolled autoregulatory mechanisms aimed at preventing the transmission of elevated blood pressure (BP) to renal microvascu-

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lature [5, 6]. Indeed, the autoregulatory vasoconstriction of the afferent arteriole prevents the transmission of systemic hypertension to glomerular microvasculature, thus maintaining constant renal blood flow and the intraglomerular pressure. This physiological mechanism preserves the glomerular filtration rate (GFR) and reduces the hypertensive renal damage [7]. However, long-term hemodynamic stress leads to the development of atherosclerotic changes of intrarenal resistance arteries and benign nephrosclerosis which interfere with protective mechanisms of renal protection. This pathological condition is frequently associated with a reduction in renal mass, both in diabetic and nondiabetic patients affected by chronic kidney disease (CKD), that accounts for their increased susceptibility to progressive glomerulosclerosis even with a moderate increase in systemic BP. Controlled BP, with target values depending to the risk profile of the patients, is essential for a proper cardiovascular and renal protection [8].

The renal effects, determined as antiproteinuric action, has been determined to be more potent with ACE inhibitors or angiotensin receptor blockers (ARBs), and more recently by gliflozins [9, 10], 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 arteriole [11, 12]. Differently, the third generation CCB seems to act more effectively on both post- and pre-glomerular vessels [13, 14]. Among these, lercanidipine has been shown to protect smaller renal vessels from hypertensive damage by dilating afferent and efferent renal glomerular arteries [11].

To provide optimal blood perfusion to the kidney, the ideal drug should effectively lower systemic BP and positively impact glomerular hemodynamics [15]. The complementary mechanisms of action of CCB and ACE inhibitors provides an effective antihypertensive action with a low rate of side effects. Results from the ACCOMPLISH trial have demonstrated the advantage of the CCB-ACE inhibitor combination in managing cardiovascular (CV) risk in obese and hypertensive patients [16].

The fixed-dose combinations of lercanidipine 10 mg and enalapril 10 or 20 mg have been available in some European countries since 2006 [17].

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

Pharmacological properties of Lercanidipine

Lercanidipine is a third generation dihydropyridine CCB (DHP-CCB) with elevated lipophilicity having a positive value of repartition coefficient (LogP) equal to 6.42 and significantly higher than other CCBs. The lercanidipine has one chiral carbon atom and similarly to other asymmetric DHP the antihypertensive action mainly derives from its (S)-enantiomer (**Figure 1**).

Lercanidipine, like the other CCBs, acts from the inner side of the cell membrane and bind more effectively to L-type calcium channels in depolarized membranes. Binding of the drug reduces the frequency of opening in response to depolarization resulting in a marked decrease in transmembrane calcium current, and thus long-lasting smooth muscle cell relaxation. This vascular effect is responsible for antihypertensive effect of the drug. More in details, the high lipophilicity of lercanidipine facilitate its binding to the membranes phospholipids prolonging its interaction with the L-type calcium channel and the duration of action compared to other DHPs [18, 19]. The high vascular selectivity of lercanidipine determine a minor cardiac negative inotropic effect compared to amlodipine and nifedipine [19]. A second layer of differentiation between lercanidipine and other DHP-CCBs is represented by its blocking activity on both the

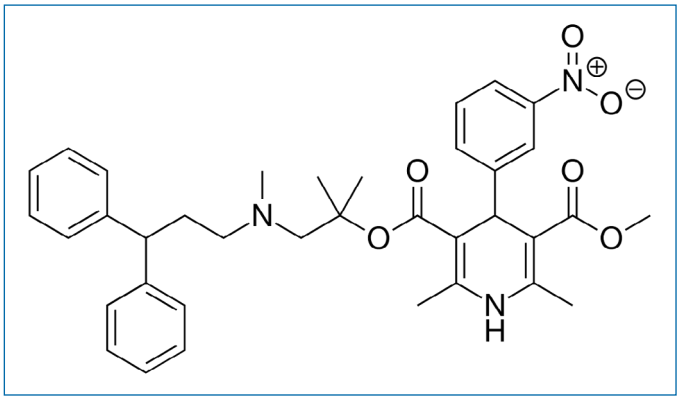

Figure 1 | Chemical structure of lercanidipine.

