

Felodipine–Metoprolol Combination Tablet: A Valuable Option to Initiate Antihypertensive Therapy?

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The aim of the present study was to assess the efficacy and tolerability of a calcium antagonist/ β -blocker fixed combination tablet used as first-line antihypertensive therapy in comparison with an angiotensin converting enzyme inhibitor and placebo. Patients with uncomplicated essential hypertension (diastolic blood pressure between 95 and 110 mm Hg at the end of a 4-week run-in period) were randomly allocated to a double-blind, 12-week treatment with either a combination tablet of felodipine and metoprolol (Logimax), 5/50 mg daily ($n = 321$), enalapril, 10 mg daily ($n = 321$), or placebo ($n = 304$), with the possibility of doubling the dose after 4 or 8 weeks of treatment if needed (diastolic blood pressure remaining >90 mm Hg). The combined felodipine–metoprolol treatment controlled blood pressure (diastolic ≤ 90 mm Hg 24 h after dose) in 72% of patients after 12 weeks, as compared with 49% for enalapril and 30% for placebo. A dose adjustment was required in 38% of patients receiving the combination, in 63% of patients allocated to placebo, and 61% of enalapril-treated patients. The overall incidence of adverse events was 54.5% during felodipine–metoprolol

treatment; the corresponding values for enalapril and placebo were 51.7% and 47.4%, respectively. Withdrawal of treatment due to adverse events occurred in 18 patients treated with the combination, in 10 patients on enalapril, and 12 patients on placebo. No significant change in patients' well-being was observed in either of the three study groups. These results show that a fixed combination tablet of felodipine and metoprolol allows to normalize blood pressure in a substantially larger fraction of patients than enalapril given alone. This improved efficacy is obtained without impairing the tolerability. The fixed-dose combination of felodipine and metoprolol, therefore, may become a valuable option to initiate antihypertensive treatment. *Am J Hypertens* 1999;12:915–920 © 1999 American Journal of Hypertension, Ltd.

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Hypertension is a common disorder in industrialized countries and is associated with an increased cardiovascular risk.¹ Antihypertensive therapy prevents to a substantial degree the occurrence of complications such as stroke and myocardial infarction.² Therefore, considerable efforts are directed worldwide to screen for hypertensive patients and to treat them. The control of blood pressure at the community level remains, however, a difficult task. This is obvious from the rather small fraction of hypertensive patients who have actually normalized their blood pressure by antihypertensive therapy.^{3,4} For example, in a recent survey carried out in the United States, less than half of treated hypertensive patients achieved a blood pressure that is generally considered as ideal (ie, a systolic [SBP] and a diastolic blood pressure [DBP] lower than 140 and 90 mm Hg, respectively, during treatment).³

How could this suboptimal blood pressure control be explained? One reason could be that the drugs currently available are not effective enough, or are not used in an optimal way. Occurrence of side effects that reduces compliance is another important factor,⁵ and in fact a lifelong compliance to treatment is difficult for many patients is another reason.

Official guidelines recommend to initiate the pharmacologic treatment of hypertension with medications given as monotherapies and, when needed, to switch from one to another class of antihypertensive agents (sequential monotherapy) or to associate two medications lowering blood pressure by different mechanisms (combination therapy).^{6,7} Recently, the concept of low-, fixed-dose combination therapy has gained increasing acceptance.^{8,9} This approach is thought to maximize the antihypertensive efficacy and to minimize the incidence of dose-dependent adverse effects and has been proposed as a valuable choice for starting antihypertensive therapy.

The present study addresses several critical issues dealing with the practical management of hypertension. First, how does a first-line monotherapy-based approach compare with a fixed-dose combination treatment in terms of efficacy and tolerability? Second, how do these two therapeutic options compare with placebo, mainly in terms of tolerability? For this purpose, patients with uncomplicated essential hypertension were randomly allocated to a double-blind, 12-week treatment with either an angiotensin converting enzyme (ACE) inhibitor (enalapril), a fixed combination tablet containing the dihydropyridine felodipine extended-release formulation and the β -blocker metoprolol controlled-release formulation (Logimax), or placebo.

