One-Year Study of Felodipine or Placebo for Stage 1 Isolated Systolic Hypertension

Henry R. Black, William J. Elliott, Michael A. Weber, William H. Frishman, Joel A. Strom, Philip R. Liebson, Clara T. Hwang, Dennis A. Ruff, Rafael Montoro, Vincent DeQuattro, Danyi Zhang, Margo M. Schleman, Michael I. Klibaner, for the Stage 1 Systolic Hypertension (SISH) Study Group

Abstract—A substantial number of older hypertensive patients have stage 1 isolated systolic hypertension (systolic blood pressure between 140 and 159 mm Hg and diastolic blood pressure <90 mm Hg), but there are currently no data showing that drug treatment is effective, safe, and/or beneficial. To compare the effects of active treatment compared with placebo on blood pressure, left ventricular hypertrophy, and quality of life among older stage 1 isolated systolic hypertensive patients, a randomized, double-blind, parallel-group, multicenter clinical trial comparing felodipine (2.5, 5, or 10 mg once daily) and matching placebo was performed in 171 patients (49% male, average age 66±7 years, with 49% white and 30% Hispanic) with a baseline blood pressure of 149±7/83±6 mm Hg. During 52 weeks of treatment, patients randomized to active treatment achieved significantly lower blood pressures (137.0±11.7/80.2±7.6 mm Hg for extended-release felodipine versus 147.5±16.0/83.5±9.7 mm Hg for placebo, \( P<0.01 \) for each), a reduced incidence of left ventricular hypertrophy (7% for extended release felodipine versus 24% for placebo, \( P<0.04 \)), and improved quality of life (change in Psychological General Well-Being index, 3.0±6.8 for extended-release felodipine versus −0.8±10.3 for placebo, \( P<0.01 \)) versus baseline. There were no clinically significant differences between treatments in tolerability or adverse effects. Stage 1 isolated systolic hypertension can be effectively and safely treated pharmacologically. Treatment reduced progression to the higher stages of hypertension, reduced the incidence of left ventricular hypertrophy, and improved an overall measure of the quality of life. Larger and longer studies will be needed to document any long-term reduction in cardiovascular event rates associated with treating stage 1 systolic hypertension.

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Key Words: hypertrophy, left ventricular ■ quality of life ■ echocardiography ■ antihypertensive therapy ■ clinical trials

Systolic blood pressure (SBP) has recently received increased recognition as a powerful, but reversible, determinant of cardiovascular risk. Although diastolic blood pressure (DBP) has traditionally received greater clinical attention,1 the 2 most recent reports from the US Joint National Committee (JNC) V2 and JNC VI3 and from international4 and British5 expert panels have given equal weight to SBP and DBP in the classification of hypertension. The decision to change from classifying by DBP was strongly supported by epidemiological6–9 and clinical trial data. A meta-analysis of 8 studies that enrolled older individuals with stage 2 or higher “isolated systolic hypertension” has shown substantial benefits of treatment.10 The JNC VI report recommended long-acting dihydropyridine calcium antagonists for older patients with isolated systolic hypertension3 because of recent clinical trial results.11,12 JNC VI did not distinguish between stage 1 isolated systolic hypertension and higher stages regarding treatment, even though the only evidence from clinical trials came from studies of the higher stages. The focus on older patients can be justified because of the higher absolute risk of cardiovascular events associated with advancing age (making treatment more cost-effective in older individuals13,14), even though such recommendations are not precisely “evidence-based.”15

The lower stages of blood pressure have recently received increased attention7,16,17. Because of the large number of individuals in these stages, “high-normal” blood pressure and “stage 1 hypertension” have the highest population-attributable risk for...
Future cardiovascular disease. Although not population-based, the Multiple Risk Factor Intervention Trial (MRFIT) noted that the largest number of excess deaths occurred in those with SBP between 130 and 159 mm Hg in the 316,099 white men screened. Significantly higher risk associated with such “mildly” elevated SBPs has been seen in both the Framingham and Physicians’ Health Studies.

