# The "LOTHAR" Study: Evaluation of Efficacy and Tolerability of the Fixed Combination of Amlodipine and Losartan in the Treatment of Essential Hypertension

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## Objective

The LOTHAR study evaluated medium and long term (one year) efficacy, tolerability and metabolic effects of the fixed combination of amlodipine and losartan compared to amlodipine or losartan alone.

## Methods

Brazilian multicenter, randomized, double-blind and comparative trial performed with 198 patients in stage 1 and 2 essential hypertension.

## Results

The fixed combination has a high antihypertensive efficacy that is sustained in the long term with very low percentage of loss of blood pressure control. This percentage is incidentally lower than that of the two monotherapy comparative regimens. In the long term, more than 60% of the patients treated with the fixed combination remained with DBP ≤ 85 mmHg, and the antihypertensive effect, when assessed by ABPM persisted for 24 hours with a trough-to-peak ratio of 76.7%. The frequency of adverse events was quite low in this group, and the long-term incidence of leg edema was approximately four-fold lower than that observed with amlodipine alone. The fixed combination did not change glucose and lipid metabolism in the medium or in the long term.

## Conclusion

Based on these results, we can say that the combination of amlodipine and losartan – the first fixed combination of a calcium channel blocker and an angiotensin II receptor blocker available in the pharmaceutical market, is an excellent option for the treatment of a wide range of hypertensive patients.

## Key words

fixed-combination of antihypertensive drugs, amlodipine, losartan, efficacy, tolerability, glucose and lipids metabolism

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Hypertension is known to be the major cardiovascular risk, and its treatment with an adequate blood pressure control significantly reduces the risk of cardiovascular morbidity and mortality[1-5].

More recently, the need for a more strict control of blood pressure has been suggested since the reduction of blood pressure to levels lower than 130/85 mmHg provides additional benefits regarding both the protection of target organs (morbidity) and cardiovascular mortality[6]. Thus, scientific normative agencies such as the American Joint National Committee, the World Health Organization, the International Society of Hypertension, and the Brazilian Society of Hypertension emphasize the need of achieving a strict control of blood pressure in the new edition of their guidelines for the treatment of hypertension, and establish a new upper limit for normal blood pressure, that is, 130/85 mmHg, which is significantly lower than the previous limit of 140/90 mmHg[3-5].

Clinical practice, however, has demonstrated that pressure levels lower than these new normal limits are very difficult to achieve through monotherapy. Large population-based studies have demonstrated that to achieve pressure levels lower than 130/85 mmHg the use of the combination of antihypertensive drugs is necessary in approximately 70% of the population with mild to moderate hypertension[6].

Among the antihypertensive drugs currently available, dihydropyridine calcium channel antagonists (DHP-CCA) and angiotensin II $AT_1$ receptor blockers (ARB) play an important role because in addition to being efficient they also have the ability to protect target organs and are associated to a low incidence of adverse events[7-11]. Incidentally, angiotensin II receptor blockers have been described to be associated to an incidence of adverse events similar to that observed with the use of placebo and which does not increase with the use of higher doses[11]. Additionally, these drugs have a favorable metabolic profile[11-14].

Clinical practice shows synergy in the reduction of blood pressure when these two classes of antihypertensive drugs are used in combination, allowing for a more adequate control of blood pressure, even when each one of the drugs is used at low doses[15].

Amlodipide – a calcium channel antagonist dihydropyridine derivative, is a potent antihypertensive drug thanks to its potent action as an arterial vasodilator; it also has natriuretic, antiproliferative, and antisclerotic effects[7,8,12].

However, this antihypertensive drug class does not promote a venodilation comparable to the arterial effect; it creates an imbalance of hydrostatic forces in peripheral capillaries, and facilitates fluid extravasation into the interstitial space, which enables the formation of lower extremity edema due to the gravity force[7,8,12,15]. Lower extremity edema has been described as a frequent adverse effect of this antihypertensive drug class, and is frequently regarded as the cause of treatment dropout.

The use of lower doses of this calcium antagonist is a way to minimize this effect, since there is a relation between dose used and frequency and intensity of adverse events[15]. However, clinical practice shows that a 50% reduction in the dose of this antihypertensive drug results in the loss of at least 20% of the hypotensive effect provided by the full dose, thus making the goal of controlling blood pressure difficult to achieve[15].

An alternative to reduce or even to prevent calcium channel antagonist-induced lower extremity edema is to combine a drug that also promotes venodilation. Similarly to ACE (angiotensin converting enzyme) inhibitors, angiotensin II $AT_1$ receptor blockers such as losartan promote both arterial and venous vasodilation, balancing hydrostatic pressure in peripheral capillaries, and thus reducing fluid extravasation into the interstitium[11].

Therefore, in addition to potentiating the reduction in blood pressure, the use of the combination of these two antihypertensive drugs may provide a lower incidence of lower extremity edema resulting from the use of a lower dose of amlodipine and from the venodilator effect of losartan[11,15,16,17].

We also know that, as a guideline, antihypertensive treatments should be simple whenever possible because the use of two or more agents is known to have a negative influence on the compliance to the long-term treatment of hypertension. Therefore, the use of fixed combinations of antihypertensive drugs has the advantage of simplifying the treatment, thus allowing a better patient compliance to the long-term hypotensive treatment[15,18,19].

Only recently has a fixed combination of a dihydropyridyne calcium channel antagonist – amlodipine, plus an angiotensin II $AT_1$ receptor blocker – losartan, become available in the Brazilian pharmaceutical market.

Finally, we know that to obtain renal and cardiovascular benefits from the antihypertensive treatment the adequate control of blood pressure should be sustained in the long term. However, clinical practice shows that this is not an easy task[15]. Thus, adjustments in the therapeutic regimen have to be made from time to time, be it in the dose, in the class of drugs, or in the progressive combination of antihypertensive drugs[15].

Many are the reasons for the need of frequent adjustments in the therapeutic regimen, such as the change in the fundamental mechanism of blood pressure increase. Thus, the analysis of the antihypertensive efficacy and of the tolerability of a therapeutic regimen in the long term becomes important.

