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ORIGINAL ARTICLE

## Dose–response effect of the lercanidipine/enalapril combination: a pooled analysis

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### ABSTRACT

**Objective:** The dose–effect relationship of fixed-dose combinations of anti-hypertensive drugs has been only poorly explored. This pooled analysis investigates the dose–response relationship of fixed-dose lercanidipine + enalapril in patients with mild-to-moderate hypertension.

**Research design and methods:** This was an individual patient data analysis of four randomized studies ( $n = 2340$ ).

**Main outcome measures:** The primary efficacy variable was the change from baseline in sitting diastolic blood pressure (SDBP). Secondary variables were change from baseline in sitting systolic BP (SSBP), proportion of responder patients, and safety.

**Results:** All fixed-dose combinations were superior to placebo in the reduction of SDBP. The greatest effect was observed with the market-available combination lercanidipine 20 mg/enalapril 20 mg ( $-15.3$  mmHg vs. baseline;  $p < 0.05$ ). The reduction in SDBP associated with the other two marketed fixed combinations of lercanidipine/enalapril were  $-10.7$  mmHg for the 10 mg/20 mg combination and  $-9.8$  mmHg for the 10 mg/10 mg combination ( $p < .05$  for both comparisons). Similar findings were reported for SSBP reduction: the greatest effect was observed with lercanidipine 20 mg/enalapril 20 mg ( $-19.2$  mmHg). The reduction in SSBP was  $-12.5$  mmHg for the 10 mg/20 mg combination and  $-11.1$  mmHg for the 10 mg/10 mg combination ( $p < .05$  for all comparisons). The highest responder rate was reported with lercanidipine 20 mg/enalapril 20 mg (75.0%); this figure was 56.1% with the 10 mg/20 mg and 53.0% with the 10/10 mg combination. No safety concerns were reported.

**Conclusion:** This pooled analysis of four randomized studies shows evidence of a dose–response effect in BP reduction with different fixed combinations of lercanidipine + enalapril. To our knowledge, this is the first analysis investigating the dose–response effect of a specific fixed-dose combination of anti-hypertensive agents. Further studies on this intriguing topic are however necessary.

### ARTICLE HISTORY

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### Introduction


Arterial hypertension is a major cause of death and disability worldwide, due also to its high prevalence in the adult population<sup>1,2</sup>. Despite this, it is widely accepted that the control of blood pressure (BP) remains suboptimal both in high- and low-income countries<sup>3</sup>. Current guidelines issued by the European Society of Hypertension (ESH)/European Society of Cardiology (ESC) recommend the use of combination therapy with antihypertensive drugs characterized by complementary mechanisms of action, as it is usually more effective than high-dose monotherapy<sup>4</sup>. In addition, combination therapy allows the use of lower doses of each drug with respect to monotherapy, thus decreasing the risk of adverse events<sup>4</sup>.

However, combination therapy requires an additional pill burden. This increased complexity of dosing may be associated with reduced adherence, and, ultimately, with poorer efficacy<sup>5,6</sup>. The use of fixed-dose combinations simplifies dosing by allowing two or more drugs to be administered as a single pill. Single administration improves adherence and, consequently, BP control<sup>6</sup>.

A number of possible combinations of antihypertensive drugs are available as fixed-dose combinations, with different doses of each component. However, to our knowledge the correlation between dose and effect of increased doses of fixed-dose combinations has been only poorly explored to date.

Among the different fixed-dose combinations used in clinical practice, the association of a calcium channel blocker (CCB) and a modulator of the renin–angiotensin system (RAS) appears an effective option<sup>4</sup>. One such combination is the third-generation vasoselective dihydropyridine CCB lercanidipine plus the angiotensin-converting enzyme inhibitor (ACEI) enalapril, which was effective and safe in clinical trials<sup>7</sup>, as well as in real-life experiences<sup>8–10</sup>. At present, the lercanidipine/enalapril combination is available at three fixed dosages: 10 mg lercanidipine/10 mg enalapril, 10 mg lercanidipine/20 mg enalapril, and 20 mg lercanidipine/20 mg enalapril. The development program of lercanidipine/enalapril fixed combination consisted of four clinical trials with similar design, which investigated different doses of the

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fixed combination<sup>7,11</sup>. The dose–response relationship of this combination therapy, however, requires further investigation, particularly for clinical purposes. In fact, when different doses of fixed combinations are available, physicians need to know in advance the expected reduction of BP at each dose increase, in order to better tailor the drug therapy to each single patient.

