Quality of Life With Three Antihypertensive Treatments
Cilazapril, Atenolol, Nifedipine

Astrid E. Fletcher, Christopher J. Bulpitt, Dagmar M. Chase, William C.J. Collins, Curt D. Furberg, Timothy K. Goggin, Andrew J. Hewett, and Albrecht M. Neiss

A multicenter, randomized double-blind study of 6 months' duration was performed in 540 patients (average age 54 years, 57% male) with mild-to-moderate essential hypertension to determine the relative effects on quality of life of cilazapril, atenolol, and nifedipine retard. Quality of life was assessed by using both a self-administered and an interviewer-administered questionnaire; the assessment included a complaint score (symptoms checklist), Health Status Index, assessment of work satisfaction, Psychological General Well-being Index, Profile of Mood States subscales, and life satisfaction assessment. Psychomotor function was measured by the Reitan Trail Making test B. At the end of the trial, diastolic blood pressure had fallen by an average of 15 mm Hg in all three groups, but significantly (p=0.01) more patients taking cilazapril required the addition of a diuretic (36%) compared with those taking atenolol (25%) or nifedipine retard (24%). No significant differences in quality of life were observed between cilazapril and atenolol during the trial. Symptomatic complaints increased on nifedipine retard (p=0.02) and contributed to a higher discontinuation rate (21% discontinued treatment compared with 13% and 14% taking atenolol and cilazapril, respectively, p=0.04). However, a possible improvement in the fatigue subscale (p=0.04) was also observed on nifedipine retard. The 95% confidence intervals showed that none of the drugs in this trial produced an effect equivalent to that previously reported between captopril and methyldopa in the Psychological General Well Being Index or between captopril and methyldopa or propranolol in Trail Making test B. We conclude that cilazapril and atenolol have equivalent effects on quality of life, but nifedipine retard was associated with more symptomatic complaints and a higher discontinuation rate. (Hypertension 1992; 19:499-507)

Key Words • quality of life • antihypertensive therapy • angiotensin converting enzyme inhibitors • calcium channel blockers • β-blockers

Antihypertensive treatment has been shown to produce a 40% reduction in fatal and nonfatal strokes when compared with placebo, but it is not known whether the benefits vary according to the specific antihypertensive drug given. Only a few trials have compared the effects of different antihypertensive treatments on mortality and morbidity; these have shown no difference between β-blocker or diuretic therapy. Even less is known about the comparative effects of newer agents, such as angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers. In the present state of knowledge, it has been suggested that the antihypertensive drug to be chosen should be the treatment that best preserves the patient's quality of life (QOL), and this perception has led to an increasing interest in the use of QOL assessments in comparative trials of antihypertensive treatments. These assessments cover the impact of known or possible drug side effects on such areas as emotional well-being, performance at work and home, and overall perception of well-being. Objective measurements of cognitive function are also important.

The aim of the present study was to compare the effects of three different classes of antihypertensive treatments on QOL: an ACE inhibitor, cilazapril, and the most widely used drugs of their class, the β-blocker atenolol and the calcium channel blocker nifedipine retard (nifedipine R).

Methods
This was a double-blind, randomized multicenter trial designed to evaluate the effects of 6 months of therapy with the ACE inhibitor cilazapril compared with the β-blocker atenolol and the calcium antagonist nifedipine R (slow-release formulation) on the QOL in
patients with mild-to-moderate hypertension. The present study was performed in 31 centers, primarily from general practices in 10 European countries (Austria, Belgium, Denmark, Finland, France, Germany, Holland, Italy, Sweden, and the United Kingdom).

Before randomization, patients entered a single-blind, 4-week placebo run-in period. Patients discontinued any previous antihypertensive therapy before entering the run-in period. Patients whose sitting diastolic blood pressure (SDBP, mean of two readings) was 95–115 mm Hg at clinic visits during the third and fourth weeks of the run-in period were randomly assigned to receive one of the active therapies for a period of 24 weeks. Patients were eligible to enter the study if they were aged 35–69 years and were able to read and write in the language of the participating country. Patients were ineligible for the study if they had severe hypertension, angina pectoris, a myocardial infarction in the 6 months before study entry, a history of heart failure or of cerebrovascular accident, atrioventricular block on the prestudy electrocardiogram, or a hemodynamically relevant heart rhythm disturbance. Patients were also ineligible if they had a history of psychiatric illness, alcoholism or drug abuse, or had clinically significant neurological, respiratory, hepatic, gastrointestinal, hematologic, autoimmune, renal, or endocrine (other than non–insulin-dependent diabetics controlled on dietary therapy only) disease. Women of childbearing potential were also excluded. During the course of the study patients were not permitted to take psychotropic or sedative drugs.

The protocol for this study was approved by ethics committees in each of the participating countries. Before taking part in the study, informed consent was obtained from the patients. Patients were informed that they would receive a placebo for 4 weeks during the study but were not informed when this would occur.