PATIENTS AND METHODS

Nine hundred forty-six patients with uncomplicated essential hypertension were included in this multicenter study. The number of randomized patients per country were: UK, 125; Belgium, 118; Sweden, 110; France, 106; Canada, 90; Norway, 82; Poland, 70; Spain, 69; Greece, 56; Switzerland, 47; Finland, 40; and Austria, 34. Patients were either untreated ($n = 494$), or had their previous treatment withdrawn ($n = 452$). They all had a mean sitting DBP between 95 and 110 mm Hg at the end of a 4-week placebo run-in period. Before inclusion, all patients gave written informed consent in accordance with the Helsinki declaration. The study was approved by all local ethics committees. All patients were considered able to understand and complete the general well-being questionnaire. Patients with a known intolerance to dihydropyridine antagonists, β -blockers, or ACE inhibitors were excluded.

The study was of parallel group design with a double-blind, random allocation to a 12-week treatment with either placebo ($n = 304$), enalapril, 10 mg/day ($n = 321$), or a fixed combination tablet of felodipine and metoprolol, 5/50 mg/day ($n = 321$). The doses were doubled after 4 or 8 weeks of treatment if mean sitting DBP was not ≤ 90 mm Hg. The dose was also doubled if, at any time after randomization, blood pressure was $>180/105$ mm Hg. In this case, an extra visit was scheduled within 7 days. The patient was discontinued from the study if he or she still had, at this extra visit, a blood pressure $>180/105$ mm Hg.

Sitting blood pressure, heart rate, and adverse events were recorded at randomization, and at each visit throughout the 12-week observation period. Blood pressure was measured 24 h after the last intake of the study medication. The measurements were always done in the same arm using a mercury sphygmomanometer and a cuff size appropriate to the patient's arm; they were performed in duplicate, with at least 1 min interval in between, to the nearest 2 mm Hg. The mean of the two readings was then calculated. Heart rate was determined by pulse palpation for 30 sec immediately after the blood pressure measurement.

Statistical Evaluation The changes in blood pressure and heart were analyzed by taking into account the change from baseline to the end of the study. The changes in the three treatment groups were compared using a two-way analysis of variance model with treatment and center as factors. Blood pressure and heart rate were also analyzed after 4 weeks of treatment. The proportion of patients with controlled blood pressure (sitting DBP ≤ 90 mm Hg) were compared between each one of the active treatment groups and placebo using the Mantel-Haenszel test stratifying

TABLE 1. CHARACTERISTICS OF THE PATIENTS AT BASELINE (MEANS \pm SD)

	Placebo (n = 304)	Enalapril (n = 321)	Felodipine– metoprolol (n = 321)
Male/female (n)	165/135	188/133	177/144
Age (years)	51.0 \pm 10.7	52.4 \pm 10.2	51.5 \pm 10.8
Weight (kg)	80.5 \pm 15.0	80.3 \pm 14.2	80.2 \pm 15.9
Height (cm)	168.3 \pm 9.8	168.8 \pm 9.4	168.9 \pm 9.9
Seated DBP (mm Hg)	101.0 \pm 4.4	100.9 \pm 4.6	101.1 \pm 4.3
Seated SBP (mm Hg)	157.2 \pm 15.3	158.0 \pm 15.4	157.6 \pm 15.3
Heart rate (beats/min)	74.9 \pm 9.1	74.7 \pm 8.6	75.1 \pm 8.8

DBP, diastolic blood pressure; SBP, systolic blood pressure.

for center. Because of multiple comparisons a *P* value less than .017 was considered significant for any pairwise comparison between treatments.

RESULTS

Table 1 shows the baseline demographic characteristics of the patients. There were no apparent differences in these parameters between the three groups.