Therefore, the objective of this multicenter, randomized, double-blind, comparative study was to evaluate the medium and long-term efficacy and tolerability of the first fixed combination of a DHP-CCA with an ARB (amlodipine + losartan) available in the pharmaceutical market for the treatment of patients with stage 1 and 2 essential hypertension in comparison with monotherapy regimens of a calcium channel antagonist (amlodipine)

or an angiotensin II receptor blocker (losartan).

The antihypertensive efficacy of these therapeutic regimens was evaluated according to international guidelines for the establishment of the efficacy of an antihypertensive drug, which is based on the degree of reduction of diastolic blood pressure and on the ability to achieve the normal levels of this blood pressure parameter. It is worth pointing out that all drugs currently available for the treatment of hypertension have had their efficacy rate established according to this international guideline.

In this study, we evaluated the antihypertensive efficacy for two different criteria of normal blood pressure: DBP ≤ 90 mmHg (classic criterion) and DBP ≤ 85 mmHg (new criterion). The latter is used as a parameter to indicate dose titration of the drugs studied. The antihypertensive effect of the three therapeutic regimens was assessed both by using blood pressure taken at the doctor's office and ambulatory blood pressure monitoring (ABPM). Finally, we also studied the influence of these treatments on glucose and lipid metabolism.

## Methods

LOTHAR (standing for "Am*L*odipino e L*O*sartana no *T*ratamento da *H*ipertensão *AR*terial" – Amlodipine and Losartan in the Treatment of Hypertension) was a Brazilian multicenter, randomized, double-blind, comparative study with the objective of evaluating the medium and long-term efficacy and tolerability, and metabolic effects of the fixed combination of amlodipine and losartan versus amlodipine or losartan alone in the treatment of stage 1 (mild) and 2 (moderate) essential hypertension. The study was conducted in seven clinical research centers, and 204 patients were selected and assigned to the three arms of the study . Six patients were excluded from the study because of protocol violation, non-compliance, and withdrawal of consent, and therefore 198 patients were effectively analyzed for efficacy and tolerability, 66 assigned in each of the arms of the study.

Following a three-week period of discontinuation of the previous antihypertensive drug (week 0), stage 1 and 2 essential hypertension patients of both genders aged between 21 and 70 years who met study inclusion and exclusion criteria were randomly and double-blindly assigned for treatment with the fixed combination of amlodipine and losartan at the initial dose of 2.5/50 mg once daily, or amlodipine 5 mg/day, or losartan 50 mg/day for six weeks.

By the end of the sixth week of treatment patients who had achieved the goal of blood pressure reduction (DBP ≤ 85 mmHg) were maintained on the drug at the same dose for six additional weeks. The dose of the drug for patients with DBP > 85 mmHg, in turn, was increased for the next six weeks of follow-up to 5.0/100 mg in the case of the fixed combination, 10 mg in the group of amlodipine alone, and 100 mg for the patients treated with losartan alone. Patients were reevaluated at week 12.

In the initial twelve-week study period, patients were evaluated every three weeks at the doctor's office for measurements of blood pressure and heart rate in the sitting and standing positions. The blood pressure recorded represents the mean of three consecutive measurements obtained with a mercury sphygmomanometer following a five-minute rest in the sitting position, and two minutes after assuming the standing position. The hypotensive effect of the three therapeutic regimens was also assessed using ambulatory blood pressure monitoring (ABPM, SpaceLabs equipment) performed in all patients at week 0 (baseline) and at the end of the 12th week of treatment.

To characterize the antihypertensive efficacy, two indexes were used: the blood pressure normalization rate (in percentage) with two cut-off points – DBP < 90 mmHg and DBP ≤ 85 mmHg, and the efficacy rate which represents the frequency of blood pressure normalization added to the percentage of patients who had a ≥ 10 mmHg reduction in DBP, despite not having achieved normal DBP levels.

At each visit, we also evaluated body weight and analysis of tolerability based on the frequency of adverse events, complemented by measurement of leg volume at the baseline period, and after six and twelve weeks of treatment (an objective index of lower extremity edema formation) assessed by the volume of fluid displaced from a full vessel when the leg was placed inside it (Archimedes' principle).

Safety biochemical parameters (complete blood count, renal function, liver function, electrolytes, protein profile, and enzymes) and electrocardiogram at rest were also determined in all patients at the baseline (week 0) and at the 12th week of antihypertensive treatment. At the same timepoints, glucose metabolism parameter values (blood glucose and blood insulin at fasting and 120 minutes following an oral 75-gram glucose overload, with calculation of insulin sensitivity index) and plasma lipids (total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides) were also recorded. Biochemical parameters were determined using an automated method, and blood insulin was determined using radioimmunoassay. Insulin sensitivity index was calculated with the formula ISI= 100,000/GCAxICA, where GCA and ICA represent glucose curve area and insulin curve area, respectively, which were determined during glucose overload.

At the end of the 12th week of treatment, for purposes of medical ethics, good clinical practice, and compliance to the Brazilian Guideline of Hypertension, only the patients who benefited from the therapeutic regimen assigned to them (those who achieved normal blood pressure defined as DBP ≤ 85 mmHg or who presented a ≥ 10 mmHg reduction in DBP) were voluntarily admitted to the double-blind extension phase of the study for forty additional weeks, and were evaluated every eight weeks in relation to antihypertensive efficacy and tolerability.

This inclusion criterion in the extension phase is justified by the fact that patients considered non-responsive were already taking the maximum allowed dose of the drug they were assigned to for at least six weeks. Since the protocol design did not allow the addition of other drugs to the therapeutic regimen, it would not be a good clinical practice to keep these patients in the study for nine additional months with the same drug regimen. In the extension period, ABPM and electrocardiogram were recorded at weeks 36 and 52 (study termination) for all patients included. Additionally, the safety biochemical parameters previously described, as well as glucose and lipid metabolism parameters were determined once more by the end of the study (week 52). Likewise, patients' leg volume was recorded at weeks 36 and 52.