The aim of this pooled analysis is to investigate the dose–response relationship of the fixed-dose combination of lercanidipine + enalapril in subjects with mild-to-moderate essential hypertension (sitting diastolic blood pressure [SDBP] between 95 and 109 mmHg, inclusive) enrolled in the studies of the development program of this combination.

## Methods

All efficacy data derived from the identified studies were merged taking into account the number of subjects (weighted analysis). This pooled analysis is an individual patient data (IPD) analysis, i.e. the individual patient data from single studies are pooled. A two-step approach was used. In the first stage, each of the identified studies is summarized by its factor (treatments and doses)/outcome association estimate and variance. In the second stage, aggregate data (pooled dataset) is then appropriately combined across studies.

The efficacy analysis was based on an intention-to-treat analysis (ITT population). The ITT population included all randomized patients who had taken at least one dose of study medication and had undergone at least one efficacy assessment for the primary efficacy endpoint after baseline.

The primary efficacy variable was the change from baseline to endpoint in mean sitting diastolic BP (SDBP). In more detail, the general linear model was used to compare the SDBP change from baseline to endpoint among the treatment groups considering in the same model the baseline value of the SDBP. The general linear model procedure provides regression analysis and analysis of variance for one dependent variable (SDBP change) by more factors (treatment groups) and covariate (baseline value of SDBP). Larger values of partial eta squared indicate a greater amount of variation accounted for by the model term, to a maximum of 1.

The goal of this pooled analysis was to assign more weight to the treatment arm with more information. Therefore, we weighted each treatment arm by the inverse of the variance. This parameter is roughly proportional to the sample size, but it is a more nuanced measure and serves to minimize the variance of the combined effect<sup>12</sup>. The variance of the combined effect is defined as the reciprocal of the sum of the weights and the standard error of the combined effect is the square root of the variance. Considering as single treatment arm – enalapril monotherapy or lercanidipine monotherapy – the adjusted mean changes from baseline to endpoint were estimated from the ANCOVA model, with treatment dose as factor and the SDBP baseline value as covariate.

Secondary efficacy variables were as follows: change from baseline in mean trough sitting systolic BP (SSBP) at

endpoint, with the same considerations as for SDBP; proportion of responder patients (SDBP <90 mmHg or decrease from baseline  $\geq 10$  mmHg and SSBP <140 mmHg or decrease from baseline  $\geq 20$  mmHg) at endpoint. In the analysis of proportion of normalized/responder patients, the last available data were been used for the final evaluation in accordance with the last observation carried forward method for subjects leaving the study prematurely.

Measurements of BP were performed according to the following standard procedures at each study center. Arterial BP measurements were taken  $24 \pm 2$  hours after dosing with a calibrated mercury sphygmomanometer and BP cuff. Phase I (beat onset) and Phase V (sound cessation) Korotkoff sounds were used as determinants of systolic and diastolic pressure, respectively. Measurement readings were taken as accurately as possible, within  $\pm 2$  mmHg. Two/three BP readings, taken 2 minutes apart were obtained and the mean was used as the BP value. The safety analysis was based on the safety population, which included all randomized patients who had taken at least one dose of study medication. The incidences of treatment-emergent adverse events among patients treated with different fixed-dose combinations of lercanidipine and enalapril, monotherapies, or placebo were compared. The results of the analysis were only descriptive, statistical inference procedures were not applied. Continuous variables were summarized by use of standard measures of central tendency and dispersion: mean, standard deviation (SD) and standard error (SE) and 95% confidence intervals (95% CIs). All tests were two-sided with a significance level fixed at 5%.

The statistical analysis was performed using SAS Version 9.2 (SAS Institute, Cary, NC, USA).

## Results

### Identified studies

Four studies were included in the pooled analyses<sup>7,11</sup>. Their design is summarized in Appendix 1 and inclusion/exclusion criteria are reported in Appendix 2.

