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Effects of Antihypertensive Medications on Quality of Life in Elderly Hypertensive Women

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Effects of Antihypertensive Medications on Quality of Life in Elderly Hypertensive Women

Sydney H. Croog, Merrill F. Elias, Theodore Colton, Robert M. Baume, Sandra R. Leiblum, C. David Jenkins, H. Mitchell Perry, and W. Dallas Hall

The impact of antihypertensive medications on the quality of life of elderly hypertensive women has rarely been systematically evaluated in large clinical trials using drugs from the new generations of pharmaceutical preparations. We carried out a multicenter, randomized double-blind clinical trial with 309 hypertensive women aged 60 to 80 years to assess effects of atenolol, enalapril, and isradipine on measures of quality of life over a 22-week period. The patients had mild to moderate hypertension. Hydrochlorothiazide was added to treatment if monotherapy was inadequate in lowering blood pressure. At the conclusion of the trial the three drug groups did not differ in degree of reduction of diastolic blood pressure or in supplementation with hydrochlorothiazide. Over the 22-week trial, linear trend analysis showed no differences between the treatment groups in change from baseline on quality of life measures of well-being, physical status, emotional status, cognitive func-

tioning, and social role participation. Regarding each of 33 physical side effects over the 22 weeks, we found no general difference between atenolol, enalapril, and isradipine groups on measures of change in distress over symptoms except for enalapril patients who worsened in distress over cough ($P = .001$) and atenolol patients who worsened in distress over dry mouth ($P = .014$). Centering on three medications that are relatively new additions to the armamentarium for blood pressure control, the findings underline the increasing opportunities for the physician to select drugs that can control blood pressure while maintaining the quality of life of elderly hypertensive women. *Am J Hypertens* 1994;7:329-339

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Over recent years increasing attention has focused on issues of treatment of the older female hypertensive. Among women 65 to 74 years old, an estimated 50% are hypertensive, with blood pressures ≥ 160 mm Hg systolic and 95 mm Hg diastolic.^{1,2} Treatment of high blood pressure in the elderly predominantly involves the female hypertensive, as women comprise approximately two-thirds of the hypertensive persons 65 years old and over. Elderly hypertensive patients are likely to differ from younger patients, in such measures as higher total peripheral resistance, lower blood volume, lower cardiac out-

put, and lower plasma renin activity.^{3,4} Some negative effects of antihypertensive medications on quality of life may lead to withdrawal from treatment or poor compliance by the patient.⁴ Drug trials with predominantly middle-aged, hypertensive patients have shown that while medications may have similar efficacy, their side effects and impact on quality of life may differ.^{5,6} However, findings from such studies cannot be generalized readily to elderly hypertensive women.

New generations of antihypertensive drugs are being developed, including refinements of calcium channel blockers, β -blockers, and angiotensin converting enzyme (ACE) inhibitors.⁷⁻¹⁰ Recently, increasing numbers of clinical trials have examined various drugs within these classes of antihypertensive medications in terms of their effects on quality of life, with most centering on either male patients or on patient populations not differentiated by sex in the analysis.¹¹⁻¹⁸ Relatively little documentation is available on the effects of such antihypertensive medications on quality of life in the elderly, as the issue has rarely been examined systematically in large, randomized clinical trials.^{19,20} Assessment of effects of the medications on elderly female hypertensives requires focus both on the pharmacologic treatment and on quality of life in the context of aging.²¹⁻²⁴

This report presents findings on measures of quality of life from a randomized, multicenter, double-blind clinical trial with 309 elderly female hypertensive patients. We assessed effects of three differing classes of antihypertensive medications, drawn from recent generations of pharmacologic agents: atenolol (a cardioselective β -blocker), enalapril (an angiotensin converting enzyme [ACE] inhibitor), and isradipine (a dihydropyridine calcium channel blocker). We examined change scores in quality of life measures after both 6 weeks and 22 weeks of treatment as well as the possible relationship of age and dosage level to the change scores. Looking beyond differences between treatment groups, we analyzed trend data for the total study group to document changes in quality of life scores during treatment with these medications. A report comparing efficacy and safety of the three drugs appears in a separate publication.²⁵

PATIENTS AND METHODS

Study Subjects and Eligibility Criteria The study subjects were postmenopausal white women aged 60 to 80 years with mild to moderate essential hypertension (ie, 95-114 mm Hg sitting diastolic blood pressure). They were recruited at 22 clinical centers throughout the United States. Eligibility criteria at initial screening included demonstrated potential for completion of the quality of life and cognitive scales used in this study: a score of 7 or lower on the Jaeger scale for the Rosenbaum Vision test,²⁶ 42 or above on

the WRAT Reading Test,²⁷ and 12 or fewer incorrect answers on the Mini Mental State Exam.²⁸

