

Managing Hypertension In Family Practice: A Nationwide Collaborative Study Of The Use Of Four Antihypertensives In The Treatment Of Mild-To-Moderate Hypertension

A Report From CEN

Abstract: The goals of this prospective, nonexperimental study were to examine the ways in which family physicians select from among four antihypertensive agents for their patients and to provide an overall perspective on how these agents perform in the management of hypertension in primary care. Three hundred seventy-eight family physicians treated 3608 mild and moderate hypertensives with one of the following medications: atenolol (n = 564 patients), enalapril maleate (n = 677), verapamil hydrochloride in sustained-release form (n = 1861), or a fixed combination, hydrochlorothiazide/triamterene (n = 506).

The resultant four groups of patients differed in several demographic and clinical measures: age, gender, race, concurrent disease, diastolic and systolic blood pressures, heart rate, and history of hypertension. The patient profiles for each group suggest appropriate matching of drugs to individual patient

needs: younger patients and those with higher heart rates more often received the beta-blocker; blacks were more frequently assigned to the diuretic and less often to the beta-blocker; patients with concurrent diseases and a longer history of hypertension were more often assigned to the angiotensin-converting-enzyme (ACE) inhibitor or the calcium channel blocker. Rates of success, defined by the percentages of patients staying on the selected drug and experiencing a reduction of at least 10 mmHg or achieving a diastolic pressure ≤ 90 mmHg, were in the same range for all four groups (55 to 62.5 percent). Patients evaluated their quality of life and gave enalapril and verapamil SR the highest ratings. The rapid completion of the study, the quality of the results, and the high rates of follow-up and compliance show that family practice is an excellent setting for conducting clinical research. (J Am Bd Fam Pract 1989; 2:172-90.)

Hypertension represents a major public health problem because nearly 1 of every 4 adults in the United States is affected by this often asymptomatic disease.^{1,2} The 1987 summary of the National Ambulatory Medical Care Survey ranked hypertension 11th and blood pressure testing 16th as principal reasons for office visits to all physicians. Moreover, hypertension was ranked 1st among the 20 most common principal diagnoses for office visits.³ The success of national programs

to promote patient awareness of hypertension and the dramatic advances in the management of it have contributed to a 45 percent decrease in deaths due to strokes since 1974, as well as a substantial reduction in the number of mildly hypertensive patients who progress to more severe forms of the disease.

The challenge to family physicians of treating hypertensive patients effectively has been expressed well by Kaplan: "The main burden of illness associated with hypertension arises not from the relatively few with severe disease, but from the masses of people with pressures that are only minimally elevated."⁴ Yet, many hypertensive adults in the United States are undiagnosed; even when they are diagnosed and treated, many are noncompliant because the prescribed medication impairs their quality of

From the Clinical Experience Network, a nationwide affiliation of family physicians. Address reprint requests to W. Jack Stelmach, M.D., Baptist Medical Center and the Goppert Family Care Center, 6601 Rockhill Road, Kansas City, MO 64131.

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life or because of economic and social factors.^{5,6} One group⁷ has reported that among 1817 asymptomatic hypertensives who were followed for 11 months, 20.4 percent did not return for follow-up care; 51.7 percent did not take the prescribed medication; and 78.9 percent did not follow medical advice to reduce risk factors, such as smoking. These findings were consistent with those reported in other studies.⁸⁻¹⁰

The changing strategies in antihypertensive therapy present new opportunities to the practicing physician. A wider choice of antihypertensive agents and fresh insights into the use of older agents have led to treatment strategies that can now control most cases of hypertension without significant side effects or negative impact on quality of life.

The 1988 report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure emphasized the need to consider a variety of factors when selecting therapy for the treatment of hypertension: "The hypertension control process must. . . take into consideration the life-styles and concomitant conditions of individual patients."¹¹ Data from tightly controlled premarketing clinical drug studies do not usually provide such practical information. While extensive clinical trials of antihypertensive agents have provided sufficient information for Food and Drug Administration marketing approval, most clinical trials are conducted under restrictive protocols designed to provide data from narrowly defined populations.¹² As a result, important questions are not asked and rare adverse effects may be missed. Family physicians often treat hypertensive patients who have varying lifestyles and may take multiple over-the-counter and prescription medications for other diseases.

Many authors have pointed out the need to conduct clinical trials of marketed drugs under conditions similar to those of actual clinical use.¹³⁻²⁰ With this in mind, the Clinical Experience Network (CEN), a nationwide affiliation of family physicians, was organized. Headed by 5 former presidents of the American Academy of Family Physicians or the American Board of Family Practice, CEN comprises more than 800 board-certified, family physicians. These physicians were selected because of their academic and professional achievements and their interest in clinical research. CEN provides qualified family physicians the opportunity to engage in comprehen-

sive, nationwide clinical investigations and to learn from their experiences in a systematic and scientific manner. The results of the clinical investigations conducted by CEN both enhance the practice of medicine and create educational opportunities.

Objectives

Because family physicians see a variety of hypertensive patients and manage various antihypertensive therapies, CEN proposed to study how antihypertensive agents are used in the family practice setting. To ensure that the study would be representative of family practice, an advisory board selected a cross section of practices with varying demographic, social, and economic characteristics. The 378 physicians who agreed to participate were practicing in medical schools, hospitals, neighborhood clinics, and private practices. Physicians from private practices made up 84 percent of our investigators. The most common sizes of private practice were 3 to 6 physicians (41 percent), solo (24 percent), and 2 physicians (16 percent). Each state was represented except New Mexico and Vermont. In our study, one of the largest clinical trials of antihypertensives, we had two objectives: (1) to learn how physicians match antihypertensives to specific types of patients, and (2) to learn what results are achieved in reducing diastolic blood pressure, reporting adverse events, compliance, and patients' estimates of their quality of life.

All investigators were apprised of the current concepts and controversies in hypertension management with a drug monograph entitled "Managing Hypertension in Modern Family Practice." In addition, an educational program for investigators was conducted in San Francisco before the trial began. This seminar stressed weight reduction, alcohol effects, sodium intake, exercise and nonpharmacologic therapy, as well as pharmacologic therapy.

To ensure the use of antihypertensives representative of each of the four classes, the guidelines from the 1988 Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure were followed. Antihypertensive therapy may be initiated with a drug from any of the four classes: diuretics, beta-adrenoceptor blocking agents (beta-blockers), angiotensin-converting-enzyme (ACE) inhibitors, and calcium channel antagonists (calcium channel blockers).¹¹ CEN is

the first group to report a large-scale trial of anti-hypertensives using drugs from each of the four classes.

Methods and Study Design

Patient Selection

Before entering this study, each patient signed an informed consent. Approvals were generated at the University of Missouri–Kansas City Adult Health Sciences Institutional Review Board and at Baptist Medical Center, Kansas City, MO (a community hospital). Selection criteria included patients aged 45 years and older having benign essential hypertension with a sitting diastolic blood pressure between 90 to 114 mmHg. Each patient qualified for initial pharmacologic therapy or a change from prior therapy. Patients were excluded who had anemia or recognized important hepatic, renal, or cardiovascular diseases other than hypertension; pregnant and nursing women; and patients whose treatment with a particular drug would be contraindicated as stated in the package insert.

Study Drugs

Drugs included in the study were: atenolol (Tenormin™), a beta-adrenoceptor blocking agent; enalapril maleate (Vasotec™), an angiotensin-converting-enzyme inhibitor; hydrochlorothiazide/triamterene (Dyazide™), a diuretic; and verapamil (Calan SR™), a calcium channel blocker in a sustained-release form. Recommended starting dosages were those in the manufacturers' package inserts: atenolol, 50 mg/d; enalapril maleate, 5 mg/d; hydrochlorothiazide/triamterene (titrated to patient need, usually 1 or 2 capsules/d); verapamil SR, 240 mg/d.

Study Design

This was a prospective, open-label, nonrandomized study with a target population of approximately 3500 patients. For each patient, the physicians recorded gender, race, age, medical history, including concurrent medications and current use of tobacco. Physicians also followed the standard Joint National Committee guidelines about weight reduction, restriction of alcohol and sodium, tobacco avoidance, and exercise. The patients, for whom pharmacologic

therapy was deemed necessary, were not pre-assigned randomly. Physicians could assign qualified patients to receive any one of the four study drugs as initial treatment, make dosage adjustments in accordance with their customary practices, and add other drugs if blood pressure was not controlled.