### General information and study populations

In total, 2868 patients were recruited in the studies. There were no relevant differences between the treatment groups in baseline characteristics (Table 1). Overall, there was a prevalence of men (1353/2368; 57.1%) and the mean age of the overall population was  $55 \pm 11$  years.

The total number of patients analyzed for efficacy was 2340 (ITT population). Following a run-in period of 2–4 weeks of single-blind placebo treatment, patients were randomly assigned to receive:

- Study #1<sup>7</sup>: placebo or enalapril monotherapy (5 or 10 mg) or lercanidipine monotherapy (5 or 10 or 20 mg) or one of six different combinations of both drugs (8 weeks of double blind treatment);
- Study #2<sup>7</sup>: lercanidipine monotherapy (10 mg) or combination therapy lercanidipine 10 mg + enalapril 10 mg

**Table 1.** Baseline characteristics.

Treatment group	Number of enrolled patients	Mean age (SD)	Males (%)
Placebo	168	55 (11)	83 (49)
Enalapril monotherapy, any dose	506	56 (10)	291 (58)
Lercanidipine monotherapy, any dose	570	54 (10)	318 (56)
Lercanidipine 5 mg/enalapril 5 mg	54	55 (12)	30 (56)
Lercanidipine 5 mg/enalapril 10 mg	52	55 (11)	35 (67)
Lercanidipine 10 mg/enalapril 5 mg	52	54 (11)	32 (62)
Lercanidipine 10 mg/enalapril 10 mg	335	55 (10)	200 (60)
Lercanidipine 10 mg/enalapril 20 mg	281	56 (10)	174 (62)
Lercanidipine 20 mg/enalapril 5 mg	64	56 (11)	44 (69)
Lercanidipine 20 mg/enalapril 10 mg	170	54 (11)	93 (55)
Lercanidipine 20 mg/enalapril 20 mg	116	56 (10)	53 (46)
Total	2368	55 (11)	1353 (57)
<i>p</i> -value		0.054	0.057

(4 weeks of single blind period with lercanidipine 10 mg and 12 weeks of double-blind treatment);

- Study #3<sup>7</sup>: placebo or enalapril monotherapy (10 or 20 mg) or lercanidipine monotherapy (10 or 20 mg) or one of four different combinations of both drugs (10 weeks of double blind treatment);
- Study #4<sup>11</sup>: enalapril monotherapy (20 mg) or combination therapy lercanidipine 10 mg + enalapril 20 mg (2 weeks of single blind period with enalapril 10 mg, 4 weeks of single blind period with enalapril 20 mg and 12 weeks of double blind treatment).

In total, 165 patients received placebo, 503 received enalapril monotherapy, 559 received lercanidipine monotherapy, and 1113 received combination therapy.

Compliance (the percentage of patients who took the prescribed amount of study drug) was excellent in all treatment groups, with the mean percentage compliance being greater than 98% with only negligible differences across studies.

### Change in SDBP

All combinations of the active drugs were found to be superior to placebo in the reduction of SDBP versus baseline values (Table 2). The greatest effect was observed with lercanidipine 20 mg/enalapril 20 mg (−15.3 mmHg vs. baseline), with this combination being consistently more effective than lercanidipine or enalapril monotherapy ( $R=0.895$ ;  $R^2=0.801$ ; Figure 1). The reduction in SDBP associated with the 10 mg/20 mg combination was −10.7 mmHg, and that reported in patients assigned to the 10 mg/20 mg combination was −9.8 mmHg. All comparisons were statistically significant ( $p < 0.05$ ).