Of the 946 randomized patients, 845 completed the study. The remaining patients discontinued prematurely because of adverse events (n = 40) or other reasons (n = 62), mainly because of blood pressure above safety criteria (n = 45). Among patients who interrupted the treatment due to adverse events, 12 (3.9%) were taking placebo, 10 (3.1%) on enalapril, and 18 (5.6%) on the felodipine–metoprolol combination, with no significant differences between groups. Two to 4 weeks after the end of the study, three patients on placebo had not yet recovered from the adverse effect (glomerulonephritis, nightmares, and urticaria). The corresponding numbers for the enalapril and the combination therapy group were three (headache, cerebral infarction, and retrosternal pain) and two (cholelithiasis and peripheral edema), respectively. During the run-in phase the incidence of adverse events was 26.3%, 29.9%, and 29.3% in the placebo, enalapril, and felodipine–metoprolol group, respectively. The corresponding values for the new onset adverse events seen during the randomized part of the trial were 42.4%, 45.8%, and 49.8%. Table 2 shows the new onset adverse events that were observed in at least 10 patients in any of the three study groups. As expected, the most common adverse events were peripheral edema, headache, and flushing in the felodipine–metoprolol group. Most patients (12 of 18) who discontinued the felodipine–metoprolol treatment did so because the occurrence of at least one of these three adverse events. This was also the case in 5 and 3 patients of the

TABLE 2. MOST COMMON NEW ONSET ADVERSE EVENTS (OCCURRING IN AT LEAST 10 PATIENTS IN ANY OF THE THREE TREATMENT GROUPS)

Adverse Event	Placebo (n = 304)	Enalapril (n = 321)	Felodipine– metoprolol (n = 321)
Headache	20 (6.6%)	16 (5.0%)	28 (8.7%)
Coughing	12 (3.9%)	23 (7.2%)	9 (2.8%)
Fatigue	10 (3.3%)	14 (4.4%)	18 (5.6%)
Edema	1 (0.3%)	3 (0.9%)	33 (10.3%)
Dizziness	9 (3%)	11 (3.4%)	15 (4.7%)
Flushing	11 (3.6%)	4 (1.2%)	17 (5.3%)
Respiratory infection	6 (2%)	16 (5%)	5 (1.6%)

12 and 10 patients who stopped prematurely placebo or enalapril treatment, respectively.

In Figure 1 the changes in blood pressure (measured 24 h after dose) from baseline to the 12th week of therapy are given. Both active treatments were significantly more effective in lowering blood pressure than placebo. This was true for SBP (*P* < .001) as well as DBP (*P* < 0.001). The reduction in blood pressure in the felodipine–metoprolol group was significantly greater than in the enalapril group (*P* < .001 for both SBP and DBP). This significant difference was observed after 4 and 12 weeks of treatment. Seventy-three percent of patients in the placebo group and 61% in the enalapril group required a dose increase compared with only 38% in the felodipine–metoprolol group.

The combined treatment controlled blood pressure in 63% of patients after 4 weeks and 72% after 12 weeks. The corresponding values were 40% and 49% for enalapril as compared with 30% and 40% for placebo. The proportion of patients with controlled DBP

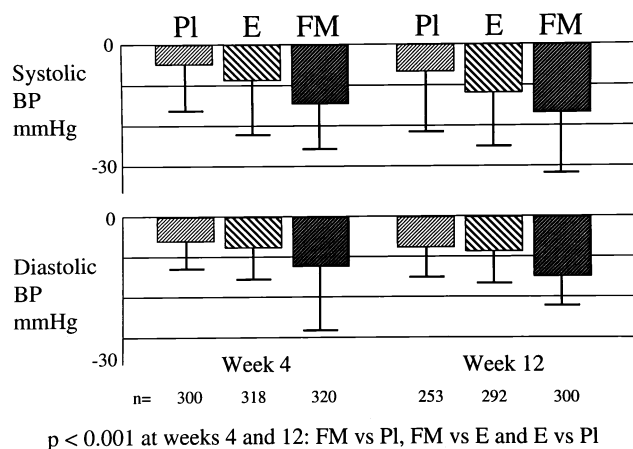


FIGURE 1. Mean (\pm 1 SD) changes in seated blood pressure (BP) after 4 and 12 weeks' treatment, 24 h after dosing. Pl, placebo; E, enalapril; FM, felodipine–metoprolol.

was significantly greater ($P < .001$) during felodipine-metoprolol treatment than enalapril or placebo administration, both after 4 and 12 weeks. In this respect, enalapril was also significantly better than placebo at 4 weeks ($P < .01$).