Patients with any of the following were excluded: severe cardiac disease, secondary hypertension, uncontrolled diabetes, recent cerebrovascular accident, bronchospasm requiring chronic treatment, significant hepatic or renal disease, intolerance to the study drugs, treatment with psychotropic drugs or any other medication that could affect blood pressure or emotional status, and presence of any other condition that could limit the patient's capacity for completion of all phases of this study. Current treatment with estrogen, progesterone, or androgens was not a reason for exclusion. If drugs for chronic conditions were essential for the patient's well-being, they were continued at the same dose throughout the study.

An 80% compliance rate was required for continuation in the study, defined as return of no greater than 20% of capsules at each visit. The research protocol was approved by appropriate institutional review boards, and informed consent was obtained from all study subjects.

Study Design After a placebo period of 4 to 8 weeks, subjects were randomized to one of the three treatment groups. The first active treatment period extended for 6 weeks (titration stage), followed by 16 weeks on maintenance therapy. Quality of life assessments were carried out at baseline at the end of the placebo period, at 6 weeks, and at 22 weeks.

Medication was titrated upward every 2 weeks until blood pressure was controlled. Control was defined as the reduction of sitting diastolic blood pressure to <90 mm Hg and at least 10 mm Hg below the baseline value. The three-step titration schedule was: atenolol 50 mg, 100 mg, 100 mg; enalapril 5 mg, 10 mg, 20 mg; isradipine 1.25 mg, 2.5 mg, and 5.0 mg. Atenolol and enalapril were prescribed once daily and isradipine was prescribed twice daily. To maintain blinding, patients receiving atenolol and enalapril took a placebo in the evening. If blood pressure was not controlled at the end of titration, open label hydrochlorothiazide (HCTZ), 25 mg daily, was added.

Patients were withdrawn from the study if their blood pressure remained uncontrolled after the administration of HCTZ, or if an intolerable adverse effect developed. Patients who withdrew during the active treatment period were requested to complete an exit interview.

Data Collection and Management Quality of life assessments were carried out by personnel who had received standardized training for the interviewing and administration of psychological testing. Interviewers were not directly involved in patient care. Patients, interviewers, and investigators were blinded to the primary treatment drug assignments.

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Quality of Life Assessment Assessment of the quality of life construct was guided by specification of five conceptual dimensions:^{29,30} (1) the sense of well-being and satisfaction with life, (2) physical state, (3) emotional state, (4) intellectual functioning, and (5) ability to perform social roles and the degree of satisfaction derived from those roles. Appendix A summarizes measures within each of the conceptual areas. Data on measures of sexual performance and work satisfaction are not included in this report because of insufficient numbers of patients with available, functional sexual partners and because of the small number of respondents who were employed.

Statistical Analyses For baseline comparisons of the three treatment groups on demographic and clinical characteristics, quality of life scales, and symptom distress scores, we used one-way analysis of variance (ANOVA). Our analyses of quality of life scales at baseline and at weeks 6 and 22 of follow-up used repeated measures ANOVA. Within these ANOVAs, we also segregated and tested for linear trends over time as well as for interaction of linear trends by treatment groups. We also conducted repeated measures analyses of covariance where we used as covariates age, titration level, and/or the addition of diuretics.³¹ We conducted these analyses both for the intent-to-treat group of all randomized patients and for that subgroup of patients who completed the entire study follow-up protocol. For pairwise comparisons among the three treatment groups, we used the Tukey multiple range test.³² In several instances, where there was indication of skewness in the distribution of individual scale results, we conducted our analyses after logarithmic transformation of the raw data.

We also conducted separate analyses of change from baseline to week 6 and from baseline to week 22 for the quality of life scales and the individual symptom distress scores. For within-group comparisons we employed paired samples *t* tests; for between-group (ie, drugs) comparisons we used ANCOVA followed by the Tukey multiple range test.³²

Power calculations with the quality of life measures indicated that the sizes of the three treatment groups in the intent-to-treat sample were sufficient to detect a 10% difference in a comparison of any of two drug groups, or a medium effect size 0.25 with 95% power³³ and a two-tailed test at the 5% level. This is equivalent to a difference of about 0.45 standard deviations in change scores across the full set of scales employed.

