

Felodipine–Metoprolol Combination Tablet: Maintained Health-Related Quality of Life in the Presence of Substantial Blood Pressure Reduction

Björn Dahlöf, Alessio Degl' Innocenti, Dag Elmfeldt, Juan Garcia Puig, Torstein Gundersen, James Hosie, Włodzimierz Januszewicz, Carl-Johan Lindström, Dieter Magometschnigg, Paul Tanser, Pavles Toutouzas, Bernhard Waeber, and Ingela Wiklund

Background: Most treated hypertensive patients do not achieve adequate blood pressure (BP) control. Initiating therapy with two drugs has been suggested when BP is >20/10 mm Hg above goal. To ensure patients' compliance, such treatment needs to be well tolerated and must not compromise health-related quality of life (HRQL). The primary objective of this study was to compare the effects on HRQL of initiating treatment with felodipine + metoprolol (F+M) fixed combination tablets, or enalapril (E), or placebo (P).

Methods: A total of 947 patients of both sexes with primary hypertension (diastolic BP 95 to 110 mm Hg), aged 20 to 70 years, participated in this randomized, double-blind, parallel group, 12-week, multicenter trial. Treatment was initiated with F+M 5 + 50 mg, or E 10 mg, or P. Doses were doubled after 4 or 8 weeks if diastolic BP was >90 mm Hg. The HRQL was measured at baseline and at the last visit using two validated questionnaires: the Psychological General Well-being Index

(PGWB) and the Subjective Symptom Assessment Profile (SSA-P). Office BP was measured at trough, that is, 24 h after the previous dose.

Results: The HRQL was high at baseline and generally well maintained during the study. For example, the mean (SD) PGWB total score was 104 (16) at baseline and 105 (16) at 12 weeks in all three treatment groups. The BP reductions after F+M (18/14 mm Hg) and E (12/9 mm Hg) were significantly greater than after P (7/7 mm Hg), and the reduction after F+M was significantly greater than after E.

Conclusions: The HRQL is maintained in the presence of substantial BP reduction during antihypertensive treatment with F+M fixed combination tablets. Am J Hypertens 2005;18:1313-1319 © 2005 American Journal of Hypertension, Ltd.

Key Words: Enalapril, felodipine, health-related quality of life, hypertension, metoprolol.

Antihypertensive drug therapy reduces cardiovascular morbidity and mortality.¹⁻³ However, many treated hypertensive patients remain at increased cardiovascular risk because of insufficient blood pressure (BP) reduction. In the US it was recently shown that the recommended target BP (140/90 mm Hg or less) was only achieved in 30% of treated Americans.³ This suboptimal

result is partly because most available antihypertensive drugs, used as monotherapy, provide adequate BP control in less than 50% of treated patients. Consequently, most patients need combinations of two or more antihypertensive drugs for adequate BP control.^{3,4}

The relationship between benefit and risk of drug treatment perceived by doctors and patients are also important for whether

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From the Clinical Experimental Research Laboratory, Department of Medicine, Sahlgrenska University Hospital/Östra (BD), Göteborg, Sweden; AstraZeneca R&D (ADI, DE, IW), Mölndal, Sweden; Hospital La Paz (JGP), Madrid, Spain; Sørlandet Hospital (TG), Arendal, Norway; Great Western Medical (JH), Glasgow, UK; Department of Hypertension of the Medical Academy in Warszawa (WJ), Warszawa, Poland; Västra Nylands kretssjukhus (C-JL), Ekenäs, Finland; Institut for hyperteniker,

Kinderspitalgasse (DM), Vienna, Austria; Department of Medicine, St Joseph's Hospital (PT), Hamilton, ON, Canada; Hippokraton Hospital of Athen (PT), Athens, Greece; and Division d'hypertension, CHUV (BW), Lausanne, Switzerland.

List of investigators appear in the Appendix.