Patients with the following conditions were not included in this study: severe or malignant hypertension; secondary hypertension; white coat hypertension, clinically manifest heart failure; myocardial infarction; coronary artery bypass grafting or stroke in the past twelve months; unstable angina; cardiac arrhythmias or atrioventricular block; diabetes; liver diseases; renal failure; blood dyscrasias; history of allergy to the drugs studied; use of medications that could interfere with the drugs studied, and use of investigational drugs in the past thirty days. Women of childbearing age who were not on a medically acceptable contraceptive method were also excluded.

The research protocol was approved by the research ethics committees of the respective institutions to which each participant center belonged and by the National Committee on Research Ethics (CONEP – *Comitê Nacional de Ética em Pesquisa*). All patients signed the informed consent.

Statistical analysis for the results of the repeated measurements was conducted using variance analysis and verified with the chi-square test. The Kruskal-Wallis non-parametric test was used to evaluate the effects of the different treatments on biochemical parameters.

## Results

The baseline characteristics of the population included in the study are shown in Table I. We can observe that the groups were not different in relation to age, body mass index and weight, heart rate, and systolic and diastolic pressure values. The percentage of female patients with stage 2 hypertension was slightly higher in the group assigned to receive losartan alone, although this difference was not statistically significant. Three patients in the amlodipine alone group were prematurely withdrawn (before completing the 12th week of treatment), two of them due to an adverse event, and one due to drug inefficacy. In the losartan alone group, four patients interrupted treatment before week 12 (one due to an adverse event, and three due to drug inefficacy). In the fixed combination of amlodipide + losartan group, no patients were prematurely withdrawn from the study.

Effects on blood pressure – Antihypertensive efficacy - *In the medium term* - The values of systolic and diastolic blood pressure in the sitting position at each visit in the three treatment groups during the first three months of treatment are shown in Figure 1. We can observe that blood pressure in the three groups which was similar in the baseline had a significant reduction as from the third week of treatment in the three groups ($p < 0.001$ versus week 0) and reached similar values in the groups treated with amlodipine alone and with the fixed combination of amlodipine and losartan (135.4 ± 12.2 / 85.7 ± 7.0 mmHg and 134.6 ± 15.0 / 86.2 ± 9.4 mmHg, respectively) by the end of week 12.

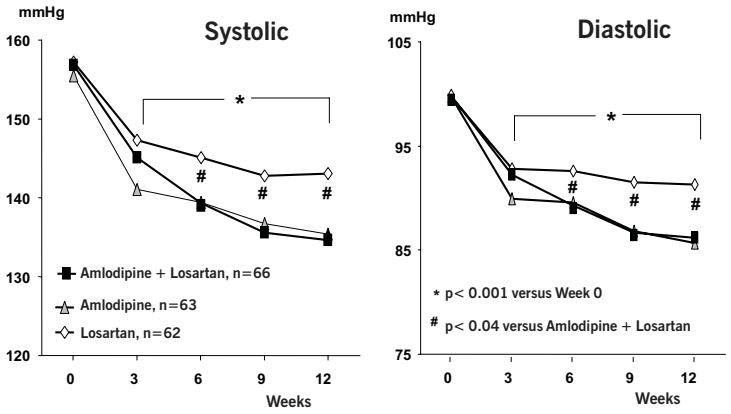
In the patients treated with losartan alone, blood pressure reduction was lower, although significant, reaching values of 143.1 ± 15.3 / 91.3 ± 9.7 mmHg ($p < 0.04$ versus amlodipine + losartan) by the end of twelve weeks of treatment. Variations in blood pressure measurement in the standing position during treatment were similar to those recorded in the sitting position, and no episode of orthostatic hypotension was reported in either of the three therapeutic regimens.

To obtain these results, dose titration was necessary for most of the patients in the three therapeutic regimens. Thus, by the end of the twelve weeks of treatment, the maximum dose was being used by 76.2% of the patients treated with amlodipine (10 mg/day), by 82.3% of the patients on losartan (100 mg/day), and by a slightly lower percentage (68.2%) of the patients on the fixed combination of amlodipine and losartan (5+100 mg/day).

**Table I – Baseline characteristics**

| | Amlodipine (n= 66) | Losartan (n=66) | Amlodipine + Losartan (n=66) |
|---|---|---|---|
| **Age (years)** | 52.0 ± 9.7 | 52.5 ± 9.6 | 54.1± 8.5 |
| **Male / Female (%)** | 42.6 / 57.4 | 25.0 / 75.0 | 32.4 / 67.6 |
| **White / Non-White (%)** | 32.4 / 67.6 | 47.1 / 52.9 | 35.3 / 64.7 |
| **Body weight (Kg)** | 70.8 ± 12.6 | 69.8 ± 11.2 | 68.8 ± 11.3 |
| **BMI (kg/m²)** | 27.5 ± 3.8 | 27.8 ± 3.4 | 27.3 ± 3.5 |
| **SBP sitting (mmHg)** | 155.5 ± 11.5 | 157.2 ± 11.5 | 156.8 ± 12.5 |
| **DBP sitting (mmHg)** | 99.7 ± 4.7 | 99.7 ± 4.1 | 99.8 ± 4.5 |
| **Stage I / II H (%)** | 36.8 / 63.2 | 45.6 / 54.4 | 33.8 / 66.2 |
| **HR sitting (bpm)** | 73.5 ± 9.0 | 74.9 ± 9.1 | 73.6 ± 9.8 |

Figure 1 **LOTHAR Study: Blood Pressure in the Sitting Position**




Therefore, by the 12th week of treatment, the mean doses of each therapeutic regimen were: 8.8 mg/day; 91.1 mg/day, and 4.1+86.2 mg/day, respectively, for amlodipine alone, losartan alone, and fixed combination of amlodipine and losartan groups.

Of the 66 patients treated with the fixed combination of amlodipine and losartan, 48 (72.2%) achieved a DBP < 90 mmHg by the end of week 12, and in 35 (53%) of them DBP was equal to or lower than 85 mmHg. Similar results were obtained in the group treated with amlodipine alone, 77.3% with DBP < 90 mmHg, and 50% with DBP ≤ 85 mmHg. Among the patients who received losartan alone, the percentage of patients who achieved values of DBP < 90 mmHg and ≤ 85 mmHg was significantly lower: 48.5% and 28.8%, respectively.

