Lercanidipine in the Management of Hypertension: An Update

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Abstract

Calcium channel blockers (CCBs), particularly dihydropyridine-CCBs, (DHP-CCBs), have an established role in antihypertensive therapy, either as monotherapy or in combination with other antihypertensive drugs. Two hundred and fifty-one papers published in PubMed in English between January 1, 1990, and October 31, 2016, were identified using the keyword "lercanidipine." Lercanidipine is a lipophilic third-generation DHP-CCB, characterized by high vascular selectivity and persistence in the smooth muscle cell membranes. Lercanidipine is devoid of sympathetic activation, and unlike the first and second generation of DHP-CCBs, it dilates both the afferent and the efferent glomerular arteries, while preserving the intraglomerular pressure. In addition, lercanidipine prevents renal damage induced by angiotensin II and demonstrates anti-inflammatory, antioxidant, and anti-atherogenic properties through an increasing bioavailability of endothelial nitric oxide. It is associated with a regression of microvascular structural modifications in hypertensive patients. The efficacy of lercanidipine has been demonstrated in patients with different degrees of hypertension, in the young and elderly and in patients with isolated systolic hypertension. In patients with diabetes and renal impairment, lercanidipine displays a renal protection with a significant decrease of microalbuminuria and improvement of creatinine clearance. Lercanidipine is well tolerated and is associated with a very low rate of adverse events, particularly ankle edema, compared with amlodipine and nifedipine. In conclusion, lercanidipine produces a sustained blood pressure-lowering activity with a high rate of responder/normalized patients, associated with a favorable tolerability profile.

Keywords: Dihydropyridine calcium channel blockers, hypertension, lercanidipine

INTRODUCTION

Hypertension is one of the most important risk factors for cardiovascular (CV) mortality and morbidity and is the most common chronic disorder seen in primary care.[1-3] Evidence from large randomized clinical trials and meta-analyses[4-6] has shown the benefits of high blood pressure (BP) reduction to prevent target organ damage, as well as mortality in elderly patients.[7,8] Lowering systolic BP (SBP) by 10 mm of mercury (mmHg) or diastolic BP (DBP) by 5 mmHg significantly decreases the risk of CV events with a larger reduction using a drug combination regimen.[4,7,9] Unfortunately, inadequate control of hypertension has been reported by several cross-sectional studies.[7,10-12] This paper aims to provide a critical review on BP-lowering, metabolic, and CV effects of lercanidipine in the treatment of hypertension, based on the results of published studies, with specific focus on the most recent data.

METHODOLOGY

A total of 251 articles available in PubMed, published in English between January 1, 1990, and October 31, 2016, using the keyword "lercanidipine," were identified (including 45 randomized controlled trials, 2 observational studies, 40 reviews, 11 case reports, and 1 editorial). The articles focused on BP-lowering, metabolic, and CV effects of lercanidipine.

GENERALITIES

With regard to antihypertensive agents, it is recognized that calcium channel blockers (CCBs) play an important role in starting and maintaining antihypertensive

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therapy, either as monotherapy or in combination with renin-angiotensin (AT)-aldosterone system (RAAS) antagonists.[13-15] CCBs are a heterogeneous class, including dihydropyridine (DHP) and non-DHP (NDHP) subgroups. Both subgroups have a similar action mechanism: they inhibit the calcium influx into vascular smooth muscle cell through the L-type voltage-gated calcium channels. The lower intracellular calcium ion concentration induces vasodilation, reduction of peripheral vascular resistance, and consequently BP. However, unlike NDHP-CCBs, DHP-CCBs have higher vascular selectivity and are devoid of pharmacological effects at the myocardium level, such as negative inotropic and chronotropic activity.[16] The antihypertensive activity of a once-daily administration of DHP-CCBs – amlodipine, lercanidipine, lacidipine, manidipine, nifedipine gastrointestinal therapeutic system (GITS, an extended-release formulation of nifedipine) – is quite similar and stable throughout the 24-h dosing interval.[16]

Different meta-analyses have shown that DHP-CCBs have cardioprotective effects decreasing the risk of CV events,[4,17,18] such as strokes (-21%), coronary artery disease (-18%), and heart failure (-28%), in patients with or without CV disease and regardless of B*P* values before treatment. Moreover, compared to β-blockers and diuretics, CCBs lead to less new-onset type-2 diabetes,[19,20] decrease SBP variability, which accounts for stroke prevention,[21] and are not associated with the risk of new-onset atrial fibrillation.[22]