L-type and T-type calcium channels, with the first mainly expressed in the afferent arterioles and the second on both afferent and efferent arterioles (**Figure 2**). This dual action determines the dilation of both the afferent and the efferent glomerular arteries, with no changes in intraglomerular capillary pressure [20, 21].

Similar to lercanidipine, amlodipine has been shown to inhibit T-type calcium channels in efferent glomerular arteries [22, 23], while lacidipine is more selective on L-type and mibefradil (not more available for clinical use) is a specific T-type blocker (**Figure 3**) [24].

Pharmacokinetic properties

Absorption

Lercanidipine, after oral administration, is completely absorbed by the gastrointestinal tract although its absolute bioavailability is relatively low (10%) due to an extensive first-pass metabolism in the liver. Under fasting condition its oral absorption is reduced to 1/3, thus lercanidipine should be administered in the presence of high-fat meals. The peak of plasma concentration is reached 1.5-3 hours after oral administration at doses of 10-20 mg (T_{max}, **Table 1**). A similar pharmacokinetic profile has been shown for the two enantiomers, although the C_{max} and AUC (area under the curve) are, on average, 1.2-fold higher for the (S) enantiomer [25].

Distribution

Lercanidipine is highly bound to serum proteins (>98%), and the free fraction is rapidly and extensively distributed from plasma to peripheral tissues. In patients with severe renal or hepatic dysfunction it is expected to have a significantly higher concentration of free lercanidipine due to lower plasma protein concentration [26].

Biotransformation

Lercanidipine is mainly metabolized by CYP3A4 to inactive metabolites, and no parent drug is found in the urine or the feces. Approximately 50% of the dose is found in the urine [26].

Elimination

Lercanidipine undergoes to a biphasic elimination phase with the first with a 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 therapeutical activity lasts for 24 hours due to its high lipophilicity and binding to the cell membrane. No accumulation has been observed after repeated administration [26]. The elimination