### Change in SSBP

Similarly to what was observed for the primary efficacy analysis of SDBP, all combinations of the active drugs were found to be superior to placebo in the reduction of SDBP versus baseline values (Table 3). The greatest effect was observed with lercanidipine 20 mg/enalapril 20 mg (−19.2 mmHg vs. baseline), with this combination being consistently more effective than lercanidipine or enalapril

**Table 2.** Mean reduction of SDBP at endpoint versus baseline values.

Treatment group	Number of evaluated patients	SDBP at baseline	Change from baseline (SE)
Placebo	165	102.2	−7.5 (0.7)
Enalapril monotherapy, any dose	503	101.2	−8.9 (0.4)
Lercanidipine monotherapy, any dose	559	101.2	−8.5 (0.4)
Lercanidipine 5 mg/enalapril 5 mg	54	100.1	−8.5 (1.0)
Lercanidipine 5 mg/enalapril 10 mg	52	100.7	−9.2 (1.0)
Lercanidipine 10 mg/enalapril 5 mg	51	100.9	−10.7 (1.0)
Lercanidipine 10 mg/enalapril 10 mg	332	100.8	−9.8 (0.4)
Lercanidipine 10 mg/enalapril 20 mg	280	100.4	−10.7 (0.5)
Lercanidipine 20 mg/enalapril 5 mg	63	100.3	−10.6 (0.9)
Lercanidipine 20 mg/enalapril 10 mg	165	102.1	−12.9 (0.8)
Lercanidipine 20 mg/enalapril 20 mg	116	103.1	−15.3 (1.0)

monotherapy ( $R=0.873$ ;  $R^2=0.702$ ; Figure 2). The reduction in SSBP associated with the 10 mg/20 mg combination was −12.51 mmHg, and that reported in patients assigned to the 10 mg/20 mg combination was −11.1 mmHg. All comparisons were statistically significant ( $p < 0.05$ ).

### Proportion of normalized/responder patients

The results of the pooled analysis for the proportion of responder patients are reported in Table 4 and Figure 3 ( $p$  values are reported in Appendix 3).

The rate of responders was greater than 50% in all fixed-combination groups. The highest responder rate was reported in the lercanidipine 20 mg/enalapril 20 mg treatment group (75.0%); this figure was 56.1% with lercanidipine 10 mg/enalapril 20 mg and 53.0% with lercanidipine 10 mg/enalapril 10 mg.

### Safety analysis

All combinations and monotherapies were safe and well tolerated; no clinically meaningful safety issues were raised in any of the analyzed studies. Overall, 681 subjects (28.8%) reported a treatment-emergent adverse event (TEAE), but only 280 subjects (11.8%) experienced a TEAE considered related to study drug. The incidence of TEAEs was overall similar across all treatment groups (Table 5). In total, 18 patients (0.76%) reported serious TEAEs.

The most frequently occurring related TEAEs were cough, tachycardia and headache. Cough ( $n=60$ ) occurred mainly with enalapril 20 mg alone (13 subjects; 4.7%) or in combination with lercanidipine 10 mg (11 patients, 3.9%), but it was reported by only two subjects (1.7%) in the lercanidipine 20 mg/enalapril 20 mg group. The percentage of patients who reported tachycardia or palpitations was highest in the lercanidipine 20 mg group (14 subjects; 8.4%); however, the use of fixed-combination therapy with lercanidipine 20 mg/enalapril 20 mg was associated with a reduced incidence of this AE (1 subject: 0.9%). The percentage of patients who reported headache ranged from 0.0% to 7.4%. Only one patient (0.9%) reported headache in the highest-dose fixed-combination group. In total, 30 patients (1%) discontinued treatment due to adverse events.