RESULTS

Patient Population We recruited 517 patients who began the placebo period. The 202 patients who did

not complete the placebo period failed to do so mainly because of blood pressure levels that did not meet study criteria, presence of concomitant illnesses, and adverse events. Upon completion of the placebo period, 315 patients were randomized. Of these, six completed only baseline interviews (1 atenolol, 2 enalapril, and 3 isradipine) and have been excluded from further analyses. The remaining 309, which we consider the "intent-to-treat" group, consisted of 103 randomized to atenolol, 101 to enalapril, and 105 to isradipine.

By week 6, 7 of the 309 intent-to-treat patients had withdrawn, and by week 22 an additional 62 patients had done so. Of the total 69 patients withdrawn, the major reasons were adverse reactions ($n = 42$) and unacceptably elevated blood pressure ($n = 19$). The number of withdrawals by treatment group were: 29 on atenolol (28.2%), 17 on enalapril (16.8%), and 23 on isradipine (20.0%). The three treatment groups did not differ significantly in rate of withdrawal. Data for the intent-to-treat analysis are based on interviews with the completer population, exit interviews with withdrawing patients, and the most recent interviews with withdrawers in the absence of formal exit interviews. Patients who withdrew did not differ in demographic characteristics or baseline quality of life measures from the remaining 240 patients who completed the entire study.

Table 1 shows the distribution of highest titrated drug level within each drug treatment group among the 240 patients who completed the study. For the atenolol group, steps 2 and 3 were identical in prescription at 100 mg/day, in accordance with a procedure to maintain blinding. Thus, in analyses relating to titration level for the atenolol group, steps 2 and 3 were combined. The percentage of patients who took the diuretic in addition to the main treatment drug did not differ between treatment groups.

Table 2 shows demographic and clinical characteristics of the three randomized treatment groups. Table 3 shows baseline means on quality of life measures in the first three columns. There were no significant differences between treatment groups at baseline in demographic or clinical variables or quality of life measures.

Effects of Drugs on Blood Pressure Reduction

Among patients completing the study, including those on monotherapy or the primary treatment plus hydrochlorothiazide, reductions in sitting diastolic blood pressure from baseline to week 22 were comparable (mean $\pm$ SE) 15.6 ± 0.7 mm Hg, 15.1 ± 0.9 mm Hg, and 16.2 ± 0.7 mm Hg for the atenolol, enalapril, and isradipine groups, respectively. These

TABLE 1. DRUG TITRATION. PATIENTS WHO COMPLETED THE TRIAL, CLASSIFIED BY HIGHEST DOSAGE LEVEL OF TREATMENT MEDICATION USED DURING THE STUDY

Titration Step	Atenolol			Enalapril			Isradipine		
	Dosage Level	n	Percent	Dosage Level	n	Percent	Dosage Level	n	Percent
1	50 mg qd	34	46.0	5 mg qd	30	35.7	1.25 mg bid	21	25.6
2	100 mg qd	28	37.8	10 mg qd	16	19.1	2.5 mg bid	29	35.4
3	100 mg qd			20 mg qd	20	23.8	5.0 mg bid	23	28.0
4	100 mg qd plus HCTZ	12	16.2	20 mg qd plus HCTZ	18	21.4	5.0 mg bid plus HCTZ	9	11.0
Total		74	100.0		84	100.0		82	100.0

HCTZ, hydrochlorothiazide; qd, every day; bid, twice daily.

changes were all statistically significant ($P < .001$). The systolic blood pressure reductions from baseline to week 22 were 15.2 ± 1.9 mm Hg, 21.3 ± 2.0 mm Hg, and 18.0 ± 1.6 mm Hg in the atenolol, enalapril, and isradipine groups, respectively. There were no significant differences between treatment groups in diastolic and systolic blood pressure reduction with the exception of a decrease in the enalapril group in systolic blood pressure that was greater than that in the atenolol group ($P = .048$).

Patient Withdrawals and Adverse Events The three treatment groups did not differ in the proportion of withdrawals because of adverse events over the 22-week trial: atenolol ($n = 17$ or 16.3%), enalapril ($n = 13$ or 12.6%), and isradipine ($n = 12$ or 11.1%).

Primary adverse events associated with withdrawal among the drug groups were: atenolol: bradycardia ($n = 5$), dyspnea ($n = 3$), and headaches ($n = 2$); enalapril: cough ($n = 3$) and orthostatic hypotension

($n = 2$); isradipine: dizziness ($n = 3$), edema of extremities ($n = 2$), headache ($n = 2$), and palpitations ($n = 2$). Miscellaneous individual adverse reactions also occurred.