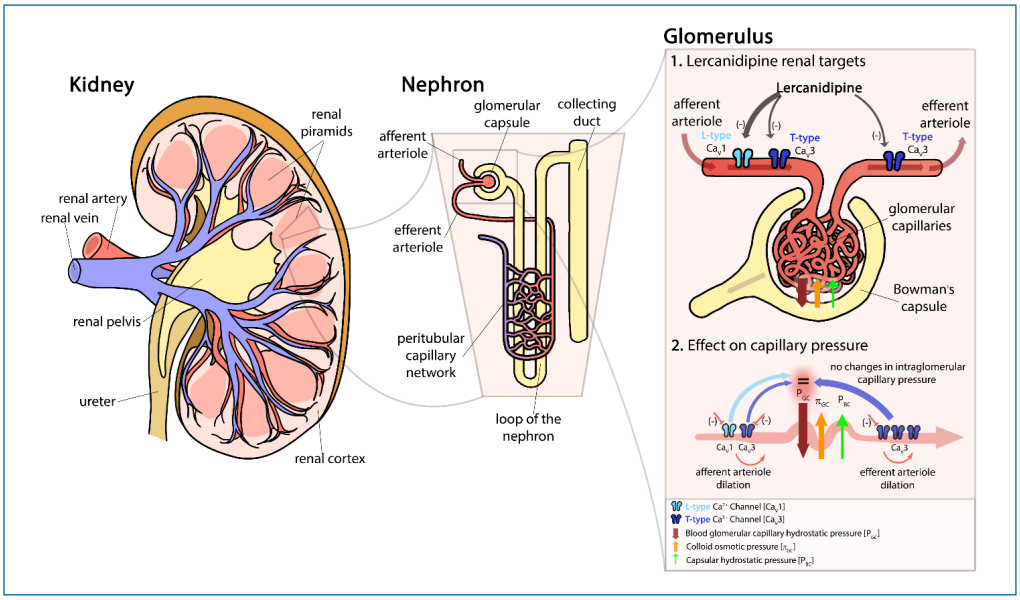

Figure 2 | Schematic representation of the localization of calcium channels (L and T) on afferent and efferent glomerular arterioles. Lercanidipine has shown to block L-type channel expressed on afferent arteriole and T-type channel present on both afferent and efferent arterioles. Source: Marbach *et al.* 2019 [40].

half-lives are superimposable, and no *in vivo* interconversion of enantiomers has been observed.

After oral administration, the plasma levels of lercanidipine are not directly proportional to the dose with a C_{max} ratio equal to 1:3:8 at the doses of 10, 20, or 40 mg, respectively. Even more pronounced saturation of first-pass metabolism was observed on AUC ratios, equal to 1, 4 and 18 for doses of 10, 20 and 40 mg of lercanidipine. Accordingly, the bioavailability increases with the dose (**Table 1**) [26].

Drug-Drug interactions

Preliminary *in vitro* data indicated that lercanidipine may inhibit both CYP3A4 and CYP2D6 activities. However, this effect has been observed at concentrations more than 40-fold higher than those reached in the plasma after administration of 20 mg of the drug.

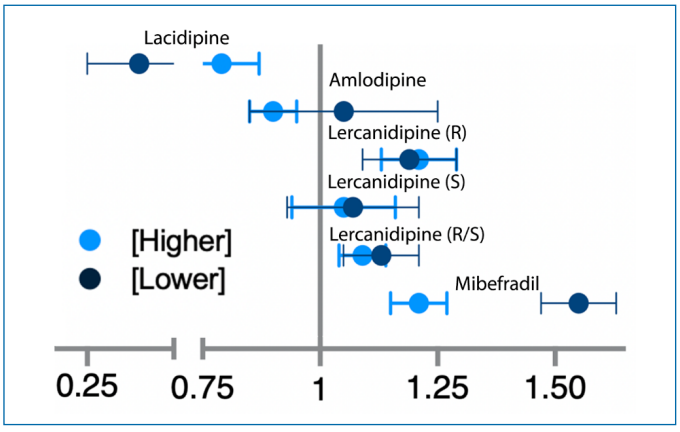

Figure 3 | Ratio of the inhibitory potencies of CCBs on L-type vs. T-type channels. High and low drug concentrations were: 1 or 10 µM for amlodipine and lercanidipine; 0.1 or 1 µM for lacidipine; 3 or 10 µM for mibefradil. Value above 1 (right side of the plot) means that the drug is more selective for T-type than L-type channel. A ratio below1 (left side) indicates selectivity for than L-type channel. Source: Cerbai *et al.* 2018 [24].

Indeed, pharmacokinetic studies in humans demonstrated that lercanidipine did not modify the plasma levels of midazolam, a typical substrate of CYP3A4, or metoprolol, a substrate of CYP2D6 [27]. Thus, lercanidipine is not predicted to alter the pharmacokinetics of drugs metabolized by CYP3A4 and CYP2D6.

On the other hand, lercanidipine is extensively metabolized by CYP3A4, such that ketoconazole (strong CYP3A4 inhibitor) increased the C_{max} of lercanidipine by eight folds and the AUC by 15 folds [27]. Similarly, ciclosporin, another strong CYP3A4 inhibitor, increased lercanidipine plasma levels by 3-fold when given concomitantly [27]. 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 [27]. Conversely, CYP3A4 inducers, such as carbamazepine, rifampicin, and St John's wort, are expected to lower the exposure and the effectiveness of lercanidipine. Thus, lercanidipine should be avoided with strong CYP3A4 inhibitors and inducers.