Patients who fulfilled the above criteria were randomly assigned to receive either cilazapril (2.5 mg once daily), atenolol (50 mg once daily), or nifedipine R (20 mg twice daily). To maintain blindness patients took identical capsules, two in the morning and one in the evening, throughout the study. Patients attended the clinics for measurement of blood pressure every 4 weeks during the active-therapy phase of the study. If during the first 12 weeks of the study, the mean SDBP at 2–8 hours after dose remained greater than 90 mm Hg, the dose was doubled once. After week 12 of the study if the mean SDBP was still greater than 90 mm Hg, hydrochlorothiazide (HCTZ), initially in a dose of 12.5 mg daily increasing if necessary to 25 mg, was added in patients already on high-dose monotherapy. Physicians were not blind to dose increases or to the addition of HCTZ.

Identical QOL questionnaires in the respective languages were administered at the beginning (week -4) and end (week 0) of the placebo run-in period and after 12 and 24 weeks of active therapy. In addition, in patients who discontinued study medication before week 24 for whatever reason, every attempt was made to administer the questionnaires as soon as possible after discontinuation. Two questionnaires, an interviewer-administered and a self-administered, were completed at each visit. The interviewer was a person, usually a nurse, who was not directly responsible for the patient's medical care. The interviewers were not aware of the results of blood pressure measurements or test drug dose alterations made during the course of the study. Details of the contents of each questionnaire are in the "Appendix."

Questionnaires were translated from the original English into seven other languages (Danish, Dutch, Finnish, French, German, Italian, and Swedish). To confirm that the meaning of the questions was not altered in the translated versions, all questionnaires were back-translated into English by persons unfamiliar with the original English version. The original English and back-translated versions were then compared for consistency of meaning, and alterations were made in the translated questionnaires as required. Further minor refinements were made in the translated versions at a 3-day prestudy training session for the interviewers organized by one of the authors (A.F.).

A total of 636 patients entered the placebo run-in period of the study. Of these, 572 were randomly assigned to receive active therapy. The principal reason for the remaining 64 patients not qualifying for randomization was failure to meet the blood pressure entry requirements. Of the randomly assigned patients, a further 32 patients (including all 18 patients from one center) were excluded from the analysis reported in this article based on quality control checks on the questionnaires performed by the Epidemiology Research Unit, Royal Postgraduate Medical School, London, during the course of the study. The main reasons for exclusion of these patients were inconsistencies in the administration of the questionnaires. All 32 patients were excluded before breaking the double-blind code. In the current report, the results are presented on the remaining 540 patients (179 given cilazapril, 182 given atenolol, and 179 given nifedipine R). The language distribution of the questionnaires used by these patients was: English 107, German 86, Danish 82, French 81, Dutch 79, Swedish 59, Finnish 28, Italian 18.

Data Management and Statistical Methods

Data management and statistical analysis of all study data was performed by an independent statistical institute (Gesellschaft für angewandte Mathematik und Informatik [GMI], Munich, FRG). Statistical analysis was performed blind to the authors; the statistical software packages, spss and sas were used. Probability values reported are based on two-tailed tests of significance. Demographic and baseline variables were compared for the three treatment groups using the $\chi^2$ test (for qualitative variables, e.g., gender) and analysis of variance or Kruskal-Wallis test according to the distribution of the variables (for quantitative variables, e.g., cholesterol).

It was calculated that with a significance level of 0.05 and a power of 90%, 200 patients per treatment group were required to detect between drug differences of 4 unit in the changes in the Psychological General Well Being Index from baseline to the end of the study and allowing for a 10% drop-out rate. This was the order of the differences observed in the trial of Croog and colleagues.9

An intent-to-treat policy was adopted for the analysis presented here, whereby all patients who had a baseline
assessment and a follow-up assessment were included. Exit interviews were conducted with all but 13 of the patients included in the analysis.

Changes in blood pressure were compared using an analysis of variance. The number of patients who required HCTZ as additional therapy were compared among the three groups using the \( \chi^2 \) test. Time from entry into the study until discontinuation was analyzed using the Kaplan-Meier method and the log-rank test. The numbers of patients with adverse events were compared using the \( \chi^2 \) test. In order not to make large numbers of comparisons and thereby compromise the significance levels obtained, the Advisory Committee decided in advance to make comparisons of the three treatment groups only between baseline and week 24 or end of study for the primary QOL variables. These were the complaint score, Health Status Index, assessment of work satisfaction, Psychological General Well-Being Index, six subscales of the Profile of Mood States, Reitan Trail Making Test B, and an overall assessment of life satisfaction (see “Appendix”). The results at the end of the monotherapy period are presented for interest but without formal statistical testing for this reason.

The changes in the QOL variables were approximately normally distributed, so that for these variables analysis of variance procedures were applicable. To correct for imbalances in baseline variables and to increase precision, potential prognostic factors (age, gender, duration of hypertension, and previous antihypertensive medication during the 3 months before the study) were considered. These were incorporated in the model as covariates if they had significant influence on the changes of the QOL variable. If significant differences at the 5% level occurred, they were analyzed by multiple \( t \) test (pairwise) comparisons; this procedure guarantees a multiple significance level of 5%. In addition, for all pairwise differences 95% confidence intervals were calculated. Actual probability values are reported.

**Results**

**Entry Characteristics**

The only statistically significant difference among the groups at baseline was a higher proportion of men in the cilazapril group as compared with the other two groups (\( p=0.02 \)) (Table 1). Otherwise there was no difference among the groups at randomization in clinical, laboratory, and psychosocial variables.