Quality of Life: Changes in Scale Scores Between Treatment Groups: Baseline to Week 6 and Week 22 In the intent-to-treat repeated measures analysis of comparisons between treatment groups, we found no differences between groups in change in scores on any of the quality of life scale measures from baseline to weeks 6 and 22. Table 3, column 7 shows results of our analyses of whether there were differences in change in scores for each quality of life measure to week 6 and week 22 as a function of drug treatment (ie, the linear trend $\times$ treatment group term). None was significant. The table also shows baseline scores and changes in mean scores on quality of life measures within treatment groups from baseline to week 22. Ninety-five percent confidence intervals are

TABLE 2. DEMOGRAPHIC AND CLINICAL VARIABLES IN THREE TREATMENT GROUPS AT BASELINE

Variable	Treatment Group		
	Atenolol (n = 103)	Enalapril (n = 101)	Isradipine (n = 105)
Demographic			
Age at entry	68.1 $\pm$ 0.5	67.7 $\pm$ 0.5	67.9 $\pm$ 0.5*
Education: median school year completed	12	12	12
Current marital status			
Percent married	58.7	61.2	50.5
Percent widowed	30.8	30.1	31.8
Household income	\$11,700	\$12,100	\$11,900
Clinical			
Height (in.)	64 $\pm$ 0.3	63 $\pm$ 0.3	63 $\pm$ 0.3
Weight (lb)	162 $\pm$ 3.1	170 $\pm$ 3.8	166 $\pm$ 3.3
Sitting systolic blood pressure (mm Hg)	161.8 $\pm$ 1.5	161.5 $\pm$ 1.5	160.5 $\pm$ 1.4
Sitting diastolic blood pressure (mm Hg)	100.1 $\pm$ 0.5	99.6 $\pm$ 0.5	99.1 $\pm$ 0.4
Estrogen use concurrent at baseline (%)	4.1	4.1	2.5

*Data on means are reported as means $\pm$ SE.

TABLE 3. QUALITY OF LIFE SCALES AT BASELINE AND CHANGE AFTER ACTIVE THERAPY FOR 22 WEEKS FOR INTENT TO TREAT PATIENTS

Scales and Areas Assessed	Baseline Mean			22 Weeks Change From Baseline Mean			P Value for Comparisons Between Groups From Baseline to Weeks 6 and 22	P Value for Linear Trend for Combined Groups From Baseline to Weeks 6 and 22
	Atenolol	Enalapril	Isradipine	Atenolol	Enalapril	Isradipine		
Well being								
General well being (+)	104.2	104.0	105.0	-1.7	-0.7	-0.9	.969	.087
Emotional status								
CESD (depression) (-)	7.5	8.5	8.4	0.1	-1.9	-0.5	.365	.728
STAI (state anxiety) (-)	29.9	31.6	29.8	0.4	-0.8	0.4	.626	.473
STAI (trait anxiety) (-)	31.6	32.9	32.3	0.1	-1.2	-0.4	.233	.009 (Im)
Level of sexual interest (+)	2.6	2.5	2.7	-0.3	-0.1	-0.4	.329	.001 (De)
Cognitive function								
Digit span forward (+)	7.5	7.6	7.5	0.1	0.5	0.3	.543	.004 (Im)
Digit span backward (+)	6.1	6.0	6.0	0.1	-0.1	0.2	.519	.570
Digit symbol score (+)	42.9	44.4	42.2	3.8	2.4	4.8	.204	.001 (Im)
Trail making A (-)	51.7	47.8	51.2	-4.6	-7.7	-7.6	.593	.001 (Im)
Trail making B (-)	112.6	112.3	120.3	-8.9	-9.9	-15.7	.255	.001 (Im)
Physical status								
Physical symptoms distress (-)	44.6	44.1	43.2	0.4	0.2	1.6	.685	.098
Sleep disturbance (-)	8.3	9.0	9.0	0.6	0.1	-0.2	.178	.691
Social roles								
Social activities (+)	22.8	22.9	23.6	0.5	0.8	0.5	.402	.011 (Im)

Baseline means and mean change to 22 weeks. Comparisons between groups based on linear trends from baseline to 6 and 22 weeks. Linear trend for total population. Atenolol (n = 103), enalapril (n = 101), isradipine (n = 105).

For assessment of changes in means, plus sign next to title of scale denotes improvement with an increasing score, and minus sign denotes improvement with a decreasing score. No mean changes were significant between groups. Significance levels for the CESD and Physical Symptoms Distress measures are based on log transformations of the data.

For linear trend assessment: "Im" indicates improvement, ie, less depression, less anxiety, improved performance on cognitive tests. "De" indicates "decline" or "decrease" as shown in Level of Sexual Interest.