The alternative analysis of the antihypertensive efficacy of the three therapeutic regimens based on the systolic blood pressure response, considering the values of 140 mmHg and 130 mmHg as normal values, revealed antihypertensive efficacy rates lower than those described for diastolic pressure in the three therapeutic regimens. Again, a higher efficacy rate was observed in the fixed combination of amlodipin + losartan group which was nevertheless not statistically different from that of amlodipine alone. The lowest efficacy rate for systolic blood pressure was observed in the losartan alone group again.

Thus, DBP < 140 mmHg was observed in 68.2%; 63.6% and 41.5% of the patients treated with the fixed combination; amlodipine alone and losartan alone, respectively. DBP < 130 mmHg was observed in only 33.8% of the patients on the combination, in 31.8% of those on amlodipine alone, and in 18.5% of those treated with losartan alone. The normalization rate of both SBP and DBP was even lower for the three therapeutic regimens, and followed the same pattern described for each blood pressure component alone. Thus, relative frequencies of patients with BP < 140/90 mmHg and < 130/85 mmHg were, respectively, 59.1% and 27.3% in the amlodipine + losartan group; 53.0% and 22.7% in the amlodipine alone group; and only 33.8% and 13.8% among the patients treated with losartan alone.

The antihypertensive effect in the three therapeutic regimens, described by blood pressure measured at the doctor's office, was confirmed by ambulatory blood pressure monitoring (ABPM). As shown in Table II, a significant and similar reduction in the 24-hour SBP, DBP and MBP was observed in the amlodipine alone group or in the fixed combination with losartan group. Similar to what was observed in the measurement taken at the doctor's office, the blood pressure reduction in the ABPM in patients treated with losartan alone, although significant, was lower ($p < 0.001$) than that observed in the other two study groups. The antihypertensive effect of the three therapeutic regimens was adequate and sustained in the 24 hours, since the trough-to-peak ratio calculated was higher than 50% in the three regimens, that is, 76.7% for the fixed combination, 92.1% for amlodipine alone, and 60.1% for losartan alone. Time profile of systolic and diastolic pressure in ABPM for the group of patients treated with the fixed combination of amlodipine and losartan is shown in Figure 2. We can observe that the treatment with the fixed combination of amlodipine at a low dose and losartan during twelve consecutive weeks provided significant reductions in systolic and diastolic pressures both during alertness and sleep, and, therefore, provided an adequate 24-hour blood pressure control.

*In the long term* - Of the 198 patients who participated in the initial phase of the study, 131 were considered eligible for the extension phase, and eleven patients were excluded from the study due to protocol violation, missing follow-up, or withdrawal of consent. Thus, 120 patients were considered in the long-term efficacy analysis of the three therapeutic regimens. Of these, 109 completed the study and were assigned as follows: 39 in the amlodipine

**Table II – Ambulatory blood pressure monitoring. Mean values of blood pressure in the 24 hours**

| | Amlodipine (n=62) | Losartan (n=63) | Amlodipine + Losartan (n=66) |
|---|---|---|---|
| **Systolic BP – 24 hours (mmHg)** | | | |
| **Baseline** | 148.7 ± 12.0 | 149.8 ± 10.7 | 149.8 ± 9.6 |
| **Week 12** | 130.6 ± 10.8 * | 140.8 ± 13.4 * † | 130.9 ± 11.4 * |
| **Diastolic BP – 24 hours (mmHg)** | | | |
| **Baseline** | 94.6 ± 6.4 | 93.8 ± 8.0 | 95.1 ± 7.0 |
| **Week 12** | 83.1 ± 5.9 * | 88.5 ± 7.8 * † | 83.2 ± 8.2 * |
| **Mean BP – 24 hours (mmHg)** | | | |
| **Baseline** | 113.3 ± 7.2 | 113.5 ± 8.1 | 114.3 ± 6.9 |
| **Week 12** | 99.2 ± 7.0 * | 106.5 ± 9.1 * † | 99.7 ± 8.5 * |
| **Trough-to-peak ratio** | | | |
| **Week 12** | 92.1% | 60.1%% | 76.7% |

** p< 0.001 versus baseline; † p< 0.001 versus amlodipine and amlodipine + losartan*

alone group, 27 in the losartan group, and 43 in the fixed combination of amlodipine and losartan group.

The drug dose was increased in a small number of patients in the three study groups during the extension phase. Thus, the mean dose by the end of weeks 12 and 52 were, respectively: amlodipine alone (8.9 and 9.2 mg/day); losartan alone (83.3 and 88.9 mg/day) and amlodipine combined with losartan (4.1+81.4 mg/day and 4.2+ 84.9 mg/day).

Mean values of systolic and diastolic blood pressure obtained in the sitting position from the baseline period to the 52nd week of treatment only for patients who completed the extension phase of the study are shown in Figure 3. We can observe that the blood pressure reduction obtained with the fixed combination of amlodipine and losartan observed in the initial phase of the study was sustained for the period of one-year follow-up, and the pattern was not different from that of the amlodipine alone group, which also remained reduced during the 52 weeks of treatment. Similar to what was observed in the initial phase of the treatment, the long-term blood pressure reduction in the losartan alone group was significantly lower than in the other groups, and a trend of return of the systolic blood pressure to higher levels throughout the treatment period was observed in this group. The same blood pressure variation pattern was observed when BP was measured in the standing position.