Importantly, metoprolol, by reducing the hepatic blood flow, reduced the bioavailability of lercanidipine by 50% [26, 28]. Consequently, lercanidipine may be safely administered with β-adrenoceptor

Table 1 | Pharmacokinetic parameters of lercanidipine.

Parameters	Assessment
Bioavailability	10% (due to first-pass effect)
Gastrointestinal 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 al.* [26].

blocking drugs, but dose adjustment may be required. On the other hand, lercanidipine does not interact with diuretics and ACE inhibitors.

Differently from other DHP-CCBs, lercanidipine increased 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 subjects and patients with mild to moderate renal and hepatic impairment, the pharmacokinetic profile of lercanidipine was similar to that of healthy controls. In patients with severe hepatic impairment, the systemic exposure of lercanidipine is expected to be increased [26]. 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 [26].

Importantly, lercanidipine pharmacokinetics is unaffected by carvedilol 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), thus supporting the rationale for its renal protection use [26].

Pharmacodynamic properties

Lercanidipine has a prolonged antihypertensive activity and is devoid of negative inotropic effects due to its high vascular selectivity [19]. The high lipophilicity of lercanidipine provides a slow onset of action, long-lasting smooth muscle relaxation, and peripheral vasodilation [19]. 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 verapamil and diltiazem, lercanidipine, like the other DHP-CCB, does not act on calcium channels in the atrioventricular node, and therefore, does not decrease heart rate [29].

Renal protection of lercanidipine: experimental evidence

In a preclinical model of hypertensive rats, the treatment with lercanidipine induced a vasodilation of both afferent and efferent arterioles of the renal microvessels (**Table 2**)[20]. Lercanidipine

Table 2 | Measures of afferent and efferent arterioles in Wistar-Kyoto normotensive and spontaneously hypertensive rats upon different treatments.

Arteriole	WKY untreated	SHR untreated	SHR lercanidipine
Afferent arteriole			
Lumen area, μm²	79.2±5.7	63.6±2.3*	79.1±3.4†
Wall area, μm²	91.6±4.5	96.6±5.1	91.1±5.2
Wall/lumen ratio	1.18±0.04	1.51±0.03*	1.16±0.07†
Efferent arteriole			
Lumen area, μm²	60.2±2.8	50.5±3.1*	60.0±3.3†
Wall area, μm²	121.4±5.1	146.2±6.7*	140.2±5.3*
Wall/lumen ratio	2.03±0.06	2.93±0.08*	2.37±0.12*†

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. Source: Sabbatini et al. [20].