Enrolled patients were evaluated at 2, 6, and 12 weeks following the beginning of treatment. At each visit, the following data were recorded: sitting diastolic and systolic pressures, heart rate, weight, adverse clinical experiences, and patient-reported compliance. At week 12, self-reported quality-of-life assessments and physicians' overall evaluation of outcomes were recorded. Table 1 lists variables that were recorded and assessed by stratification (see Analytical Methods) as possible contributors to diastolic blood pressure outcomes.

Self-reported quality of life was assessed by six measures: energy/exercise tolerance, daily routine/lifestyle, mood/mental function, sexual function, appetite, and general well-being. Ratings were designated as "improved," "somewhat improved," "no change," "somewhat worse," or "worse."

Data Collection and Management

Standardized data collection forms were completed by participating physicians. Twenty-two of the participants functioned as regional coordina-

Table 1. Factors Assessed as Possible Contributors to Diastolic Blood Pressure Outcomes.

Factor
Age (years)
Gender
Race
Baseline diastolic blood pressure (mmHg)
Baseline systolic blood pressure (mmHg)
Concurrent cardiovascular disease
Concurrent diabetes
Other concurrent diseases
Concurrent medications
Previously diagnosed (yes, no)
Duration of hypertension (<1 year, ≥1 year)
Previously treated (with antihypertensive) (yes, no)
Heart rate (count/min)
Tobacco use (yes, no)

tors, ensuring that the data were collected properly. Authors of this report served as senior monitors, answering questions about the protocol and patient qualifications. The data were collected on a series of forms, and each was sent, as completed, to an independent clinical research firm, Health Learning Systems, Inc., Lyndhurst, NJ, for review, coding, data entry and analysis, and manuscript preparation. Incomplete and questionable data were verified by telephone, either by the coordinators or Health Learning Systems. Discrepancies were detected by personal observations and a computer program that edited entries.

Analytic Methods

For the purpose of analyzing blood pressure changes, patients were considered to be hypertensive if the entry diastolic blood pressure was ≥ 95 mmHg. Changes in diastolic blood pressures were assessed by two scales: (1) diastolic blood pressure reduced to ≤ 90 mmHg,¹¹ and (2) diastolic blood pressure decreased by at least 10 mmHg. The number and percent of patients in these categories were calculated for each treatment group and for the subgroups defined in Table 1.

All of the patients enrolled in the study were included in the safety analysis. Each adverse clinical event was recorded, but physicians did not attempt to correlate individual events with a specific study drug. Further, a baseline profile of adverse events was not established. During the study, adverse clinical events were tabulated for each treatment group. Because no previously unreported adverse events associated with these drugs were noted, we report here only the more frequently occurring adverse events (≥ 1.0 percent).

Statistical Analysis

This study was not designed as a controlled study for the purpose of comparing the absolute pharmacologic efficacies of the drugs. This study included the broad population of patients seen in family practice, and the exclusion criteria were not severely restrictive. Therefore, in line with the nonexperimental design of the study, the groups were not homogeneous for all variables, and numerous factors might have affected the treatment outcomes.

To assess the homogeneity of the four treatment groups at baseline, differences between pairs (e.g., enalapril group:atenolol group) were compared by the t-test for continuous variables and by the chi-square test for categorical variables.

Statistical analyses of diastolic blood pressure changes were pairwise comparisons; i.e., diastolic blood pressure results for patients receiving verapamil SR versus results for each of the three other treatment groups (atenolol, enalapril, and hydrochlorothiazide/triamterene). Probabilities of differences were assessed by chi-square analyses. To increase the power of these pairwise comparisons, the sample size of the verapamil SR group was approximately three times larger than any other group. The validity of this approach is given by Miller.²¹ The diastolic blood pressure results were compared after dichotomizing the results at 2, 6, and 12 weeks by two definitions of success: a decrease of ≥ 10 mmHg or a decrease to ≤ 90 mmHg. Statistical comparisons between groups were also analyzed by specific risk factors or strata (Table 1).

Quality-of-life responses were evaluated on a 5-point ordinal scale corresponding to the five possible responses, and an ordinal chi-square test, the Wilcoxon Rank-sum Test, was used to analyze the pairwise comparisons.²²

The majority of patients in this study met the entry guidelines. Because the groups were very large, the inclusion of the few patients who did not fit each guideline did not markedly affect the results or conclusions. Furthermore, in this nonexperimental study, the groups were subdivided by various criteria, and specific ranges of data were analyzed separately; e.g., age 56 to 71 years. For completeness, all patients' results were analyzed.

Results

Assignment of Patients

Three hundred seventy-eight family physicians enrolled 3608 patients in the study. Initial treatment groups consisted of atenolol, 564 patients; enalapril, 677 patients; hydrochlorothiazide/triamterene, 506 patients; verapamil SR 1861 patients; multiple antihypertensives, 189 patients (Figure 1). As the study progressed, some patients who had used a single antihypertensive required the addition of another drug for blood pressure control, and these patients were included in the group "multiple antihypertensives." Fourteen

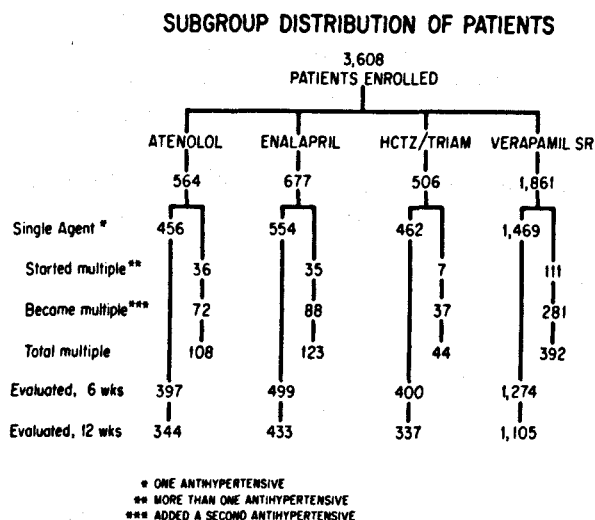


Figure 1. Subgroup Distribution of Patients.

percent of the patients had a second antihypertensive added to the regimen: 13.6 percent of those receiving atenolol, 13.7 percent receiving enalapril, 16.1 percent receiving verapamil, and 7.4 percent receiving hydrochlorothiazide/triamterene.

The reasons for patient dropout are listed in Tables 2 and 3. The reason reported most frequently was an adverse clinical event (285 [9.7 percent] patients receiving a single antihypertensive and

104 [15.6 percent] patients receiving multiple antihypertensives). Very few patients were lost to follow-up (6.2 percent of the single antihypertensive group and 1.9 percent of the multiple antihypertensive group). Discontinuation because of poor compliance was notably low (0.6 percent in the single antihypertensive group and 0.5 percent in the multiple antihypertensive group). Discontinuation because of inadequate blood pressure control was 1.6 percent in the single drug treatment group and 5.1 percent in the multiple antihypertensive group. There were few illnesses and few deaths to reduce the numbers of patients. Costs of drugs were the least reported cause of discontinuation. Patients treated with multiple antihypertensives were not analyzed except for safety.

Demographic Variables

There were marked variations in patient populations (Table 4). In each group at entry, there were more women than men; this ratio was 1.4:1. Notably, the group treated with hydrochlorothiazide/triamterene had twice as many women as men. The mean ages of patients in the enalapril, hydrochlorothiazide/triamterene, and verapamil SR groups were comparable (60 years). However, the mean age of patients assigned to atenolol was 3 years lower than that of the other patient groups. The majority of patients in the study

Table 2. Discontinuations from Study for Patients on Single Antihypertensive by Treatment Group.