Percentage rates of blood pressure normalization (cut-off points for DBP $< 90$ and $\leq 85$ mmHg) and antihypertensive efficacy (DBP $\leq 85$ mmHg or $\Delta$ DBP $\geq 10$ mmHg) observed at the weeks 12th and 52nd weeks of treatment with each therapeutic regimen only for patients participating in the extension phase of the study are shown in Table III. As can be observed, efficacy and blood pressure normalization rates were quite high at week 12 for the three therapeutic regimens, unlike the results presented for the total group at week 12. This fact results from the selection criterion of patients for the

Figure 2

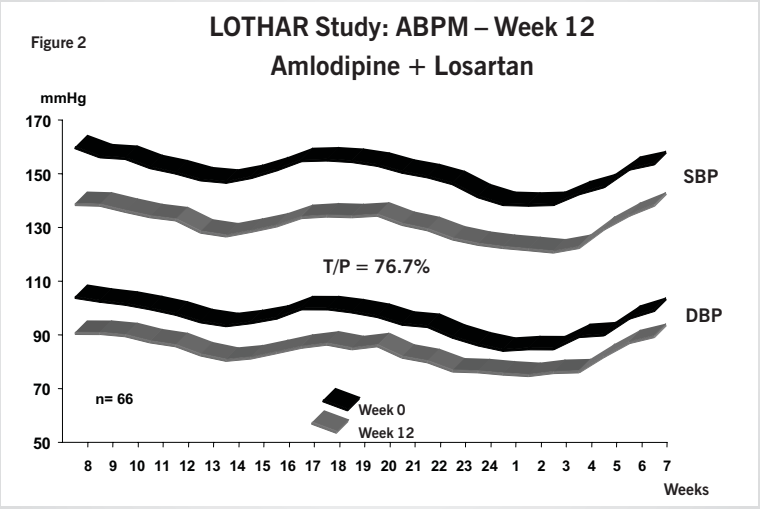
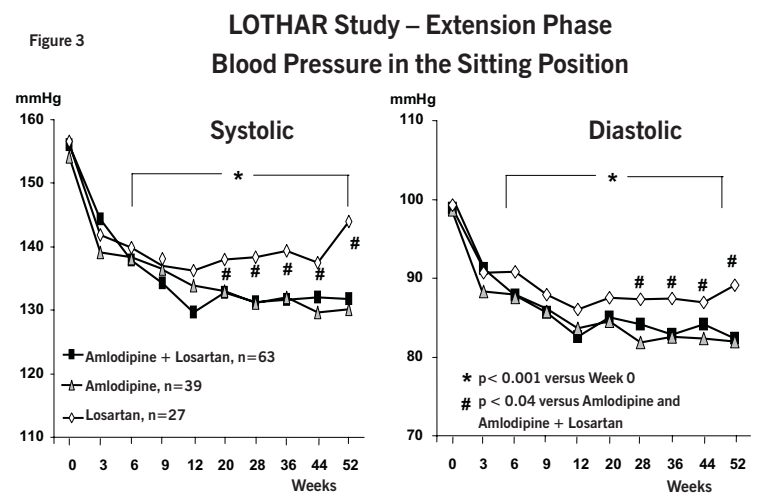


Figure 3




extension phase, of which only patients who had obtained a clinically significant benefit from the treatments of the initial phase of the study could participate, for purposes of ethics and good clinical practice, as previously explained in details in the methodology section.

In Table III we can observe that a significant loss of antihypertensive efficacy occurs (a reduction in the percentage of patients with antihypertensive efficacy) in the long term, especially in the groups treated with losartan alone (from 79.3% to 51.7%) or amlodipine alone (from 97.7% to 75%). In the patients treated with the fixed combination of amlodipine and losartan, the long-term efficacy loss was much lower (from 93.6% to 87.2%) than that observed with the other two therapeutic regimens, which means that with this modality of treatment the maintenance of high rates of antihypertensive efficacy is feasible even in the long term.

The long-term antihypertensive efficacy of the fixed combination of amlodipine and losartan was confirmed with repeated recordings of ABPM performed during the one-year follow-up. As we can see in Figure 4, the degree of reduction of systolic and diastolic blood pressure during the 24 hours – during alertness and sleep, observed after 12 weeks of treatment, was sustained in the same level in the ABPM performed in these patients at weeks 32 and 52 of the study, thus corroborating the long-term maintenance of pressure control.

No significant variations in heart rate were observed with the different therapeutic regimens, both in the medium and in the long term.

Tolerability: adverse events - The absolute and relative frequencies of patients with adverse events in general and with the two major events (lower extremity edema and headache) reported in the twelve weeks of treatment with the three therapeutic regimens are shown in Table IV. We can observe that in the group treated with losartan alone there was a reduction in the frequency of patients who presented adverse events when compared to the baseline. On the contrary, in the groups treated with the fixed combination and with amlodipine alone, an increase in the absolute and relative frequencies of patients with adverse events was observed, and this increase was slightly higher, although not significant, among patients who received amlodipine alone. The incidence of headache decreased with the three therapeutic regimens and an increase trend in the frequency of patients with lower extremity edema was observed in the patients who received calcium channel antagonist alone or in combination with losartan. The frequency of patients with edema tended to be slightly higher, although not significantly in the amlodipine alone group.

No significant variation in leg volume measurement was observed among the groups studied during the twelve first weeks of treatment.

When the long-term tolerability of the three antihypertensive regimens was evaluated, we observed that in the group of patients treated with amlodipine

**Table III – Medium (three months) and long-term (twelve months) antihypertensive efficacy**

| | Criterion 1 Normalization (DBP < 90 mmHg) | | Criterion 2 -Normalization (DBP ≤ 85 mmHg) | | Efficacy (DBP ≤ 85 mmHg + Δ DBP ≥ 10 mmHg) | |
|---|---|---|---|---|---|---|
| | Week 12 | Week 52 | Week 12 | Week 52 | Week 12 | Week 52 |
| **Amlodipine** | 88.6% | 77.3% | 63.6% | 61.3% | 97.7% | 75.0% |
| **Losartan** | 79.3% | 55.2% | 51.7% | 31.0 % | 79.3% | 51.7% |
| **Amlodipine+Losartan** | 87.2% | 85.1% | 66.0% | 63.8% | 93.6% | 87.2% |

