CAPTOPRIL, ENALAPRIL, AND QUALITY OF LIFE

To the Editor: Testa et al. (April 1 issue) compared two antihypertensive medications, captopril and enalapril, with regard to their effects on quality of life in men. Patients treated with captopril had more favorable changes in overall quality of life, general perceived health, vitality, health status, sleep, and emotional control. The authors state that previous research had not employed sufficiently sensitive instruments or studied samples large enough to detect meaningful differences.

The findings of published studies of enalapril and quality of life are not consistent with these conclusions. Steiner et al. randomly assigned 360 men with hypertension to treatment with amlodipine, captopril, enalapril, or propranolol. The quality-of-life scales used by those investigators were similar to or the same as those used by Testa et al. Captopril and enalapril did not differ in their effects on quality of life, except that, as compared with captopril, enalapril significantly improved values on subscales for general health, restlessness, and sleep-onset latency; enalapril improved vitality.

Omvik et al. studied 461 men and women with hypertension randomly assigned to treatment for 50 weeks with either amlodipine or enalapril. No significant differences in quality of life were found between the treatments, and no decreases from baseline values were noted with enalapril treatment. In fact, there were significant improvements in values on subscales for anxiety, psychological well-being, general health perceptions, and vitality and on the Psychological Well-Being index.

In the Treatment of Mild Hypertension study, 902 patients with hypertension were randomly assigned to one of six treatment groups, including groups taking enalapril and placebo for 12 months. Values on seven scales for quality of life showed no statistically significant decrement with enalapril relative to placebo or the other treatments. Dahlöf and Dimentä studied the effects of enalapril and captopril in two placebo-controlled, double-blind studies of 80 healthy volunteers. No differences in quality of life, including vitality and sleep, were found for captopril or enalapril relative to placebo. Eight other published studies, involving over 3000 patients, reported either no change or improvement in quality of life with enalapril treatment. Surprisingly, Testa et al. did not present their findings in the context of this previous research.

In general, studies of enalapril have shown either no decrement in measures of quality of life or, in some cases, statistically significant improvements either from baseline values or with enalapril treatment as compared with captopril treatment. In the context of existing data on quality of life and enalapril, the results reported by Testa et al. are most likely reflective of the large number of statistical tests performed without adjustments for multiplicity.

Nancy C. Santanello, M.D., M.S.
HARRY GUESS, M.D., Ph.D.
JOSEPH F. HEYSE, Ph.D.
West Point, PA 19486
Merck Research Laboratories

Editor's Note: All the authors of this letter are employees of Merck Sharp & Dohme, the manufacturer of enalapril.


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To the Editor: Since captopril was given twice daily and enalapril once daily in the trial of Testa et al., were the investigators and patients blinded? The study states that hydrochlorothiazide was administered in a blinded fashion, but says nothing about the other drugs. Also, how many patients had to have hydrochlorothiazide added to treatment with an angiotensin-converting-enzyme inhibitor? These investigators have previously observed that the addition of hydrochlorothiazide markedly decreased quality of life. Could this be at least a partial explanation for the differences in results between the two angiotensin-converting-enzyme inhibitors?

NORMAN M. KAPLAN, M.D.
University of Texas Southwestern Medical Center
Dallas, TX 75235


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To the Editor: In the study by Testa et al., could the differences observed have reflected differences between the vehicles for the antihypertensive agents, rather than differences between the drugs themselves? Indeed, the package inserts suggest that the two drug manufacturers involved use different vehicles for their tablets. For example, enalapril apparently contains magnesium, an ion with effects on nerve cells. The obvious way to avoid this weakness in a study is to test pure substances, not commercial preparations from different companies. Have the authors done this?

DOUGLAS R. WAUD, M.D., D.PHIL.
University of Massachusetts Medical School
Worcester, MA 01655

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To the Editor: Testa et al. considerably modified standard instruments such as the Psychological General Well-Being scale, making it impossible to compare their results directly with those of other trials of antihypertensive treatments that have used this instrument. 1-4 Absolute changes in scores and confidence intervals are not given for the main results; data on quality of life at the 8-week and 18-week points are not presented. Reporting raw data is particularly important, since different measures of responsiveness can be used. The choice of denominator for the responsiveness index should represent the underlying variability of the instrument in a stable situation. Testa et al. used the standard deviation for the treatment period (changes at 18 to 24 weeks) in preference to the standard deviation for the pretreatment period. Over 20 percent of the patients withdrew during the trial. Therefore, the standard deviation for the latter part of the treatment period reflects a smaller and more homogeneous
group and inflates the responsiveness index. Using the standard deviation determined at base line or, if available, that for the run-in period would lead to a more representative measure of the underlying variability of the measurement instrument.