**Blood Pressure Control**

There was no significant difference in the reduction of mean SDBP or sitting systolic blood pressure among the three groups at any clinic visit. The mean decrease from baseline in diastolic blood pressure (±SD) was \(-14.7 (8.7)\) for cilazapril, \(-15.5 (8.8)\) for atenolol, and \(-14.7 (8.5)\) for nifedipine R at the end of the study. The number of patients requiring the addition of HCTZ during the study was 65 (36.3%) in the cilazapril group, 45 (24.7%) in the atenolol group, and 42 (23.5%) in the nifedipine R group (\( p=0.01 \)).

**Incidence of Discontinuation of Therapy (All Reasons)**

The results are shown in Figure 1. The cumulative drop-out rate was significantly higher for nifedipine R compared with that for cilazapril or atenolol (\( p=0.04 \)) with no difference between cilazapril and atenolol. The higher drop-out rate for nifedipine R was already manifest at the week 4 assessment, with six patients (3.3%) discontinuing treatment from cilazapril, seven (3.8%) from atenolol, and 15 (8.4%) from nifedipine R. By the end of the study, 25 (14.0%) patients had discontinued treatment from cilazapril, 23 (12.6%) patients from atenolol, and 38 (21.2%) patients from nifedipine R.

**Adverse Events (Spontaneously Reported to the Investigator)**

Table 2 lists all adverse events spontaneously reported by more than six patients in any one treatment group during the active therapy period of the study. The adverse events are grouped into those commonly associated with an ACE inhibitor, a \( \beta \)-blocker, and a calcium antagonist, followed by nonspecific adverse events. Fifty-two percent of the patients (\( n=93 \)) in the cilazapril group reported one or more adverse events during the study, whereas 62% (\( n=112 \)) of the patients in the atenolol group and 64% (\( n=115 \)) in the nifedipine R group reported one or more adverse events. The total number of adverse events reported was 161 for the cilazapril group, 194 for the atenolol group, and 242 for the nifedipine R group. An adverse event was cited as the reason for early discontinuation of therapy for nine (5%) patients in the cilazapril group, 15 (8%) patients in the atenolol group, and 31 (17%) patients in the nifedipine R group. The difference among the three treatment groups was significant (\( p=0.001 \)).

Cough and sore throat were most common in the cilazapril group, fatigue and cold hands and feet in the atenolol group, and edema and flushing in the nifedi-
Flushing and edema were the adverse events most often cited as a reason for discontinuation of therapy. Serious clinical events were uncommon. Atrial fibrillation developed in one patient in the atenolol group, two patients in the cilazapril group suffered a stroke and two patients suffered a myocardial infarction, one in the atenolol group and one in the nifedipine R group. One patient in the cilazapril group died during the study. Although an autopsy was not performed, the death was classified as a cardiac death and was considered by the investigator as unrelated to trial medication.

**Quality of Life Variables**

The changes in QOL variables from baseline to end of study or termination before week 24 are shown in Table 3, together with the changes in these variables from baseline to the week 12 assessment or to termination before week 12. The change in the complaint score from baseline to week 24 or early termination, using an analysis of covariance, was different among the three drugs \((p=0.02)\). The analysis included as covariates age, gender, duration of hypertension, and previous antihypertensive medication during the 3 months before the study. The covariates that influenced the outcome were gender and previous medication. Complaint scores were generally higher in women and in patients who had been taking antihypertensive medication during the 3 months before the study. The adjusted mean values are shown in Table 3. The 95% confidence intervals for change, comparing each drug with the other two, (baseline to end of study or termination before week 24) are shown in Table 4. The complaint score was greater for nifedipine R compared with atenolol; the score was also higher for nifedipine R than for cilazapril, but the difference was not statistically significant. There was no statistical difference between cilazapril and atenolol. Therefore, nifedipine R caused significantly more symptoms than cilazapril or atenolol as reported by individual patients.

There was a significant difference among the three treatment groups for the fatigue/inertia subscale of the Profile of Mood States. Nifedipine R was associated with a significant improvement in fatigue compared with cilazapril and atenolol at the end of the study \((p=0.04)\). There was no difference between cilazapril and atenolol.

For all other QOL variables (Health Status Index; assessment of work satisfaction; Psychological General Well-Being Index; the subscales tension, depression, anger, vigor; and confusion of the Profile of Mood States; Reitan Trail Making Test B; and life satisfaction assessment) there were no differences among the