Stage 1 systolic hypertension (SBP between 140 and 159 mm Hg and DBP < 90 mm Hg) is the remaining subgroup in hypertension that lacks evidence demonstrating that lowering blood pressure is both possible and beneficial. Therefore, we conducted a year-long study with a placebo control to compare the potential benefits of blood pressure lowering in this as-yet-unstudied group of hypertensive patients.

**Methods**

Eligible patients, ≥ 55 years old, met JNC V and VI criteria for stage 1 systolic hypertension (while taking placebo): sitting SBP (SiSBP) between 140 and 159 mm Hg, and sitting diastolic blood pressure (SiDBP) < 90 mm Hg. All participants signed written informed consent documents approved by local institutional review boards. None had diseases presenting safety hazards or used medications that would influence efficacy or safety.

This study had 3 phases: ≤ 8-week washout, 4-week single-blind placebo run-in, and 52-week double-blind treatment. After randomization, either felodipine extended-release (ER) 2.5 mg or matching placebo was given once daily between 6:00 and 9:00 AM. If at either week 8 or week 16, SiSBP remained > 140 mm Hg or was not reduced at least 10% from baseline, the dose of felodipine ER (or placebo) was doubled. All patients were maintained at the highest dose for the remaining 36 weeks.

ECG, laboratory, and quality-of-life assessments were performed at the beginning and end of double-blind treatment. Blood pressure was measured using a mercury sphygmomanometer. Each trough value was the mean of 3 readings taken 1 minute apart, 22 to 26 hours after dosing. Left ventricular mass index (LVMI) was measured by 2D echocardiograms and the area-length algorithm, by 2 independent echocardiographers viewing blinded videotapes at a centralized laboratory. Quality-of-life was assessed by the Psychological General Well-Being (PGWB) questionnaire.

The primary efficacy end point was reduction in trough SiSBP at week 52 compared with baseline in randomized patients who took ≥ 1 dose of medication and had ≥ 1 efficacy measurement during treatment, using last-observation carried-forward techniques. All statistical tests were 2 sided. Data are reported as mean ± SD. A significance level of $P = 0.05$ was accepted for differences between treatment groups and a significance level of $P = 0.100$ was accepted for interactions.

Based on $α = 0.05$ and a SD of 12 mm Hg, 62 patients per group provided 90% power to detect a primary efficacy end point of 7 mm Hg. This estimated SD was based on previous studies of stage 2 hypertension, because of the paucity of data specific to stage 1.

An ANOVA model with site and treatment as factors was used to analyze the reductions from baseline using SAS (SAS Institute): trough SBP and DBP; echocardiogram and quality-of-life measurements; and heart rate, weight, and ECG measurements. The proportion of subjects achieving SBP < 140 mm Hg or a 10% reduction in SBP compared with that of baseline (ie, responders) was calculated for each treatment group. Subgroupings by age (< 65, ≥ 65 years), gender, or race/ethnicity on blood pressure and echocardiogram measurements were examined using the ANOVA model with subgroup and treatment as factors. ANOVA was used to assess the effects of weight, body mass index, and blood pressure at baseline on the change from baseline in LV mass. Echocardiograms were analyzed only if both the baseline and the end-of-study examinations for a given participant were of acceptable technical quality. Fisher’s exact test was used for efficacy and safety comparisons between treatment groups.

An expanded Methods section can be found in an online data supplement available at http://www.hypertensionaha.org.