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Address correspondence and reprint requests to Dr. Alessio Degl' Innocenti, Medical Science, AstraZeneca R&D, SE-431 83 Mölndal, Sweden; e-mail: alessio.deglinnocenti@astrazeneca.com

or not the recommended BP target is achieved. Hypertension is generally an asymptomatic condition, whereas antihypertensive drug therapy may elicit adverse drug reactions and compromise the patient's health-related quality of life (HRQL).^{5,6} Such possible drawbacks of drug therapy will negatively affect the doctor's willingness to prescribe effective treatment, and also impair the patient's compliance. Many doctors and patients fear that the substantial BP reductions needed to achieve the recommended BP target, and the drug combinations necessary to reach this goal, may affect HRQL negatively.

Thus, for best possible prevention of cardiovascular complications, antihypertensive drug regimens need to be both effective and well tolerated, and must not compromise the patients' HRQL. Combinations of drugs with complementary mechanisms of action may be particularly useful in this context, as they can provide improved BP reduction with maintained tolerability and HRQL, and current guidelines on the management of hypertension do recommend fixed combinations.^{3,4} The American guidelines suggest consideration should be given to initiating therapy with two drugs, either as separate prescriptions or in fixed dose combinations when BP is more than 20/10 mm Hg above goal.³

Controlled release combination tablets containing felodipine, a vascular selective dihydropyridine calcium antagonist, and metoprolol succinate, a β_1 -selective adrenoceptor antagonist, reduce the BP more effectively than any of its components, without compromising tolerability.⁷ The effect of felodipine + metoprolol combination tablets on HRQL in hypertensive patients has so far not been specifically studied.

The rationale behind this placebo-controlled study was the assumption that felodipine + metoprolol combination tablets reduce BP substantially in patients with primary hypertension without compromising HRQL. It was decided to compare felodipine + metoprolol not only with placebo, but also with a commonly used, effective, and well-tolerated monotherapy. This comparison could indicate whether the combination would be a possible alternative for initiating treatment. The primary objective was to compare the effects of the three treatments (felodipine + metoprolol, enalapril, or placebo) on HRQL. Other objectives were to compare the BP-lowering effects and tolerability (adverse events). This article presents the HRQL part of the study together with brief data on BP. Detailed results on BP and tolerability have been published previously.⁸

Methods

Study Population

Men and women, aged 20 to 70 years, with primary hypertension and sitting diastolic BP 95 to 110 mm Hg after a 4-week single-blind, run-in period with placebo treatment, were eligible for inclusion in the study. A further inclusion criterion was that patients should be able to understand and complete the HRQL questionnaires. Patients with known intolerance to any of the study drugs

were excluded, as were patients with a history of recent psychiatric or cardiovascular disease, insulin-treated diabetes, impaired liver function, renal artery stenosis, or any condition associated with poor compliance. A total of 947 patients from 96 study sites (mostly general practices) in 12 countries were randomized: Austria ($n = 34$), Belgium ($n = 118$), Canada ($n = 90$), Finland ($n = 40$), France ($n = 106$), Greece ($n = 56$), Norway ($n = 82$), Poland ($n = 70$), Spain ($n = 69$), Sweden ($n = 110$), Switzerland ($n = 47$), and UK ($n = 125$). Before inclusion all patients gave written informed consent in accordance with the Helsinki declaration. The study was conducted according to Good Clinical Practice and was approved by all local Ethics Committees.

Study Design and Conduct

This was a randomized, placebo-controlled, double-blind, parallel group study. Eligible patients were randomized to 12 weeks of double-blind treatment with either felodipine + metoprolol, enalapril, or placebo. All treatments were given once daily. The initial dosage of felodipine + metoprolol was 5 + 50 mg and that of enalapril was 10 mg. The doses were doubled to a maximum of 10 + 100 mg and 20 mg, and corresponding placebo, at check-up visits after 4 or 8 weeks of treatment if sitting diastolic BP was not ≤ 90 mm Hg. The doses were also doubled if, at any time after randomization, BP was >180 mm Hg systolic or >105 mm Hg diastolic. If the BP remained at this high level after 7 d, the patient was discontinued from the study.

