The effectiveness and tolerability of lercanidipine is independent of body mass index or body fat percent. The LERZAMIG study

This study, carried out in primary care, looked at whether the effectiveness and tolerability of an antihypertensive drug is affected in overweight and obese patients.

Abstract

This study set out to assess whether the effectiveness and tolerability of lercanidipine for the treatment of essential hypertension in daily clinical practice is affected by body mass index (BMI) or body fat percent (BFP). A total of 2,793 outpatients (mean age 59.8 years) with mild-to-moderate hypertension participated in a multi-centre, prospective, open-label study. All patients received oral treatment over 12 weeks with lercanidipine 10 mg, which was titrated to 20 mg if blood pressure (BP) control was not attained. They were visited at baseline and at four, eight and 12 weeks. BFP was measured by the bioelectrical impedance analysis using an Omron BF-302 body fat monitor. Patients who were overweight or obese were also prescribed a hypocaloric diet.

Results showed that, at baseline, sytolic BP was 159.4±11.7 mmHg, diastolic BP was 94.5±7.5 mmHg, BMI was 30.9±8.4 kg/m^2, and BFP 27.7±6.3%. At 12 weeks, BP was lowered to 138±10.1 mmHg (systolic) and 81±7.2 mmHg (diastolic) ($p<0001$). BMI and BFP significantly decreased to 29.3±8 kg/m^2 and 27.3±4.1% ($p<0.05$), respectively, which was most likely to be diet-related. Antihypertensive effectiveness was independent of baseline BMI and BFP values. There was a low incidence of adverse effects (5.5%), with headache (3.4%) and pedal oedema (1.5%) being the most frequent. Some 93% of patients completed the 12-week treatment period.

The study showed that lercanidipine is an effective and well tolerated antihypertensive drug in daily clinical practice and its antihypertensive properties are not influenced by BMI and BFP.

Key words: lercanidipine, hypertension, obesity, body mass index, body fat percent.

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Introduction

Lercanidipine is a third-generation dihydropyridinic calcium channel blocker (CCB), which causes systemic vasodilation by blocking the influx of calcium ions through L-type calcium channels in cell membranes.[1-3] This vasoselective drug is a highly lipophilic dihydropyridine that has a slower and smoother onset, and a longer duration of action than other CCBs.[4] Furthermore, lercanidipine may exert an antiatherogenic activity unrelated to its antihypertensive effect.[5-7] Lercanidipine is well tolerated, with fewer vasodilator-related adverse events than other dihydropyridines.[8] Its efficacy has been evaluated in non-comparative and comparative studies versus other CCBs[9-11] and other antihypertensive drugs[12-15] in mild-to-moderate hypertension. In addition, some studies[16] suggest that lercanidipine is useful in patients with severe or resistant hypertension, elderly patients, hypertensive patients with type 2 diabetes, and in post-menopausal women.

> ***'We aimed to determine in daily clinical practice whether antihypertensive effectiveness is affected by two different body composition variables, BMI and BFP'***

High blood pressure is very frequent in obese subjects.[17] Complex mechanisms link increasing body weight with increasing blood pressure (BP). In obese individuals, sympathetic nervous and renin-angiotensin-aldosterone system activation appear to play an important role in the following: sodium and water retention, the rightward shift in pressure-natriuresis, and BP elevation.[18-21] A leptin-dependent increase in sympathetic nerve activity may contribute to obesity-related hypertension.[22] Although weight reduction, together with salt restriction and increased physical exercise, can lower BP, antihypertensive medication is usually required in overweight or obese hypertensive patients.[23] Since antihypertensive efficacy may be reduced in overweight or obese patients,[24] we aimed to determine in daily clinical practice whether the antihypertensive effectiveness of lercanidipine may be

Table 1. The study protocol

Procedure	Visit 0 baseline	Visit 1 4 weeks	Visit 2 8 weeks	Visit 3 12 weeks
SBP, DBP, HR	X	X	X	X
Eligibility criteria	X			
Demographic data	X			
Patient history and physical examination	X			
Height measurement	X			
Weight measurement	X	X	X	X
Body mass index (BMI)	X	X	X	X
Body fat percent (BFP)	X	X	X	X
Blood tests	X			X
Study medication (lercanidipine) supplied	X	X	X	X
Diet recommendations	X	X	X	X
Adverse events		X	X	X
Compliance with treatment		X	X	X

Key: SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate

influenced by two different body composition variables:[25] body mass index (BMI) and body fat percent (BFP).