Lercanidipine hydrochloride (HCl) is a third-generation DHP-CCB characterized by high vascular selectivity and high lipophilicity, which enables easy penetration and considerable concentration and persistence in the phospholipids bilayer of the smooth muscle cell membranes, from which it is gradually released to reach the L-type calcium channels.[23,24] *In vitro* lercanidipine has shown a lower negative inotropic effect than other DHPs such as lacidipine, amlodipine, nitrendipine, nifedipine, and felodipine.[24]

PHARMACOKINETICS

Unlike other DHP-CCBs, the high lipophilicity of lercanidipine HCl provides a slow onset of action, a long-lasting smooth muscle relaxation, and a peripheral vasodilation.[23,24] After oral administration, lercanidipine is well absorbed by the gastrointestinal tract, with a peak plasma concentration reached after 1.5–3 h. The drug appears to have a biphasic elimination profile: first phase with elimination plasma half-life of 3–5 h,[23,25,26] followed by a second phase with terminal half-life of 10.5 h.[23,27] In hypertensive patients, the mean terminal elimination half-life after a single oral dose of 10–20 mg is 8–10.5 h.[27,28] However, the prolonged duration of the pharmacological activity is not dependent on the plasma drug half-life, but on the smooth muscle membrane kinetics;[25] therefore, despite the short plasma half-life, the pharmacodynamic action covers 24 h.

Lercanidipine is metabolized in the liver by cytochrome CYP3A4 and converted into inactive metabolites which are eliminated in urine and feces.[27,28] Lercanidipine should not be administered with inhibitors of CYP3A4 or cyclosporine.[28]

Pharmacokinetic properties are not modified by age or mild or moderate hepatic or renal impairment,[26] whereas in patients with severe renal insufficiency – estimated glomerular filtration rate (eGFR) <30 ml/min/m² – the dosage has to be reduced to avoid high plasma concentrations.[25-28] The absorption of lercanidipine is increased by high-fat meals, and it should thus be administered before eating.[26,28] Concomitant administration of cimetidine or digoxin does not modify the pharmacokinetics of lercanidipine, whereas as with other DHP-CCBs, an interaction with simvastatin has been reported (increased plasma concentration of simvastatin). It is therefore recommended to administer simvastatin in the evening and lercanidipine in the morning.[28,29]

Taken together, these findings show that lercanidipine is a long-acting CCB allowing for once-daily administration. This effect is not dependent on plasma drug half-life but on smooth muscle membrane kinetics.

RELEVANT PHARMACOLOGICAL AND CLINICAL PHARMACOLOGICAL ASPECTS OF LERCANIDIPINE

Sympathetic activation

Unlike nifedipine GITS and felodipine, lercanidipine decreases sympathetic overdrive associated with hypertension. During chronic treatment in hypertensive patients, at similar BP reduction, norepinephrine plasma concentration was not modified by lercanidipine (10–20 mg/daily), whereas it was increased by nifedipine GITS and felodipine.[30,31] Moreover, muscle sympathetic nerve traffic, assessed via microneurography, was decreased by lercanidipine and increased by felodipine, suggesting that lercanidipine as monotherapy,[31] or combined with enalapril[32] during chronic administration, does not induce sympathetic activation, secondary to peripheral vasodilation. This aspect has an important clinical relevance considering that sympathetic overdrive can be associated with the development and progression of target organ damage and CV events in hypertensive patients.[30,33]

Antioxidant and anti-inflammatory activity

Lercanidipine increases nitric oxide (NO) bioavailability and endothelium-dependent vasodilation in hypertensive patients.[34] It also reduces the markers of oxidative stress, such as plasma lipoperoxides, isoprostanes, myeloperoxidase, a leukocyte-derived vascular NO oxidase,[35] malondialdehyde,[34,36] asymmetric dimethylarginine (ADMA), an endogenous NO synthase inhibitor,[34,36,37] and metalloproteinase-9.[38] In addition, the drug inhibits vascular neointimal and smooth muscle cell proliferation as well as cholesterol accumulation through the reduction of cellular reactive oxygen species.[37,39-41]

In hypertensive patients, lercanidipine decreases the plasma white blood cells, C-reactive protein, E-selectin, P-selectin,[42]

lipoprotein-a, and intracellular adhesion molecules involved in thrombotic process and vascular/tissue injury.[43]

Lercanidipine may exert anti-atherogenic effects as well as antihypertensive activity. A significant reduction of atherosclerotic lesions and cholesterol accumulation has been demonstrated in animals,[39,40] and a 35% decrease of low-density lipoprotein-cholesterol (LDL-C) oxidation has been observed in hypertensive patients with diabetes mellitus.[44]