---

**Table 2. Adverse Events Spontaneously Reported by More Than Six Patients in Any One Treatment Group**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Cilazapril ((n=179))</th>
<th>Atenolol ((n=182))</th>
<th>Nifedipine ((n=179))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>11 (2)</td>
<td>7 (0)</td>
<td>3 (0)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>7 (0)</td>
<td>3 (0)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Cold hands/feet</td>
<td>3 (0)</td>
<td>6 (2)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1 (0)</td>
<td>6 (2)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (0)</td>
<td>19 (0)</td>
<td>7 (0)</td>
</tr>
<tr>
<td>Flushing</td>
<td>4 (1)</td>
<td>20 (4)</td>
<td>23 (5)</td>
</tr>
<tr>
<td>Headache</td>
<td>10 (0)</td>
<td>5 (0)</td>
<td>40 (13)</td>
</tr>
<tr>
<td>Edema</td>
<td>1 (0)</td>
<td>6 (0)</td>
<td>4 (0)</td>
</tr>
<tr>
<td>Palpitations-tachycardia</td>
<td>6 (1)</td>
<td>1 (0)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Polyuria</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6 (0)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>13 (1)</td>
<td>14 (2)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Skin rash</td>
<td>6 (1)</td>
<td>4 (0)</td>
<td>4 (0)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7 (0)</td>
<td>7 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Sweating increased</td>
<td>5 (0)</td>
<td>6 (1)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (0)</td>
<td>6 (1)</td>
<td>4 (0)</td>
</tr>
<tr>
<td>Back pain</td>
<td>10 (0)</td>
<td>3 (0)</td>
<td>4 (0)</td>
</tr>
<tr>
<td>Infection</td>
<td>20 (0)</td>
<td>26 (0)</td>
<td>20 (0)</td>
</tr>
<tr>
<td>Total events (No.)</td>
<td>161</td>
<td>194</td>
<td>242</td>
</tr>
<tr>
<td>Total patients with one or more events (No.)</td>
<td>93</td>
<td>112</td>
<td>115</td>
</tr>
<tr>
<td>Total patients withdrawn due to events (No.)</td>
<td>9</td>
<td>15</td>
<td>31</td>
</tr>
</tbody>
</table>

Values are the number of patients who reported each adverse event; values in parentheses are the number of patients in whom the adverse event was cited as a reason for discontinuation of therapy. Because more than one adverse event may have occurred in one patient the totals may not add.
TABLE 3. Change in Quality of life Scales

<table>
<thead>
<tr>
<th>Quality of life measure</th>
<th>Cilazapril</th>
<th>Atenolol</th>
<th>Nifedipine</th>
<th>Statistical significance (wk 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complaint score (−)</td>
<td>1.29</td>
<td>0.26</td>
<td>0.44</td>
<td>−0.73</td>
</tr>
<tr>
<td>Activity</td>
<td>0.47</td>
<td>0.98</td>
<td>−0.81</td>
<td>−0.17</td>
</tr>
<tr>
<td>Health Status Index</td>
<td>−0.18</td>
<td>−0.89</td>
<td>−0.03</td>
<td>−0.19</td>
</tr>
<tr>
<td>Work satisfaction (−)</td>
<td>1.73</td>
<td>1.70</td>
<td>0.11</td>
<td>−0.01</td>
</tr>
<tr>
<td>Psychological state</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGWB (+)</td>
<td>−0.44</td>
<td>1.02</td>
<td>−0.54</td>
<td>0.29</td>
</tr>
<tr>
<td>POMS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tension (−)</td>
<td>0.14</td>
<td>0.01</td>
<td>0.02</td>
<td>−0.11</td>
</tr>
<tr>
<td>Depression (−)</td>
<td>0.36</td>
<td>0.14</td>
<td>0.29</td>
<td>0.27</td>
</tr>
<tr>
<td>Anger (−)</td>
<td>−0.18</td>
<td>−0.21</td>
<td>−0.47</td>
<td>−0.04</td>
</tr>
<tr>
<td>Vigor (+)</td>
<td>0.60</td>
<td>0.42</td>
<td>0.65</td>
<td>0.33</td>
</tr>
<tr>
<td>Fatigue (−)</td>
<td>−0.05</td>
<td>−0.14</td>
<td>0.21</td>
<td>−0.14</td>
</tr>
<tr>
<td>Confusion (−)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychomotor function</td>
<td>−3.73</td>
<td>−7.31</td>
<td>−4.29</td>
<td>−8.73</td>
</tr>
<tr>
<td>Life satisfaction</td>
<td>−0.02</td>
<td>−0.14</td>
<td>0.04</td>
<td>−0.06</td>
</tr>
</tbody>
</table>

Change in quality of life scales from baseline (week 0) to week 12 (including premature terminations before week 12) and to week 24 (including all terminations during active therapy). Statistical significance shown is from baseline to week 24. (+) Indicates positive values are an improvement; (−) indicates negative values are an improvement. PGWB, Psychological General Well-Being Index; POMS, Profile of Mood Status.

TABLE 4. Ninety-Five Percent Confidence Interval of Change for Comparison of Drugs From Baseline to Week 24