Patients and methods

LERZAMIG (¿Es LERcanidipino igual de eficaZ en todos los pacientes con hipertensión Arterial independientemente de la Masa e Indice de Grasa corporal?) was a prospective, multicentre, open-label, non-comparative study set up to assess the effectiveness and tolerability of lercanidipine and the potential influence of BMI and BFP on the effect of the drug. The study was conducted in a Spanish primary care setting. Patients were treated with lercanidipine 10–20 mg o.d. and followed for a 12-week period. Eligible patients were men and women aged 18 years, with previously treated or newly diagnosed mild or moderate essential hypertension, which was defined as a systolic BP (SBP) of ≥ 140 mmHg (≥ 130 mmHg in patients with diabetes) and < 180 mmHg, and a diastolic BP (DBP) of ≥ 90 mmHg (≥ 80 mmHg in patients with diabetes) and < 110 mmHg.

Exclusion criteria were: severe hypertension (SBP > 180 mmHg or DBP > 110 mmHg),[26,27] known hypersensitivity or history of severe adverse events to any dihydropyridine, evidence of unstable angina or decompensated congestive heart failure, myocardial infarction within the previous 30 days, left ventricular outflow obstruction, severe rhythm disturbances with no pacemaker, liver dysfunction (serum aminotransferases > 2-fold increase or serum bilirubin > 1.5-fold increase above upper limit of normality), renal insufficiency (serum creatinine concentration > 1.5 mg/dL [132.6 mmol/L] in men and > 1.4 mg/dL [123.8 mmmol/L in women]), and any contraindication for prescribing treatment with lercanidipine (as stated in the technical form of the product or if the investigator considered the patient should be excluded). Pregnant women, nursing mothers, or women of childbearing potential not using adequate contraception methods were also excluded. Informed consent was obtained from all participants.

SBP and DBP were measured with a mercury sphygmomanometer in patients in a sitting position with their back supported after 10 minutes of resting. Patients were advised not to smoke or to drink coffee in the 30 minutes prior to BP assessment. Visit BPs were recorded as the average of two separate measurements (a third measurement was obtained when there was a difference of 5 mmHg between the two readings). Adequate BP control was defined as a SBP < 140 mmHg and a DBP < 90 mmHg for patients without diabetes, and a SBP < 130 mmHg and a DBP < 80 mmHg for patients with diabetes.[26,27]

All patients underwent a complete physical examination and their BMI and BFP was calculated. Overweight was defined as a BMI > 25 kg/m^2 and obesity as a BMI > 30 kg/m^2. BFP was measured using a practical and reliable device for primary care clinical practice, the OMRON BF 302 body fat monitor (Omron Healthcare Europe, Hoofdoorp, The Netherlands). This device works by bioelectrical impedance and analyses the electrical resistance of the body tissues by sending an extremely weak insensitive electrical current through the body. Since fat tissue has little or no electric conductivity, it is possible to determine the ratio of fat tissue compared with other tissues. To make the measurement as accurate as possible, the measurement is taken in the upper body where most fat is located. BFP is calculated by how much of the total body weight is made up by fat and the corresponding per cent of total weight. Fat obesity is considered when BFP is > 30%.