	Treatment Group				
	Atenolol (n = 456)	Enalapril (n = 554)	Hydrochlorothiazide Triamterene (n = 462)	Verapamil SR (n = 1469)	Total (n = 2941)
	n (%)	n (%)	n (%)	n (%)	n (%)
Adverse events	41 (9.0)	38 (6.9)	50 (10.8)	156 (10.6)	285 (9.7)
Lost to follow-up	28 (6.1)	29 (5.2)	32 (6.9)	93 (6.3)	182 (6.2)
Inadequate blood pressure control	4 (0.9)	10 (1.8)	8 (1.7)	24 (1.6)	46 (1.6)
Other illness	3 (0.7)	4 (0.7)	5 (1.1)	9 (0.6)	21 (0.7)
Poor compliance	4 (0.9)	4 (0.7)	3 (0.7)	7 (0.5)	18 (0.6)
Other	4 (0.9)	3 (0.5)	2 (0.4)	2 (0.1)	11 (0.4)
Death*	1 (0.2)	2 (0.4)	1 (0.2)	4 (0.3)	83 (0.3)
Cost	0 (0)	1 (0.2)	0 (0)	2 (0.1)	3 (0.1)
Total	85 (18.6)	91 (16.4)	101 (21.9)	297 (20.2)	574 (19.5)

*No deaths were related to study drugs.

Table 3. Discontinuations from Study: Patients Receiving Multiple Antihypertensives ($n = 667$).

Reason for Discontinuation	n (%)
Adverse events	104 (15.6)
Inadequate blood pressure control	34 (5.1)
Lost to follow-up	13 (2.0)
Poor compliance	4 (0.6)
Other	3 (0.5)
Other illness	2 (0.3)
Death*	2 (0.3)
Cost	2 (0.3)
Total patients	164 (24.6)

*No deaths were related to study drugs.

groups was white (85 to 92 percent). The highest percentage of blacks was in the hydrochlorothiazide/triamterene group (12.9 percent); the lowest, in the atenolol group (5.3 percent). The proportion of smokers in the atenolol and the hydrochlorothiazide/triamterene groups (19 percent) was slightly higher than in the other two groups (17 percent).

Clinical Variables

The atenolol group had a smaller percentage of patients with concurrent disease (41.0 percent), and both the atenolol and hydrochlorothiazide/triamterene groups had smaller percentages of pa-

tients taking concurrent nonantihypertensive medications (43.0 percent and 42.3 percent, respectively) than did the other groups (Table 5). The verapamil SR group had the highest percentage of patients with cardiovascular disease (15.0 percent), and both the verapamil SR and enalapril groups had higher percentages of diabetic patients (10.2 percent and 9.3 percent, respectively) than did the other groups.

Hypertensive Profile

With respect to clinical variables and history related to hypertension, the patients in the enalapril and verapamil SR groups were similar (Table 6). However, patients in the verapamil SR group were more likely to have been diagnosed as hypertensive for more than a year. The other two groups were quite different from the enalapril and verapamil SR groups. Patients in the atenolol and hydrochlorothiazide/triamterene groups had, on average, lower systolic blood pressures and higher heart rates, and they were less likely to have been previously diagnosed or treated for hypertension. The highest mean diastolic pressure (99.0 mmHg) and the highest mean heart rate (81.1 counts/min) were in the atenolol group.

Dosages

Throughout the study, the majority of the patients in each group was taking the recommended start-

Table 4. Selected Demographic Variables at Entry by Treatment Group.

	Treatment Group			
	Atenolol (n = 564)	Enalapril (n = 677)	Hydrochlorothiazide/ Triamterene (n = 506)	Verapamil SR (n = 1861)
Gender				
Men (%)	47.1	45.3	32.6*	45.7
Women (%)	52.8	54.6	67.3*	54.3
Age (years)				
Range	28-87	24-94	36-95	34-92
Mean	56.8*	59.8	59.7	60.3
Race				
White (%)	92.4	90.8	85.2*	90.7
Black (%)	5.3	7.1	12.9*	7.5
Other (%)	2.3	2.1	2.0	1.8
Tobacco use				
Yes (%)	19.1	16.8	19.4	17.2

*Statistically significant difference from other groups. $P < 0.001$.

Table 5. Percentage of Patients with Selected Clinical Variables at Entry by Treatment Group.

	Treatment Group			
	Atenolol (n = 564)	Enalapril (n = 677)	Hydrochlorothiazide/ Triamterene (n = 506)	Verapamil SR (n = 1861)
	%	%	%	%
Concurrent diseases	41.0†	48.0	47.4	52.0
Concurrent medications	43.0*	51.0	42.3†	48.5
Cardiovascular disease	11.0*	11.7*	8.3†	15.0
Diabetes	3.9†	9.3	5.7†	10.2

*Statistically significant difference compared with verapamil SR, $P \leq 0.05$.

†Statistically significant difference compared with verapamil SR, $P \leq 0.005$.

ing dosage (Table 7). There were, however, marked differences between the groups. Very few patients in the hydrochlorothiazide/triamterene group used more than two capsules. In both the atenolol and verapamil SR groups, there was an increase in the percentage of patients using a higher dosage at week 6 and week 12. The largest percentage of patients taking greater than starting dosages was in the enalapril group (34.3 percent at week 12).

Blood Pressure Results

The percentages of patients who had an entry diastolic blood pressure of 95 mmHg or greater and who achieved defined reductions in diastolic pressure are given in Table 8. The increases in the

percentages of patients reaching the defined reductions at weeks 6 and 12 reflect primarily a decrease in the number of unsuccessfully treated patients; some left the study because of inadequate blood pressure control, or they received a second antihypertensive. At week 12, the proportion of remaining patients achieving a diastolic blood pressure of ≤ 90 mmHg or at least a 10 mmHg decrease was the same for the enalapril, hydrochlorothiazide/triamterene, and the verapamil SR groups. In contrast, the atenolol group had a higher percentage of patients who achieved defined reductions; however, these patients were distinctly different from those in the other groups. As shown in Table 9, when patients in each group were evaluated at 12 weeks and their variables were compared with variables at entry, the atenolol

Table 6. Hypertensive Profile of Patients at Entry by Treatment Group.

	Treatment Group			
	Atenolol (n = 564)	Enalapril (n = 677)	Hydrochlorothiazide/ Triamterene (n = 506)	Verapamil SR (n = 1861)
Mean diastolic blood pressure (mmHg)	99.0†	97.6	96.8	97.3
Mean systolic blood pressure (mmHg)	162.1*	163.5	160.4†	163.2
Heart rate (mean count/min)	81.1†	77.8	78.3*	77.6
Previously diagnosed (%)	52.4†	65.3*	41.3†	69.7
Duration ≥ 1 year‡ (%)	56.9†	65.4*	46.8†	71.4
Previously treated	46.6†	62.3	30.6†	64.9

*Statistically significant difference compared with verapamil SR, $P < 0.05$.

†Statistically significant difference compared with verapamil SR, $P < 0.005$.

‡Information was not reported for 11 patients: 5 atenolol, 1 enalapril, 2 hydrochlorothiazide/triamterene, and 3 verapamil SR.

Table 7. Dosage Ranges at Weeks 2, 6, 12 by Treatment Group.

Drug (Starting dose)	Week	Percentage of Patients on Starting Dose Recommended in Manufacturer's Package Insert			Percentage of Patients on Higher than Starting Dose Recommended in Manufacturer's Package Insert		
		0-2	2-6	6-12	0-2	2-6	6-12
Atenolol (50 mg)		81.93	76.35	74.19	8.59	13.02	14.66
Enalapril (5 mg)		66.02	56.79	53.41	24.33	30.93	34.28
Hydrochlorothiazide/triamterene (1, 2 capsules)		95.24	93.37	94.83	1.0	0.69	0.81
Verapamil SR (240 mg)		82.95	77.13	74.11	5.54	10.27	11.84

lol patients and the verapamil SR patients were not homogeneous populations. The atenolol patients were younger (55.8 versus 58.9 years) and had, on average, a higher initial heart rate (82.2 versus 78.4 counts/min, with 45 percent versus 35 percent in excess of 80). The verapamil SR group had a larger proportion of patients with previously diagnosed hypertension (58.8 percent versus 43.2 percent), a longer history of hypertension (62.1 percent versus 49.6 percent), and concurrent diseases (47.4 percent versus 40.1 percent).

Blood Pressure Results by Risk Factor

To determine whether any of the variables (Table 1) might have affected the blood pressure outcomes, each treatment group was stratified by each variable. This procedure created 128 subgroups (32 in each of four treatment groups). Each subgroup within a treatment group was

compared with the corresponding subgroup in the other treatment groups to determine differences in blood pressure reduction.