For all 13 baseline sets of means, the standard error differed by no more than 0.2 points across the three drug groups, except Trail Making A (0.7) and Trail Making B (0.4).

For all 13 sets of means of change, the standard error differed by no more than 0.3 points except for Trail Making A (0.6) and Trail Making B (0.4).

shown in Table 4, reporting on comparisons of each pair of drug treatment groups in degree of change from baseline.

We also carried out separate supplementary repeated measures analysis of variance for the 240 patients who completed three interviews and 22 weeks of treatment. Results of the trend analysis mirrored those deriving from analysis of the intent-to-treat population. In addition, to look specifically at short-term drug effects we compared the treatment groups at 6 weeks, including all patients who were present at that time (n = 302). No differences between treatment groups at that time were found in change on the quality of life scale scores.

Drug Groups Combined Considering mean scores for the three drug groups combined, there were several significant linear trends over the 22 weeks for the total population, as seen in the final column of Table 3. They included decrease (improvement) on the Trait

Anxiety ($P = .009$) and decline in Level of Sexual Interest ($P = .001$). Improvements were seen in the Digit Span Forward test ($P = .004$), Digit Symbol ($P < .001$), and the Trailmaking A and B tests ($P < .001$, $P < .001$, respectively). The Social Activities Scale showed an increase in activity ($P < .01$).

With regard to indicators of physical health, we found no change in scores on the Physical Symptoms Distress Index over the 22 weeks. Examination of two subscales of the General Well Being Adjustment scale, ie, vitality and general health, showed no significant time trends in scores for the patient groups combined, and no between-group differences over the 22 weeks. Results were similar in the analysis of the 240 patients in the "completer" group.

Change in Quality of Life Measures to Week 22: Influence of Age, Titration, and Diuretics as Covariates Through analysis of covariance, we explored whether there was significant between-group change in the quality

TABLE 4. NINETY-FIVE PERCENT CONFIDENCE INTERVALS FOR COMPARISON BETWEEN DRUG TREATMENT GROUPS IN CHANGE SCORES FROM BASELINE TO WEEK 22

Scales and Areas Assessed	Atenolol v Enalapril	Atenolol v Isradipine	Enalapril v Isradipine
Well being			
General well being	(-6.0, 1.7)	(-3.1, 4.4)	(-5.5, 2.6)
Emotional status			
CESD (depression)	(-2.0, 3.9)	(-2.6, 1.7)	(-2.6, 3.6)
STAI (state anxiety)	(-1.6, 5.8)	(-4.5, 1.9)	(-2.5, 4.1)
STAI (trait anxiety)	(-0.9, 2.8)	(-2.6, 1.0)	(-1.6, 1.9)
Level of sexual interest	(-0.5, 0.1)	(-0.3, 0.3)	(-0.5, 0.1)
Cognitive function			
Digit span forward	(-0.1, 0.8)	(-0.5, 0.4)	(-0.1, 0.8)
Digit span backward	(-0.7, 0.2)	(-0.7, 2.9)	(-0.9, 2.7)
Digit symbol score	(-1.9, 2.1)	(-0.5, 4.1)	(-0.4, 4.2)
Trail making A	(-6.4, 2.7)	(-5.5, 5.3)	(-6.9, 3.0)
Trail making B	(-48.8, 7.8)	(-21.8, 40.8)	(-40.4, 18.4)
Physical status			
Physical symptoms distress	(-2.2, 1.9)	(-0.1, 3.6)	(-0.5, 3.7)
Sleep disturbance	(-0.4, 1.5)	(-1.6, 0.3)	(-1.0, 0.9)
Social roles			
Social activities	(-1.3, 0.8)	(-0.9, 0.9)	(-1.3, 0.9)

of life measures when age, titration level, or the addition of diuretics was covaried with treatment groups. We found no evidence of an effect of these variables on change in any of the quality of life scale measures.

Distress Over Symptoms: Changes During Therapy

While the total scores for the Physical Symptoms Distress Index showed no between-group differences at weeks 6 or 22, we compared the drug groups in distress on the 33 individual perceived symptoms that comprise the Index. (See Appendix A for symptoms

list.) Results showing significant comparisons are shown in Table 5. Ninety-five percent confidence intervals appear in Table 6 reporting on comparisons of each pair of drug groups in degree of change from baseline.