'The antihypertensive efficacy of some drugs may be reduced in overweight or obese patients'

Lercanidipine was administered at an initial daily dose 10 mg once daily, taken immediately after waking up. Patients with overweight or obesity were also prescribed a hypocaloric diet. Four visits were scheduled: at baseline and after four, eight and 12 weeks of treatment. At each visit, BP, heart rate

Table 2. Baseline characteristics of the study population

Baseline characteristics (n=2,793)		
Data	**%**	**Mean±SD**
Total patients (n=2,793)		
Age, years		59.8±10.7
Patients > 65 years	32	
Sex		
- men	47.2	
- women	52.8	
Height, cm		164.5±8.7
Weight, kg		76.1±12.1
Body mass index (BMI), kg/m^2		28.2±4.3
> 25 kg/m^2 (n=1,489)	53.3	
Body fat percent (BFP), %		27.7±6.3
> 30% (n=1,452)	52.0	
SBP, mmHg		159.4±11.7
DBP, mmHg		94.5±7.6
HR, beats/min		76.0±8.6
Mild (grade I) hypertension	44	
Moderate (grade II) hypertension	56	
Cardiovascular risk factors		
- smoking	39.9	
- hypercholesterolaemia	29.5	
- excessive alcohol intake	17.2	
- diabetes mellitus	12.2	
- family history of cardiovascular disease	1.6	
Concomitant diseases	34.1	
- peripheral arterial disease	14.5	
- ischaemic heart disease	12.2	
- cerebrovascular disease	5.8	
- congestive heart failure	5.6	
- renal insufficiency	2.9	
- other	68.8	

Key: SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate

Table 3. Previous antihypertensive medication and reasons for the prescription of lercanidipine

Data	Number of patients	%
Total patients	2,793	100
Naïve patients (newly treated)	1,269	45.4
Previously treated with antihypertensive drugs	1,524	54.6
Previous antihypertensive medication		
Diuretics	698	45.6
Angiotensin-converting enzyme (ACE) inhibitors	675	44.3
Beta blockers	166	10.9
Calcium channel blockers	154	10.1
Angiotensin II receptor blockers	141	9.3
Other medications	44	2.9
Reasons to prescribe lercanidipine (n=1,524, 54.6%)		
Uncontrolled blood pressure	1,086	38.9
Adverse events	350	12.5
Other	88	3.1

(HR), BMI, and BFP were measured, compliance was checked, and adverse events were recorded. If BP control was not attained with lercanidipine 10 mg at four weeks, the drug was uptitrated to 20 mg once daily; if BP was uncontrolled, add-on drugs were allowed. The investigator designated any adverse events as either potentially drug related or not drug related. Two blood tests including fasting glucose, uric acid, ions and a complete lipid profile were performed at baseline and after the 12 weeks of therapy. At study end, the effectiveness and tolerability of treatment with lercanidipine were assessed by both patients and investigators as 'poor', 'regular', 'good', and 'very good'. The study protocol is shown in table 1.

Statistical analysis

Categorical data were expressed as numbers and per cents and continuous data as mean (standard deviation). The Student's *t* test for paired and unpaired data was used to assess the effects of treatment on continuous variables. Categorical variables were analysed with the chi-square ($\chi 2$) test. In order to study differences in the quantitative variables over time as well as progression, or between group differences, the analysis of variance (ANOVA) for repeated or independent measurements was used. The analysis of covariance (ANCOVA) was used to assess the effect of lercanidipine in subsets of the study population divided according to BMI, age (≤ 65 years *vs.* > 65 years), and diabetes mellitus (yes/no). Statistical significance was set at $p<0.05$. The SPSS statistical software package for Windows (version 9.1) was used to analyse the data.

Results

Baseline characteristics of study population are shown in table 2. The study included 2,793 mild-to-moderate essential hypertensive patients with a mean age of 59.8±10.7 years and 893 (32%) were more than 65 years. Over half of the patients (53.3%) had overweight or obesity (BMI > 25 kg/m^2) and 52% had excessive body fat (BFP > 30%). Mild (grade I) hypertension was diagnosed in 44% and moderate (grade II) in 56% of patients, respectively. Baseline SBP was 159.4±11.7 mmHg and DBP was 76.0±8.6 mmHg.