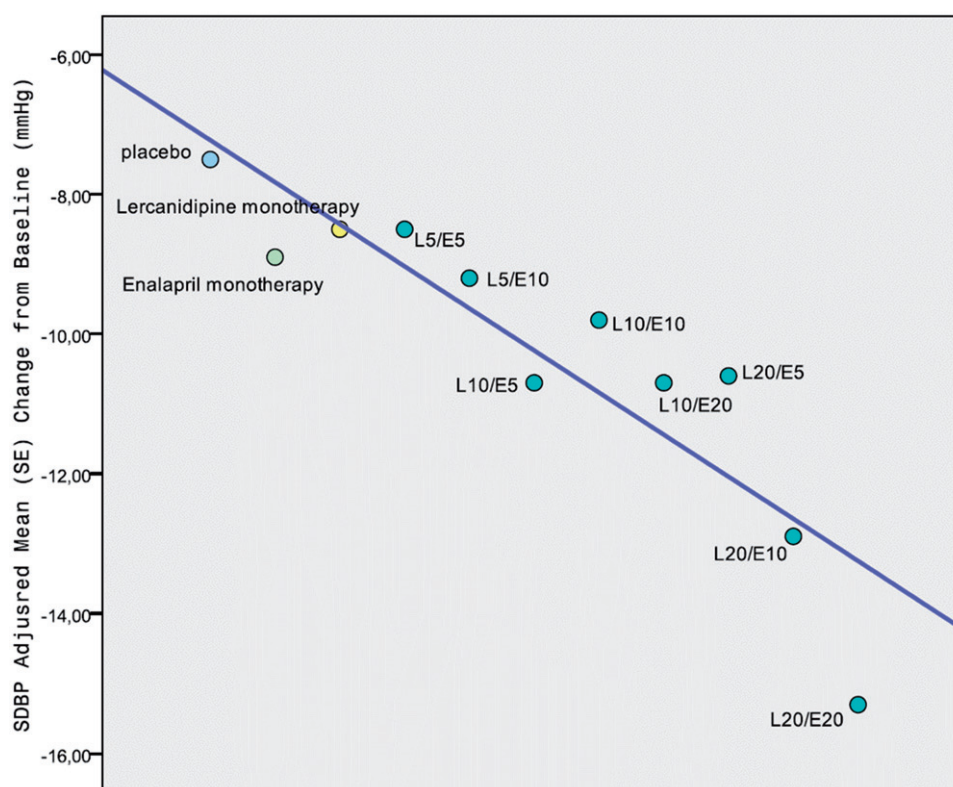


Figure 1. Linear regression analysis for lercanidipine/enalapril dose and SDBP change versus baseline.

Table 3. Reduction of SSBP versus baseline values.

Treatment group	Number of evaluated patients	SSBP at baseline	Change from baseline (SE)
Placebo	165	159.3	-7.9 (1.1)
Enalapril monotherapy, any dose	503	156.6	-10.3 (0.6)
Lercanidipine monotherapy, any dose	559	155.8	-9.7 (0.5)
Lercanidipine 5 mg/enalapril 5 mg	54	155.5	-13.2 (1.6)
Lercanidipine 5 mg/enalapril 10 mg	52	157.8	-9.6 (1.6)
Lercanidipine 10 mg/enalapril 5 mg	51	156.7	-13.4 (1.7)
Lercanidipine 10 mg/enalapril 10 mg	332	155.0	-11.1 (0.8)
Lercanidipine 10 mg/enalapril 20 mg	280	156.1	-12.5 (0.9)
Lercanidipine 20 mg/enalapril 5 mg	63	157.6	-15.6 (1.5)
Lercanidipine 20 mg/enalapril 10 mg	165	157.5	-15.9 (1.1)
Lercanidipine 20 mg/enalapril 20 mg	116	159.0	-19.2 (1.4)

Overall, there were no clinically relevant changes in mean values for any of the laboratory variables analyzed in any treatment group.

## Discussion

Combination treatment of high blood pressure may provide substantial advantages in terms of antihypertensive efficacy, target organ protection and tolerability<sup>4</sup>. Fixed-dose combinations may increase adherence<sup>6</sup> and, consequently, clinical efficacy. However, there is a marked heterogeneity in discontinuation rate among different classes of antihypertensive agents, and also among drugs belonging to the same class<sup>13</sup>. It should also be noted that both lercanidipine and enalapril are among the drugs showing the lowest rates of discontinuation in their respective classes<sup>13</sup>.

Adherence to treatment and discontinuation rates are relevant prognostic factors. In addition, a shift from

monotherapy to combination treatment is associated, in clinical practice, with improved cardiovascular protection, likely due to increased adherence<sup>13</sup>. Therefore, there are many reasons to believe that an effective and well tolerated fixed-dose combination treatment may provide substantial clinical benefits to a large population of hypertensive patients<sup>14</sup>.