As shown in Table 10, for newly diagnosed patients, there were no differences between the atenolol and verapamil SR groups in respect to reduction in diastolic blood pressure. In all comparisons of the blood pressure outcomes of the verapamil SR subgroups with those of enalapril or hydrochlorothiazide/triamterene, the results were equal with one exception. For patients whose entry diastolic pressure was ≥ 105 mmHg, a higher percentage of the hydrochlorothiazide/triamterene patients achieved a 10 mmHg or greater reduction. However, analysis of the two groups shows that the verapamil SR patients had a higher mean heart rate (79.2 versus 76.0 counts/min, $P < 0.001$) and were more likely to have been previously diagnosed (56.0 percent versus 16.3 percent, $P < 0.001$) and to have had a longer his-

Table 8. Percentage of Patients with Defined Reductions in Diastolic Blood Pressure by Week and Treatment Group.*

Drug	2 Weeks		6 Weeks		12 Weeks	
	A %	B %	A %	B %	A %	B %
Atenolol	73.2	73.4	78.4	82.3	84.8†	85.1†
Enalapril	65.0	65.7	73.0	74.8	78.7	77.6
Hydrochlorothiazide/ Triamterene	63.0	68.6	70.6	79.5	82.1	80.7
Verapamil SR	66.6	63.7	72.3	73.6	78.7	77.2

A = Achieving a ≥ 10 mmHg decrease in diastolic pressure.

B = Achieving a diastolic pressure ≤ 90 mmHg.

*Patients evaluated had an entry diastolic pressure of at least 95 mmHg. The percentages refer to the percentage of patients still in the groups at a given time period and not the percentage of patients who had entered the study.

†Statistically significant difference compared with verapamil SR, $P < 0.05$.

Table 9. Selected Entry Characteristics of Patients with Initial Diastolic Blood Pressure ≥ 95 mmHg, Atenolol and Verapamil SR Treatment Groups (12-Week Evaluation).

	Treatment Group		P Value
	Atenolol (n = 257)	Verapamil SR (n = 743)	
Mean age (years)*	55.8	58.9	0.001
Heart rate >80/min (%)*	45.2	34.8	0.003
Previously diagnosed (%)*	43.2	58.8	0.001
Hypertension duration ≥ 1 year (%)*	49.6	62.1	0.001
Mean heart rate (count/min)	82.2	78.4	
Concurrent disease (%)*	40.1	47.4	0.043

*Statistically significant difference $P < 0.05$.

tory of hypertension (64.6 percent versus 38.0 percent, $P < 0.001$).

In comparing the blood pressure outcomes of subgroups using atenolol and verapamil SR, in many cases, the atenolol group had a higher percentage of patients reaching the defined levels. However, as already noted, the atenolol group evaluated at 12 weeks comprised a much different population of patients (Table 9).

Overall Success

Overall success was defined as the percentage of patients who stayed on the initially prescribed drug and who at 12 weeks had achieved a diastolic blood pressure ≤ 90 mmHg. The results by group were: atenolol, 64 percent; hydrochlorothiazide/triamterene, 63 percent; enalapril, 58 percent; and verapamil, 55 percent.

Adverse Events

An adverse event was any sign or symptom that the physician reported as an unintended or unexpected outcome of therapy.

Each reported adverse clinical event was recorded by treatment group, although causal relations between drugs and events were not established. The number of patients with reported adverse experiences (Table 11) ranged from 145

(26.2 percent, enalapril group) to 337 (50.5 percent, multiple antihypertensives group). Multiple adverse events were often reported for a single patient. The mean number of adverse events per patient ranged from 1.4 (enalapril and verapamil SR groups) to 1.7 (multiple antihypertensives group). The severity of the adverse events is indicated by the percentage of patients with such an event who discontinued the study (26.2 percent to 38.2 percent).

While more than 100 different kinds of adverse events were reported, not one was new or different from what had been reported previously. Twenty-two different adverse events that reached ≥ 1.0 percent are presented in Table 12.

Certain adverse events were reported at the ≥ 1 percent level for only one group: atenolol (cold extremities, irregular heart rate, depression, drowsiness, and dyspnea); enalapril (palpitations); hydrochlorothiazide/triamterene (musculoskeletal cramps and dry mouth); verapamil SR (tremor, nervousness). Each of these associations has been previously reported. At the 1 percent level, edema was reported by all drug groups except the diuretic, and nausea by all except the enalapril group. Men from three groups reported impotence at a 1 percent or higher rate: atenolol (4.5 percent), hydrochlorothiazide/triamterene (5.4 percent), and verapamil SR (1.5 percent). Dizziness, fatigue, and headache were reported frequently in each treatment group. Two adverse events were reported with notably high frequency: constipation in the verapamil group (17.3 percent) and fatigue in the atenolol group (12.5 percent).

Frequencies of adverse events ≥ 1 percent in the multiple antihypertensives group are given in

Table 10. Comparison of Blood Pressure Outcomes between Atenolol Group and Verapamil SR Group at 12 Weeks — Patients with Newly Diagnosed Hypertension (Entry Diastolic Blood Pressure ≥ 95 mmHg).

	A	B
	n (%)	n (%)
Atenolol	125 (85.62)	123 (84.83)
Verapamil SR	263 (85.95)	252 (82.35)
Chi-square probability	0.925	0.509

A = ≥ 10 mmHg reduction in diastolic blood pressure.
B = A diastolic blood pressure ≤ 90 mmHg.

Table 11. Adverse Clinical Events That Were Noted at Any Time in Course of Study by Treatment Group.

	Treatment Group				
	Atenolol n = 456	Enalapril n = 554	Hydrochlorothiazide/ Triamterene n = 462	Verapamil SR n = 1469	Multiple n = 667
Patients with AEs* (%)	144 (31.6)	145 (26.2)	131 (28.4)	563 (38.3)	337 (50.5)
Number of AEs	216	207	204	826	569
Number/patient	1.50	1.43	1.56	1.47	1.69
Patients with AEs who discontinued (%)	41 (28.5)	38 (26.2)	50 (38.2)	156 (27.7)	104 (30.9)

*AEs = Adverse events. (A clear association with the antihypertensive was not confirmed in all cases.)

Table 13. As anticipated, this group showed a higher percentage of adverse events, and certain events reached a level of 1.0 percent only in the

multiple antihypertensives group: abnormal feelings, flatulence, flushing, malaise, and sleep disorders.

Table 12. Percentages of Adverse Events (AEs) Occurring in 1.0 Percent or More of Patients Receiving Single Antihypertensive by Treatment Group.*

	Atenolol (n = 456) (%)	Enalapril (n = 554) (%)	Hydrochlorothiazide/ Triamterene (n = 462) (%)	Verapamil SR (n = 1469) (%)
I.†				
Cold extremities	1.1			
Irregular heart rate	1.1			
Depression	1.3			
Drowsiness	1.3			
Dry mouth			1.3	
Dyspnea	1.5			
Palpitations		1.1		
Cramps, musculoskeletal			2.4	
Tremor				1.0
Nervousness				1.0
II.†				
Constipation			1.1	17.3
Cough	1.1	1.4		
Diuresis (excessive)			3.3	1.1
Dyspepsia			1.7	
Weakness	1.1		2.0	
III.†				
Edema	1.5	2.4		2.2
Impotence‡	4.5		5.4	1.5
Nausea	1.5		3.7	1.4
IV.†				
Dizziness	5.5	5.2	5.2	5.5
Fatigue	12.5	4.2	6.1	4.1
Headache	2.4	3.6	2.0	4.4

*Percentage of AEs in patients receiving multiple antihypertensives are presented separately.

† I. AEs occurring in only one treatment group.

II. AEs occurring in two treatment groups.

III. AEs occurring in three treatment groups.

IV. AEs occurring in all treatment groups.

‡Impotence: atenolol, n = 224; hydrochlorothiazide/triamterene, n = 147; verapamil SR, n = 699.

Table 13. Percentages of Adverse Events (AEs) Occurring in 1.0 Percent or More of Patients Receiving Multiple Antihypertensive Agents (n = 667).

Adverse Events	Percentage
Constipation	11.4
Fatigue	8.4
Headache	7.0
Dizziness	6.8
Edema	6.8
Impotence (n = 253)	4.7
Abnormal feelings	2.7
Dyspnea	2.6
Nausea	2.4
Palpitations	2.3
Weakness	2.3
Depression	1.7
Nervousness	1.7
Flushing	1.4
Sleep disorders	1.4
Dry mouth	1.2
Dyspepsia	1.2
Flatulence	1.2
Tremor	1.2
Cough	1.1
Malaise	1.0
Cramps, musculoskeletal	1.0

Compliance

Based on physicians' assessments, patients complied well with the prescribed regimens. Only 18 patients were discontinued because of poor compliance (Table 2), and physicians reported overall compliance at 92.8 to 95.8 percent. There were no significant differences between groups or across time. The patients themselves reported compliance rates of 93.7 percent to 96.3 percent.