Table 4. Changes in blood pressure, heart rate, body mass index, and body fat percent through the 12-week study period

Data	Visit 0 baseline	Visit 1 4 weeks	Visit 2 8 weeks	Visit 3 12 weeks
SBP, mmHg	159.4±11.7	146.6±11.7	140.8±10.7	138.1±10.2*
DBP, mmHg	94.5±7.6	86.1±7.8	82.6±7.4	81.0±7.3*
HR, beats/min	76.0±8.6	74.8±7.8	73.9±7.6	73.5±7.5
Weight, kg	76.1±12.1	75.2±11.8	74.4±11.6	74.1±11.5
BMI, kg/m²	28.2±4.3	27.8±4.2	27.5±4.1	27.4±4.1
BFP, %	27.7±6.3	30.1±8.3	29.7±8.3	29.4±8.2

Data as mean±standard deviation.
*p<0.01 baseline *vs.* visit 3.
Key: SBP = systolic blood pressure; DPB = diastolic blood pressure; HR = heart rate; BMI = body mass index; BFP = body fat percent

Table 5. Changes in blood pressure in different subgroups according to age and presence of diabetes

Data	Age, years		Diabetes mellitus	
	≤ 65	> 65	Yes	No
Visit 0, baseline				
SBP, mmHg	158.1±11.5	162.2±11.7	161.4±12.7	159.1±11.6
DBP, mmHg	94.8±7.3	93.8±7.9	94.5±8.1	94.5±7.5
Visit 1, 4 weeks				
SBP, mmHg	145.8±11.6	148.5±11.7	148.8±12.7	146.3±11.5
DBP, mmHg	86.3±7.6	85.5±8.1	86.7±8.3	85.9±7.7
Visit 2, 8 weeks				
SBP, mmHg	140.1±10.7	142.4±10.5	142.0±11.6	140.7±10.5
DBP, mmHg	82.8±7.4	82.4±7.4	83.1±7.3	82.6±7.4
Visit 3, 12 weeks				
SBP, mmHg	137.4±10.2	139.7±9.9	138.9±10.9	138.0±10.1
DBP, mmHg	81.2±7.3	80.8±7.3	80.9±7.1	81.1±7.3

Key: SBP = systolic blood pressure; DBP = diastolic blood pressure

Some 45.4% of patients had newly diagnosed essential hypertension. All received lercanidipine as initial therapy. In previously treated patients (54.6%), lercanidipine was prescribed due to uncontrolled hypertension in 38.9%, and to drug-related adverse events with other agents in 12.5% (table 3). At study end, 42% of patients were uptitrated to 20 mg/day of lercanidipine and 18% needed to add more antihypertensive medication to achieve BP goals. The per cent of patients who required add-on therapy was not significantly different in the subsets of patients with high or low BMI or high or low BFP.

SBP and DBP was reduced from 159.4±11.7 mmHg and 94.5±7.6 mmHg, respectively, at baseline, to 138.1±10.2 mmHg and 81.0±7.3 mmHg, respectively, at study-end (p<0.0001). Final BP reductions were –21.3±11.6 mmHg for SBP and –13.6±8.2 mmHg for DBP. Heart rate reduced from 76.0±8.6 beats/minute to 74.1 ± 11.5 beats/minute, with a reduction of -2.6±6.7 beats/min (p=ns). Table 4 shows the changes in BP, HR, weight, BMI and BFP through the study period. No significant changes were observed with lercanidipine in fasting glucose, serum creatinine, uric acid, ions or lipid profile.

Weight was reduced from 76.1±12.1 kg at baseline to 74.1±11.5 kg at study end while BMI decreased from 28.2±4.3 kg/m² to 27.4±4.1 kg/m², and BFP increased from 27.7±6.3 % to 29.4±8 .2 % (all, p=ns). The SBP and DBP reductions were statistically significant, not only in the subsets of patients with a BMI ≤ 25 kg/m² and in those with a BFP < 30%, but also in those patients with a BMI > 25 kg/m² and with a BFP > 30% (p<0.001, intra-group differences). Although the magnitude of SBP and DBP reductions were non-significant, the effect was slightly higher in non-obese than in obese patients.