Renal effects

At renal level, lercanidipine acts differently from other first- and second-generation DHP-CCBs. It dilates both the afferent and the efferent glomerular arteries, with intraglomerular capillary pressure remaining unchanged.[45-47] This ability is thought to be a consequence of inhibition of both L-type (preglomerular) and T-type (postglomerular) calcium channels at renal level. Postglomerular arteries are rich in T-type calcium channels, and the third-generation CCBs have been proved to inhibit T-type channels in postglomerular vessels.[48,49] In addition, lercanidipine decreases tubule-interstitial fibrosis and microalbuminuria in spontaneously hypertensive rats,[46,47] demonstrating a renal protection independent of BP reduction. The renal protection of lercanidipine has been confirmed in a double-transgenic rat (dTGR) model, with overexpression of human renin and angiotensinogen genes.[37] Lercanidipine treatment prevented renal damage and mortality induced by AT-II. In treated animals, proteinuria decreased and plasma creatinine levels were maintained in the normal range compared with untreated dTGR rats. Moreover, a decrease of monocyte infiltration, extracellular matrix formation, and fibrosis was observed in renal vessels. These effects may result from inhibition of tissue inflammation and from improved NO bioavailability. At cellular level, the action of lercanidipine in this experimental model seems related to intracellular protein kinase C isoforms inhibition and activation of the dimethylarginine dimethylaminohydrolase enzyme involved in ADMA metabolism, as demonstrated by reduced ADMA plasma concentration in dTGR animals. Consequently, intracellular NO bioavailability increases since ADMA is an inhibitor of NO synthase. These intracellular effects of lercanidipine are caused by reduced intracellular calcium concentration.

Effects on microvascular structure in hypertensive patients

In hypertensive patients, lercanidipine treatment is associated with a regression of microvascular structural changes,[50] the effect being confirmed through the evaluation of the retinal arteriolar morphology.[51] The wall-to-lumen ratio of retinal arterioles was assessed using scanning laser Doppler flowmetry to evaluate the retinal perfusion. The results show that lercanidipine significantly decreases the wall-to-lumen ratio [Figure 1], as well as the wall thickness and the wall cross-sectional area of the retinal arteries.[51] This effect may be related to the antioxidant and anti-inflammatory properties of lercanidipine. These effects, together with BP reduction, have a high clinical relevance, considering the role of endothelial
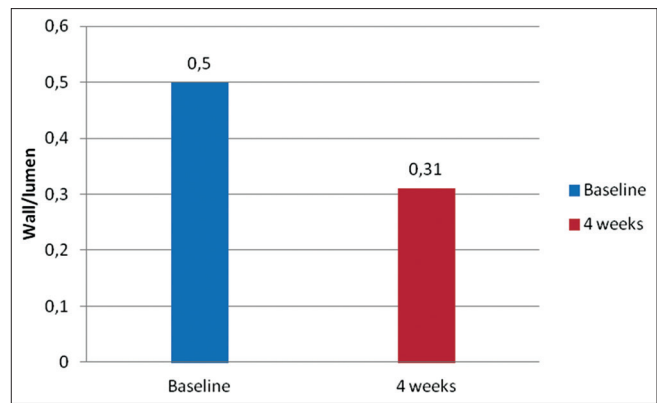

Figure 1: Reduction in the wall-to-lumen ratio after lercanidipine treatment (4 weeks) ($P < 0.001$ vs. baseline)[51]

dysfunction, oxidative stress, low-grade inflammation, and arterial stiffness in the pathogenesis of atherosclerosis and the importance of organ damage in long-term CV disease.

Preclinical data demonstrate that lercanidipine is highly selective for vascular tissue and produces smooth muscle relaxation through binding to L-type calcium channels. Moreover, it has a lower negative inotropic effect compared with other DHP CCBs, does not cause significant reflex tachycardia, shows a renal protection, and exerts anti-atherogenic, anti-inflammatory, and antioxidant effects.

ANTIHYPERTENSIVE ACTIVITY

The therapeutic efficacy of lercanidipine (10–20 mg/daily) has been evaluated in double-blind, randomized, comparative trials and in large observational studies, in patients with mild-to-moderate hypertension, severe hypertension, isolated systolic hypertension, hypertensive patients with diabetes mellitus, kidney disease, or concomitant different CV risk factors, as well in elderly subjects.

In patients with mild-to-moderate hypertension or with isolated systolic hypertension,[52] lercanidipine significantly reduces the augmentation index, as well the central SBP and pulse pressure [Figure 2].