Heart rate was significantly decreased by the felodipine-metoprolol combination by 3.1 ± 8.5 beats/min after 4 weeks and 5.6 ± 9.4 beats/min after 12 weeks, whereas placebo and enalapril had no effect ($P < .001$, felodipine-metoprolol versus placebo and enalapril). No significant change in body weight was observed during the course of the study.

DISCUSSION

One of the purposes of this large double-blind, placebo-controlled multicenter trial was to apply a new approach of pharmacologic treatment of hypertension (ie, the use of a low-dose combination as first-line therapy). To this end a fixed-dose combination tablet of the vasoselective dihydropyridine calcium antagonist felodipine (5 mg/day)¹⁰ and the cardioselective β -blocker metoprolol (50 mg/day)¹¹ was compared with a medication lowering blood pressure by another mechanism, the ACE inhibitor enalapril (10 mg/day)¹², and placebo. All drugs were administered once daily. Enalapril was chosen as a reference single-agent therapy because of its wide acceptance as a first-line antihypertensive drug. The active treatments were significantly more effective than placebo, with a clearcut advantage for the felodipine-metoprolol combination over the enalapril monotherapy. Overall adverse events had the same incidence in patients receiving placebo as in those allocated to enalapril or the felodipine-metoprolol combination.

Combination therapy has advantages related to differing mechanisms of action of the individual drugs, which include the potential to produce additive antihypertensive effects. The association of a dihydropyridine with a β -blocker is logical, especially because blockade of cardiac β -adrenoceptor prevents the occurrence of any reflex heart rate acceleration induced by the calcium antagonist-mediated peripheral vasodilation. Actually, the felodipine-metoprolol combination is known to be more effective than the individual components given alone, while being as well tolerated.¹³ The fixed-dose combination used in the present study contains an extended-release formulation of felodipine and a controlled-release formulation of metoprolol. This preparation has been shown to provide smooth drug plasma concentrations as well as smooth blood pressure and heart rate effects over the 24-h dosing interval when administered once a day.¹⁴ For example, the trough-to-peak ratio for this long-acting felodipine-metoprolol combination is 84% for SBP and 65% for DBP,¹⁵ which falls within the guidelines suggested by the US Food and Drug Adminis-

tration for administration of once-daily antihypertensive drugs.¹⁶

The initial dosing of the active treatments was conventional and could be doubled if needed after 4 weeks. It has to be pointed out that the dose increase was required in clearly more patients randomized to enalapril (61%) than in those receiving the drug combination (38%). In this study, the dose adjustment allowed to increase the fraction of patients with a DBP ≤ 90 mm Hg by about 10%. The recommended dosing of enalapril in essential hypertension is 10 to 20 mg given once daily.¹⁷ It should be kept in mind in this context that enalapril is rather short-acting. Therefore, it is possible that a better blood pressure control would have been achieved by increasing the dose of enalapril to 20 mg twice a day.¹⁸

The lowering in blood pressure induced by the felodipine-metoprolol combination, on the average of 18/14 mm Hg after 3 months of treatment, are practically identical to what has been previously observed with the same preparation.¹³ The placebo arm was, as anticipated, of crucial importance as blood pressure was substantially lowered in the control group of patients, by a mean of 7/7 mm Hg at completion of the trial (ie, to the same extent achieved by the ACE inhibitor). Blood pressure was measured conventionally at the doctor's office, like in all interventional mega-trials performed so far. It should be emphasized, however, that the blood pressure readings were always obtained at trough, 24 h after the last dosing. This may lead to an underestimation of the blood pressure response prevailing during most of the day.

Regarding the quality of blood pressure control, the main message of the present study is that starting therapy with a low-dose calcium antagonist/ β -blocker combination makes it possible to normalize blood pressure in a greater number of patients than with an ACE inhibitor as initial drug. Several other studies have demonstrated the superiority of low-dose combinations of antihypertensive agents over monotherapy with the individual components (even in higher doses). This is, for example, the case for ACE inhibitor/diuretic,^{19,20} ACE inhibitor/calcium antagonist,^{21,22} and β -blocker/diuretic²³ combinations. It is pertinent to note in this context that a low-dose combination of the β_1 -adrenoceptor blocker bisoprolol and hydrochlorothiazide²³ has been approved by the Food and Drug Administration in United States as a first-line therapy.²⁴ Furthermore, the low-dose reserpine-thiazide combination, which is generally viewed as obsolete, is more effective in lowering blood pressure than a modern calcium antagonist like nifedipine given in monotherapy, while inducing fewer side effects.²⁵