Calibration of changes in quality-of-life scores with life events is difficult to interpret because of the large standard error of the regression slope below -0.1 and the presentation of only negative changes rather than the entire distribution. The results do not appear intuitively sensible; the average change in general perceived health in the enalapril group was a decrease of 8 units (less than 2 percent of the base-line score); apparently, this change was large enough to produce an effect equivalent to that of imprisonment. This is not compatible with accepted notions that effect sizes of 0.2 represent small treatment effects (fifth of a standard deviation).

Astrid Fletcher, Ph.D.
London School of Hygiene and Tropical Medicine
London WC1E 7HT, United Kingdom


To the Editor: Testa et al. randomly assigned men with mild-to-moderately-severe hypertension to treatment with captopril or enalapril and found no differences in blood pressure, rates of withdrawal from treatment, or the incidence of major side effects. The quality of life at 24 weeks was improved in patients with low initial scores for quality of life who were treated with captopril and enalapril, but the improvement was significant only in those treated with captopril. This finding led to speculation that captopril improves quality of life. The differences in the magnitude of improvement across treatment groups were not statistically significant among patients with low initial scores.

To address the question of whether an improvement in quality of life could be expected without a change in treatment in patients with initially low scores for quality of life, we compared changes in patients with initially low, medium, and high scores in the Medical Outcomes Study. I report the results in 481 men and 168 women with uncomplicated hypertension who were drawn from 367 practices in three cities. Approximately 91 percent were aware of their condition, 87 percent were receiving antihypertensive medication, and all were free of any serious coexisting medical condition. The "natural course" of their quality of life, without intervention by the study, was determined by comparing initial assessments with follow-up assessments after 24 weeks. Because the measures of distress and well-being analyzed by Testa et al. are highly correlated and because these measures produced the same pattern of results in their study and ours, these measures were combined to define one mental-health scale (documented elsewhere). Table 1 compares the results on the Psychological Distress scale reported by Testa et al. with the results of the Medical Outcomes Study. To facilitate comparisons, changes in scores in both studies were standardized by dividing the difference between follow-up values and base-line values by the standard deviation. (Because the results were the same among the men in the Medical Outcomes Study as those among the women, the values were combined.) The average improvement in the scores of our patients with initially low scores was large (0.45 SD unit), as well as larger than the improvements in the patients of Testa et al. who had initially low scores (0.31 SD unit in the captopril group and 0.12 SD unit in the enalapril group). Whereas the scores of patients in both groups who had initially high scores declined, especially in the enalapril group (0.18 SD unit), the score in the comparable group in our study declined even more (0.29 SD unit).

Neither the average improvement in quality of life in the patients with initially low scores nor the decline observed in patients with initially high scores who were treated with captopril and enalapril were qualitatively different from the comparable changes in similar groups in the Medical Outcomes Study. Thus, the improvement reported in the captopril group with low initial scores, which was not significantly different from that in the comparable enalapril group, is unlikely to be due to treatment. It is not clear why a significantly greater decline was observed in the patients in the enalapril group who had initially high scores than in the comparable patients in the captopril group. Determining whether side effects of medication explain this difference may require more sensitive measures of side effects than those used by Testa et al. Given the magnitude of the regression to the mean observed in both patients with low and patients with high initial scores in the Medical Outcomes Study, it is risky to draw conclusions about whether captopril or enalapril offers a pharmacologic advantage in terms of quality of life, without comparisons with control groups with initially high and low scores.

John E. Ware, Jr., Ph.D.
Boston, MA 02111
New England Medical Center

Table 1. Changes in Quality-of-Life Scores in Groups with Initially Low, Medium, and High Scores in the Study by Testa et al. and the Medical Outcomes Study.

<table>
<thead>
<tr>
<th>Testa et al.</th>
<th>Difference in Psychological Distress Scale</th>
<th>Medical Outcomes Study</th>
<th>Difference in SF-36 Mental Health Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>Score</td>
<td>Change in score</td>
<td>SD units†</td>
</tr>
<tr>
<td>Low</td>
<td>457</td>
<td>53</td>
<td>19.78</td>
</tr>
<tr>
<td>Medium</td>
<td>533</td>
<td>60</td>
<td>6.2</td>
</tr>
<tr>
<td>High</td>
<td>577</td>
<td>71</td>
<td>-3.5</td>
</tr>
</tbody>
</table>

†The difference was calculated by subtracting the initial values from follow-up values.
†The standard deviation was 64.
†The standard deviation was 59.
†Value was significantly different from zero (P<0.05).
†Value was significantly different from that in the comparison group (P = 0.04 to 0.01).
†The standard deviation was 14.3.
**P<0.001 by two-tailed test.
††P<0.05 by two-tailed test.