Figure 4

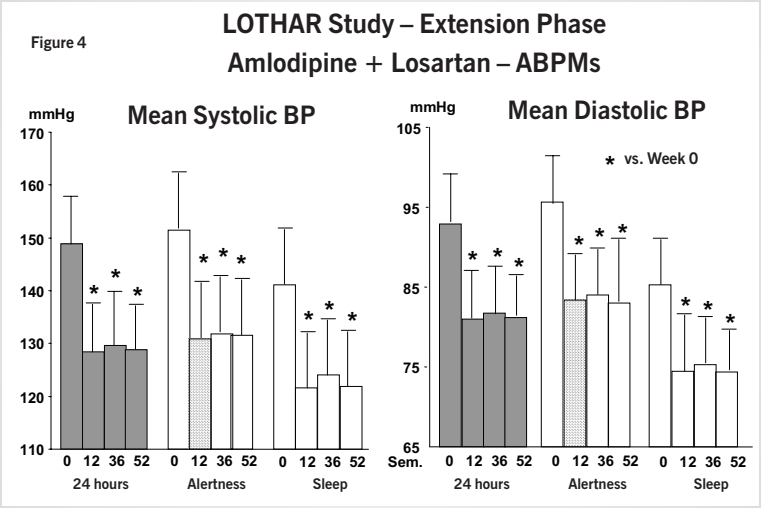



**Table IV – Frequency of adverse events at the baseline period and after twelve weeks of treatment**

| | Amlodipine (n=66) | Losartan (n=66) | Amlodipine + Losartan (n=66) |
|---|---|---|---|
| **Patients with adverse events** | | | |
| **Baseline** | 11 (16.7%) | 15 (22.7%) | 12 (18.2%) |
| **Week 12** | 17 (25.8%) | 10 (15.4%) | 15 (22.7%) |
| **Patients with headache** | | | |
| **Baseline** | 6 (9.1%) | 14 (21.2%) | 6 (9.1%) |
| **Week 12** | 2 (3%) | 4 (6.1) | 3 (4.5%) |
| **Patients with lower extremity edema** | | | |
| **Baseline** | 0 (0%) | 2 (3%) | 0 (0%) |
| **Week 12** | 5 (7.5%) | 0 (0%) | 3 (4.5%) |

alone a progressive increase occurred both in the number of adverse events and in the number of patients who presented at least one adverse event. Differently, in the group who received the fixed combination, and especially in the group treated with losartan alone, we observed stabilization or even reduction both in the number of events and in the number of patients with adverse events. Thus, by the end of the treatment in the amlodipine group, nineteen adverse events had been reported by thirteen patients, representing a 29.5% incidence of patients with adverse events. In the losartan-alone group only two patients (6.9%) with adverse events were recorded at the last visit (one event per patient). In the fixed combination of amlodipine and losartan group only seven adverse events were reported by 10.6% of the patients (n = 5).

The relative frequency of patients with lower extremity edema and headache in all visits performed during a one-year follow-up of the patients treated with the three therapeutic regimens is shown in Figure 5. As we can see, no difference in the incidence of headache among the three drug regimens was observed. In relation to lower extremity edema, we can see that its incidence was progressive and significantly higher in the group of patients treated with amlodipine alone, when compared to losartan alone, and to the fixed combination. This incidence became stable as of approximately the 20th week of treatment.

Thus, from week 20 the relative frequency of lower extremity edema ranged from 15.9% to 18.2% of the patients treated with amlodipine alone. Differently, in the group treated with the fixed combination of amlodipine and losartan the incidence of this adverse event was four to five-fold lower than that observed in the patients treated with amlodipine alone, ranging from 2.1% to 4.3% of the population in this group. No patient of the group treated with losartan alone had lower extremity edema.

Again, also in the extension phase, no significant

variations or differences were observed among the study groups as regards leg volume measurement.

Effects on glucose and lipid metabolism - Glucose and plasma lipid metabolism parameter values assessed at the baseline and at the 12th week of treatment with the three drug regimens are shown in Table V.

As can be seen, no significant variations of blood glucose and blood insulin during fasting and following glucose overload were observed in the three groups. The sensitivity to insulin index was not influenced by any of the antihypertensive treatment regimens either. Likewise, no significant changes in the different parameters of lipid profile were observed during the twelve weeks of treatment with any of the three antihypertensive regimens used.

Thus, the drug regimens used may be considered neutral as regards glucose and plasma lipid metabolism.

The metabolic neutrality of the fixed combination of amlodipine and losartan was sustained in the long term as can be seen in Figure 6, in which the values of blood glucose and blood insulin during fasting and following glucose overload, of insulin sensitivity index, and of the different parameters of the lipid metabolism remained stable and were not different from those of the baseline during the 52 weeks of treatment with the combination.

## Discussion

The results of this multicenter study demonstrated that the fixed combination of amlodipine and losartan has a high antihypertensive efficacy that is sustained in the long term with a quite reduced percentage of loss of blood pressure control. Based on our results we can state that the long-term antihypertensive efficacy of the fixed combination of amlodipine at low doses with higher doses of losartan was higher than that of the two comparative monotherapy regimens using high doses of those drugs alone. Thus, although we could achieve pressure levels similar to those observed with the fixed combination by using amlodipine at high doses (more than double the dose used in the fixed combination), we detected a significant loss rate in the long term, with loss of efficacy and blood pressure normalization endpoint in a significant number of patients treated with this monotherapy, which is a relevant fact because it implies maintenance of the cardiovascular risk in these patients, and frequent adjustments in the therapeutic regimen.

The high antihypertensive efficacy rate of amlodipine alone at high doses observed in our study, which was similar to that of the fixed combination, had already been described in comparative studies of other fixed combinations of antihypertensive drugs, but always using high doses of this calcium channel antagonist at high doses[20,21]. In relation to losartan alone, the superior efficacy of the fixed combination was even more evident. Thus, not only did blood pressure remain at upper levels during the treatment with losartan, but also medium and long-term blood pressure normalization rates were quite lower among patients who received this monotherapy treatment. We also observed a significant rate of loss of blood pressure control with losartan alone throughout time.