Overall, the results of this pooled analysis of four randomized studies – which constituted the development program of the fixed-dose combination of lercanidipine/enalapril – show clear evidence of a dose–response effect in the mean reduction of SDBP (primary measure of efficacy) and SSDP (secondary measure of efficacy) from baseline to endpoint in patients with mild-to-moderate hypertension treated with different doses of the fixed-combination of lercanidipine + enalapril. To our knowledge, this is the first analysis to investigate the dose–response effect of a specific fixed-dose combination of anti-hypertensive agents, while Gupta *et al.*, in their landmark meta-analysis published in 2010, did not focus on any specific therapy<sup>5</sup>. However, it must be acknowledged that the number of included studies is small, and therefore the statistical power of the analysis is limited. However, we decided to include only the four studies constituting the development program of the fixed-dose combination since they presented a similar design – thus adding robustness to the comparison of the results – and as they investigated a number of different dosages of lercanidipine and enalapril, therefore allowing an *ad hoc* analysis of the dose–response effect.

The fixed-combination of lercanidipine 20 mg and enalapril 20 mg provided superior results in reduction of BP and in terms of responder rate compared with the other doses

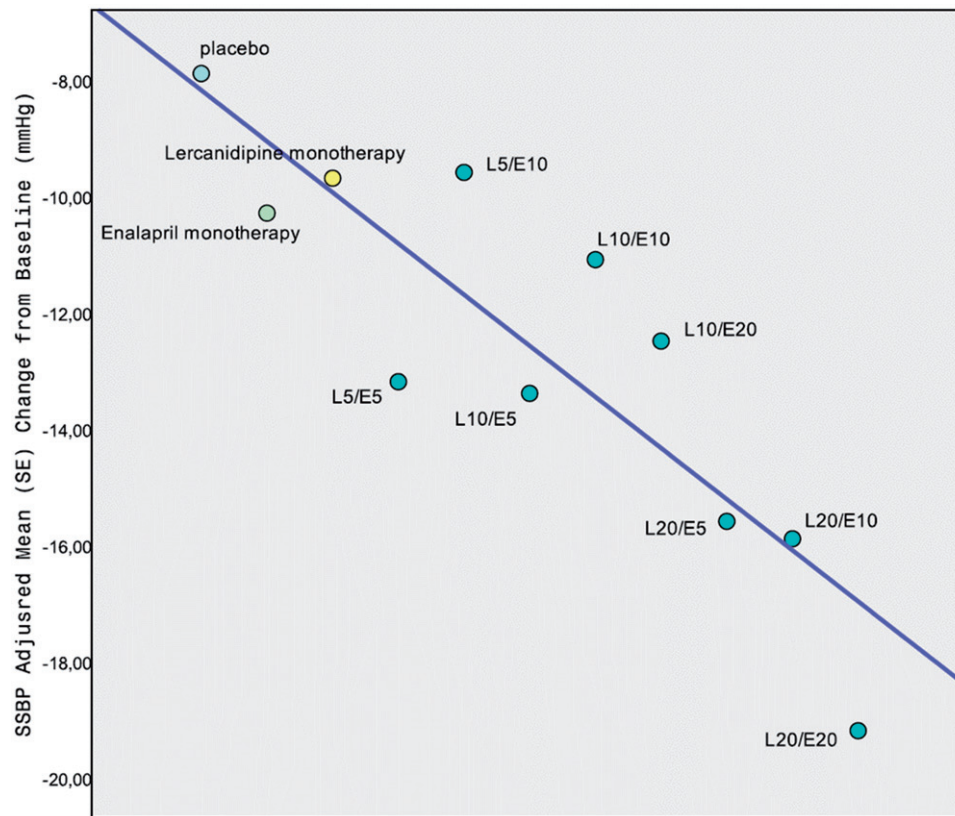


Figure 2. Linear regression analysis for lercanidipine/enalapril dose and SSBP change versus baseline.

Table 4. Proportion of normalized/responder patients.