<table>
<thead>
<tr>
<th>Quality of life measure</th>
<th>Cilazapril vs. atenolol</th>
<th>Cilazapril vs. nifedipine</th>
<th>Atenolol vs. nifedipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complaint score (−)</td>
<td>(−1.1, 2.4)</td>
<td>(−3.4, 0.1)</td>
<td>(−4.0, −0.5)*</td>
</tr>
<tr>
<td>Activity</td>
<td>(−1.4, 3.7)</td>
<td>(−0.4, 4.8)</td>
<td>(−1.6, 3.6)</td>
</tr>
<tr>
<td>Health Status Index</td>
<td>(−1.7, 0.3)</td>
<td>(−1.9, 0.1)</td>
<td>(−1.2, 0.8)</td>
</tr>
<tr>
<td>Work satisfaction (−)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological state</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGWB</td>
<td>(−1.9, 3.4)</td>
<td>(−2.2, 3.1)</td>
<td>(−2.9, 2.4)</td>
</tr>
<tr>
<td>POMS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tension (−)</td>
<td>(−0.9, 1.1)</td>
<td>(−0.6, 1.4)</td>
<td>(−0.7, 1.3)</td>
</tr>
<tr>
<td>Depression (−)</td>
<td>(−1.3, 1.0)</td>
<td>(−0.8, 1.5)</td>
<td>(−0.6, 1.7)</td>
</tr>
<tr>
<td>Anger (−)</td>
<td>(−1.2, 0.9)</td>
<td>(−0.5, 1.5)</td>
<td>(−0.3, 1.7)</td>
</tr>
<tr>
<td>Vigor (−)</td>
<td>(−0.6, 1.5)</td>
<td>(−1.2, 0.9)</td>
<td>(−1.7, 0.4)</td>
</tr>
<tr>
<td>Fatigue (+)</td>
<td>(−0.8, 1.0)</td>
<td>(0.1, 1.9)†</td>
<td>(0.1, 1.8)†</td>
</tr>
<tr>
<td>Confusion (−)</td>
<td>(−0.6, 0.6)</td>
<td>(−0.6, 0.6)</td>
<td>(−0.6, 0.6)</td>
</tr>
<tr>
<td>Psychomotor function</td>
<td>(−3.1, 6.0)</td>
<td>(−2.4, 6.7)</td>
<td>(−3.7, 5.3)</td>
</tr>
<tr>
<td>Life satisfaction</td>
<td>(−0.3, 0.2)</td>
<td>(−0.3, 0.2)</td>
<td>(−0.2, 0.3)</td>
</tr>
</tbody>
</table>

Ninety-five percent confidence intervals of change for all quality of life measures comparing each pair of treatments. Calculated as change in cilazapril group minus change in atenolol group; change in cilazapril group minus change in nifedipine retard group; and change in atenolol group minus change in nifedipine group. PGWB, Psychological General Well-Being Index; POMS, Profile of Mood Status.

*In favor of atenolol.
†In favor of nifedipine.
was added as needed to control the blood pressure. After 6 months of treatment, a significant benefit for captopril compared with methyldopa was shown in measures of overall well-being, in physical symptoms, in self-rated work performance, in a measure of cognitive function, and in overall life satisfaction. There were fewer differences between captopril and propranolol, with significant differences being found in favor of captopril in general well-being, sexual function, and physical symptoms. Patients taking propranolol did better than did those taking methyldopa in work performance.

Several trials have recently examined whether these benefits for the ACE inhibitor are also found when compared with newer drugs.\textsuperscript{10-14} The trials have found no differences among the ACE inhibitors (captopril, lisinopril, or enalapril) when compared with atenolol, nifedipine, or verapamil in global measures of psychological and general well-being and life satisfaction. The adverse effect of propranolol suggested in the original 1986 study of Croog and colleagues\textsuperscript{8} was confirmed in the trial by Steiner and colleagues.\textsuperscript{12} A possible criticism of these other trials is that they failed to detect effects because they were too short in duration (less than 6 months) or included too few subjects. We do not consider that the duration of the trial is a likely explanation. Short trials are able to detect differences: for example, in a 4-month comparison of verapamil and propranolol\textsuperscript{15} and a 2-month comparison of ACE inhibitors and propranolol,\textsuperscript{12} while in a comparison of methyldopa and rimelidemine, the greatest differences were observed in the first month of treatment.\textsuperscript{16} Lack of power may be a factor in certain trials.\textsuperscript{10-13} The suggestion, however, that atenolol, at least in low doses, may have minimal adverse effects on QOL is supported by the results of a large 6-month trial comparing patients taking atenolol (n=238) with those taking placebo (n=232).\textsuperscript{17}

One measure of overall well-being, the Psychological General Well-Being Index was used both in the present trial and three of the other trials. In the original Croog study\textsuperscript{9} significant differences of 3.8 unit were observed between captopril and methyldopa and of 2.5 unit between captopril and propranolol, a positive difference indicating in favor of captopril. When ACE inhibitors were compared with atenolol, much smaller differences were observed than between captopril and propranolol or captopril and methyldopa. In Steiner's study the differences were 0.3 unit between captopril and atenolol and 0.7 unit between enalapril and atenolol.\textsuperscript{12} In a trial of black hypertensive patients, differences were reported by gender: a difference of 1.0 unit was found between captopril and atenolol for men and a difference of $-0.8$ unit (therefore in favor of atenolol) for women.\textsuperscript{13} The present trial comparing cilazapril with atenolol and nifedipine was one of the largest of the recent trials and of the same duration as the trial of captopril, methyldopa, and propranolol. The 95% confidence intervals for the between-drug differences exclude an effect between cilazapril and atenolol ($-1.9$, $+3.4$) and between cilazapril and nifedipine ($-2.2$, $+3.1$) of the size seen previously between captopril and methyldopa (3.8 unit) but do not exclude the difference of 2.5 unit between captopril and propranolol. However, the average differences between cilazapril and atenolol