Six Weeks From baseline to 6 weeks enalapril patients worsened in their distress over cough as compared with atenolol ($P < .001$) and isradipine patients ($P < .001$). The atenolol patients as compared with isradipine patients worsened in their degree of distress concerning tiredness and shortness of breath (P

TABLE 5. MEAN CHANGES ($\times 10$) IN REPORTED DISTRESS OVER SELECTED SYMPTOMS FROM BASELINE TO WEEK 6 AND WEEK 22 BY BETWEEN-GROUP COMPARISONS AND WITHIN-GROUP CHANGES FOR INTENT TO TREAT SAMPLE†

Symptom‡	Week 6 Change From Baseline			Comparison Between Groups in Changes From Baseline (P Value)	Week 22‡ Change From Baseline			Comparison Between Groups in Changes From Baseline (P Value)
	Atenolol (n = 103) (A)	Enalapril (n = 101) (B)	Isradipine (n = 105) (C)		Atenolol (n = 103) (A)	Enalapril (n = 101) (B)	Isradipine (n = 105) (C)	
Cough	-0.9	+5.0***	+0.9	B > A,C***	+0.3	+5.0***	+0.8	B > A,C***
Dry mouth	+1.1	+0.1	-0.1	NS	+0.9	-1.0*	-0.4	A > B***
Tiredness or fatigue	+3.3**	-0.2	-0.2	A > B,C**	+0.5	-1.7	+0.1	NS
Shortness of breath	+1.9*	+0.5	-0.1	A > C*	0	-0.7	+0.7	NS
Sensitivity to cold in extremities	+1.5*	-0.7	0	A > B,C*	+0.7	-0.3	+0.3	NS

†The results for each physical symptom distress measure were based on a 5-point scale (1-5). Plus sign shows worsening for the symptom. Minus sign shows improvement. Within-group comparisons show significance level of degree of change from baseline by asterisks.

‡Week 22 groups contain all patients without segregation by diuretic. With effects of diuretic controlled through ANCOVA, results at 22 weeks showed no differences in levels of significance other than those reported in the table.

* $P < .05$.

** $P < .01$.

*** $P < .001$.

TABLE 6. NINETY-FIVE PERCENT CONFIDENCE INTERVALS ($\times 10$) FOR COMPARISONS BETWEEN TREATMENT GROUPS IN CHANGE SCORES IN DISTRESS OVER SYMPTOMS, FROM BASELINE TO WEEK 6 AND WEEK 22

Symptom	Week 6			Week 22		
	Atenolol v Enalapril	Atenolol v Isradipine	Enalapril v Isradipine	Atenolol v Enalapril	Atenolol v Isradipine	Enalapril v Isradipine
Cough	(-9.0, -2.7)*	(-0.8, 4.3)	(-7.0, -1.3)*	(-7.9, -1.5)*	(-2.2, 3.2)	(-7.2, -1.4)*
Dry mouth	(-1.1, 2.9)	(-3.0, 0.8)	(-2.4, 2.0)	(-0.3, -4.0)*	(-3.5, 1.0)	(-1.5, 2.7)
Tiredness or fatigue	(0.7, 6.3)*	(-6.5, -0.5)*	(-2.9, 2.9)	(-0.8, 5.1)	(-3.4, 2.7)	(-1.2, 4.8)
Shortness of breath	(-0.5, 3.2)	(-3.7, -0.2)*	(-2.2, 1.0)	(-1.3, 2.8)	(-1.4, 2.8)	(-0.6, 3.4)
Sensitivity to cold in extremities	(0.3, 4.2)*	(-3.5, -0.5)*	(-1.6, 2.9)	(-1.3, 3.1)	(-2.4, 1.6)	(-1.7, 2.8)

*For the direction of differences between drug groups and levels of significance, see Table 5.

= .016, $P = .019$). As compared with both enalapril and isradipine patients, atenolol patients also had more distress over cold extremities ($P = .020$).

Twenty-Two Weeks Review of changes from baseline to 22 weeks showed a reduction in the number of symptoms on which the treatment groups differed. There was a worsening in distress over cough among enalapril patients as compared with those on atenolol or isradipine ($P < .001$). In addition, there was increased distress over dry mouth in atenolol patients as compared with those taking enalapril ($P < .014$).

Repeated measures analysis of the linear trend in symptoms distress item scores from baseline to weeks 6 and 22 was carried out (Table 5). Differences between drug groups appeared in cough ($P = .001$) and tiredness ($P = .048$) with distress increasing in the enalapril group for cough and atenolol for tiredness. Supplementary analysis of only the 240 patients in the "completer" population produced results that duplicated those in the intent-to-treat analysis in terms of absence of significant differences.