Treatment group	Number of evaluated patients	Responders (%)
Placebo	165	79 (47.9)
Enalapril monotherapy, any dose	503	268 (53.3)
Lercanidipine monotherapy, any dose	559	254 (45.4)
Lercanidipine 5 mg/enalapril 5 mg	54	32 (59.3)
Lercanidipine 5 mg/enalapril 10 mg	52	28 (53.8)
Lercanidipine 10 mg/enalapril 5 mg	51	28 (54.9)
Lercanidipine 10 mg/enalapril 10 mg	332	176 (53.0)
Lercanidipine 10 mg/enalapril 20 mg	280	157 (56.1)
Lercanidipine 20 mg/enalapril 5 mg	63	35 (55.6)
Lercanidipine 20 mg/enalapril 10 mg	165	106 (64.2)
Lercanidipine 20 mg/enalapril 20 mg	116	87 (65.0)

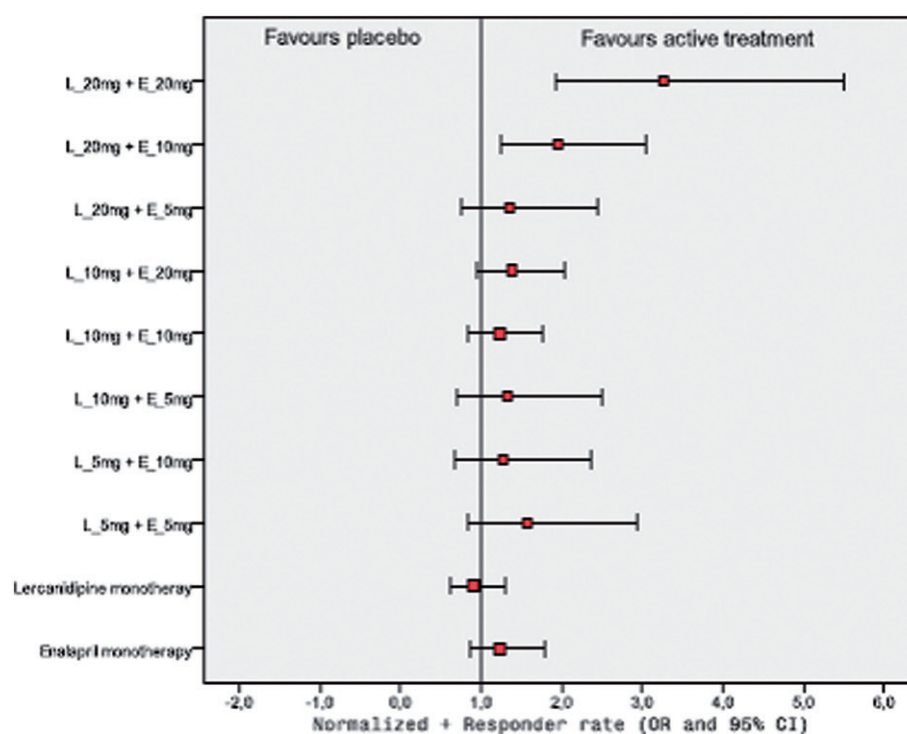
tested. Although a specific statistical analysis was not possible, a linear dose–response relationship in all these parameters was evident when comparing the 20 mg/20 mg combination with the other two fixed-dose combinations currently available, i.e. the 10 mg/10 mg and the 10 mg/20 mg combinations. The 20 mg/20 mg combination was not associated with a more severe burden of AEs compared with the other combinations tested. Notably, the most important class-related side effects of each monotherapy – i.e. cough for enalapril and peripheral edema for lercanidipine – were reduced with the combination therapy, thus supporting the hypothesis that the combination of two different classes of drugs might neutralize the unsolicited effects of each single component.

The findings of this pooled analysis may have immediate implications for clinical practice. Fixed combinations of

antihypertensive agents are recommended for the first-line treatment of mild-to-moderate hypertension, but often clinicians prefer lower doses of each component in order to limit the potential onset of AEs<sup>4</sup>. The greater efficacy without a worsening of the safety profile observed with higher-dose combinations of lercanidipine and enalapril provides robust evidence against this assumption.

In addition, the linear dose–response effect observed in our analysis for the three fixed-dose combinations currently marketed could allow antihypertensive treatment to be tailored to the specific needs of each patient. The clinician may therefore select the fixed dose most suitable to achieve the desired BP reduction. Moreover, the selected dose – if different from the 20/20 mg dosage – can be increased as necessary to enhance the anti-hypertensive efficacy and reach the target BP levels, without any additional risk of adverse events.