Health-Related Quality of Life Assessments

The patients answered two validated, self-administered HRQL questionnaires at randomization and after 12 weeks of double-blind treatment to assess both general well-being and specific subjective symptoms. The questionnaires were also used at study enrolment (ie, before randomization) to familiarize the patients with the procedures. The patients answered the questionnaires during the clinic visit before any other measurements or examinations were made. To promote quality and avoid missing values, the questionnaires were checked for completeness before the patient left the clinic.

General well-being was evaluated using the Psychological General Well-Being (PGWB) Index.⁹ This questionnaire measures subjective well-being or distress, and is well-documented in terms of reliability and validity.^{10,11} It contains 22 items that, apart from giving a total score, combine into six dimensions: anxiety, depressed mood, positive well-being, self-control, general health, and vitality. The patient rates each item on a six-point scale (with 6 as the most positive option and 1 as the most negative). The PGWB total score gives a maximum of 132 and a minimum of 22.

Subjective symptoms were evaluated using the validated Subjective Symptom Assessment Profile (SSA-P).¹²

Table 1. Demographics, clinical data, and medical history at baseline

| | Placebo (n = 304) | Enalapril (n = 321) | Felodipine-Metoprolol (n = 321) |
|-----------------------------------|----------------------|------------------------|------------------------------------|
| Male/female (n) | 169/135 | 188/133 | 177/144 |
| Age (yr) | 51.0 (10.7) | 52.4 (10.2) | 51.5 (10.8) |
| Seated DBP (mm Hg) | 101.0 (4.4) | 100.9 (4.6) | 101.1 (4.3) |
| Seated SBP (mm Hg) | 157.2 (15.3) | 158.0 (15.4) | 157.6 (15.3) |
| History of | | | |
| Myocardial infarction (n) | 6 (2.0%) | 7 (2.2%) | 3 (0.9%) |
| Cerebrovascular disease (n) | 5 (1.6%) | 2 (0.1%) | 5 (1.6%) |
| Diabetes mellitus (n) | 10 (3.3%) | 21 (6.5%) | 12 (3.7%) |
| Obstructive pulmonary disease (n) | 6 (2.0%) | 3 (0.9%) | 3 (0.9%) |
| Renal disease (n) | 7 (2.3%) | 17 (5.3%) | 16 (5.0%) |
| Liver disorder (n) | 13 (4.3%) | 6 (1.9%) | 11 (3.4%) |
| Allergy (n) | 38 (12.5%) | 36 (11.2%) | 26 (8.1%) |

Means (SD) where applicable.

The SSA-P considers subjective symptoms that are commonly reported among treated and untreated hypertensive patients. It contains 42 symptoms (items). A visual analog scale is used to rate each item (ie, a 100-mm straight line with its end-points defined in words denoting the extreme poles). Highly correlated items are categorized into six dimensions: emotional distress (7 items), gastrointestinal symptoms (6 items), peripheral vascular symptoms (5 items), cardiac symptoms (3 items), sex life (2 items), and dizziness (2 items). The remaining 17 items are presented as single items. The scale ranges from 0 to 100. A low value indicates few or less pronounced symptoms, whereas a high score indicate severe symptoms, or poor functioning.

BP Measurements

At all clinical visits, BP was measured 24 h after the last intake of study medication. Blood pressure was measured after 5 min of rest in the seated position, and always in the same arm, using a mercury sphygmomanometer and a cuff size appropriate to the patient’s arm. The measurements were made in duplicate and the mean was calculated and used in all analyses.

Statistical Analysis

The study was analyzed using the intention-to-treat approach. Changes in HRQL variables and BP, from baseline to the last visit (12 weeks), were compared between treatments using a two-way analysis of variance model with treatment and country as factors. Country rather than center was used in the model because of the large number of centers, some of which had only a few patients.

The change in PGWB total score was the primary efficacy variable. Using Bonferroni’s method to adjust for multiple tests, a P value less than .017 was considered significant. Accordingly, the 98.3% confidence intervals (CI) for the true mean differences between treatments are given in the results. Two hundred patients per treatment

group were required to demonstrate a difference in change in PGWB total score of 3.5 or more between any two treatments, with an α error of 5% and 80% power, assuming a standard deviation of 12.5.