Age, Titration, Diuretics, and Change in Symptoms Distress In comparisons between drug treatment groups, when we considered age, drug titration level, and diuretic usage by means of analysis of covariance, we found no evidence that these three covariates accounted for differences in change in reported symptoms distress for any of the 33 items.

DISCUSSION

A primary finding in regard to the changes in scores of the quality of life measures was the lack of significant differences between drug treatment groups in measures of general well being, cognitive function, emotional status, and social role performance from baseline to week 6 and to week 22. This was seen

in the intent-to-treat analysis and in the analysis of completers.

The rate of withdrawal from a clinical trial because of adverse reactions to the medications is often a ready index of negative impact on quality of life, insofar as it suggests that the effects of the drugs were so negative they could not be tolerated. We found, however, no significant differences between drug groups in the percentage of withdrawals over the 22 weeks of treatment.

Considering the total patient group without drug classification, we found reduction in trait anxiety as well as improvement in cognitive test scores. Without a placebo control group we cannot attribute such improvement to antihypertensive drug treatment. Small decline in anxiety with repeated office visits and the positive effects of practice on cognitive test scores are well-known phenomena in psychological studies.

We did not find relationships between age or dosage level and change in quality of life scale measures. Previous research has shown that the addition of diuretics to monotherapy may reduce differences between the drug groups in changes in quality of life scale scores.³⁴ However, the number of patients taking hydrochlorothiazide in each treatment group was relatively small and we did not find such effects of diuretics in this study.

In terms of change in reported distress over symptoms, there were no significant differences between the drug groups in scores on the total Physical Symptoms Distress Index at weeks 6 or 22.

Among the 33 individual symptoms distress items examined, however, we identified a small subset in which (a) patients from the three treatment groups differed in response, and (b) the nature of response differed by the length of treatment. Some symptoms distress reported at 6 weeks with atenolol was improved at 22 weeks. This improvement cannot be ex-

plained by selective withdrawal because of the side effects. Notably, at 22 weeks the three groups differed in change on only two symptoms—worsening of cough among enalapril patients and dry mouth among atenolol patients. In the isradipine treatment group no worsening in distress over symptoms appeared from baseline to week 6 or week 22 on any of the physical symptoms distress items for which differences between drug groups were detected. The data on linear trends in distress over dry mouth in atenolol patients and cough in enalapril patients are consistent with known effects of these agents.

With negative findings there is the question of adequate statistical power to detect meaningful differences. The power analysis showed failure to detect a medium effect (95% power) to be highly unlikely. Further, as indicated in the footnote to Table 3, the standard errors of the mean changes are relatively small for each of the quality of life scales.

This clinical trial examined a group of elderly hypertensive women who fit a specified demographic and clinical profile, and the results do not necessarily generalize to other populations. Our findings regarding atenolol, enalapril, and isradipine are specific to those drugs and the assigned dosages.

The measures selected for this study and for earlier clinical trials in which the first author participated were chosen in line with a conceptualization of the dimensions of quality of life and of the construct.^{5,13,29} In this research several primary measures of areas of quality of life are the same as were employed in those previous clinical trials, having been selected on the basis of wide usage, reliability, validity, and relevance.³⁵⁻³⁸ For assessment of additional dimensions of cognitive functioning and of mood state, ie, anxiety and depression, we also added established instruments that are widely employed in aging studies and in studies of the effects of hypertension on behavior.³⁹⁻⁴² Additional measures for this study necessarily had to be either adapted from other instruments or developed to fit the special requirements of research on this elderly female population and this particular set of antihypertensive drugs.⁴³⁻⁴⁵

Considering recent large randomized clinical trials concerned with quality of life that have included female patients, and one or more of the antihypertensive medications examined here,^{11-15,17,20} it is notable that reported findings have been generally similar to ours concerning the relatively minimal impact of the medications on quality of life measures. Although caution must be exercised in drawing conclusions about comparisons between clinical trials, such findings appear to emerge despite diversity in methods, study populations, research design, quality of life measures, and assessment of perceived symptoms

and side effects. Given that in this study the three treatment drugs appear similar in their efficacy and in their effects on the series of quality of life measures, our findings may suggest that the clinician increasingly has a broader range of choices and can more closely tailor the treatment to specific characteristics of the elderly female patient and to the desired additional secondary effects of the medications.

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APPENDIX A: MEASURES USED TO ASSESS AREAS OF QUALITY OF LIFE

WELL-BEING

Sense of Well-Being³⁵⁻³⁷ The General Well-Being Adjustment Scale (Rand) consists of 22 questions on the following subscales: anxiety, depression, general health, positive well-being, self-control, and vitality. Patients rate each question on a 6-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. The internal consistency reliability (Cronbach's α) is 0.94 for the full scale.