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|}
\hline
Symptom & Cilazapril & Atenolol & Nifedipine \\
\hline
Dry cough & 14.4 & -9.1 & 0.6 \\
Sore throat & 8.1 & -5.7 & 5.1 \\
Cold hands and feet & -5.8 & 1.7 & -14.0 \\
Sweating more than usual & 8.1 & 13.1 & -1.7 \\
Heartburn & -2.9 & 8.5 & 8.7 \\
Racing heart & -4.7 & -12.5 & -6.3 \\
Headaches & -19.0 & -23.3 & -5.2 \\
Swollen ankles & 0.6 & 3.4 & 32.0 \\
Itching & -2.9 & -2.8 & 9.8 \\
Cramps in legs & 3.5 & 1.7 & 20.0 \\
Flushing of face & -4.7 & -4.0 & 7.0 \\
Getting up at night to pass urine & 4.1 & -7.3 & 14.0 \\
\hline
\end{tabular}
\caption{Individual Symptoms Complaint Rate}
\end{table}

\textbf{Discussion}

The results of this trial showed little difference between the ACE inhibitor cilazapril and the $\beta$-blocker atenolol in their effects on measures of QOL, whereas the effects of the calcium channel blocker nifedipine R were mixed. Symptomatic complaints were more frequent in the nifedipine R group throughout the trial and also accounted for a significantly higher discontinuation rate in this treatment group (17% discontinued compared with 8% and 5% in the atenolol and cilazapril groups, respectively). On the other hand, nifedipine R patients reported significantly fewer items in the Profile of Mood States fatigue score than patients in either the cilazapril or atenolol group. These unexpected and unexplained trends in fatigue were also apparent at the end of the 12-week monotherapy period and therefore are unlikely to be explained by the addition of HCTZ. Although the greater number of patients in the nifedipine R group who discontinued treatment may bias the interpretation of the end-of-trial data, most discontinuations associated with an adverse effect were due to flushing and edema; fatigue was not given as a reason for discontinuation in any of the treatment groups. Spontaneous reports to the physicians of fatigue occurred for 19 patients in the atenolol group and seven patients each in the cilazapril and nifedipine R groups.

We cannot make a direct interpretation of the absolute effects on QOL of the antihypertensive agents without a comparison with a placebo group. Our interpretation is based on the relative effects of the drugs in this trial. Overall our results suggest that when an ACE inhibitor is compared with atenolol, neither drug appears to offer any important benefits over the other in measures of QOL. How does this finding compare with those of other trials in hypertension using an ACE inhibitor?

Croog and colleagues\textsuperscript{9} published in 1986 the results of a major trial using QOL evaluation methods; this was a double-blind trial of 6 months' duration in 626 men with mild-to-moderate hypertension randomly assigned to captopril, methyldopa, or propranolol groups. HCTZ
ences ranged from —7 to +2, thus excluding the size of patients. The 95% confidence intervals for the differences of 4 unit or more, was achieved since the 95% confidence limits for between-drug differences were 3.4 unit or less.

These results suggest that atenolol appears to have similar effects on overall well-being as the ACE inhibitors; the benefits originally observed for captopril on QOL derived from the comparisons with methyldopa and propranolol. Cilazapril and atenolol were, however, different from nifedipine in several respects: there were more withdrawals and symptomatic side effects with nifedipine R, but nifedipine R reduced fatigue compared with atenolol and cilazapril. A similar finding of an increase in side effects has been reported for nifedipine R compared with verapamil and with lisinopril. In the present trial, the main individual side effects that increased with nifedipine R were edema, flushing, and headache and were sufficiently troublesome to lead to discontinuation. Heartburn, leg cramps, and nocturia or polyuria were also associated with nifedipine R.

Testa and colleagues reported the results of a 24-week comparison of atenolol with nifedipine gastrointestinal therapeutic system. This study differed in several respects from ours. Only men were included and nifedipine was used in a novel preparation. Their results, showing significant benefits for nifedipine compared with atenolol across a range of QOL dimensions, were based only on the patients who completed the trial, although a large proportion of patients taking nifedipine (40%) and atenolol (32%) withdrew. Analysis of all randomly assigned subjects indicated very little difference in QOL between the two drugs. Withdrawal due to adverse effects was more common in the nifedipine group (16%) compared with the atenolol group (4%), p<0.001, as was also shown in our trial. In a very large 10-week trial (n=828) of men and women randomly assigned to lisinopril or nifedipine, higher withdrawal rates in the nifedipine group were also reported. The trial found no differences between the drugs in measures of QOL other than symptoms.

There was no evidence in the present trial for a differential effect of any of the treatments on cognition. Both self-reported problems and a simple test of psychomotor function (Trail Making B) showed improvements of a similar magnitude across all groups. Croog et al found a significantly greater improvement of 19 seconds in the captorpril group compared with 11 seconds in the methyldopa group in the time needed to complete the Trail Making B. There was only a small difference between captorpril and propranolol (2 seconds). In the present study very small differences were observed between cilazapril, atenolol, and nifedipine with atenolol- and nifedipine-treated patients performing the test 2—3 seconds faster than cilazapril-treated patients. The 95% confidence limits for the differences ranged from —7 to +2, thus excluding the size of difference earlier found between captorpril and methyldopa. Again, this suggests that the differences previously observed reflected adverse effects of methyldopa rather than improvements with captorpril.