Results

A total of 947 patients were randomly allocated to treatment with felodipine + metoprolol (n = 321), or enalapril (n = 321), or placebo (n = 305). The baseline demographics, BP, and medical history in the three treatment groups are given in Table 1. The patient flow is shown in Fig. 1. One hundred two patients discontinued the study prematurely (40 due to adverse events, 45 because of too high BP, and 17 due to other reasons. One randomized patient who received two different sets of blinded medication (intended for different patients) was excluded from the

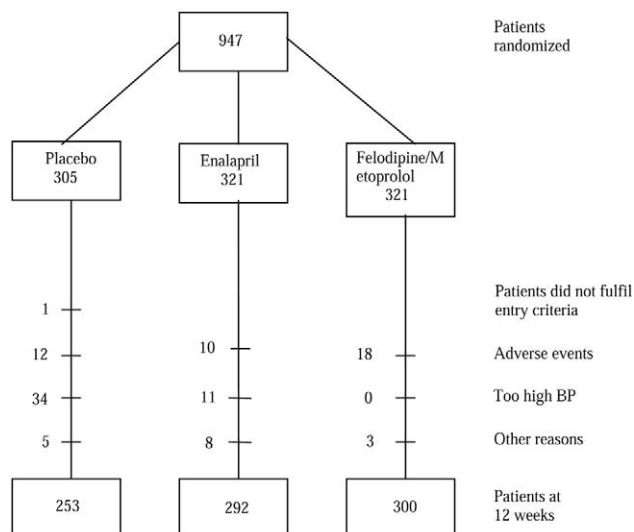


FIG. 1. Flow chart of patients. Numbers of patients randomized, discontinued, and followed for 12 weeks (end of study).

Table 2. The Psychological General Well-Being Index (the higher the score the higher the well-being)

| | n | Baseline | | 12-week | | Difference 12-week – Baseline | | Comparison | 98.3% CI |
|-----------------------|-----|----------|------|---------|------|-------------------------------------|------|------------|---------------|
| | | Mean | SD | Mean | SD | Mean | SD | | |
| Total score | | | | | | | | | |
| Placebo | 249 | 103.6 | 15.4 | 104.8 | 16.0 | 1.2 | 14.3 | PI-FM | –2.349; 2.815 |
| Enalapril | 289 | 104.3 | 16.6 | 105.5 | 15.6 | 1.2 | 11.4 | PI-E | –2.520; 2.672 |
| Felodipine–Metoprolol | 297 | 104.3 | 16.3 | 105.5 | 16.2 | 1.2 | 12.0 | E-FM | –2.321; 2.636 |
| Anxiety | | | | | | | | | |
| Placebo | 249 | 23.5 | 4.4 | 23.9 | 4.6 | 0.5 | 4.4 | PI-FM | –0.699; 0.928 |
| Enalapril | 288 | 23.8 | 4.5 | 24.4 | 4.1 | 0.6 | 3.7 | PI-E | –0.919; 0.719 |
| Felodipine–Metoprolol | 297 | 23.8 | 4.7 | 24.2 | 4.5 | 0.4 | 3.8 | E-FM | –0.567; 0.996 |
| Depressed mood | | | | | | | | | |
| Placebo | 249 | 15.9 | 2.4 | 15.9 | 2.4 | 0.0 | 2.4 | PI-FM | –0.453; 0.421 |
| Enalapril | 289 | 16.0 | 2.4 | 16.0 | 2.4 | 0.0 | 2.0 | PI-E | –0.460; 0.418 |
| Felodipine–Metoprolol | 296 | 15.8 | 2.5 | 15.8 | 2.4 | 0.0 | 2.0 | E-FM | –0.415; 0.424 |
| Positive well-being | | | | | | | | | |
| Placebo | 249 | 16.6 | 3.3 | 16.7 | 3.6 | 0.1 | 3.1 | PI-FM | –0.630; 0.536 |
| Enalapril | 288 | 16.8 | 3.7 | 16.9 | 3.6 | 0.1 | 2.7 | PI-E | –0.529; 0.643 |
| Felodipine–Metoprolol | 296 | 16.7 | 3.6 | 16.9 | 3.7 | 0.2 | 2.7 | E-FM | –0.664; 0.456 |
| General health | | | | | | | | | |
| Placebo | 249 | 14.6 | 2.7 | 14.9 | 2.4 | 0.4 | 2.5 | PI-FM | –0.174; 0.760 |
| Enalapril | 289 | 14.5 | 2.7 | 14.8 | 2.5 | 0.2 | 2.2 | PI-E | –0.338; 0.601 |
| Felodipine–Metoprolol | 297 | 14.8 | 2.6 | 14.9 | 2.5 | 0.1 | 2.2 | E-FM | –0.287; 0.609 |
| Self Control | | | | | | | | | |
| Placebo | 249 | 15.5 | 2.2 | 15.7 | 2.3 | 0.2 | 2.2 | PI-FM | –0.411; 0.502 |
| Enalapril | 289 | 15.5 | 2.5 | 15.5 | 2.5 | 0.1 | 2.1 | PI-E | –0.365; 0.553 |
| Felodipine–Metoprolol | 297 | 15.4 | 2.5 | 15.6 | 2.5 | 0.1 | 2.3 | E-FM | 0.487; 0.389 |
| Vitality | | | | | | | | | |
| Placebo | 248 | 17.6 | 3.7 | 17.7 | 3.8 | 0.0 | 3.4 | PI-FM | –0.772; 0.446 |
| Enalapril | 289 | 17.8 | 3.7 | 17.9 | 3.7 | 0.1 | 2.8 | PI-E | –0.677; 0.548 |
| Felodipine–Metoprolol | 297 | 17.8 | 3.6 | 18.1 | 3.5 | 0.2 | 2.6 | E-FM | –0.683; 0.485 |