Quality of Life

Patients (93 percent) reported their own evaluation of quality of life. Representative responses about energy level/exercise tolerance are given in Table 14. The lowest percentage of patients reporting improvement was in the atenolol group (39.7 percent), and the highest was in the verapamil SR group (49.5 percent).

Results were tabulated for each of the six quality-of-life variables. Each of the treatment groups was then compared with the others for each of the six measures of quality of life (Table 15). There

were no statistically significant differences reported for quality of life between the verapamil SR and enalapril groups or between the atenolol and hydrochlorothiazide/triamterene groups. Patients in both the enalapril and verapamil SR groups reported a higher degree of satisfaction than those in the atenolol group. The verapamil SR group reported a higher positive response than the hydrochlorothiazide/triamterene group for energy/exercise tolerance and general well-being. The enalapril group reported a higher positive response than did the hydrochlorothiazide/triamterene group for sexual function.

Physicians' Overall Assessment

In assessing the usefulness of the four antihypertensives, the physicians' ratings showed no differences between the four groups. On the 5-point rating scale, the mean scores given to each drug were not statistically different.

Discussion

Demographics

While the patient population was similar to that seen in practice, the assignment of patients to specific antihypertensives created heterogeneous groups. The distribution of patients by gender and race in this study was generally consistent with statistics published recently by an agency of the United States government about characteristics of patients visiting family physicians.³ These data indicated that in 1985, more women than men (in a ratio of 1.56:1) consulted family physicians in the continental United States.³ In our study, each group had more women than men, and the average ratio of all groups was 1.4:1. However, the group treated with hydrochlorothiazide/triamterene had twice as many women as men. The data from the subgroup stratification did not indicate that the women were more likely to have a particular disease or condition that made them more likely to receive the diuretic. It is not apparent from our data why a high proportion of women was selected to receive the diuretic.

The published data on physician office visits by race were: white, 90.0 percent; black, 8.2 percent; other, 1.8 percent.³ Our population data were very similar: white, 90.2 percent; black, 7.9 percent; other, 1.9 percent. Black patients were more likely to receive hydrochlorothiazide/triamterene and least likely to receive the beta-blocker. This

Table 14. Self-Reported Quality of Life — "Energy/Exercise Tolerance."

Group	Rank				
	1	2	3	4	5
	Improved	Somewhat Improved	No Change	Somewhat Worse	Worse
	n (%)	n (%)	n (%)	n (%)	n (%)
Atenolol	71 (17.97)	86 (21.77)	197 (49.87)	34 (8.61)	7 (1.77)
Enalapril	109 (21.67)	123 (24.45)	246 (48.91)	18 (3.58)	7 (1.39)
Hydrochlorothiazide/ triamterene	66 (19.47)	84 (24.78)	165 (48.67)	22 (6.49)	2 (0.59)
Verapamil SR	316 (24.31)	328 (25.23)	585 (45.00)	58 (4.46)	13 (1.0)

reflects the generally accepted observation that blacks tend to respond well to diuretics and less well to beta-blockers.¹¹

While the mean age of the groups at entry was the same (60 years) for enalapril, hydrochlorothiazide/triamterene, and verapamil SR, the mean age in the atenolol group at entry was more than 3 years younger.

Clinical Characteristics of Patients

The treatment groups were also heterogeneous clinically. Physicians tended to assign the patients to treatment groups based on certain clinical characteristics. Patients in the enalapril and verapamil SR groups were similar in their proportions having concurrent diseases and taking medications other than antihypertensives; however, 3.3 percent fewer patients had cardiovascular disease in the enalapril group than the verapamil SR group.

In contrast, patients in the atenolol and hydrochlorothiazide/triamterene groups were much less likely to have other cardiovascular diseases or diabetes or to be taking other medications. Those in the atenolol group were less likely to have concurrent disease. This finding is not unexpected: beta-blockers are contraindicated in patients with sinus bradycardia, heart block, and overt cardiac failure, and there is a relative contraindication to hydrochlorothiazide/triamterene for diabetics. The general tendency was to assign patients with concurrent medications and those who had prior drug therapy for hypertension to the newer antihypertensives, enalapril and verapamil SR.

Hypertensive Profile of Patients

Differences in the populations of patients selected to each treatment group were most evident in the hypertension profiles. Patients selected to receive

Table 15. Comparisons of Patient Self-Evaluation of Quality of Life by Group.

Measure	Comparison by Pairs — Higher Rated Drug of Pair (P Value)					
	V-E	A-H	V-A	E-A	V-H	E-H
Energy/exercise tolerance	—	—	V† 0.000	E* 0.010	V* 0.037	—
Daily routine	—	—	V 0.058	E 0.085	—	—
Mood	—	—	V* 0.019	E* 0.019	—	—
Sexual function	—	—	V* 0.011	E† 0.001	—	E* 0.013
Appetite	—	—	—	—	—	—
General well-being	—	—	V* 0.029	—	V 0.092	—

*Statistically significant difference in pairwise comparison $P < 0.05$.

†Statistically significant difference in pairwise comparison $P < 0.005$.

A = atenolol; E = enalapril; H = hydrochlorothiazide/triamterene; V = verapamil.

verapamil SR were more often previously diagnosed as hypertensive, had a longer history of hypertension, and were more often previously treated with drugs than were those patients in the beta-blocker and diuretic groups.

This shifting of previously treated hypertensives from their earlier drug therapy to another agent indicates that the patients were either refractory or had experienced unacceptable side effects with the prior therapy. Such a shift toward the new drugs is not surprising. Verapamil SR and enalapril represent new classes of drugs for hypertension, and physicians now have the opportunity to try these drugs in patients for whom older agents had proved less satisfactory.

Another notable difference in the hypertension profiles was the mean heart rates. The higher mean heart rates in the diuretic group and especially in the beta-blocker treatment group suggest the possibility that a significant number of patients in these groups had an elevated cardiac output contributing to the elevated blood pressure. The selection of the beta-blocker is often the most appropriate therapy for such patients.

Patient Selection to Study Groups

A general pattern of drug selection emerges from these data. For newly diagnosed hypertensive patients whose only medical problem was hypertension, physicians tended more often to use the beta-blocker or the diuretic. Young patients and those with higher heart rates also were assigned more often to the beta-blocker. Physicians used the diuretic as a single agent most often for women. In contrast, the calcium channel blocker and the ACE inhibitor were more often prescribed for patients who had other diseases and medications and had been diagnosed and treated for hypertension previously; i.e., the more refractory patients.

Dosages

Consistent with the long-recognized use of the diuretic, dosage changes greater than the recommended starting doses were infrequent. In the other groups, higher doses were used in 12 percent to 34 percent of patients. The most frequently titrated drug was enalapril; only 53.4 percent were on the initial recommended dose at week 12, whereas 74 percent of the patients on atenolol or verapamil SR remained on the starting dose

through week 12. The more frequent change of dosage for patients on enalapril did not result in poor compliance in this 12-week study. However, with the increased dosages, the higher price of this drug might become a factor in poor compliance.

Diastolic Blood Pressure Results

Because the design of the study created heterogeneous treatment groups, statistically significant differences in changes of diastolic blood pressure reflected primarily differences in the patient populations, not necessarily differences in drug efficacy.

As shown in Table 8, the majority of patients who were evaluated at 2, 6, and 12 weeks experienced ≥ 10 -mmHg reductions in diastolic blood pressure or reached a diastolic pressure of ≤ 90 mmHg. While the proportion of the atenolol patients reaching the defined reductions was somewhat higher, it should be recalled that it was not the intent of this study to compare the absolute efficacies of the drugs employed but, rather, to gain a better understanding of the way in which the drugs were prescribed in family practice.