The most important clinical studies are reported in Tables 1 and 2. A significant reduction of SBP and DBP, associated with a high rate of responder patients and BP normalizations, was obtained after 4–6 weeks of therapy.[53] The antihypertensive effect is maintained for 24 h, with a favorable smoothness index and a significant decrease of morning BP rise as well as BP variability [Figure 3].[51,54-57]

Recently, an international, multicenter, randomized, placebo-controlled, parallel group, factorial design study[58] was performed in 1000 patients with Stage 2 hypertension with lercanidipine (10–20 mg/daily) as monotherapy or combined with enalapril. The results have shown that in patients treated with 10 mg of lercanidipine office and home, SBP/DBP decreased by 11.0/10.4 mmHg and 8.8/4.6 mmHg with a responder rate (defined as office SBP and DBP reductions
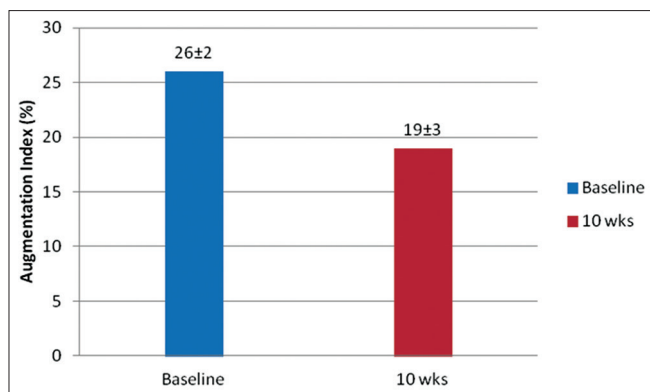
Figure 2: Effects of 10 weeks' lercanidipine treatment on augmentation index ($P < 0.005$ vs. baseline)

of >20 and >10 mmHg) of 47% and 53%, respectively. The values obtained with the 20 mg dose of lercanidipine were -13.0/-13.0 mmHg and -7.7/-5.5 mmHg with a responder rate of 46% and 62%, respectively.

Large-scale, open observational studies performed in clinical practice in patients treated with lercanidipine10 mg as monotherapy uptitrated to 20 mg in 36%–47% of patients[59,60] reported a high percentage of patients (46.4%–63.0%) with normalized BP.

Comparison with other dihydropyridine calcium channel blockers

Globally, the antihypertensive efficacy of lercanidipine, assessed either as office BP and 24-h BP monitoring, does not differ statistically from other DHP-CCBs such as amlodipine, felodipine, nifedipine GITS, lacidipine, and manidipine, as reported in two meta-analyses of comparative studies.[61,62] Lercanidipine has also been compared with other drug classes such as atenolol,[63] hydrochlorothiazide,[64] captopril,[65] losartan,[66] and candesartan,[67] showing a similar antihypertensive efficacy.

Direct comparison trials with amlodipine show equivalence of the antihypertensive efficacy between the two drugs,[68-70] a finding recently confirmed in a controlled randomized trial performed in acute stroke patients.[54] In these patients, lercanidipine and amlodipine significantly reduced clinical BP, as well mean 24-h, day-time, and night-time BP and decreased early morning BP surge. No statistically significant difference was observed in BP reduction, trough-peak ratio, smoothness index, and response and normalization rates between lercanidipine and amlodipine.

The clinical efficacy of lercanidipine is also similar to that of felodipine,[71,72] nifedipine GITS,[72-74] and lacidipine.[56,70,74]

ANTIHYPERTENSIVE ACTIVITY IN SPECIFIC PATIENTS

Elderly patients

The antihypertensive efficacy of lercanidipine in elderly patients with mild-to-moderate hypertension has been evaluated in three multicenter, double-blind randomized trials, as well as in other studies and surveys.[70,74-77]
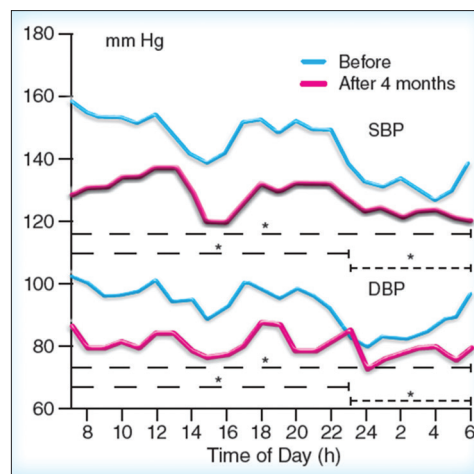

Figure 3: Twenty-four hours ambulatory blood pressure monitoring-Fourier analysis for systolic (upper panel) and diastolic (lower panel) blood pressure before and after 4 months lercanidipine treatment. Asterisks refer (*$P < 0.05$) to the between curves statistical significance both for 24-h and for the day and night periods[57]

The COHORT study[70] compared lercanidipine with amlodipine and lacidipine in hypertensive patients with a mean age of 69–70 years. After 6 months, BP significantly decreased with lercanidipine (−29.6/−14.5 mmHg) as well as with amlodipine and lacidipine, with no significant difference between drugs. Similar results were observed with regard to the responder rate also (around 50% at lower dose–up to 80% after increasing the dose).