As previously mentioned, the rate of BP control in the real world setting is far from being optimal, ranging from less than 20% to about 40–50% in different countries<sup>3</sup>. Among the main causes of poor BP control, therapeutic inertia and onset of real or perceived side effects should be mentioned<sup>15</sup>. The present study, suggesting the substantial linearity of the dose–response effect with the investigated fixed dose combinations, could help physicians establish more aggressive treatment, being more comfortable with a partly predictable BP response with higher doses of the drugs<sup>16</sup>. In addition, a more pronounced BP reduction with higher doses of the fixed combinations was obtained without paying the price of an increased incidence of AEs; this would favor



Treatment versus placebo	OR (95% CI)
enalapril monotherapy (5, 10, 20 mg)	1.24 (0.86-1.79)
lercanidipine monotherapy (5, 10, 20 mg)	0.91 (0.63-1.30)
lercanidipine 5 mg + enalapril 5 mg	1.58 (0.85-2.95)
lercanidipine 5 mg + enalapril 10 mg	1.27 (0.68-2.37)
lercanidipine 10 mg + enalapril 5 mg	1.33 (0.71-2.49)
lercanidipine 10 mg + enalapril 10 mg	1.23 (0.85-1.78)
lercanidipine 10 mg + enalapril 20 mg	1.39 (0.94-2.04)
lercanidipine 20 mg + enalapril 5 mg	1.36 (0.76-2.44)
lercanidipine 20 mg + enalapril 10 mg	1.96 (1.26-3.04)
lercanidipine 20 mg + enalapril 20 mg	3.27 (1.94-5.49)

Figure 3. Forest plot for responder patients at endpoint.

Table 5. Safety results.

Treatment group	Number of evaluated patients	Number of patients with $\geq 1$ TEAE (%)		
		Any TEAEs	Serious TEAEs	Treatment-related TEAEs
Placebo	168	47 (28.0)	2 (1.2)	11 (6.5)
Enalapril monotherapy, 5 mg	58	18 (31.0)	0	9 (15.5)
Enalapril monotherapy, 10 mg	173	44 (25.4)	0	21 (12.1)
Enalapril monotherapy, 20 mg	275	88 (32.0)	6 (2.2)	27 (9.8)
Lercanidipine monotherapy, 5 mg	54	17 (31.5)	0	8 (14.8)
Lercanidipine monotherapy, 10 mg	349	101 (28.9)	2 (0.6)	24 (6.9)
Lercanidipine monotherapy, 20 mg	167	40 (24.0)	0	20 (12.0)
Lercanidipine 5 mg/enalapril 5 mg	54	17 (31.5)	0	17 (31.5)
Lercanidipine 5 mg/enalapril 10 mg	52	13 (25.0)	0	8 (15.4)
Lercanidipine 10 mg/enalapril 5 mg	52	16 (30.8)	0	10 (19.2)
Lercanidipine 10 mg/enalapril 10 mg	335	90 (26.9)	0	34 (10.1)
Lercanidipine 10 mg/enalapril 20 mg	281	90 (32.0)	4 (1.4)	43 (15.3)
Lercanidipine 20 mg/enalapril 5 mg	64	27 (42.2)	0	15 (23.4)
Lercanidipine 20 mg/enalapril 10 mg	170	44 (25.9)	2 (1.2)	23 (13.5)
Lercanidipine 20 mg/enalapril 20 mg	116	29 (25.0)	2 (1.7)	10 (8.6)

TEAE, treatment-emergent adverse event.



patients' adherence to treatment and compliance, and, consequently, BP control.

Other studies specifically aimed at investigating the dose-effect relationship of the lercanidipine/enalapril combination are however required to further confirm our findings. In addition, specific analysis on other fixed-dose combinations included in the pharmacological armamentarium for the treatment of hypertension are required to investigate whether the observations collected on lercanidipine/enalapril, and in particular the linear dose-response relationship of the available combinations – can be extended also to other molecules. Last, given the marked pleiotropic effects of lercanidipine, other cardiometabolic variables (e.g. lipids, renal function, electrolytes, obesity, glucose) may be investigated in dedicated meta-analyses.

### Transparency

### Declaration of funding

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### Declaration of financial/other relationships

D.R. has disclosed that he has no significant relationships with or financial interests in any commercial companies related to this study or article.

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