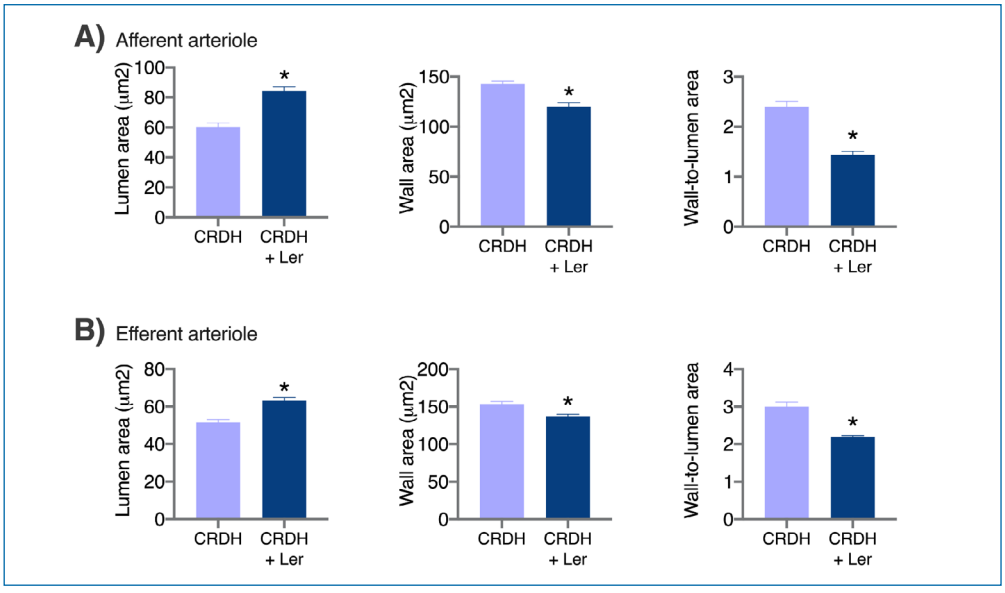

Figure 4 | Effect of lercanidipine on glomerular arterioles morphology in Cohen-Rosenthal Diabetic-Hypertensive Rats. CRDH = Cohen-Rosenthal diabetic-hypertensive rats; LER = lercanidipine. *p<0.05 vs CRDH. Source: Rosenthal *et al.* 2007 [30].

Table 3 | Clinical studies on the renal effects of lercanidipine as monotherapy or as an add-on on ACE inhibitors/ARBs.

Author (Ref.)	Study	Patients (n)	Treatments	Follow-up	Outcome
Dalla Vestra (2004) [34]	DIAL	277	Lercanidipine 10/20 mg *vs.* ramipril 5/10mg	9-12 months	AER: -17.4 *vs.* -19.7 µg/min
Robles (2005) [36]	ZAFRA	203	Lercanidipine 10mg + ACE-inhibitor or ARB	6 months	SBP/DBP: -30.4/-15 mmHg Prot: -0.7 g/die (-20%)
Robles (2010) [37]		68	Lercanidipine 20 mg + ACE-inhibitor or ARB	6 months	SBP/DBP: -17/-9 mmHg Prot: -0.54 g/day (-33%)
Robles (2016) [35]	RED LEVELS	35	Lercanidipine 10-20 mg + ACE-inhibitor vs Amlodipine 5 mg + ACE- inhibitor	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, Angiotensin-converting enzyme; ARB, Angiotensin II receptor blocker; AT-II, angiotensin-II. SBP, systolic blood pressure; DBP, diastolic blood pressure (mm/Hg).

administration prevented wall thickening and luminal narrowing in small-sized arteries and glomerular arterioles of Cohen-Rosenthal diabetic hypertensive rats (**Figure 4**) [30].

These results could have relevant clinical implications. It is well established that traditional DHP-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 microvessels [11], 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 proteinuria [23]. A similar renal protection effect by lercanidipine was observed in a double-transgenic rat model overexpressing human renin and angiotensinogen genes associated to a reduction in mortality induced by angiotensin II [31].

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

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 renin angiotensin-aldosterone system (RAAS) [12]. The combination of these agents should provide complementary effects since CCBs and RAAS inhibitors do not share the same mode of action.

CCBs are potent vasodilators that induce an autonomous activation of the sympathetic system and the RAAS system that can be dampened by ACE inhibitors. Further, 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. The concomitance of both treatments may reduce the incidence of adverse events, particularly peripheral edema, indeed 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 vessels [32]. Thus, lercanidipine in fixed combination with enalapril has a strong rationale for controlling hypertension and hypertension-associated renal damage.