A large battery of tests of memory were assessed during the trial in some centers and will be reported in detail in a separate publication. Briefly, the results indicated no differential drug effects on memory. Steiner and colleagues also found no differences between atenolol, propranolol, enalapril, or captorpril in a variety of measures testing delayed and immediate recall.

Previous suggestions of an antidepressant, or indeed a euphoric effect of ACE inhibitors, were not supported by our results. Cilazapril-treated patients tended to show a small increase (3%) in measures of depression and little change in the subscales of tension and vigor. The relation between β-blockers and depression has been frequently described in case reports and cross-sectional studies, but it is not clear whether this is produced only by lipophilic β-blockers such as propranolol or also by hydrophilic β-blockers like atenolol. In the present trial, the depression scores on atenolol showed an increase of 6% compared with an increase of 3% on cilazapril and a fall of 3% on nifedipine R. The difference between cilazapril and atenolol was therefore small, with the 95% confidence interval for the difference ranging from —29% to +22%. Thus, on both instruments, differences in depression of greater than 30% between an ACE inhibitor and atenolol were excluded.

Fatigue is a frequently reported side effect of the β-blocker class and was a major reason for discontinuation of propranolol in the Medical Research Council trial of mild hypertension. In the present study, spontaneous reports to the physician of fatigue occurred in 10% of patients in the atenolol group compared with 4% in both the cilazapril and nifedipine R group; the Profile of Mood Status subscale of fatigue increased significantly for patients taking atenolol compared with a decrease in those taking nifedipine R. More unexpectedly, the same increase in fatigue scores was also found for patients taking cilazapril. However, these adverse effects of fatigue in the current trial did not appear to reduce compliance since no patient withdrew for this reason.

Individual adverse events in this trial confirmed previous studies. There was a 14% increase from baseline of dry cough with cilazapril. An association of ACE inhibitors with cough has been reported since 1982, although the size of the problem varies according to different methods of ascertainment. Estimates from post-marketing survey studies give prevalence figures of 0.2%, 0.8%, and 1.1% based on spontaneous reports of suspected adverse reactions with captopril and enalapril. Much higher figures have been reported in controlled studies using a standard side-effects questionnaire. The percent increase in cough over baseline was between 14% and 25% and was much higher than the 2% or less reported for the comparator drug. Similarly, in the current study a net increase of 14% of reports of dry cough was found in the cilazapril group.

The present trial was conducted in 10 European countries. Most of the instruments used in the trial were developed in the United States, but we think it unlikely that the use of the questionnaires is invalid. Considerable care was taken using standard methods of transla-
tion and back-translation into non-English languages. Some modifications to the English were also made for use in the United Kingdom. The reliability of the QOL instruments was examined for each language with standard psychometric measures such as Cronbach’s α and split-half reliability. Very high values of reliability were found, most close to 0.9. This provides considerable reassurance on the use of QOL instruments in diverse European languages. An interaction between treatment and language was not found.

Falls in mean blood pressures, both systolic and diastolic, were similar in all three groups throughout the study. Significantly more patients in the cilazapril group (36%) required the addition of a diuretic compared with those in the atenolol (25%) or nifedipine R (24%) group.

Although all three drugs were associated with increases in the overall number of symptomatic complaints and of specific side effects, other components of QOL such as work satisfaction, psychological well-being, and overall life satisfaction tended to improve. The side effects of nifedipine R (headache, flushing, and edema) led to patients discontinuing treatment. This suggests that, in this trial, the main impact of specific symptoms was to lower compliance.

In conclusion, the results of this large, randomized controlled trial showed that patients treated with cilazapril had the same QOL as those who received atenolol, although the side effect profile of the two drugs differed. Nifedipine R group had increased symptomatic complaints and discontinuation rate despite a possible reduction in fatigue.

Appendix

Self-Administered Questionnaire

**Psychological General Well-Being Index.** This consists of 22 questions on the following six subscales: anxiety, depression, general health, positive well-being, self control, and vitality. Patients rate each question on a five-point scale. The total index, consisting of the sum of the subscales, ranges from 22 to 132 with a high score indicating greater well-being. **Life satisfaction assessment.** Three global questions assessing overall life satisfaction and satisfaction with social roles. These questions were developed by the Rand Corporation, Santa Monica, Calif. **Profile of Mood States.** This is a 65-item scale consisting of six subscales: tension, depression, anger, vigor, fatigue, and confusion. Patients rate each item on a five-point scale. **Complaint score.** This is a list of 32 symptoms and includes those of which hypertensive patients frequently complain, particularly those patients being treated with β-blockers, calcium antagonists, ACE inhibitors, or diuretics. Patients rate the severity of the symptoms on a five-point scale. **Sleep dysfunction assessment.** This consists of a list of seven questions, four of which have been derived from the Crown-Crisp experiential index and three from Bulppt and Fletcher.