**Results**

**Demographic Variables and Patient Disposition**

Demographic and clinical characteristics of the 2 randomized treatment groups are shown in Table 1; none of the differences achieved statistical significance. Nearly half of the patients were age ≥ 65 years, which is typical of isolated systolic hypertension. The majority of the enrolled pa-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Felodipine ER (n=85)</th>
<th>Placebo (n=86)</th>
<th>Total (n=171)</th>
<th>P for Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Male</td>
<td>48 (56)</td>
<td>36 (42)</td>
<td>84 (49)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>37 (44)</td>
<td>50 (58)</td>
<td>87 (51)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>White</td>
<td>40 (47)</td>
<td>44 (51)</td>
<td>84 (49)</td>
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<tr>
<td>Hispanic</td>
<td>27 (32)</td>
<td>24 (28)</td>
<td>51 (30)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>12 (14)</td>
<td>9 (10)</td>
<td>21 (12)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>5 (6)</td>
<td>9 (10)</td>
<td>14 (8)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>Mean ± SD, y</td>
<td>66 ± 6.9</td>
<td>66 ± 6.8</td>
<td>66 ± 6.8</td>
<td></td>
</tr>
<tr>
<td>55–64.9 y</td>
<td>40 (47)</td>
<td>47 (55)</td>
<td>87 (51)</td>
<td></td>
</tr>
<tr>
<td>≥ 65 y</td>
<td>45 (53)</td>
<td>39 (45)</td>
<td>84 (49)</td>
<td></td>
</tr>
<tr>
<td>Duration of hypertension, y</td>
<td>8.1 ± 9.1</td>
<td>9.8 ± 9.3</td>
<td>8.9 ± 9.2</td>
<td>0.15</td>
</tr>
<tr>
<td>Baseline SBP, mm Hg</td>
<td>149 ± 7.0</td>
<td>150 ± 7.7</td>
<td>149 ± 7.3</td>
<td>0.48</td>
</tr>
<tr>
<td>Baseline DBP, mm Hg</td>
<td>83 ± 5.5</td>
<td>84 ± 5.6</td>
<td>83 ± 5.6</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Values are mean ± SD or number (percent).

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patients were either white (49%) or Hispanic (30%). The majority of the 79 people screened but not randomized did not meet the enrollment criteria for sustained stage 1 systolic hypertension. During randomized treatment, significantly more patients withdrew from placebo (21 [24%] of 86) than from felodipine ER (8 [9%] of 85, *P*<0.05). The most common reasons for discontinuation were withdrawal of patient consent (5%), lack of therapeutic response (4%), or adverse events (4%). After 52 weeks of treatment, the distribution of patients across doses was as follows: felodipine ER 2.5, 5, or 10 mg (n=17, 22, or 39, respectively); placebo 2.5, 5, or 10 mg (n=5, 10, or 51, respectively).

**Antihypertensive Efficacy**

Active treatment with felodipine ER was associated with significantly greater reductions from baseline in mean trough SBP at all time points (Figure 1). Mean reductions in trough sitting SBP at week 52 compared with baseline were 11.7±11.8 mm Hg (felodipine ER) and 2.0±14.4 mm Hg (placebo); this was a significant difference (*P*<0.01) by ANOVA. Significant between-group differences were also found for mean reductions in trough DBP at all time points except week 8 (data not shown). After 52 weeks of treatment, mean reductions in trough DBP were 3.0±7.1 and 0.1±8.7 mm Hg in the felodipine ER and placebo groups, respectively (*P*<0.01). Subgroup analyses of trough SBP and DBP indicated that patients randomized to felodipine ER consistently showed greater mean reductions in blood pressure, regardless of age (<65 years, ≥65 years), gender (male, female), or race/ethnicity (white, Hispanic, black/Asian/other).

Patients in the group randomized to felodipine ER showed statistically significant (*P*<0.01) differences compared with the placebo group in response rates, defined for this protocol as SBP <140 mm Hg or at least a 10% reduction in SBP compared with baseline. This included all time points except week 8, when all patients were on the lowest dose of study medication (Figure 2). After 52 weeks of double-blind treatment, response rates were significantly different (*P*<0.01) between randomized groups: 62% (felodipine ER) versus 34% (placebo).

**LV Mass Index**

At baseline, the mean LVMI by 2D echocardiography did not differ between the 2 groups (felodipine ER 96.4±18.2 g/m², n=54; placebo 99.9±29.9 g/m², n=57). LVH, predefined for the present study as LVMI >116 g/m² for males and >104 g/m² for females, was present in 15 of the placebo-treated patients and 9 of the felodipine ER–treated patients (or 22% prevalence overall) at baseline. After 52 weeks of treatment, neither group demonstrated an overall significant change in mean LVMI (felodipine ER 0.5±16.1 g/m², placebo 3.0±14.8 g/m²). However, both the prevalence and incidence of LVH were significantly different across treatment groups. Only 7 (13%) of 54 patients randomized to felodipine ER had LVH after 52 weeks of treatment compared with 19 (33%) of 57 placebo-treated patients (*P*=0.014). Three (7%) of 45 felodipine ER–treated patients without LVH at baseline developed LVH during 52 weeks of treatment compared with 10 (24%) of 42 placebo patients (*P*=0.035, Figure 3).