Several clinical studies have investigated the renal protective effect of lercanidipine or lercanidipine/enalapril (**Table 3**). In the DIAL study, patients with type 2 diabetes, mild to moderate hypertension, and persistent microalbuminuria were randomized to receive either lercanidipine (10-20 mg/day) or ramipril (5-10 mg/day) [33]. After a follow-up of 9-12-months, lercanidipine reduced 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, $p<0.05$) [33]. The effect of lercanidipine as monotherapy or in combination with RAAS inhibitors has also been investigated in patients with CKD and/or albuminuria [34-36]. Robles *et al.* investigated the renal protective effect of lercanidipine (10 mg/day) in patients with CKD and uncontrolled BP levels already in treatment with either ACE inhibitors or ARB [35]. Overall, 175 patients with CKD and higher than recommended BP were evaluated (63% on ACE inhibitors and 37% on ARB). Over a 6-month follow-up period, lercanidipine 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/

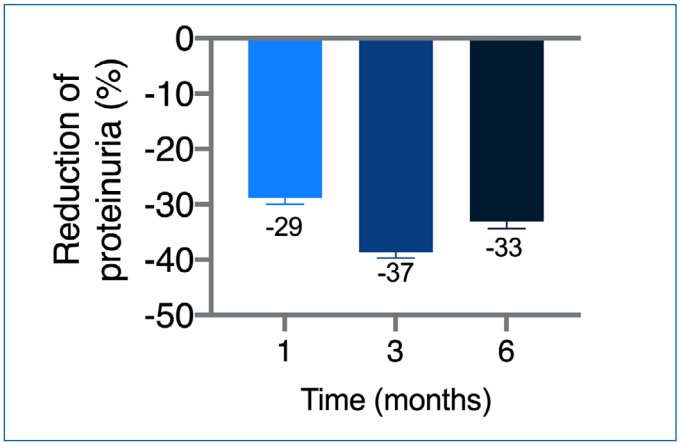

Figure 5 | Percentage reduction in proteinuria after 1, 3 and 6 months of treatment with lercanidipine 20 mg/day, in addition to ACE-inhibitors or ARB, in previously uncontrolled hypertensive patients with CKD. P<0.001 for all values. Source: Robles *et al.* 2010 [36].

day) [35]. Plasma creatinine levels were not affected by the treatment while its clearance increased (41.8±16 at baseline *vs.* 45.8±18 mL/min after 6 months, p=0.019) [35]. The same group reported a similar open label study in 68 hypertensive patients with CKD [36]. Patients already receiving an ARB or an ACE inhibitor without attaining target BP levels were further treated with lercanidipine (20 mg/day) as add-on therapy and followed-up for 6 months. Although systolic and diastolic BP were reduced (from 152/86 mmHg at baseline to 135/77 mmHg after 6 months, with a mean reduction -16.8/-9.3 mmHg) to a lesser extent than in the ZAFRA study [35, 36], proteinuria was reduced by lercanidipine almost twofold, with a dose-response effect, which seems partially to be independent of BP changes [34]. 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 5**). In addition, creatinine clearance did not significantly change after lercanidipine treatment (43.5±10.6 *vs* 44.0±1.0 mL/min) [36]. 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 [36].

Finally, the effects of lercanidipine/enalapril and amlodipine/enalapril combinations were directly compared in a 12-month, prospective, multi-center, randomized, open-label, blinded-endpoint study conducted on hypertensive patients with albuminuria (RED LEVEL and PROBE study) [34, 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 differences [34, 37]. Thus, while ACE inhibitors and ARBs remain first-line antihypertensive drugs in CKD patients, as stated by 2021 KDIGO guidelines [38]. We believe that the above-mentioned studies suggest a potential for further renal protection by lercanidipine especially in combination treatment.

Expert Opinion

Beyond BP reduction efficacy of different classes of antihypertensive drugs, their effect on end-organ protective properties (both cardiovascular and renal) can be distinguished. CCBs have traditionally been considered as powerful antihypertensive agents but less effective than RAAS inhibitors and gliflozins in long-term kidney function preservation. Lercanidipine is a third generation CCB that shows a unique pharmacological profile, different from first- and second-generation. This drug shows a prolonged antihypertensive activity and is devoid of negative inotropic effects due to its high vascular selectivity [19]. It is an effective and safe antihypertensive drug and can be used in special populations including elderly, diabetics, and patients at renal damage risk [26]. Lercanidipine is highly lipophilic and inhibits both L and T types of calcium channels eliciting a direct dilation on both afferent and efferent glomerular arteries, preserving the intraglomerular pressure. This activity translates into favourable renal hemodynamic changes, also in monotherapy, and may provide a clinical benefit superior to other CCBs which showed protective effect only when administered in combination with an ACE inhibitor or an ARB.