In the ELderly and LErcanidipine trial[74] performed on patients with a mean age of 73 years, lercanidipine and nifedipine GITS decreased DBP more than lacidipine, whereas the efficacy on SBP was not different. The AGATE study investigated the antihypertensive activity of lercanidipine in patients aged <65 and ≥65 years,[77] showing a similar antihypertensive effect in the two groups (SBP/DBP -17/9 and -21/10 mmHg, respectively).

This finding has been confirmed in a large survey in general practice,[59] with a similar reduction of SBP/DBP in patients <65 or ≥65 years old (-24/14 mmHg vs. -29/13 mmHg) and similar rate of BP normalization (65% and 60%). Moreover, this survey demonstrated comparable changes in BP (SBP/DBP -26/-14 mmHg and -24/-14 mmHg) and in BP normalization rate (66% and 61%) in females and males, respectively. Overall, the responder rate was 72% with a 10 mg dose, whereas 29% of subjects needed the 20 mg dose to obtain BP control.

Therefore, the therapeutic activity of lercanidipine is not age or gender dependent. This finding has an important therapeutic relevance if we consider that: (a) the majority of hypertensive patients are older than 65 years, (b) it is more difficult to achieve BP control in elderly women than in elderly men,[7] and (c) international guidelines suggest that CCBs are suitable drugs for treating hypertension in the elderly.[15]

Table 1: Comparative randomized studies versus other calcium channel blockers

Reference	*n*	Design	Drug (s) and dose (mg)	Duration	Main efficacy results
De Giorgio, 1999	20	DB, CO	Lercanidipine 20 Amlodipine 10	4 weeks	Lercanidipine equivalent to amlodipine in 24-h ABPM reduction
Macchiarulo, 2001	110	R	Lercanidipine 10 Felodipine ER 10 Amlodipine 10 Nifedipine 40-60 Verapamil 240	4 months	Percentage BP reduction: Nifedipine > lercanidipine > amlodipine > verapamil > felodipine

Romito, 2002
LEAD study
	250	R	Lercanidipine 10-20
			Felodipine 10-20
			Nifedipine GITS 30-60
				8 weeks	Lercanidipine equivalent to felodipine and nifedipine
					Switch to higher dose
					  Lercanidipine 20 mg=15.7%
					  Felodipine 20 mg=13%
					  Nifedipine 60 mg=13.4%

Leonetti, 2002
Zanchetti, 2003
COHORT study (elderly >60 years)
	828	R, DB	Lercanidipine 10-20
			Amlodipine 5-10
			Lacidipine 2-4
				12 months	Response rate
					  Lercanidipine 10 mg=52%
					  Amlodipine 5 mg=56%
					  Lacidipine 2 mg=47%
					Switch to higher dose
					  Lercanidipine 20 mg=22%
					  Amlodipine 10 mg=23%
					  Lacidipine 4 mg=24%
					Add on
					  Lercanidipine=26%
					  Amlodipine=21%
					  Lacidipine=29%

Cherubini, 2003
ELLE study (elderly)
	324	R, DB	Lercanidipine 5-10
			Lacidipine 2-4
			Nifedipine GITS 30-60
				24 weeks	Switch to higher dose
					  Lercanidipine=14%
					  Lacidipine=19%
					  Nifedipine=11%

Grassi, 2003	28	R, DB	Lercanidipine 10 Felodipine 10	3 months	Lercanidipine > felodipine in reducing sympathetic activation Lercanidipine=felodipine in reducing BP

Millar Craig, 2003 (elderly)	222	R, DB, DD	Lercanidipine 10-20
			Lacidipine 2-4
				4-5 months	Lercanidipine=lacidipine in reducing BP
					Switch to higher doses
					  Lercanidipine=61%
					  Lacidipine=67%
					  No differences in 24 h ABPM

Lund Johansen, 2003	92	R	Lercanidipine 10-20 Amlodipine 10-20	8 weeks	Lercanidipine 20 mg equivalent to Amlodipine 10 mg

Casiglia, 2004	54	R	Lercanidipine 10-20
			Manidipine 10-20
				3 months	Lercanidipine=Manidipine in reducing BP
					Switch to 20 mg
					  Lercanidipine=22%
					  Manidipine=28%
					  No differences in 24 h ABPM

Barrios, 2008 TOLERANCE study	650	R	Lercanidipine 20 Amlodipine 10	At least 1 month	Lercanidipine 20 mg equivalent to Amlodipine 10 mg

ABPM=Ambulatory BP monitoring, BP=Blood pressure, CO=Controlled, DB=Double-blind, DD=Double-dummy, R=Randomized, ER=Extended release, GITS=Gastrointestinal therapeutic system