**Quality of Life**

At baseline, the mean quality-of-life score (as assessed by the PGWB index) was not different between the 2 treatment groups (Table 2). After 52 weeks of treatment, there was a significant (*P*<0.01) difference across treatment groups in the change in PGWB index from baseline: 3.0±6.8 (felodipine ER) versus −0.8±10.3 (placebo). The felodipine ER group scored significantly better than did the placebo group on both anxiety (*P*<0.05) and depression (*P*<0.01) subscales, but there were no significant between-group differ-
ences in the other indices of positive well being, self-control, health, or total vitality.

Safety
There was 1 death from colon cancer in the placebo group during the study, which was assessed by the investigator to be unrelated to study participation. Only 7 patients discontinued participation in the study because of adverse events: 2 (2%) assigned originally to felodipine ER versus 5 (6%) assigned to placebo. Exactly the same numbers of subjects discontinued participation because of lack of therapeutic response. There were no significant between-group differences in the incidence of the most frequently reported specific adverse events (Table 3) or adverse events pertaining to specific body systems. There was a nonsignificant trend for dizziness, back pain, and headache that was more common in placebo-treated subjects, whereas hematuria, rhinitis, and dyslipidemia were more commonly reported among those randomized to felodipine ER. There were no clinically meaningful changes from baseline at week 24 or week 52 for any of the laboratory parameters assessed, including aspartate aminotransferase, alanine aminotransferase, total and HDL cholesterol, triglycerides, or potassium (data not shown).

Discussion
These data from the first placebo-controlled, 1-year clinical trial to enroll only patients with stage 1 isolated systolic hypertension show that pharmacological treatment is effective, safe, well tolerated, and associated with beneficial effects on LVH and quality of life. Active treatment with felodipine ER reduced both SBP and DBP significantly better than did placebo at all but 1 time point throughout the 52 weeks of the study and did so irrespective of age, gender, or race/ethnicity of the patients. The superiority of active treatment was observed in all analyses, as well as in comparisons of regimens across response rates and the prevalence of controlled hypertension.

The potential benefits of controlling stage 1 systolic hypertension, as demonstrated in the present study, include both a reduction in the incidence and prevalence of LVH and an improvement in the quality of life. Although the change in mean LVMI did not differ significantly across randomized groups at the end of the 52 weeks of treatment, there was an overall reduction in LVMI in those randomized to active treatment compared with an increase in LVMI in those receiving placebo. Some data suggest that patients whose LVMI increases over time suffer a larger number of adverse cardiovascular events than do those whose LVMI decreases.25 The finding of improved quality of life among actively treated patients is consistent with several recent studies26–28 and argues against the commonly held theory that antihypertensive drugs cause many adverse effects in patients who are usually asymptomatic. Although the diuretic-treated and β-blocker–treated groups had the largest improvement in Quality-of-Life in the Treatment of Mild Hypertension

Table 2. Results of PGWB Questionnaires

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Felodipine ER (n=81)</th>
<th>Placebo (n=73)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total PGWB index</td>
<td>95.7±8.7</td>
<td>96.5±10.0</td>
<td>0.82</td>
</tr>
<tr>
<td>Change after 52 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total PGWB index</td>
<td>3.0±6.8</td>
<td>−0.8±10.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Anxiety subscale</td>
<td>1.7±3.2</td>
<td>0.3±4.7</td>
<td>0.05</td>
</tr>
<tr>
<td>Depression subscale</td>
<td>0.2±1.6</td>
<td>−0.4±1.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Positive well-being subscale</td>
<td>0.3±2.6</td>
<td>−0.4±2.5</td>
<td>0.40</td>
</tr>
<tr>
<td>Self-control subscale</td>
<td>0.1±1.9</td>
<td>0.0±2.7</td>
<td>0.36</td>
</tr>
<tr>
<td>Health subscale</td>
<td>0.6±2.8</td>
<td>−0.1±2.7</td>
<td>0.11</td>
</tr>
<tr>
<td>Total vitality subscale</td>
<td>0.0±2.6</td>
<td>−0.2±3.0</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Values are mean±SD. A negative mean indicates an overall worsening from baseline.