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 micro-albuminuria and improvement of creatinine clearance was demonstrated in patients with diabetes and CKD, representing a population at high risk of organ damage. Alone or in combination with ACE inhibitors, lercanidipine has been shown to provide renal vascular protective effects in the experimental setting and reduce proteinuria in clinical studies. 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 [34, 36]. The reduction of oxidative stress obtained by administration of lercanidipine was associated to inhibition of vascular neointimal and smooth muscle cell proliferation and cholesterol accumulation [39]. As lercanidipine is well tolerated and is associated with a low risk of ankle edema, it may be considered a safe 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 CKD demonstrated protective effects on the kidneys due to the capability of lercanidipine to dilate the afferent and efferent glomerular arteries and 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/enalapril [34]. Indeed, it is possible that the vasodilatory effect of lercanidipine of afferent arteriole may avoid the reduction of filtration fraction due to RAAS blockers because of efferent arteriole vasodilation. However, RED LEVEL represents the only head-to-head comparison study among different CCBs in terms of renal protection [34]. 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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References

[1] Mancia G, Kreutz R, Brunstrom M, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens 2023; 41:1874-2071.

[2] Kario K, Okura A, Hoshide S, Mogi M. The WHO Global report 2023 on hypertension warning the emerging hypertension burden in globe and its treatment strategy. Hypertens Res 2024; 47:1099-102.

[3] Leoncini G, Viazzi F, Pontremoli R. Chronic kidney disease and albuminuria in arterial hypertension. Curr Hypertens Rep 2010; 12:335-41.

[4] Pontremoli R, Leoncini G, Ravera M, et al. Microalbuminuria, cardiovascular, and renal risk in primary hypertension. J Am Soc Nephrol 2002; 13 Suppl 3:S169-72.

[5] Carlstrom M, Wilcox CS, Arendshorst WJ. Renal autoregulation in health and disease. Physiol Rev 2015; 95:405-511.

[6] Mennuni S, Rubattu S, Pierelli G, et al. Hypertension and kidneys: unraveling complex molecular mechanisms underlying hypertensive renal damage. J Hum Hypertens 2014; 28:74-9.

[7] 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.

[8] Viazzi F, Leoncini G, Grassi G, Pontremoli R. Antihypertensive treatment and renal protection: Is there a J-curve relationship? J Clin Hypertens (Greenwich) 2018; 20:1560-74.

[9] The E-KCG, Herrington WG, Staplin N, et al. Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2023; 388:117-27.

[10] Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2020; 383:1436-46.

[11] Burnier M. Renal protection with calcium antagonists: the role of lercanidipine. Curr Med Res Opin 2013; 29:1727-35.

[12] Sabbatini M, Leonardi A, Testa R, et al. Effects of dihydropyridine-type Ca2+ antagonists on the renal arterial tree in spontaneously hypertensive rats. J Cardiovasc Pharmacol 2002; 39:39-48.

[13] Tocci G, Palano F, Pagannone E, et al. Fixed-combination therapies in hypertension management: focus on enalapril/lercanidipine. Expert Rev Cardiovasc Ther 2009; 7:115-23.

[14] 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; 30:843-54.

[15] Bakris G. Are there effects of renin-angiotensin system antagonists beyond blood pressure control? Am J Cardiol 2010; 105:21A-9A.

[16] Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med 2008; 359:2417-28.

[17] Barrios V, Escobar C, Echarri R. Fixed combinations in the management of hypertension: perspectives on lercanidipine-enalapril. Vasc Health Risk Manag 2008; 4:847-53.