analysis. Thus 845 patients were available for the 12-week analysis.

Health-Related Quality of Life

General Well-Being The mean PGWB scores at baseline and the 12-week visit in the treatment groups, and the mean changes from baseline, are given in Table 2. The table also shows the 98.3% CI for the between-group comparisons. The mean PGWB total scores were similar and relatively high in all three treatment groups at baseline, and remained fairly constant during the study. The same applied to all PGWB dimensions. In fact, there was no change or a slight numerical increase in all scores in all treatment groups (ie, the general well-being was not compromised by any of the treatments, and there were no treatment differences).

Subjective Symptoms The mean scores in the SSA-P dimensions at baseline and the 12-week visit in the treatment groups, and the mean changes from baseline, are given in Table 3. The table also shows the 98.3% CI for the between-group comparisons. The mean scores were similar and relatively low at baseline in all three treatment groups, and the mean changes during the study were generally small. However, there was a slight increase in the gastrointestinal symptoms score during treatment with

felodipine + metoprolol (mean +1.8), which differed significantly from the slight decreases recorded during treatment with enalapril (mean –1.4) or placebo (mean –2.0).

The mean scores in SSA-P single items were relatively low and similar in the three treatment groups and at baseline. The mean changes from baseline to the 12-week visit were generally modest, with two exceptions; the score for swollen ankles increased by 8.9 (from 12.5) during treatment with felodipine + metoprolol, and the score for dry cough increased by 8.3 (from 17.0) during treatment with enalapril. However, these symptoms were mild or moderate in the majority of patients and caused few discontinuations. Five patients discontinued due to swollen ankles in the felodipine + metoprolol group, and only one patient discontinued due to cough in the enalapril group.