Patients of different populations

Efficacy and tolerability of antihypertensive drugs may vary between populations. In clinical studies with antihypertensive drugs, most of the patients are Caucasians. African-Americans are more likely to have chronic kidney diseases and end-stage renal disease than Caucasians.[78] In general, the former have a better response in terms of BP reduction treatment with CCB monotherapy and diuretics than β-blockers and inhibitors of the renin-AT axis.[79] BP response to CCB monotherapy is qualitatively similar in Blacks and Whites.[80]

There are limited data specifically evaluating BP-lowering and long-term outcomes in Asian populations, but the response to antihypertensive drugs is likely to be similar to Caucasians.[81]

Table 2: Large, effectiveness studies in real-life setting

Reference	*n*	Dose (mg)	Duration	Main results
Barrios, 2002 ELYPSE	9059	10	12 weeks	Responders 10 mg=70%
Barrios, 2006 LAURA	3175	10-20	24 weeks	CO=82% 45% of patients=20 mg Need add on=18%
Barrios, 2006 LERZAMIG	2793	10-20	12 weeks	Very good response=51% (physician rating) 42% of patients=20 mg Need add on=18%
Burnier, 2007	2199	10-20	8 weeks	Responders=72% On target=59% 39% of patients=20 mg Need add on=13.5%
Barrios, 2007 ELECTRA	1523	10	12 weeks	Responders=76% Need add on=24%

CO=Controlled

A dedicated study with lercanidipine has been performed among Asians of different ethnic groups (Chinese, Malays, and Indians) and the results confirm that lercanidipine is effective in lowering BP in the Asian population, similarly to other studies involving Caucasians.[82]

It therefore can be stated that the therapeutic effect of lercanidipine is not race or ethnicity dependent.

Patients with isolated systolic hypertension

In patients with isolated systolic hypertension,[56] the responder rate after 8 weeks of treatment was significantly higher with lercanidipine than with lacidipine (65% vs. 50% *P* = 0.04), whereas no significant difference was observed at the end of the study (67% vs. 58%). Another placebo-controlled study[83] reported a high percentage of patients with normalized BP (62%) after treatment with lercanidipine.

Patients with concomitant cardiovascular risk factors: Obesity, metabolic syndrome, dyslipidemia, diabetes, target organ damage

The LERZAMIG study,[84] performed in obese or overweight patients, showed that the antihypertensive efficacy of lercanidipine is independent of body mass index or excessive body fat. At the end of treatment, a "very good response" was rated by 51% of evaluating physicians. In this high-risk population, 42% of patients required the 20 mg dose.

This finding has been recently confirmed by the results of a study performed on hypertensive patients with severe obesity, in which the 24-h BP-lowering effects of lercanidipine, combined with enalapril, were shown to be similar in magnitude to those detected with the felodipine-enalapril combination.[32] In the lercanidipine/enalapril combination-treated group, the antihypertensive effects were associated with a much

lesser tachycardia and sympathetic activation than in the felodipine/enalapril-treated group.

The LAURA study,[85] a multicenter, observational, open-label investigation performed on 3175 patients in a real-life setting, evaluated lercanidipine effectiveness in patients with hypertension and concomitant CV risk factors, such as dyslipidemia, smoking, family history of CV disease, and target organ damage. After 6 months of lercanidipine treatment, BP significantly decreases by 18.5/13.8 mmHg in patients at low risk and by 23/15.2, 24.4/16.1, and 27.4/17.4 mmHg in patients with medium, high, and very high risk, respectively. A BP control rate was achieved in 55% of patients treated with 10 mg/day of lercanidipine and in 82% of those uptitrated to 20 mg/day. Therefore, a significant antihypertensive effect was obtained across all CV risk levels, more evident in patients at highest risk.

Data obtained in hypertensive patients with type-2 diabetes have shown that the antihypertensive efficacy of lercanidipine as monotherapy was not associated with impairment of glucose homeostasis. In these patients, fasting blood glucose significantly decreased from 153 to 133 mg/dl, as well as the glycosylated hemoglobin level (5.8%–5.5%), fructosamine (from 280 to 230 mg/dl), and the area under the curve obtained during the oral glucose tolerance test, without significant differences between 10 and 20 mg/day of lercanidipine. At baseline, patients were randomized to receive 10 mg or 20 mg of lercanidipine. The dose could be increased after 4 weeks to 20 mg or 30 mg according to the clinical response. At the study end, 55% of patients responded to 10 mg and 50% of patients responded to 20 mg. The response reached 95% of the patients after uptitration to 20 mg.[86]

Patients with chronic renal disease/albuminuria

CCBs could be particularly indicated for renal protection during long-term treatment of hypertension.[87,88] However, DHP-CCBs have a heterogeneous impact on renal hemodynamics. Unlike other DHP-CCBs, which dilate only the afferent artery, lercanidipine dilates both the afferent and the efferent glomerular arteries[46] avoiding the increase of intraglomerular capillary pressure involved in renal damage and progression. While amlodipine displays a renal protection only when combined with angiotensin-converting enzyme (ACE) inhibitors or with angiotensin receptor blockers, otherwise lercanidipine, thanks to its renal hemodynamic effects, protects renal function as single-drug regimen.