[18] Gasser R, Klein W, Köppel H. Lercanidipine, a new third generation Ca-antagonist in the treatment of hypertension. Journal of Clinical and Basic Cardiology 1999; 2:169-74.

[19] Brixius K, Gross T, Tossios P, et al. Increased vascular selectivity and prolonged pharmacological efficacy of the L-type Ca2+ channel antagonist lercanidipine in human cardiovascular tissue. Clin Exp Pharmacol Physiol 2005; 32:708-13.

[20] Sabbatini M, Leonardi A, Testa R, et al. Effect of calcium antagonists on glomerular arterioles in spontaneously hypertensive rats. Hypertension 2000; 35:775-9.

[21] Grassi G, Robles NR, Seravalle G, Fici F. Lercanidipine in the Management of Hypertension: An Update. J Pharmacol Pharmacother 2017; 8:155-65.

[22] Hayashi K, Homma K, Wakino S, et al. T-type Ca channel blockade as a determinant of kidney protection. Keio J Med 2010; 59:84-95.

[23] Hayashi K, Ozawa Y, Fujiwara K, et al. Role of actions of calcium antagonists on efferent arterioles--with special references to glomerular hypertension. Am J Nephrol 2003; 23:229-44.

[24] Cerbai E, Mugelli A. Lercanidipine and T-type calcium current. Eur Rev Med Pharmacol Sci 2018; 22:4025-31.

[25] Jabor VA, Coelho EB, Lanchote VL. Enantioselective pharmacokinetics of lercanidipine in healthy volunteers. J Chromatogr B Analyt Technol Biomed Life Sci 2004; 813:343-6.

[26] Barchielli M, Dolfini E, Farina P, et al. Clinical Pharmacokinetics of Lercanidipine. J Cardiovasc Pharmacol 1997; 29:S1-S15.

[27] Klotz U. Interaction potential of lercanidipine, a new vasoselective dihydropyridine calcium antagonist. Arzneimittelforschung 2002; 52:155-61.

[28] Zamir A, Hussain I, Ur Rehman A, et al. Clinical Pharmacokinetics of Metoprolol: A Systematic Review. Clin Pharmacokinet 2022; 61:1095-114.

[29] Dinnendahl V, Fricke U. Dinnendahl, V; Fricke, U, eds. (2015). Arzneistoff-Profile (in German). 6 (28 ed.). Eschborn, Germany: Govi Pharmazeutischer Verlag. ISBN 978-3-7741-9846-3.2015.

[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; 12:145-52.

[31] Menne J, Park JK, Agrawal R, et al. Cellular and molecular mechanisms of tissue protection by lipophilic calcium channel blockers. FASEB J 2006; 20:994-6.

[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; 6:449-55.

[33] Dalla Vestra M, Pozza G, Mosca A, et al. 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; 17:259-66.

[34] Robles NR, Calvo C, Sobrino J, et al. Lercanidipine valuable effect on urine protein losses: the RED LEVEL study. Curr Med Res Opin 2016; 32:29-34.

[35] Robles NR, Ocon J, Gomez CF, et al. Lercanidipine in patients with chronic renal failure: the ZAFRA study. Ren Fail 2005; 27:73-80.

[36] Robles NR, Romero B, de Vinuesa EG, et al. Treatment of proteinuria with lercanidipine associated with renin-angiotensin axis-blocking drugs. Ren Fail 2010; 32:192-7.

[37] Hansson L, Hedner T, Dahlof B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. Blood Press 1992; 1:113-9.
[38] Kidney Disease: Improving Global Outcomes Glomerular Diseases Work G. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int 2021; 100:S1-S276.
[39] Wu JR, Liou SF, Lin SW, et al. 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.
[40] Marbach S, Bocquet L. Osmosis, from molecular insights to large-scale applications. Chem Soc Rev 2019; 48:3102-44.