Antihypertensive Effect

A lower proportion of patients treated with felodipine + metoprolol (38%) required a dose increase compared to those treated with enalapril (61%) or placebo (73%). The mean reductions in sitting BP from baseline to the 12-week visit were 18/14 mm Hg (systolic BP/diastolic BP) after felodipine + metoprolol, 12/9 mm Hg after enalapril,

Table 3. Subjective Symptoms Assessment Profile (SSA-P) dimensions (the lower the value the less symptoms)

| | n | Baseline | | 12-week | | Difference 12-week – Baseline | | Comparison | 98.3% CI |
|------------------------------------|-----|----------|------|---------|------|-------------------------------------|------|------------|----------------|
| | | Mean | SD | Mean | SD | Mean | SD | | |
| Emotional distress | | | | | | | | | |
| Placebo | 247 | 26.1 | 18.7 | 25.1 | 18.6 | -1.1 | 16.0 | PI-FM | -3.973; 2.209 |
| Enalapril | 287 | 24.5 | 18.7 | 23.5 | 17.7 | -0.9 | 14.6 | PI-E | -3.360; 2.845 |
| Felodipine–Metoprolol | 293 | 24.4 | 17.8 | 24.1 | 18.1 | -0.3 | 14.4 | E-FM | -3.591; 2.341 |
| G-1 Symptoms | | | | | | | | | |
| Placebo | 247 | 15.7 | 12.4 | 13.7 | 10.9 | -2.0 | 10.8 | PI-FM | -5.908; -1.715 |
| Enalapril | 287 | 14.7 | 13.4 | 13.4 | 10.8 | -1.4 | 10.1 | PI-E | -2.711; 1.506 |
| Felodipine–Metoprolol | 295 | 12.0 | 9.6 | 13.9 | 10.3 | 1.8 | 9.5 | E-FM | -5.221; -1.197 |
| Peripheral circulatory symptoms | | | | | | | | | |
| Placebo | 247 | 16.2 | 15.3 | 15.9 | 15.0 | -0.2 | 15.5 | PI-FM | -5.540; 0.176 |
| Enalapril | 287 | 16.1 | 13.7 | 16.0 | 13.8 | -0.1 | 12.2 | PI-E | -3.059; 2.693 |
| Felodipine–Metoprolol | 296 | 14.9 | 12.8 | 17.3 | 15.3 | 2.4 | 14.0 | E-FM | -5.241; 0.243 |
| Cardiac symptoms | | | | | | | | | |
| Placebo | 246 | 16.1 | 16.4 | 14.0 | 13.8 | -2.1 | 15.3 | PI-FM | -4.431; 1.698 |
| Enalapril | 287 | 14.4 | 15.1 | 12.6 | 13.4 | -1.8 | 14.0 | PI-E | -3.440; 2.724 |
| Felodipine–Metoprolol | 295 | 13.2 | 15.1 | 12.4 | 13.1 | -0.7 | 15.3 | E-FM | -3.946; 1.929 |
| Sexual life | | | | | | | | | |
| Placebo | 237 | 32.1 | 21.3 | 35.0 | 24.2 | 2.9 | 22.0 | PI-FM | -1.103; 7.786 |
| Enalapril | 274 | 30.7 | 20.1 | 32.4 | 22.8 | 1.7 | 21.1 | PI-E | -3.382; 5.553 |
| Felodipine–Metoprolol | 281 | 35.5 | 22.3 | 35.0 | 22.7 | -0.5 | 19.7 | E-FM | -2.013; 6.525 |
| Dizziness | | | | | | | | | |
| Placebo | 245 | 17.9 | 20.3 | 15.7 | 18.3 | -2.3 | 18.3 | PI-FM | -7.351; 0.590 |
| Enalapril | 287 | 17.6 | 18.8 | 16.5 | 18.3 | -1.1 | 19.0 | PI-E | -5.107; 2.856 |
| Felodipine–Metoprolol | 292 | 15.8 | 18.7 | 17.1 | 19.6 | 1.2 | 19.9 | E-FM | -6.057; 1.546 |

and 7/7 mm Hg after placebo. The reductions were significantly greater in both active treatment groups than in the placebo group. The BP reduction was also significantly greater in the felodipine + metoprolol group than in the enalapril group (mean difference 6/5 mm Hg; $P < .001$). The proportion of responders after 12 weeks (ie, patients with diastolic BP ≤ 90 mm Hg or a reduction in diastolic BP ≥ 10 mm Hg) were 82%, 57%, and 46% in the felodipine + metoprolol, enalapril, and placebo groups, respectively.