**Sexual function assessment.** This is a list of six questions, covering various aspects of sexual function, three from Crown and Crisp and three from Bulppt and Fletcher.

Interviewer-Administered Questionnaire

**Work satisfaction.** A series of seven questions from which a Total Work Index can be calculated. In addition, two subscales can be calculated: job satisfaction-morale and mental acuity at work.

**Life events.** These consist of eight questions designed to detect major life events, other than medical treatment, that could significantly affect the patient’s QOL. **Raven Trail Making Tests (A & B).** This is a two-part instrument for assessing visual–motor speed and integration. The score is based on the total number of seconds required to accomplish the task of connecting images by drawing lines. **Health Status Index.** Five questions supplemented by information from the Complaint score and adverse events during the trial.

Acknowledgments

We are indebted to the following clinical investigators and interviewers for their contribution to this research.

**Austria**
- Dr. Alexander Windsor-Topolsky, Wiener Gebietskrankenhau, Wien; Maria Enzfelder, (interviewer); Dr. Hans Walek, Florisdorfer Hauptstr., Wien, Susanne Mraz (interviewer); Dr. Dieter Klinger, Praktischer Arzt, Moelding; Ingrid Rupp (interviewer).

**Belgium**
- Dr. Diamon Gangji, Hôpital Universitaire Erasme, Bruxelles; Brigitte Noyelle (interviewer); Dr. Pierre Mbuyamba, Department of Cardiology, Clinique André Renard, Herstal; Nicole Delfosse (interviewer); Dr. Jean-Paul Meurant, La Louvière; Francine David (interviewer); Dr. Jean-Jacques DeTiege, Bruxelles; Martine Dumont-Mergeay (interviewer).

**Denmark**
- Dr. Kund Andreasen, Aarhus C; Dr. T. Knudsen, Arden; Dr. Jørgen Munck, Ørsted; Merete Andreasen, (interviewer).

**Finland**
- Dr. Olavi Vänskä, Joensuu Health Center, Joensuu; Marja-Leena Palviainen (interviewer); Dr. Martti Helin, Säveri Oy, Kuopio; Helena Hyrynen (interviewer).

**France**
- Dr. Pierre Simon, Centre Hospitalier La Beauchée, St. Brieuc Cedex; Jacqueline Le Mee (interviewer); Dr. Faiez Zannad, CHR-Hospital Central, Nancy-Cedex; Nicole Franco (interviewer).

**Germany**
- Dr. Herbert Mauersberger, Schwenningen, Gitta Mauersberger (interviewer).

**Holland**
- Dr. Harry W.C. van den Brekel, Honsbroek; Nenette van den Brekel-Poels (interviewer); Dr. Lars Jan Jansen, Bovenij Ziekenhuis, Amsterdern; Gerard Brands (interviewer); Dr. Kenneth Jie, Bleuland Ziekenhuis, Gouda; Agnes M.M.C. Jie-Boog (interviewer); Dr. Hans Wolters, Sint Jozef Ziekenhuis, Kerkrade; Carla Stefelmans (interviewer); Dr. Jaap Smul, Diagnosing huis, Haarden; Joke G. Ubbens (interviewer); Dr. Willem A.J.J. Bogaers, Sint Nicolaas, Ziekenhuis, Waalwijk; Albertine E. Kraaij-Zeven (interviewer).

**Italy**
- Dr. Roberto Sega, Clin. Medica Generale dell’Università, Ospedale Sacco, Milano; Dr. Pierluigi Pittana (interviewer); Prof. Eugenia Marchesi, Clinica Medica I, Policlinico S. Matteo, Pavia; Dr. Paola Centoeghe (interviewer).
References


33. Reitam RM: Trail Making Manual for Administration, Scoring and Interpretation. Indianapolis, Ind, Department of Neurology, Section of Neuropsychology, Indiana University Medical Center, 1958

Sweden

Dr. Tore Schjönberg, Nacka Kommuns FHV, Nacka; Eva Almquist (interviewer), Yvonne Lundin (interviewer); Dr. Per-Olof Andersson, Höglandsjukhuset, Näshög; Inga Rofors (interviewer); Dr. Kay Skogström, Regionssjukhuset, Oerebro; Solveig Pettersson (interviewer).

United Kingdom

Dr. Yasine Karim, St. Barnabas House, Gillingham, Kent; Ann Hill (interviewer); Dr. Richard Simmons, Dr. John Adam, Dr. Suchit-Mohau Sen, Invicta Research, Wilmington, Dartford, Kent; Marie Rooks (interviewer); Joan Ranson (interviewer); Dr. Nigel Gostick, Central Surgery, Rugby, Warwickshire; Mary Rushall (interviewer).

We are also indebted to Astrid Bauleke, Karen Hollander, Judi Horrocks, and Pablo Muñoz of GM3, Munchen, Germany; and Margot Daymond of Royal Postgraduate Medical School, London, UK, for their assistance in the administration and data management of the trial.
Quality of life with three antihypertensive treatments. Cilazapril, atenolol, nifedipine.
A E Fletcher, C J Bulpitt, D M Chase, W C Collins, C D Furberg, T K Goggin, A J Hewett and A M Neiss

doi: 10.1161/01.HYP.19.6.499

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/19/6_Pt_1/499