The effect of the unequal selection of patients to the drug groups is reflected in differences in blood pressure reduction. The higher percentage of atenolol patients achieving defined levels of blood pressure reduction is not surprising. On average, this group was comprised of a higher percentage of younger patients and patients with elevated heart rates. Younger patients tend to be more responsive to beta-blocker therapy. Similarly, in the subgroup analyses,* among patients with an entry diastolic blood pressure ≥ 105 mmHg, the hydrochlorothiazide/triamterene group had the highest percentage of patients achieving ≤ 90 mmHg diastolic pressure, indicating a difference in the selection of patients for this treatment. Indeed, the comparison group, verapamil SR, had significantly more patients who had been previously diagnosed and treated, suggesting that refractory patients were more likely to have been assigned to receive verapamil SR than the diuretic. Despite being the group with the greatest proportion of concurrent diseases and the highest proportion with previously diagnosed and treated hypertension, the percentage of verapamil SR patients who achieved a reduction ≥ 10 mmHg or a diastolic blood pressure

*Data not presented.

≤ 90 mmHg was the same as in the other groups at weeks 2 and 6 and equal to all but atenolol at week 12 (Table 8).

Matched to individual patients, each of the drugs studied reduced diastolic blood pressure to ≤ 90 mmHg in the majority of patients who remained on single antihypertensives. Large differences in the effectiveness would not be expected in this practice setting. Each drug has been previously reported to reduce pressures, and the treatment groups were highly heterogeneous.

Adverse Events

The overall numbers of adverse events reported by treatment group were rather high, ranging from 26.2 to 50.5 percent. For comparison, the discontinuation rate from antihypertensives reported for the Hypertension Detection and Follow-up Program (HDFP) trial was 32.7 percent.²³ The higher percentage reported by patients taking multiple antihypertensives is expected, not only because of the number of drugs taken, but because these patients had not been successfully treated for their hypertension. The 38.3 percent rate for verapamil SR was heavily influenced by the 17.3 percent rate of constipation. This figure was higher than reported in the manufacturer's package insert; however, we made no correction for the number of patients who entered the study with a problem of constipation, and Bulpitt and Fletcher have reported a high rate of constipation in the general population.²⁴ The frequency of fatigue in patients who received atenolol (12.5 percent) is notable. While fatigue is a common problem associated with all four treatment groups, the rate with the beta-blocker was twice as high as in any other group. This might be related to the greater number of younger patients who are assumedly more active.

These adverse events have been reported in other studies of antihypertensives. Many of the associations are expected from the action of the drug: diuresis, fatigue, weakness, etc. The only experiences reported by 1 percent or more of patients that were not in the manufacturers' package inserts were impotence and edema with atenolol and impotence with verapamil SR. Each one had been reported previously, but not at these levels. Because a baseline profile was not established, some patients may have entered the study with these complaints.

Compliance

The compliance rates reported here indicate that, at least for the first 3 months of antihypertensive treatment, compliance was less a problem than has been reported elsewhere.⁴⁻⁷ Some studies have shown that physicians tend to overestimate the compliance rates of their patients,^{25,26} which were reported without an objective criteria, such as pill counts. In other studies, patient-reported compliance rates were consistent with changes in blood pressure.²⁷⁻³⁰ The high compliance rate reported here (> 92 percent) suggests that the family practice setting is well suited for clinical studies. Ongoing physician-patient relationships appear to enhance follow-up and compliance.

Quality of Life

In their assessments, the physicians did not note any differences in the overall clinical success of patients in any group. However, the patients reported differences in their self-evaluation of quality of life. Most changes reported were neutral or positive; i.e., patients tended to report "no change" (sexual function and appetite) or "improvement" (energy, routine, mood, and general well-being). By each of the six measurements, enalapril and verapamil SR were indistinguishable; there were no significant differences. Similarly, atenolol and hydrochlorothiazide/triamterene were given the same ratings by the patients. However, when the two newer drugs, enalapril and verapamil SR were compared with the older drugs, clear differences were seen, which favored the newer drugs.

It could be argued that patients receiving enalapril and verapamil SR were more likely to be suffering from long-standing hypertension and concurrent diseases; therefore, any changes for the better would result in positive responses. It also could be likely that the newer agents were better tolerated than the older drugs. With a variety of agents available to reduce blood pressure, patient satisfaction with the prescribed drug often becomes a determining factor in the selection process.

Overall Assessment

The results of this study show that in treating hypertension, family physicians selected antihypertensives in a manner congruent with current recommendations, which were based on the individual needs of patients. In the treatment of a heterogeneous population of hypertensives, each of

the drugs studied was effective in reducing diastolic blood pressures without significant adverse events in 55 to 64 percent of all patients and in 79 to 85 percent of those who stayed on therapy for 12 weeks. Enalapril and verapamil SR were judged to be better than atenolol and hydrochlorothiazide/triamterene for quality-of-life measures.

The success of the Clinical Experience Network is noteworthy. The physicians enrolled the patients, accurately completed the reports, and compiled the data within 9 months. The excellent follow-up-rates and level of compliance reflect the rapport that exists between family physicians and their patients and suggest that family practices are an excellent resource for clinical studies.

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Managing Hypertension Study Authors
 W. Jack Stelmach, M.D., Kansas City, MO;
 David R. Rush, Pharm.D., Kansas City, MO;
 Paul C. Brucker, M.D., Philadelphia, PA;
 Harmon Holverson, M.D., Emmett, ID;
 B. Leslie Huffman, Jr., M.D., Toledo OH;
 William J. Kane, M.D., Potomac, MD;
 and Michael F. Ryan, Ph.D., Lyndhurst, NJ.

Panel Physician Investigators

Abraham, George E. II, Vicksburg, MS
 Adams, Robert C., Van Wert, OH
 Alexander, Bruce D., Presque Isle, ME
 Allen, James Y., Jr., Fort Worth, TX
 Amundson, Loren H., Sioux Falls, SD
 Anderson, Larry R., Wellington, KS
 Atkinson, John W., Tacoma, WA
 Ausmus, Michael S., Kansas City, MO
 Avant, Robert F., Rochester, MN
 Bagley, Bruce A., Latham, NY
 Baker, Charles E., Jr., Crossnore, NC
 Baker, Stephen D., Pittsburgh, PA
 Ballard, Evan A., Jonesville, NC
 Balzer, Larry D., Hooker, OK
 Barber, Frederick A., Elmwood Park, IL
 Barco, Daniel H., Durham, NC
 Beasley, John W., Madison, WI
 Beaver, Walter P., Noblesville, IN
 Becker, Donald L., Lodi, CA
 Beever, Steven C., Dillon, MT
 Benski, Raymond, Nederland, TX
 Benton, David E. II, Mesa, AZ
 Bergan, James R., Minneapolis, MN
 Berglund, Thomas R., Portage, MI
 Bloomfield, Richard A., Newport, NC
 Blue, Brent A., Jackson, WY
 Bodenhausen, Gary E., Blue Springs, MO
 Booth, John P., Florence, SC
 Bope, Edward T., Columbus, OH
 Bostick, Robert M., Golden Valley, MN
 Bounds, Charles W., Moncks Corner, SC
 Boyd, John A., Durango, CO
 Boyken, Mark E., St. Croix Falls, WI
 Bradley, J. Douglas, St. Joseph, MO
 Brady, Forrest S., Spearfish, SD
 Brewer, Stephen C., Madeira, OH
 Brignac, Raymond N., Selma, AL
 Brodie, Gordon L., Manchester, CT
 Brody, Arnold G., St. Louis, MO
 Brown, David M., Tacoma, WA
 Brown, Lauren M., Barberton, OH
 Brownstein, Bernard A., Philadelphia, PA
 Brubeck, Ellen T., Mt. Olive, NC
 Buhr, James B., Valley City, ND
 Buie, Steven E., Lees Summit, MO
 Buser, Donald H., Belleville, IL
 Buxman, James H., Portland, OR
 Byler, Philip R., Williamsport, PA