Discussion

This double-blind, placebo-controlled study shows that HRQL is maintained in the presence of substantial BP reduction during antihypertensive treatment with felodipine + metoprolol combination tablets.

The study population was recruited from general practices in Europe and Canada and consisted of more than 900 men and women, aged 20 to 70 years, with mild-to-moderate primary hypertension. Thus, the patients studied can be regarded as representative for the ordinary white hypertensive patient.

The PGWB and the SSA-P were selected for the assessment of HRQL on the basis of being well recognized and validated.⁹ The large number of patients in this study

ensured high statistical power to detect also small differences between study treatments in effects on HRQL. In fact, a retrospective power analysis confirmed that the study had 92% power to detect a difference of 3.5 units in PGWB total score.

More patients were discontinued in the placebo group ($n = 52$) than in the felodipine + metoprolol group ($n = 21$) or the enalapril group ($n = 29$). The most common reasons were too high BP in the placebo and enalapril groups, and adverse events in the felodipine + metoprolol group. It is unlikely that these differences in discontinuation rates between the treatment groups have introduced any serious bias in the analysis of the study and caused erroneous conclusions. First, the number of patients discontinued was low in relation to all patients in each treatment group. Second, exclusion of more patients with too high BP in the placebo group leads to the BP-lowering effect of active treatments being underestimated. Third, patients who were discontinued because of too high BP most likely had low rather than high HRQL, and exclusion of more such patients in the placebo group results in their HRQL being overestimated.

The patients' HRQL was generally high at baseline. The mean PGWB total scores of 104 indicate high general well-being, and are similar to those previously observed in a general population sample.¹³ In addition, the mean

SSA-P scores were generally low, and few mean values were above 20 on the 0 to 100 scale. Thus, most patients had no or only mild symptoms. The high HRQL at baseline observed in this study is in agreement with findings in other studies of hypertensive patients¹⁴ and supports previous statements that hypertensive patients constitute an asymptomatic population.

The mean PGWB and SSA-P scores were generally well maintained during the study in all three treatment groups (ie, HRQL was not negatively affected by treatment). The only significant difference between treatments in the present study was the slight increase in the SSA-P dimension “gastrointestinal symptoms” during felodipine + metoprolol treatment that differed from the slight decreases during enalapril or placebo treatment. The occurrence of expected class-specific side effects in some patients (eg, swollen ankles with felodipine + metoprolol and cough with enalapril) did not influence the general well-being in most patients, as there was no decrease in mean PGWB scores. These symptoms were mild or moderate in the majority of patients and caused few discontinuations.

A number of previous comparative studies have shown only small, if any, changes in HRQL during treatment with calcium antagonists, β -blockers, or angiotensin-converting enzyme (ACE) inhibitors.^{6,14–22} However, these studies did not exclude an effect on HRQL of the studied drugs, as they were not placebo controlled.

Health-related quality of life was as well maintained during treatment with felodipine + metoprolol as with enalapril or placebo in spite of a considerably greater BP reduction with felodipine + metoprolol. Thus, there should be no concern that effective BP reduction with felodipine + metoprolol would compromise HRQL. In this context, it is notable that HRQL may even be positively related to BP reduction, as indicated in the Hypertension Optimal Treatment study.²³ It may be argued that HRQL should preferably be measured at similar BP reduction in studies comparing different drugs to assess possible differences in HRQL between treatments.⁶ However, the aim of this study was to test the assumption that felodipine + metoprolol combination tablets reduce BP substantially without compromising HRQL, and not to compare HRQL at similar BP reductions.

In conclusion, this double-blind, placebo-controlled study shows that HRQL is maintained in the presence of substantial BP reduction during antihypertensive treatment with felodipine + metoprolol fixed combination tablets. The comparison with enalapril monotherapy supports current recommendations that initiating therapy with combination treatment may be considered in patients who need considerable BP reduction.