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The authors reply:

To the Editor: We appreciate Dr. Kaplan’s request for details lost during revision. The medication was administered in double-blind, double-dummy fashion. The number of patients who also received hydrochlorothiazide was 44 in the captopril group and 39 in the enalapril group.

We agree with Dr. Ware that regression to the mean influenced our results; we emphasized that in our paper. Indeed, this effect is maximized (data from the Medical Outcomes Study) when the base-line classification and dependent variables are one and the same. Unambiguous conclusions cannot be drawn about absolute changes from base line. On the other hand, regression to the mean does not explain differences in the patterns of change between the two drug treatments.

The interval suggested by Dr. Fletcher to estimate the reliability constant to calculate responsiveness varies because patients were being weaned from previous treatment during the initial phase of the study. Also, analyses are invariant with respect to the constant chosen. As for calibration, Fletcher ignores the difference between a total scale and an operative scale. To cite an unrelated example, a rise in body temperature by 4°C may seem slight on a total scale but large on an operative scale. In our study, single large stressors were very rare, and stress scores more often reflected small stressors that accumulated over many years, thereby allowing coping and adaptation of quality of life.

Finally, Santanello et al. cite a number of studies. Conclusions about absolute “worsening” or “improvement” in trials without placebos seem unjustified. Furthermore, we know from Croog et al. that studies with observation periods of two weeks (Dahlöf and Dimenäs) and four weeks (Steiner et al.) are too short for quality-of-life assessment; both were also underpowered for this purpose. Our study suggests that 200 patients are required per group for sufficient power. The study by Omvik et al. and the Treatment of Mild Hypertension study did not include captopril comparison groups and pooled men and women. This makes interpretation difficult. The thousands of other patients seem to have been treated in two open-label studies, which do not merit discussion.

Santanello et al. criticize us for selective citation. We also did not cite a small (40-patient), randomized, double-blind study of depressed patients with hypertension, in whom captopril, as compared with enalapril, reduced both depression (P<0.001, Hamilton Depression Scale) and anxiety (P<0.01, Hamilton Anxiety Scale).

As for multiplicity of tests, our analysis was conservative. Univariate comparisons were made only after the overall multivariate hypothesis had been rejected. Global tests magnified treatment differences, since the direction of effects was uniform. Values for the factor combining positive affect, vitality, general health, work, and sleep demonstrated significant differences in favor of captopril as compared with enalapril (+9.7 vs. −18.6 units, P = 0.007). Treatment differences were too consistent and durable to be dismissed as merely due to chance.

MARCIA A. TESTA, M.P.H., PH.D.
NORMAN K. HOLLERNBERG, M.D., PH.D.
Harvard School of Public Health
Boston, MA 02115
Harvard Medical School

The study by Manning et al. on magnetic resonance imaging (MRI) coronary angiography (March 25 issue) is an important first step toward identifying a noninvasive method of visualizing coronary anatomy. I am concerned, however, about the analysis performed in the study. Is it reasonable to exclude nine coronary segments from the analysis of the MRI studies because of technical limitations (uninterpretable and time constraints)? Should not MRI study of all 156 segments of coronary arteries intended for analysis have been compared with conventional methods according to “intention-to-analyze” principles? If all segments were uninterpretable, the sensitivity and specificity of MRI angiography would be zero.

I also wonder whether it is fair to compare two methods according to different standards. MRI coronary arteriography was judged according to its ability to identify a stenosis of 50 percent or more at any point in the imaged coronary tree. Conventional contrast coronary arteriography, on the other hand, has consistently provided submillimeter resolution of the entire coronary tree, giving information about the location, severity, and morphologic characteristics of stenoses. Thus the best MRI angiogram is only 88 to 90 percent as good as the worst coronary angiogram. If MRI angiography were truly 88 to 90 percent as good as conventional coronary angiography, would this be adequate? Can we afford to be wrong more than 10 percent of the time in patients with coronary artery disease? I hope that current efforts in MRI angiography focus on improving the quality of the images.

JOHN A. BITTLE, M.D.
Brigham and Women’s Hospital
Boston, MA 02115


To the Editor: Dr. Steinberg’s editorial accompanying the preliminary report on MRI coronary angiography (March 25 issue) very appropriately points out that the clinical benefit of noninvasive MRI coronary angiography will be determined by its ability to identify those local arterial lesions that have important physiologic consequences. . . . Translating the appearance of anatomical lesions into a sense of their functional importance and consequences.