Byrne, Stephen, Moorestown, NJ
 Cairns, Craig B., Newark, OH
 Campbell, Wayne L., Novato, CA
 Carrazzone, Peter L., Wayne, NJ
 Carrico, Virgil N., Bryan, OH
 Carter, Darrell L., Granite Falls, MN
 Carter, John Z., Tucson, AZ
 Casey, Michael R., Laurel, MS
 Castro, Miguel A., Jr., Baltimore, MD
 Chappell, Robert W., Jr., Huntsville, AL
 Chatterton, Howard T., Ladysmith, WI
 Christensen, Jan F., Gunnison, UT
 Cline, Robert S., Sanford, NC
 Clouse, Robert C., Fremont, MI
 Condie, Scott D., Shelby, NC
 Cook, James A., Wheaton, IL
 Cooper Herbert P., Jr., Clemson, SC
 Copeland, Donald L., Davidson, NC
 Coronado, Raul, Summit, NJ
 Coughlin, Timothy D., Reno, NV
 Cozine, Robert L., Emmetsburg, IA
 Craemer, Chris W., Lees Summit, MO
 Cronan, Thomas L., Trumbull, CT
 Crotwell, Henry F., York, SC
 Crowley, Michael D., Easton, MD
 Crump, William J., Jr., Huntsville, AL
 Cullison, Samuel W., Monroe, WA
 Cummings, Cynthia L., Los Gatos, CA
 D'Agostino, Robert L., Canton, MA
 Dailey, Loraine M., Pasadena, MD
 Daniels, Timothy K., Storm Lake, IA
 Dascoli, Thomas C., Indianapolis, IN
 David, Alan K., Lexington, KY
 Davis, Carl S., Lees Summit, MO
 Davis, Harry N., Canton, GA
 Davis, Larry E., Knoxville, TN
 Davis, Robert W., Raceland, LA
 De Jesus, Marian, Isla Verde, PR
 Dennis, Daniel P., Blue Springs, MO
 Derryberry, John S., Shelbyville, TN
 Dibala, Richard P., Storrs, CT
 Dieterich, Steven R., East Granby, CT
 Dodge, Frederick A., Waianae, HI
 Donnell, William S., Jr., Bolivar, MO
 Douglas, Kaaren C., Kansas City, MO
 Duckett, Charles H., Greenville, NC
 Dudley, James R., Steamboat Springs, CO
 Eikenberry, Joel L., N. Manchester, IN
 Erbstoesser, John W., Mount Vernon, WA
 Fahrenholtz, Herbert D., Kingman, KS
 Falencki, John J., New York, NY
 Fall, Gordon F., Seattle WA
 Ferrante, James A., Pittsburgh, PA
 Ferrera, Robert D., Sacramento, CA
 Fields, Larry S., Ashland, KY
 Filipi, David H., Omaha, NE
 Fish, William W., Liberty, MO
 Flanner, Frank R., Hoisington, KS

Ford, Brian R., Spirit Lake, IA
 Frantz, Kurt S., Enid, OK
 Franz, Robert, Oklahoma City, OK
 Frazzano, Arthur A., Portsmouth, RI
 Frederick, Kenneth A., Cincinnati, OH
 Freeland, Arthur G., Klamath Falls, OR
 Friedmann, Karl R., Old Lyme, CT
 Fuller, Woodson C., Rockford, IL
 Garb, Leslie J., Houston, TX
 Gardner, Henry J., Ogden, UT
 Garver, Paddy R., Show Low, AZ
 Gay, George L., Cambridge, WI
 Gettinger, Joshua S., Madisonville, TN
 Gilmore, Stephen R., Hixson, TN
 Glover, David W., Warrensburg, MO
 Goldberg, Alan H., Pottstown, PA
 Goldberg, Richard S., New York, NY
 Gordon, Harry W., Scottsdale, AZ
 Govi, Joseph R., Latrobe, PA
 Grace, Nicholas T., Healdsburg, CA
 Grant, Phyllis F., New Castle, IN
 Greenstein, Seymour, Houston, TX
 Griffin, Eugene W. III, Jonesville, NC
 Gross, Thomas E., Presque Isle, ME
 Grossman, Ronald D., Hopewell, NJ
 Gruca, Paul G., Alma, MI
 Hackney, Terry L., Louisville, CO
 Haddock, Douglass A., Kalamazoo, MI
 Hadley, David M., Plainfield, IN
 Hahn, Jan T., Lenoir City, TN
 Hammond, Betty L., East Brunswick, NJ
 Handley, Dennis M., Boonville, MO
 Handshy, Stanley E., Erie, KS
 Hansen, Peter O., Kenai, AK
 Harmon, Gerald E., Georgetown, SC
 Harrell, Frank W., Louisville, KY
 Hartlage, Randell J., Tallahassee, FL
 Harvey, William G., Jr., Beaver, OK
 Hay, Robert F., Lawton, OK
 Haynes, William W., Jr., Walterboro, SC
 Hehn, Rudolph J., Thomasville, GA
 Henley, Douglas E., Hope Mills, NC
 Hickman, Gerald, Boulder, CO
 Hitz, David L., Newtown Square, PA
 Hixson, Constance T., Lexington, KY
 Hoch, John R., Westchester, IL
 Hocutt, John E., Jr., Wilmington, DE
 Holden, David C., Peoria, IL
 Holder, Robert E., Bentonville, AR
 Holstein, Lana L., Flagstaff, AZ
 Hooper, Allen S., Oberlin, KS
 Hotz, Roy J., Jr., Kingsville, TX
 Howard, Jerome, Charlotte, NC
 Howard, Paul O., Sanford, NC
 Hubbell, Patricia A., Delaware, OH
 Hubbell, Thomas P., Delaware, OH
 Hudson, Charles P., San Antonio, TX
 Hurst, Charles R., Tyler, TX

Ingram, James R., Sumter, SC
 Irvine, Willis J., Portland, OR
 Jalowsky, Herbert R., Tucson, AZ
 James, Gary V., Marion, KY
 James, Trenton L. II, Baton Rouge, LA
 Janney, James G. III, White Salmon, WA
 Jayakody, Frank L., Shelbyville, TN
 Jebaily, Gerard C., Florence, SC
 Jones, Champ M., Jr., Winston-Salem, NC
 Jones, David D., Presque Isle, ME
 Jones, Graham P., Medford, NJ
 Jones, Howard D., Milford, NJ
 Jones, Michael A., Carson City, NV
 Joy, Dennis M., Charlevoix, MI
 Kahler, Mark R., Overland Park, KS
 Kane, Frank L., Wayne, NJ
 Kasten, Mark C., Cape Girardeau, MO
 Kaufman, Harvey L., Voorhees, NJ
 Keane, James W., Minneapolis, MN
 Keene, Robert J., Trenton, PA
 Kelly, Carmel M., North Pembroke, MA
 Kendall, Thomas W., Greenville, SC
 Kennally, Kevin P., Sabetha, KS
 Kenny, John J., Manahawkin, NJ
 Kipfer, Roger K., Louisville, CO
 Kiteck, Stephen S., Somerset, KY
 Klamm, Richard D., Menasha, WI
 Koida, Robert K., Sonoma, CA
 Kolesk, Stephen J., Mt. Laurel, NJ
 Konzen, Dennis W., Mattawan, MI
 Koontz, Peter S., Minneapolis, MN
 Kramer, Michael S., Dallas, TX
 Krienke, Russell B., Auston, TX
 Krier, David B., Carlton, OR
 Kuter, David P., Baraboo, WI
 Lackey, Charles W., Frisco, CO
 Laker, Richard J., Fort Wayne, IN
 Lammers, Keith A., Amherst, NH
 Langston, Edward L., Indianapolis, IN
 Larimore, Walter L., Kissimmee, FL
 Lean, Edward W., Paw Paw, MI
 Leeds, Gary E., New York, NY
 Levalley, Gary L., Fort Dodge, IA
 Leventhal, Walter D., Summerville, SC
 Levites, Kenneth B., West Sayville, NY
 Levy, Albert, New York, NY
 Little, Clarence J., Anchorage, AK
 Little, Robert G., Harrisburg, PA
 Loomis, Norman R., Ontario, NY
 Loschen, Darroll J., York, NE
 Lucas, John F., Jr., Fort Worth, TX
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 Lushbough, Bruce C., Brookings, SC
 Lyons, Daniel C., Hamburg, PA
 McCallum, Oscar M., Henderson, TN
 McGahee, Ollie O., Jr., Jesup, GA
 McMahon, William E., Springville, NY
 McMinn, Charles E., Omaha, NE