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Appendix Investigators

Austria: Kurt Huber, Vienna; Prof. Jörg Slany, Vienna; Bruno Tiso, Vienna; Werner Klein, Graz; Sven Torbjörn Wällstedt, Sierning.

Belgium: Jean-Francois Noel, Verviers; Marchindise, Godinne; Jean-Marc Joris, Montignies-sur-Sambre; Georges Saad, Liège; Xavier Warling, Liège; Francis Charlier, Liège; Patrick Bacart, Bruxelles; André Némery, Soignies; Richard Martens, Braine-L'Alleud; Ignace Haumont, Mont-Ste-Aldegonde; Philippe Robert, Wareme; Jean-Paul Melchoir, Bruxelles; Bernard Bosquart, Bruxelles; Albert Lecocq, Jemappes; Luc Martens, Brussel.

Canada: Luisa Scholar, Regina; Dan Dattani, Saskatoon; Michael Baird, Ottawa; Kim-Weng Tan, Orleans; Luis Salgado, Regina; Marcel Fournier, Montreal; Emile Marcotte, Poine Claire; David Spence, London; Robert G. Luton, London.

Finland: Timo Sinkkonen, Kouvola; Raimo Rytkönen, Iisalmi; Stefan Strang, Korsholm; Pekka Saarinen, Helsinki.

France: Charles Cousin, Chateau Thebaud; Hervé Feuillet, Vallet; George Delamare, Blois; Michel Masieri, Besle

sur Vilaine; Ronald Lucas, Guemene Penfao; Jacques Tondut, Angers; Sylvain Kichelewski, Saint Ouen; Michel Chelly, Ablon sur Seine; Francis Dupont, Saint-Denis; Jean-Michel Huet, Villeneuve le Roi; Jacques Sicard, Saint Romain sur Cher.

Greece: Vyssoulis, Athens; K. Siamopoulos, Loannina; V. Votteas, Athens; Maria Papavassikiou, Athens; Apostolos Achimastos, Athens; Chrysanthos Zamboulis, Thessaloniki; Dim Athanassiadis, Athens; Achileas Tourkandonis, Thessaloniki.

Norway: Haakon Istad, Oslo; Ove Hjort, Oslo; Per Schelderup Mathiesen, Halden; Haakon Gunnar Klaeboe, Tonsberg; Egil Vaage, Stavanger; Reidar Retzius, Haugesund; Oyvind Digranes, Minde; Kristin Löland Jacobsen, Ålesund; Terje Wessel Aas, Trondheim; Erik Seegård, Lillestrom.

Poland: Andrzej Szczeklik, Krakow; Kalina Kawecka-Jaszcz, Krakow.

Spain: Josefina Olivan, Sevilla; Bil Extremera, Granada; Lopez Jimenez, Madrid; Castro Beiras, Madrid.

Sweden: Ole Borgholst, Kungsör; Per Winberg, Göteborg; Gösta Eliasson, Falkenberg; Inga Grundestam, Gävle; Britt Isberg, Göteborg; Suzanne Londré, Ljungskile; Rolf Malmström, Sandviken; Lars Nilsson, Särö; Åke Sjöstrand, Tranås; Christina Nerbrand, Lund; Rachel Tengel, Skene; Anders Tisell, Vetlanda.

Switzerland: Milos Dimic, Altendorf; Silvio Knill, Zürich; Walter Haefeli, Basel; Jürg Frank, Solothurn; Gilbert Abetel, Orbe; Thi Nguyen, Lausanne; Jean-Jacques Pauchard, Rossens.

United Kingdom: J. J. Langan, Bailleston; Mairi G. B. Scott, Glasgow; L. Malcolm Campbell, Kirkintill; Anne Knox, Paisley; John P. Vernon, Dundee; Alan James Dawson, Dundee; Robert Rosbottom, Dundee; Roger Smith, Dundee; Duncan Andrew A. Reid, Edinburgh; Hamlim A. M. Nasr, Bexley.