The "Diabete Ipertensione Albuminuria Lercanidipina" study[89] which evaluated the effectiveness of lercanidipine monotherapy in comparison with ramipril in mild-to-moderate hypertensive patients with type-2 diabetes and persistent microalbuminuria, showed a >50% reduction of microalbuminuria) in 34.2% and 22.2% of patients treated with lercanidipine and ramipril, respectively. This finding can explain the improvement of creatinine clearance in hypertensives, with or without type-2 diabetes and with chronic mild renal failure, uncontrolled with ACE inhibitors or AT receptor blockers, observed in the

ZAndip en Function Renal Alterada study.[90] Lercanidipine and RAAS inhibitors have a synergic effect in reducing microalbuminuria.[91] Indeed, 10–20 mg/day of lercanidipine as add-on to renin-AT axis blocking drugs significantly reduces proteinuria by 20%–35% in patients with proteinuric renal disease.[92,93] Most recently, the REnal Disease: LErcanidipine Valuable Effect on urinary albumin Loses trial compared the effects of lercanidipine associated with enalapril versus the amlodipine plus enalapril combination; investigators found a reduction of albuminuria in the lercanidipine-treated patients but not in the group treated with amlodipine.[94]

The ability of lercanidipine 20 mg to reduce albuminuria in patients with hypertension can be a protective effect against renal damage since the kidney is one of the targets for end-organ damage in hypertensive and diabetic patients.[15] The improvement of renal function with lercanidipine has been evaluated in patients after renal artery intervention for atherosclerotic lesions.[95] Six months after the intervention, the eGFR significantly increased from 71 ± 21 ml/min/1.73 m^2 to 78 ± 23 ml/min/1.73 m^2 and 24-h urine protein excretion decreased significantly from 0.03 g to 0.02 g. This evidence, while confirming the renal protection of lercanidipine, has important clinical relevance because it has been demonstrated that microalbuminuria/proteinuria in hypertensives is an important predictor of CV disease and chronic renal impairment.[96]

Therefore, lercanidipine significantly improves BP in young and elderly hypertensive patients, as well as in patients with diabetes, or CV risk factors. The antihypertensive efficacy does not differ statistically from other DHP-CCBs.

In patients with kidney disease, lercanidipine improves creatinine clearance and reduces microalbuminuria, particularly when associated with renin AT system inhibitors.

TOLERABILITY
Adverse events
The most frequent adverse events (AEs) induced by DHP-CCBs are related to systemic vasodilation and include ankle edema, dizziness, headache, flushing, palpitations, and vertigo. Numerous studies have shown that treatment with lercanidipine is associated with a very low rate of AEs[53] [Table 3] and withdrawal from the therapy. Even if the rate of AEs differs across studies, overall 11.5%–11.8% of patients reported AEs[53,85] and a very low percentage (1%–2%) discontinued lercanidipine treatment due to AEs.[59] In the ELYPSE study,[97] which included 9000 patients, AEs were recorded in 6.5% of patients.

Compared with other DHP-CCBs (amlodipine, felodipine, lacidipine, nifedipine, and nitrendipine), the tolerability of lercanidipine was globally higher,[53,70,74,98] providing again a strong evidence of a good tolerability during prolonged therapy.

The "lercanidipine challenge trial,"[99] performed in patients with AEs during treatment with different DHP-CCBs and who

Table 3: Adverse effects of lercanidipine compared with placebo

AE	Lercanidipine (%)	Placebo (%)
Flushing	1.1	0.4
Ankle edema	0.9	1.3
Palpitations	0.6	0.4
Headache	2.3	1.3
Vertigo	0.4	0.4
Asthenia	0.4	0.4

Data from Borghi. AE=Adverse events

switched to lercanidipine, showed lercanidipine treatment to be associated with a significant reduction of flushing, headache, dizziness, and particularly ankle edema.