Mallozzi, Angelo, Stamford, CT
 Marieneau, Fred E., Sandpoint, ID
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 Martin, Mark W., Lees Summit, MO
 Mathews, Michael W., Olathe, KS
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 Mead, William F., Port Angeles, WA
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 Meisner, Carl R., Stafford, TX
 Messner, Stan A., Wichita, KS
 Mestan, Robert E., Princeton, IL
 Meyer, Albert A., Durham, NC
 Micek-Galinat, Laura A., Rahway, NJ
 Miller, Ronald A., Whitefish, MT
 Miller, William D., St. Joseph, MO
 Milligan, William L., Cherry Hill, NJ
 Millman, Robert, Rockville, MD
 Mohr, John J., Boise, ID
 Mold, James W., Oklahoma City, OK
 Moquist, Dale C., Grand Forks, ND
 Morris, Glenn F., Jackson, MS
 Morrow, Robert, Yonkers, NY
 Moss, Richard N., Augusta, GA
 Munger, Michael L., Kansas City, MO
 Munger, Robert S., Jr., Exeter, NH
 Murphy, John E., Lees Summit, MO
 Myers, Carl M., Platt City, MO
 Myers, Douglas A., Zanesville, OH
 Nash, Bruce D., Bennington, VT
 Nicholson, Benjamin E., Edgefield, SC
 Nordstrom, Carl R., Boone, NC
 Noren, Thomas F., Escanaba, MI
 Novak, Dennis E., Forked River, NJ
 Novak, Larry I., Syracuse, NY
 Ogonek, Joseph A., Barberton, OH
 Okosky, Paul J., Saratoga Springs, NY
 Ortiz, Richard, Savannah, MO
 Orzano, A. John, Flemington, NJ
 O'Shea, John M., Clinton, IA
 Papadopoulos, Demetrios A., Mt. Pleasant, SC
 Parker, Mark T., Enfield, NH
 Parker, Robert W., Overland Park, KS
 Paulding, Stephen B., Cumberland Center, ME
 Pickering, William J., Unionville, CT
 Pilchman, Martha D., Bay Shore, NY
 Pittard, Marion D., Toccoa, GA
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 Plessman, Paul E., Seward, NE
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 Rainsford, George L., Edgefield, SC
 Rattenne, Mitzi E., Wellington, KS
 Ratts, Larry D., Bloomington, IN
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 Rhodes, Charles E., Goose Creek, SC
 Richardson, Bruce W., Havre, MT

Roberts, Daniel D., Central Point, OR
 Roberts, John H., Sioux City, IA
 Robinson, Sloan A., Cherry Hill, NJ
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 Rooney, William R., Monett, MO
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 Rude, Gilbert A., Kearney, NE
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 Ruoff, Gary E., Kalamazoo, MI
 Rutledge, Rion M., Rock Hill, SC
 Sachere, Andrew B., East Brunswick, NJ
 Sacks, Lee B., Glenview, IL
 Salanski, Stephen C., Lees Summit, MO
 Salyards, Phyllis S., Hastings, NE
 Sample, Jerry J., Rock Hill, SC
 Sandberg, Chris B., St. Joseph, MO
 Sarlin, Milton D., Spartanburg, SC
 Saylor, Stephen, Topeka, KS
 Scherger, Joseph E., Dixon, CA
 Scherger, William E., Lima, OH
 Schlabach, Jay L., Goshen, IN
 Schleinkofer, Robert M., Fort Wayne, IN
 Schrader, Jane, West Des Moines, IA
 Schubert, Stephen E., Mendota, IL
 Schuchardt, Robert L., St. Louis, MO
 Schwarz, Robert L., Menomonee Falls, WI
 Shackelford, Robert H., Mt. Olive, NC
 Sherrill, Leroy, Chattanooga, TN
 Shropshire, Richard W., Monona, WI
 Silko, Gary J., Washington, PA
 Simpson, Kirk W., Minneapolis, MN
 Smith, Charles W., Jr., Huntsville, AL
 Smith, Johnny Y., Jr., Columbia, SC
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 Snipes, Garrett E., Winter Haven, FL
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 Sobelson, Gary A., Concord, NH
 Spence, William D., Bethany, OK
 Stallings, Joe H., Jr., Jonesboro, AR
 Stangland, David G., Tonasket, WA
 Stanley, Richard E., Greeneville, TN
 Stirman, Edward M., Kingsport, TN
 Stolee, Curtis N., St. Peter, MN
 Stringer, Kenton L., Aurora, MO
 Suenram, Mark R., Lees Summit, MO
 Sullivan, James S., Dothan, AL
 Swee, David E., New Brunswick, NJ
 Sweiger, David W., Maple Valley, WA
 Talley, Ernest A., Gresham, OR
 Tamarin, Steven B., New York, NY
 Tarr, Jack H., Knoxville, TN
 Tavani, Nicholas J., Jr., Laurel, MD
 Thanel, Fredric H., Buffalo, WY
 Thomas, Jo E., Exeter, NH
 Thompson, John E., Nekoosa, WI
 Tobin, Marla J., Higginsville, MO
 Tobin, Richard S., Ithaca, NY
 Tocks, Jonathan B., Enola, PA

Vander Woude, Larry B., Sioux Falls, SD
 Van Es, Gerald L., Sioux Center, IA
 Vedder, Arthur K., Santa Cruz, CA
 Vickery, Linda C., Sussex, NJ
 Villavicencio, Olmedo E., Annandale, VA
 Vinton, Thomas J., Liberty, MO
 Waldrige, Ronald E., Shelbyville, KY
 Wall, Kevin K., Manhattan, KS
 Waltz, Miles E., North Conway, NH
 Ware, James E., Victoria, TX
 Warnick, Craig A., Brockton, MA
 Watson, David H., Yoakum, TX
 Watson, James R., Lafayette, IN
 Weber, James R., Jacksonville, AZ
 Weible, Nancy E., Bonne Terre, MO
 Welch, Anna L., Lafayette, IN
 West, David M., Grand Junction, CO
 White, George H., Rock Hill, SC
 Whiting, Robert R., Jr., Hardin, MT
 Wilhoit, Gordon B., Moncks Corner, SC
 Wilker, John F., St. Cloud, FL
 Wilkerson, Leonard A., Kissimmee, FL
 Winslow, James W., Tarboro, NC
 Withrow, Susan J., Rockville, MD
 Witters, Gregory D., Sedro Wooley, TN
 Wittig, Geoffrey G., Dansville, NY
 Woeste, David M., River Falls, WI
 Wolf, Howard C., Lafayette, CO
 Wolff, L. Thomas, Syracuse, NY
 Wood, Eugene G., Jackson, MS
 Woodring, Mary A., Middlesboro, KY
 Woods, Norman P., San Jose, CA
 Wopat, Richard C., Lebanon, OR
 Wright, Keith A., Bolivar, MO
 Wunder, William E., Jr., Noblesville, IN
 Yaeger, Thomas A., Cloverdale, CA
 Yaussy, Kenneth A., Newton, NC
 Yoder, Steven M., Goshen, IN
 Young, Kevin I., Plymouth, NH
 Zagory, Conrad, San Francisco, CA

Editorial Comment

There would appear to be specific advantages in the use of collaborative networks to study certain questions relevant to family practice. In the study reported above, the Clinical Experience Network (CEN) demonstrates some of these advantages. The large number of patients drawn from realistic

clinical settings over a broad geographic area and from multiple practice types could be expected to minimize some of the inherent problems that often exist in studies of smaller populations in more highly selected practices. In addition, the data are derived in the crucible of realistic practice settings rather than from the more artificial circumstances of the academic environment. The heterogeneity of the investigators, as well as the population studied, could reasonably be expected to simulate the environment in which most primary care by family physicians is delivered.

In this study, a relatively unselected population (as we commonly see in family practice) is divided into four cohorts based on the physicians' selection of drug therapy for hypertension. Several variables are then examined for similarities and differences among those cohort groups. Although the study is subject to certain biases, these biases are those that are likely to exist in actual practice.

The reader is cautioned to avoid inferring conclusions that are not warranted. This is a descriptive study and should be regarded as such. In my opinion, it does, however, represent a meritorious achievement that holds great promise for practice-based research. It describes in some detail how interested family physicians use basic drug therapy with reasonable success in the treatment of a common disorder. There appears to be a dominance of appropriate prescribing behaviors in these settings.

I am aware that there are several networks of practicing physicians in the country devoted to the study of important health problems. I hope that the publication of this study will encourage sponsors to support well-designed studies by these networks. I also implore readers to be prudently critical as they interpret the results of these kinds of studies. It is reasonable to expect that there will appear an increasing number of studies of this genre in the literature. Accurate interpretation can sometimes be as challenging as the experiment itself.

Paul R. Young, M.D.
 Lexington, KY