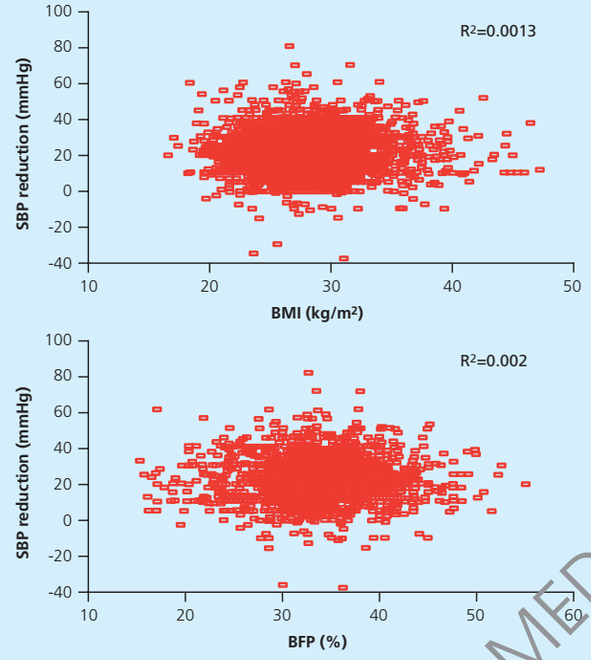
At the final visit, 11.8% of previously overweight patients showed a BMI < 25 kg/m² or a BFP < 30%. BP

'The antihypertensive effectiveness of lercanidipine was consistent in older and younger patients'

was similarly reduced in the study cohort, regardless of BMI or BFP. No statistical correlation was found between SBP or DBP reductions and the two variables (figures 1 and 2). Table 5 shows that the antihypertensive effectiveness of lercanidipine was consistent in older (> 65 years) and younger (< 65 years) patients, and in patients with or without diabetes with statistically significant SBP and DBP reductions (p<0.001). The effectiveness of lercanidipine was rated by the investigators as 'good' and 'very good' in 43.8% and 50.9% of cases, respectively. In addition, patients rated the effectiveness as 'good' in 47.3% and 'very good' in 47.4% of cases.

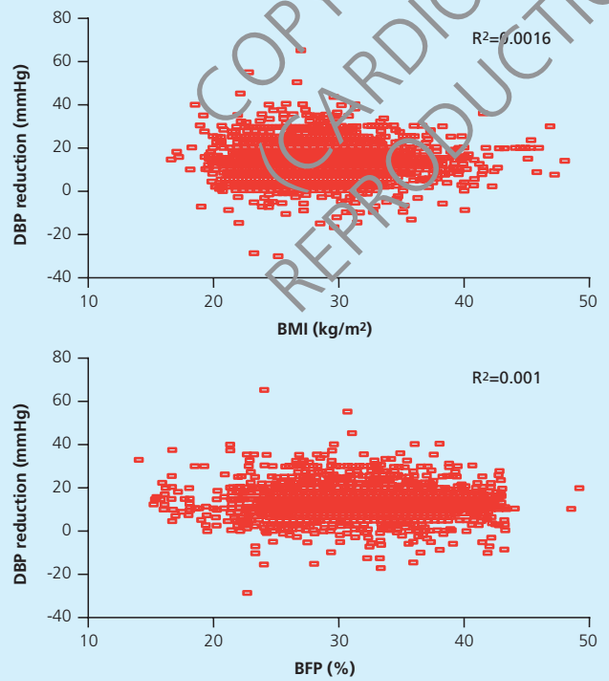
Some 93% of patients completed the 12-week treatment period with lercanidipine. There was a low incidence of adverse events (5.5%) with the most frequent being oedema (2.9%), headache (2.6%), flush (1.9%), dizziness (0.6%), asthenia (0.5%), skin rash (0.3%), and palpitations (0.4%). The rate of events was

Figure 1. Correlations between SBP reduction and BMI and between SBP reduction and BFP



Key: SBP = systolic blood pressure; BMI = body mass index; BFP = body fat percent

Figure 2. Correlations between DBP reduction and BMI and between DBP reduction and BFP



Key: DPB = diastolic blood pressure; BMI = body mass index; BFP = body fat percent

similar in patients with BMI > 25 kg/m² or with BMI ≤ 25 kg/m² and with BFP > 30% or < 30%. Fifty-nine (2.1%) patients discontinued the study due to side effects. No serious adverse events were reported. The tolerability of antihypertensive treatment with lercanidipine was rated as 'good' or 'very good' by 97% of physicians and 95% of patients.