Finally, the need for combining drugs acting by different mechanisms to better control blood pressure

is substantiated by the preliminary results of the Hypertension Optimal Treatment study.²⁶ In this morbidity and mortality trial, patients were randomized to three different target groups of either ≤ 90 , ≤ 85 , or ≤ 80 mm Hg. The treatment was started in all patients with felodipine, and a β -blocker or an ACE inhibitor could then be added if the goal blood pressure was not reached. At 6 months, 83% of the patients of the ≤ 90 mm Hg target group had achieved their target. The corresponding figures for the ≤ 85 and ≤ 80 mm Hg target group were 71% and 57%, respectively. Consequently, more aggressive therapy was required for the lower blood pressure targets, which is reflected by the fact that combination therapy was used in 48%, 59%, and 66% of the ≤ 90 , ≤ 85 , and ≤ 80 mm Hg target groups, respectively.

When dealing with the pharmacologic treatment of hypertension, a crucial issue is the tolerability of drugs. Each antihypertensive agent might have basically two types of adverse effects: those that are or those that are not dose dependent within the therapeutic dosing range.²⁷ Combining low doses of drugs with different modes of action on the cardiovascular system minimizes the incidence of dose-dependent side effects and could prevent the occurrence of some adverse reactions triggered by the other constituent of the combination.^{7–9} This pharmacologic rationale is to some extent substantiated by the results of the present study. Thus, there were no more clinical adverse experiences in patients allocated to the combined treatment than in those administered enalapril. In terms of compliance, fixed-dose combinations also offer an advantage by enabling patients to follow a simple and convenient therapeutic regimen.

Interestingly, the profile of adverse effects observed from the felodipine–metoprolol treatment corresponded to that expected during calcium entry blockade using a dihydropyridine (ie, edema, headache, and flushing). These adverse effects are most likely attributable to the felodipine-induced vasodilation. In the present trial, they were by far the leading cause of treatment discontinuation. Also interestingly, these adverse effects have been shown previously to be less frequent when felodipine is combined with metoprolol, as in this study, than when it is given alone.²⁶

In conclusion, the present data show that the felodipine–metoprolol combination tablet allows to normalize blood pressure in a larger number of hypertensive patients than enalapril used as a single agent. They also show that this better antihypertensive efficacy is not obtained at the expense of a decreased tolerability. Low-dose fixed combinations, because of their excellent efficacy, good tolerability, and simplicity of use, are very useful to treat patients not adequately controlled by monotherapy and therefore,

may become a valuable option to initiate antihypertensive therapy.