We observed that, in the long term, more than 60% of the patients treated with the fixed combination of amlodipine and losartan remained with diastolic blood pressure levels equal to or lower than 85 mmHg, thus achieving the goals recommended by current guidelines for the treatment of hypertension[3,4,5]. Still regarding antihypertensive efficacy, we observed that when it was assessed using systolic blood pressure normalization alone or in combination with diastolic blood pressure, the percentages obtained were lower than those reported when only diastolic blood pressure was considered for the three therapeutic regimens, reflecting the low efficacy of the drugs available for the treatment of hypertension in reducing and controlling systolic blood pressure. Again,

Figure 5

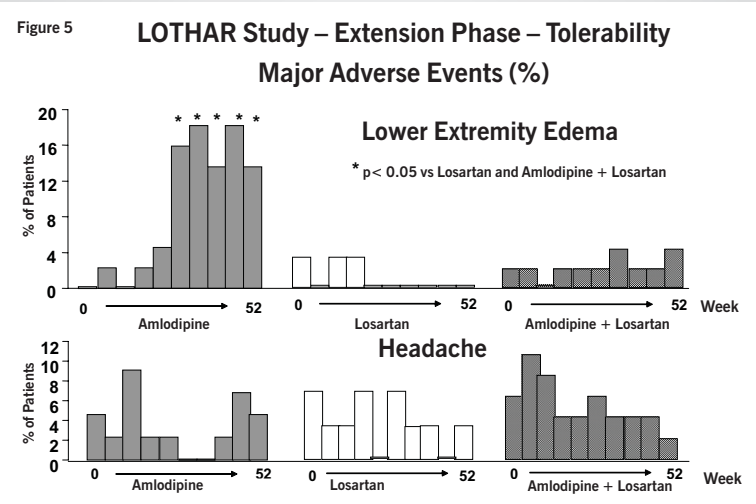
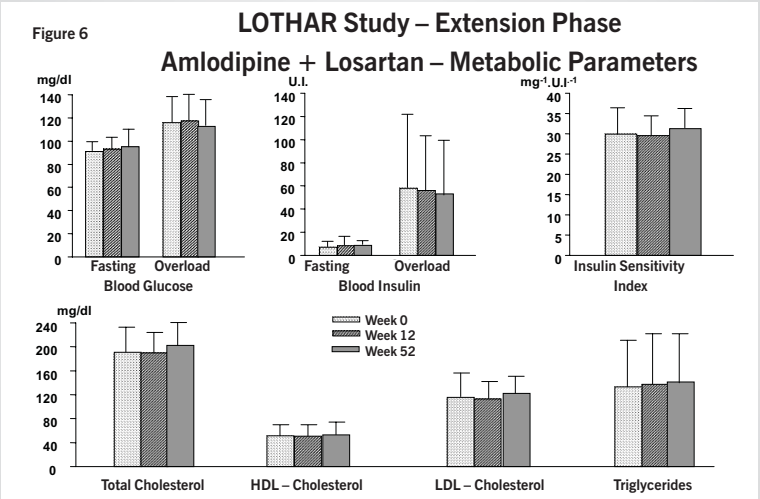


**Table V - Glucose and lipid metabolism parameters**

| | Amlodipine (n=63) | Losartan (n=62) | Amlodipine + Losartan (n=66) |
|---|---|---|---|
| | Fasting blood glucose (mg/dl) | | |
| **Baseline** | 96.0 ± 11.6 | 95.6 ± 9.7 | 93.6 ± 9.1 |
| **Week 12** | 97.0 ± 11.8 | 95.4 ± 11.0 | 96.7 ± 10.8 |
| | **Blood glucose – two hours – After-overload (mg/dl)** | | |
| **Baseline** | 124.4 ± 37.9 | 120.9 ± 39.9 | 115.8 ± 28.7 |
| **Week 12** | 117.2 ± 33.9 | 119.6 ± 36.6 | 117.8 ± 30.5 |
| | **Fasting blood insulin** | | |
| **Baseline** | 8.3 ± 4.8 | 9.7 ± 6.5 | 7.7 ± 4.3 |
| **Week 12** | 8.9 ± 5.2 | 10.2 ± 6.9 | 9.6 ± 7.3 |
| | **Blood insulin – two hours – After-overload** | | |
| **Baseline** | 60.7 ± 58.6 | 71.4 ± 80.0 | 58.7 ± 54.4 |
| **Week 12** | 53.8 ± 40.2 | 72.0 ± 73.6 | 56.9 ± 44.9 |
| | **Total cholesterol (mg/dl)** | | |
| **Baseline** | 192.0 ± 42.4 | 194.9 ± 34.9 | 192.9 ± 40.2 |
| **Week 12** | 201.6 ± 45.4 | 192.9 ± 36.4 | 188.2 ± 34.2 |
| | **LDL – cholesterol (mg/dl)** | | |
| **Baseline** | 114.8 ± 36.0 | 117.9 ± 29.5 | 114.0 ± 33.6 |
| **Week 12** | 124.1 ± 39.9 | 114.4 ± 30.9 | 109.2 ± 27.3 |
| | **HDL – cholesterol (mg/dl)** | | |
| **Baseline** | 50.6 ± 12.6 | 49.7 ± 11.3 | 51.1 ± 12.2 |
| **Week 12** | 51.9 ± 11.3 | 50.3 ± 12.7 | 114.8 ± 36.0 |
| | **Triglycerides (mg/dl)** | | |
| **Baseline** | 135.1 ± 89.5 | 144.8 ± 96.2 | 151.3 ± 122.9 |
| **Week 12** | 134.6 ± 88.6 | 153.5 ± 97.3 | 150.2 ± 115.2 |

Figure 6




patients treated with the fixed combination of amlodipine and losartan showed the highest rates, which were statistically different from that observed with losartan, but not from that reported for patients who received amlodipine alone.

The difficulty to control systolic blood pressure observed in our study is supported by a review recently published by Professor Giuseppe Mancia[22] in which he reports that in almost the totality of the studies on endpoints of hypertension alone or associated with diabetes, the target-goal of systolic blood pressure was not achieved, despite the use of multiple antihypertensive drugs. Moreover, this difficulty to achieve the goal of controlling systolic blood pressure explains why the international guidelines for studies on antihypertensive drugs still use criteria based on diastolic blood pressure to describe the antihypertensive efficacy of a drug, in spite of the fact that guidelines indicate the real need to control systolic blood pressure as well.

We currently know that the anti-hypertensive efficacy of a drug should be assessed considering not only the blood pressure measured at the doctor's office, but also the 24-hour effects of the drug on blood pressure, assessed by ambulatory blood pressure monitoring (ABPM). Our results demonstrate that the antihypertensive effect of the fixed combination, as well as of the monotherapies, is sustained during the 24 hours. We observed a 76.7% trough-to-peak ratio with the fixed combination of amlodipine and losartan, which allows the use of this medication in a single daily dose, thus facilitating the long-term compliance to treatment, since studies demonstrate that the higher the number of daily doses, the higher the treatment dropout rate[23].