Ankle edema is the most common AE during treatment with DHP-CCBs and may reduce patients' compliance to the therapy and favor drug withdrawal. Globally, the incidence of ankle edema during lercanidipine treatment is between 0.6% and 9%,[53,70] much lower than the 23%–29% reported with other DHP-CCBs.[100,101] Three studies[69,102,103] have assessed the ankle edema intensity and the incidence induced by lercanidipine using an objective measurement: leg volume (water-displacement volume) and pretibial subcutaneous tissue pressure. The increase in leg volume after 8 weeks of treatment was significantly lower in the lercanidipine group compared with amlodipine,[69,103] and a significantly lower percentage of patients had clinical signs of leg edema with lercanidipine than with amlodipine (9.8% vs. 33.3%). Similar findings have been obtained comparing lercanidipine with nifedipine GITS during 12 weeks of therapy. Ankle-foot volume and pretibial subcutaneous tissue pressure were significantly lower with lercanidipine than with nifedipine.[102] This objective evidence confirms the observations reported in clinical trials and particularly in two meta-analyses of randomized trials.[61,104] Compared with the pooled data reported for amlodipine, nifedipine, and felodipine,[61] lercanidipine was associated with a significantly lower percentage of patients with peripheral edema (7.0% vs. 14.0%, $P < 0.001$), with 56% relative risk reduction, while compared with the pooled data of lacidipine and manidipine, there were no significant differences (8.5% vs. 6.6%). Therefore, lipophilic DHP-CCBs induce a significant 57% risk reduction for ankle edema compared with hydrophilic DHP-CCBs.[104] The low incidence of ankle edema with lercanidipine is independent of age,[70,74,99] gender,[59,69] ethnic group,[82] presence of concomitant CV disease,[59,85] or BP reduction.[69,102]

Withdrawal rate and persistence
In all probability, the good tolerability profile of lercanidipine has given a very low withdrawal rate for AEs of 2.1%–<1%.[59,70,97] Compared with amlodipine, nifedipine, and felodipine,[61,105] lercanidipine treatment was associated with a 76% decrease in the relative risk of withdrawal. A very high adherence and persistence to therapy (90%–99%) during lercanidipine treatment[59,60,97,106] have been reported, compared with the 39%–72% reported with other DHP-CCBs.[106,107]

Metabolic adverse events

Overall, no clinically meaningful changes in any of the laboratory parameters during treatment with lercanidipine have been reported during the studies. Chronic therapy with lercanidipine has a neutral effect on glucose or lipid metabolism. On the contrary, it has been shown to have a favorable effect on fasting glucose, glucose tolerance test, insulin sensitivity, glycosylated hemoglobin – both in diabetics and not diabetics – total cholesterol, LDL-C, high-density lipoprotein-cholesterol, and triglycerides.[27,60,84,93,86] The absence of negative effects of lercanidipine on lipid and glucose metabolism is an added advantage in the treatment of hypertension, frequently associated with impaired metabolic parameters.

Globally, lercanidipine is well tolerated with a significantly lower incidence of AEs, particularly peripheral edema, compared with amlodipine, nifedipine, and felodipine. No clinical changes in laboratory parameters have been reported during the studies.

Conclusions
Pharmacological characteristics

Lercanidipine is a third-generation lipophilic DHP-CCB. Due to its high lipophilicity, lercanidipine has an easy penetration and a considerable concentration and persistence in the phospholipids bilayer of the smooth muscle cell membranes, from which it is gradually released to reach the calcium channels; therefore, despite its relatively short half-life, the pharmacological activity of lercanidipine is prolonged.

Antihypertensive efficacy

Globally, the antihypertensive efficacy of lercanidipine is not inferior, and in some studies even superior, to that of other DHP-CCBs or other antihypertensive agents. The dosage of lercanidipine in the different studies was 10–20 mg/day. The antihypertensive efficacy of lercanidipine has been demonstrated in patients with mild-moderate hypertension, as well in patients with type-2 diabetes, renal disease, and isolated systolic hypertension or with several concomitant CV risk factors.

Renal effects

Studies in hypertensive patients with diabetes or renal impairment have shown that lercanidipine has protective effects on the kidneys because it dilates the afferent and efferent glomerular arteries, preserving the intraglomerular pressure. Unlike other CCBs, lercanidipine has also been shown to reduce albuminuria, a recognized risk factor for CV events in hypertensive patients.

Tolerability

Lercanidipine has a favorable tolerability profile with lower incidence of adverse effects, particularly peripheral edema, and withdrawals because of peripheral edema, compared with amlodipine, nifedipine GITS, and felodipine. Moreover, the adherence of patients to lercanidipine therapy is higher than that reported with first- and second-generation DHP-CCBs.

These evidences are of great value for everyday clinical practice and can help physicians to better tailor the treatment according to patients' needs and therapeutic response.

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Conflicts of interest
There are no conflicts of interest.

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