Table 3. Adverse Events With Incidence >5% in Either Randomized Group During 52 Weeks of Treatment

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Felodipine ER (n=85)</th>
<th>Placebo (n=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Body as a whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Back pain</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Metabolic/nutritional</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipemia</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Central/peripheral nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All between-group comparisons were not statistically significant.</td>
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</tbody>
</table>
Study, a sub-study of the Hypertension Optimal Treatment Trial (which used felodipine as first-line treatment) has demonstrated that the most intensively treated hypertensive patients achieve the best quality-of-life scores. The quality-of-life data from the present study are corroborated internally by the finding that discontinuations from blinded study medication were significantly less likely among patients randomized to active treatment and that adverse effects were similar, if not slightly better, among patients treated with felodipine ER compared with placebo. The adverse events associated with felodipine ER in the present study were similar in frequency to those associated with placebo and were unremarkable with respect to either nature or severity. There was no evidence of an association between long-term use of felodipine ER and any deleterious effects on laboratory test results.

There are several novel or unusual findings in the present study. Our study is the first to demonstrate specifically that control of stage 1 isolated systolic hypertension is achievable by pharmacological treatment. Although the importance of achieving blood pressure control has been emphasized by JNC VI, Healthy People 2000, and the new HEDIS “yardsticks,” SBP is not currently controlled in many patients. The data from the present study should encourage physicians and patients to use effective antihypertensive agents to control SBP. Although the sample size in the present study was too small to detect a difference in clinical events between treatments, there was a significant difference in both the prevalence and incidence of LVH, a strong predictor of future cardiovascular morbidity and mortality among hypertensive patients. The 22% prevalence of LVH at baseline among the enrolled subjects with stage 1 systolic hypertension in the present study suggests that target-organ changes are present in a substantial proportion of patients who often currently go untreated. The observed baseline prevalence is similar to that seen in the Treatment of Mild Hypertension Study, in which 24% of men and 45% of women had LVMI’s higher than then-accepted norms. Regression of LVH has been seen previously after a year’s treatment with any of several effective antihypertensive drugs, including felodipine.

There are a number of limitations to the present study that may limit enthusiasm for widespread treatment of stage 1 isolated systolic hypertension. There are, as yet, no outcome studies proving that drug treatment of hypertension in this range prevents cardiovascular events. Clearly, such treatments will incur cost, and there is little evidence that such a strategy will be cost-effective. Higher-risk patients generally have a better cost-effectiveness ratio, and unless the pulse pressure is large, patients with stage 1 isolated systolic hypertension would be expected to have lower risk than those with hypertension at higher stages. The data on LVH gathered in the present study were limited by the usual technical problems, and good quality baseline and follow-up echocardiograms were obtained in only 65% of the randomized patients (or 77% of those completing 52 weeks of treatment). The present study was also unusual because the enrolled patients with stage 1 isolated systolic hypertension were generally free of other risk factors, including diabetes mellitus and renal impairment, which greatly increase cardiovascular risk and would require more intensive lowering of blood pressure, according to JNC VI and British guidelines. Perhaps because of the limited 52-week treatment period, relatively few of the placebo-treated patients progressed to stage 2 hypertension; this has not been the experience in the Framingham study, in which low levels of hypertension have often been found to progress into higher stages and to result in a higher rate of cardiovascular events.

The results of the present study provide further evidence in favor of the recommendations of JNC VI and the British Hypertension Society for the use of long-acting dihydropyridine calcium channel blockers for the management of isolated systolic hypertension. However, longer and longer studies will be needed to demonstrate that treating stage 1 isolated systolic hypertension in older individuals results in reduced cardiovascular morbidity and mortality.

Acknowledgment

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References


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