It is important to point out that blood pressure reduction provided by the treatment with the fixed combination of amlodipine and losartan did not cause any secondary increase in sympathetic activity, since no significant variations of heart rate occurred. This fact is beneficial and also helps explain the long-term maintenance of the antihypertensive efficacy with a low rate of loss of blood pressure control.

In addition to a high efficacy in reducing blood pressure, keeping it at controlled levels, an antihypertensive drug should also have a good tolerability profile, since the presence of adverse effects may decrease the degree of compliance of the patient to the therapeutic regimen, thus ultimately leading to treatment dropout[24]. Our results demonstrate that the fixed combination of amlodipine at low doses and losartan at higher doses has a very good tolerability profile with a low incidence of adverse events. Moreover, when present, the great majority of these adverse events were mild, given that only for a very small proportion of those who presented with adverse events was treatment discontinuation necessary. The frequency of adverse events was significantly higher among patients treated with amlodipine alone especially in the long term. In the losartan alone group, as expected[24], we observed a lower incidence of adverse events, confirming the excellent tolerability of this class of antihypertensive drugs.

The most frequent adverse events in this multicenter study with the fixed combination of amlodipine and losartan, and with the monotherapies were lower extremity edema and headache[7,8,25]. The incidence of lower extremity edema was particularly significant among patients treated with amlodipine alone, reaching rates higher than 18% in the long term. With the fixed combination of amlodipine and losartan, the incidence of this adverse event was much lower, approximately four-fold less frequent than in the amlodipine alone group.

On one hand, the good tolerability of the combination may be explained by the use of lower doses of each of the hypotensive drugs, since the existence of a strong relation between the dose of the hypotensive drug and the frequency of adverse events is known[15,23]. On the other hand, the lower incidence of lower extremity edema observed with the combination – approximately one fourth of that observed in the amlodipine group, results not only from the use of lower doses of this calcium channel antagonist, but also from its synergistic interaction with losartan.

Thus, dihydropyridine calcium antagonists are known to be potent arterial vasodilators, but less effective as venodilators. Moreover, these agents have been demonstrated to be able to cause secondary sympathetic stimulation in varying degrees, thus increasing catecholamine release which ultimately promotes venoconstriction[7,8,16,25]. Consequently, in patients treated with dihydropyridine drugs there would be an increase in hydraulic pressure in the capillary region, exceeding the oncotic pressure with a resulting fluid extravasation into the interstitial space and, therefore, with edema formation. By gravity action, this edema tends to be located in the lower extremities, especially in the malleolus region, although even anasarca has already been described in patients using dihydropyridine calcium antagonists. This adverse event of dihydropyridine calcium antagonists has usually a late onset (after six to eight weeks of treatment), and becomes more intense during the day and in the summer.

On the other hand, the dilation effectiveness both arterial and venous of angiotensin II receptor blockers is well known[11]. Thus, when an ARB is combined with a calcium antagonist venular dilation is facilitated and hydraulic pressure in capillaries is reduced, and consequently the likelihood of edema formation also decreases. The better tolerability of the combination, as previously mentioned, will surely benefit treatment compliance[24].

However, patient compliance to treatment is also known to be influenced by countless factors such as the doctor-patient relationship, the knowledge of the disease, the absence of symptoms, the development of adverse events with antihypertensive medication, the number of pills to be taken, and others[15,17,18,19,23]. Thus, the fixed combination of amlodipine and losartan assessed in the present study has a second positive point in relation to patient compliance to treatment, which is its convenient posology; that is, the two antihypertensive drugs are packed in the same galenic formulation with a 24-hour duration of action, thus allowing the use of a single daily dose of the medication.

We are aware that, in addition to the aspects of efficacy and tolerability of an antihypertensive drug, we should also evaluate its effects on metabolic parameters, especially of glucose and lipids, because alterations in these parameters are very frequently observed in hypertensive patients. Incidentally, hypertension is frequently associated to the metabolic syndrome; also, the frequency of this association increases with age[26,27,28,29,30].

However, some drugs used in the treatment of hypertension, such as diuretics and beta blockers, are

known to be able to promote harmful alterations in lipid metabolism, especially in glucose metabolism[13,14,28,29,30]. The pharmacologic agents of the class of calcium channel antagonists, in turn, have a neutral metabolic profile, and in some studies using angiotension II receptor blockers for the treatment of hypertensive patients a positive impact on glucose metabolism was reported, with improvement of sensitivity to insulin[11,13] and a significant reduction in the risk of development of new cases of diabetes[9,10,13].

In our study we observed that the use of the fixed combination of amlodipine and losartan did not change parameters of either glucose metabolism or plasma lipids, thus having a neutral metabolic profile even when used in the long term. Based on these results we can conclude that this therapeutic modality is safe and adequate for the treatment of hypertension in patients with metabolic syndrome, diabetes mellitus and dyslipidemias.

In brief, the results of this multicenter study demonstrated that the fixed combination of amlodipine and losartan – the first galenic combination of these two classes of antihypertensive drugs available in the pharmaceutical market, has a high antihypertensive efficacy, allowing approximately 60% of the patients treated to achieve and maintain, in the long term, the new goal of blood pressure control. The antihypertensive effect of the combination is sustained in the 24 hours, thus allowing its use in a single daily dose, which benefits the compliance to treatment. The tolerability of this fixed combination of antihypertensive drugs is also very good, with a low incidence of adverse events further facilitating compliance.

Based on our results, we can suggest that thanks to the high antihypertensive efficacy sustained in the long term, and to the very good tolerability profile, in addition to the adequate metabolic profile, the fixed combination of amlodipine and losartan is an excellent option for the treatment of hypertension in a wide range of hypertensive patients, with a high potential to reduce cardiovascular risks since significant cardiovascular benefits have already been demonstrated with the use of each of the components of this fixed combination of antihypertensive drugs.

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