EMOTIONAL STATUS

CESD-Depression Scale^{39,40} The CESD Scale (Center for Epidemiologic Studies-Depression) is designed to measure depressive symptomatology in the general population. The scale centers on 20 dysphoric and somatic complaints that often accompany depressive mood but which may not constitute criteria for the clinical syndrome of depression. Patients rate each symptom on a 4-point scale indicating the

number of days the symptom was experienced during the previous week. Responses range from "less than 1 day" to "5 to 7 days." Total scores for the scale range from 0 (low) to 60 (high).

State Anxiety Scale; Trait Anxiety Scale⁴¹ The STAI (Spielberger) consists of two sets of 20 questions to assess state anxiety and trait anxiety. In responding to the State Anxiety scale, the patient rates each self-descriptive item in regard to how she is feeling "right now." For the Trait Anxiety scale the patient rates a series of descriptors in regard to how she feels generally. Ratings are made on a 4-point scale, ranging from "Not at all" to "Very much so." Scores for each scale range from 20 (low) to 80 (high).

Level of Sexual Interest This is a single item scale to which all patients responded. It consists of the question: "During the past month, how would you rate your current level of sexual interest? Consider the frequency of your sexual urges, fantasies, and thoughts." The scale ranges from no interest (0) to very high interest (7).

COGNITIVE FUNCTION

Digit Span Test⁴² The Digit Span test is a subtest from the Wechsler Adult Intelligence Scale that measures memory retentiveness. It involves repetition of digits in the same order as they are spoken by the examiner and repetition of digits in the reverse order. Higher scores indicate higher retentiveness.

Digit Symbol⁴² The Digit Symbol test is a subtest of the Wechsler Adult Intelligence Scale and requires the subject to associate symbols with other symbols, testing speed and accuracy in the task. Higher score indicates higher performance.

Trail Making A; Trail Making B³⁸ The Reitan Trail Making Test is a two-part instrument for assessing visual-motor speed and integration. The Trail Making A test requires the patient to connect circles by consecutive number. The Trail Making B test requires that the subject connect circles by alternate consecutive numbers and alphabet letters. The score for each test is based on the total number of seconds required to accomplish the task of connecting images by drawing lines.

PHYSICAL STATUS

Physical Symptoms Distress Index—EW Patients rate each of 33 reported symptoms in regard to the degree of distress they experienced during the previous month because of the symptoms. The symptoms are based in part on items used in questionnaires in the National Heart, Lung, and Blood Institute Hypertension Detection Follow-up Program, in part on side effects reported in the literature on the three treatment drugs.⁴³ The items include: tiredness or fatigue, feeling weak, headaches, feeling nauseous, vomiting, diarrhea, constipation, feeling flushed, feeling dizzy or lightheaded when standing up quickly, fainting, skin rash, stuffy nose, feeling swelling in throat, tongue, or face, swelling of ankles, cough, trouble falling asleep, nightmares, feeling anxious, heart beating unusually slowly, heart beating unusually fast, feeling sensitive to cold in hands or feet, feeling depressed and blue, wheezing or difficulty breathing, blurry vision, pain in joints, upset stomach or heartburn, excessive dry mouth, frequent urination, heart pounding or fluttering, muscle cramps, shortness of breath, pains in heart or chest, loss of taste or

change in taste sensations. The ratings are on a 5-point scale, ranging from "Not at all" to "Extremely," with a range in scores from 33 (low) to 165 (high), $\alpha = 0.82$. The format is based on the Brief Symptom Inventory.⁴⁴ The Index is a modification of the Physical Symptoms Distress Index earlier employed elsewhere.⁵

Sleep Disturbance Index⁴⁵ The Sleep Disturbance scale, which was adapted from previous work, consists of four questions that measure number of days in which there were problems in falling asleep, staying asleep, early awakening, and awakening tired. Scores range from 4 (no sleep disturbance) to 20 (high sleep disturbance). Cronbach's $\alpha = 0.79$.

Vitality, General Health These measures are subscales of the General Well-Being Adjustment Scale cited above.³⁶

SOCIAL ROLES

Social Participation Activities Scale This is a 9-question scale which assesses frequency of participation during the past month in a series of common social and recreational activities, including such items as visiting with friends or relatives, community activities, hobbies, and telephone conversations with friends or relatives. Ratings on a 6-point scale range from "Not at all" (0) to "Daily" (4), and scores for the total scale range from 0 (low) to 45 (high). Cronbach's $\alpha = 0.66$.

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