REFERENCES

1. MacMahon S, Peto R, Cutler J, et al: Blood pressure, stroke, and coronary heart disease. Part I. Prolonged differences in blood pressure: prospective observational studies corrected for the regression, dilution bias. *Lancet* 1990;335:765–777.
2. Collins R, Peto R, MacMahon S, et al: Blood pressure, stroke and coronary heart disease. Part 2. Short-term reductions in blood pressure: overview of randomized drug trials in their epidemiological context. *Lancet* 1990;335:827–838.
3. Burt VL, Cutler JA, Higgins M, et al: Trends in prevalence, awareness, treatment and control of hypertension in the adult US population: data from the health examination surveys 1960–1991. *Hypertension* 1995;26:60–69.
4. Mancia G, Sega R, Milesi C, et al: Blood pressure control in the hypertensive population. *Lancet* 1997;349:454–457.
5. Lüscher TF, Vetter H, Siegenthaler W, Vetter W: Compliance in hypertension: facts and concepts. *J Hypertens* 1985;3(suppl 1):3–9.
6. 1993 Guidelines for the Management of Mild Hypertension: Memorandum from a World Health Organization/International Society of Hypertension Meeting. *Hypertension* 1993;22:392–403.
7. Brunner HR, Ménard J, Waeber B, et al: Treating the individual hypertensive patient: considerations on dose, sequential monotherapy and fixed-dose combinations. *J Hypertens* 1990;8:3–11.
8. Waeber B, Brunner HR: Main objectives and new aspects of combination treatment of hypertension. *J Hypertens* 1995;13(suppl 2):S15–S19.
9. Epstein M: Newer approaches to antihypertensive therapy. *Arch Intern Med* 1996;156:1969–1978.
10. Todd PA, Faulds D: Felodipine. A review of the pharmacology and therapeutic use of the extended-release formulation in cardiovascular disorder. *Drugs* 1992;44:251–277.
11. Houtzagers JJR, Smilde JG, Creyten G, Westergren G: Efficacy and tolerability of a new controlled-release formulation of metoprolol: a comparison with conventional metoprolol tablets in mild to moderate hypertension. *Eur J Clin Pharmacol* 1997;33:39–44.
12. Todd PA, Heel RC: 1986. Enalapril. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension and congestive heart failure. *Drugs* 31:198–248.
13. Dahlöf B, Jönsson L, Borgholst O, et al: Improved antihypertensive efficacy of the felodipine-metoprolol extended-release tablet compared with each drug alone. *Blood Pressure* 1993;2(suppl1):37–45.
14. Abrahamsson B, Edgar B, Lidman K, Wingstrand K: Design and pharmacokinetics of Logimax, a new extended-release combination tablet of felodipine and metoprolol. *Blood Pressure* 1993;2(suppl 1):10–15.
15. Venables TL, Akhtar W, Campbell LM, et al: Antihy-

- pertensive efficacy of a combination of felodipine and metoprolol. *J Hum Hypertens* 1995;9(suppl 2);53.
16. Meredith PA: Through/peak ratios for antihypertensive agents. The issues in perspective. *Drugs* 1994;48:661-666.
 17. Gavras I, Gavras H: Enalapril, *in* Messerli, FH (ed): *Cardiovascular Drug Therapy*. Philadelphia, WB Saunders, 1990, pp 792-799.
 18. MacFadyen RJ, Meredith PA, Elliott HL: Enalapril: clinical pharmacokinetics and pharmacokinetic-pharmacodynamic relationships. An overview. *Clin Pharmacokinetics* 1993;25:274-282.
 19. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Low-dose captopril for the treatment of mild to moderate hypertension. *Hypertension* 1983;5(suppl 3):139-144.
 20. Chrysant SG, for the Lisinopril-Hydrochlorothiazide Group: Antihypertensive effectiveness of a low-dose lisinopril-hydrochlorothiazide combination. *Arch Intern Med* 1994;154:737-743.
 21. Gennari C, Nami R, Pavese G, et al: Calcium-channel blockade (nitrendipine) in combination with ACE inhibition (captopril) in the treatment of mild to moderate hypertension. *Drugs Ther* 1989;3:319-325.
 22. Fitscha P, Meisner W, Hitzemberger G: Antihypertensive effects of isradipine and captopril as monotherapy or in combination. *Am J Hypertens* 1991;4:151s-153s.
 23. Frishman WH, Bryzinski BS, Coulson LR, et al: A multifactorial trial design to assess combination therapy in hypertension. Treatment with bisoprolol and hydrochlorothiazide. *Arch Intern Med* 1994;154:1461-1468.
 24. Fenichel RR, Lipicky RJ: Combination products as first-line pharmacotherapy. *Arch Intern Med* 1994;154:1429-1430.
 25. Krönig B, Pittrow DB, Kirch W, et al, for the German Reserpine in Hypertension Study Group, 1997: Different concepts in first-line treatment of essential hypertension: comparison of a low-dose reserpine-thiazide combination with nitrendipine monotherapy. *Hypertension* 1997;29:651-658.
 26. Hansson L, Zanchetti A, for the HOT Study Group: The Hypertension Optimal Treatment (HOT) Study—patient characteristics: randomization, risk profiles, and early blood pressure results. *Blood Pressure* 1994;3:322-327.
 27. Fagan TC: Remembering the lessons of basic pharmacology. *Arch Intern Med* 1994;154:1430-1431.