Discussion

This study was designed to assess whether the antihypertensive effectiveness of lercanidipine might be influenced by obesity. The latter was measured using two different body composition variables,[25] BMI and BFP, that can be assessed in daily clinical practice. Our results show that lercanidipine is effective and well tolerated regardless of BMI or BFP. These data are in agreement with those previously reported in randomised trials[16,28] and in the post-marketing ELYPSE (Eficacia de Lercadipino Y su Perfil de Seguridad [Efficacy of Lercanidipine and its Safety Profile]) study.[10]

Lee *et al.*[29] showed that the relative risks of hypertension were 2.56 times greater in men and 3.17 times greater in women whose BMIs were greater than 27 kg/m². It has been shown that BMI is an independent factor associated with the incidence of hypertension,[30] and that weight gain is closely related to cardiovascular morbidity, in particular in association with hypercholesterolaemia, diabetes, and hypertension.[31] It has been estimated that a 1 kg increase in body weight implies a 3.1% rise in global cardiovascular risk.[32] Notably, around 50% of our study population were overweight or had body fat increase (BMI > 25 kg/m² or BFP > 30%), confirming that lercanidipine is a useful antihypertensive medication in obesity. Although the magnitude of BP reduction was mildly higher in thin-normal than in overweight-obese patients, the reductions in SBP and DBP achieved in both subgroups after 12 weeks of treatment with lercanidipine were statistically significant.

This is clinically relevant given the

Key messages

- Lercanidipine is an effective and well tolerated antihypertensive drug in clinical practice
- Its good clinical efficacy is not significantly modified in overweight or obese patients or in those with increased body fat percent
- These results are consistent with other previous studies and confirm that lercanidipine appears a useful drug for most hypertensive patients

implication that obesity is a risk factor for hypertension and the fact that the antihypertensive efficacy of some drugs (e.g. beta blockers) may be reduced in overweight or obese patients.[24] Guidelines underline the importance of avoiding overweight in order to achieve better BP control.[26,27] Pathophysiological changes found in obese patients may differ substantially from those found in lean patients. Obese patients have increased cardiac output, volume expansion, and lower total peripheral resistance compared with lean patients.[33] Moreover, hypertension appears to be related to increased activity of both the renin–angiotensin and sympathetic nervous systems in obese patients.[34,35] It is reasonable to suggest, therefore, that some antihypertensive medications may differ in their blood pressure-lowering efficacy in obese patients,[36] so it is important to find a drug that can control BP regardless of obesity. Our data show that lercanidipine is effective regardless of BMI and BFP. In addition, our results also support the usefulness of lercanidipine in patients over 65 years and in patients with type 2 diabetes, which has been previously observed in these populations.[18,37]

Lercanidipine was found to be a well-tolerated antihypertensive drug regardless of BMI or BFP. In fact, only 59 patients (2.1%) discontinued the treatment due to adverse events. The good tolerability profile implies a low withdrawal rate, indicating satisfactory patient compliance. Moreover, lercanidipine appears to be associated with a better tolerability profile and less risk of vasodilator-related adverse reactions compared to other dihydropyridines in the clinical practice setting.[12-14,38] This seems to be related to its differential effect on the vascular bed. Lercanidipine exhibits less discrepancy between capillary and venous dilatation, a lesser impairment of the veno-arteriolar reflex, and a reduced effect on vascular permeability. These characteristics may result in a better tolerability profile, including a significantly lower incidence of pedal oedema.[39]

'Our results show that lercanidipine is effective and well tolerated regardless of BMI or BFP'

In conclusion, despite the limitations of open and non-comparative observational intervention studies, LERZAMIG shows that lercanidipine is an effective and well-tolerated antihypertensive drug in lean or obese hypertensive patients. Its results confirm the findings from previous randomised controlled trials and surveillance studies, and suggest that lercanidipine appears to be a useful option for hypertension management in daily clinical practice.

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Conflict of interest

The study was funded by Recordati Spain, of which AN is the Medical Director. VB, CE, AC and LMR have no conflicts of interest to declare.

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