

SINGLE-DRUG THERAPY FOR HYPERTENSION IN MEN

A Comparison of Six Antihypertensive Agents with Placebo

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Abstract Background. Characteristics such as age and race are often cited as determinants of the response of blood pressure to specific antihypertensive agents, but this clinically important issue has not been examined in sufficiently large trials, involving all standard treatments, to determine the effect of such factors.

Methods. In a randomized, double-blind study at 15 clinics, we assigned 1292 men with diastolic blood pressures of 95 to 109 mm Hg, after a placebo washout period, to receive placebo or one of six drugs: hydrochlorothiazide (12.5 to 50 mg per day), atenolol (25 to 100 mg per day), captopril (25 to 100 mg per day), clonidine (0.2 to 0.6 mg per day), a sustained-release preparation of diltiazem (120 to 360 mg per day), or prazosin (4 to 20 mg per day). The drug doses were titrated to a goal of less than 90 mm Hg for maximal diastolic pressure, and the patients continued to receive therapy for at least one year.

Results. The mean (\pm SD) age of the randomized patients was 59 ± 10 years, and 48 percent were black. The average blood pressure at base line was $152 \pm 14/99 \pm 3$

mm Hg. Diltiazem therapy had the highest rate of success: 59 percent of the treated patients had reached the blood-pressure goal at the end of the titration phase and had a diastolic blood pressure of less than 95 mm Hg at one year. Atenolol was successful by this definition in 51 percent of the patients, clonidine in 50 percent, hydrochlorothiazide in 46 percent, captopril in 42 percent, and prazosin in 42 percent; all these agents were superior to placebo (success rate, 25 percent). Diltiazem ranked first for younger blacks (<60 years) and older blacks (≥ 60 years), among whom the success rate was 64 percent, captopril for younger whites (success rate, 55 percent), and atenolol for older whites (68 percent). Drug intolerance was more frequent with clonidine (14 percent) and prazosin (12 percent) than with the other drugs.

Conclusions. Among men, race and age have an important effect on the response to single-drug therapy for hypertension. In addition to cost and quality of life, these factors should be considered in the initial choice of a drug. (N Engl J Med 1993;328:914-21.)

THE initial treatment for hypertension has changed as drugs with pharmacologic properties permitting single-drug therapy have become available. In their 1988 report, the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure¹ considered the selection of initial treatment on the basis of demographic characteristics.

Previous cooperative studies by the Department of Veterans Affairs have supported the recommendations of the Joint National Committee, such as proposing that beta-blockers be considered equal to thiazide diuretics in the initial antihypertensive therapy of white patients^{2,3} and recommending the use of captopril as initial single-drug therapy.^{4,5} We and others have also observed differential racial responses to antihypertensive drugs.²⁻⁸ Speculation that demographic characteristics would predict clinically important differences in the antihypertensive efficacy of various drugs and permit better selection of single-drug therapy has not been substantiated by a placebo-controlled,

prospective randomized trial of representative drugs from each of the major therapeutic classes.

We studied different classes of antihypertensive drugs used as single-drug therapy. Our primary objectives were to determine the efficacy of each drug in lowering blood pressure, the ability to control blood pressure over time, and the incidence of termination of treatment for medical reasons. We also compared short-term efficacy and long-term control in the various drug classes according to age and race. Neither cost nor quality-of-life issues were studied.

METHODS

Study Design and Selection of Patients

Male veterans being evaluated as outpatients entered a washout phase lasting from four to eight weeks before randomization, during which they received one placebo tablet twice daily administered in a single-blind fashion. The criteria for inclusion were an age of 21 years or older, written informed consent, and a reasonable expectation that the patient's diastolic blood pressure would be between 95 and 109 mm Hg with placebo. Patients were excluded from the study if they had any of a number of medical conditions listed elsewhere.* Each patient underwent routine laboratory testing and electrocardiography. Interviews to gather information on side effects were conducted at the second visit and each subsequent visit.

The base-line blood pressure was calculated as the average of the readings obtained at the last two clinic visits in the period before

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*The members of the study group are listed in the Appendix.

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randomization. Compliance was determined on the basis of the patient's clinic attendance and a count of pills. Patients were randomized if their mean diastolic blood pressure on two consecutive visits was between 95 and 109 mm Hg and if the values did not differ by more than 6 mm Hg between visits.

At the time of randomization, the patients were assigned in a double-blind manner⁷ to receive placebo or one of the six study drugs. They then entered a titration phase of four to eight weeks. The drugs and their doses (listed from low to medium to high) were hydrochlorothiazide (12.5, 25, and 50 mg daily), atenolol (25, 50, and 100 mg daily), clonidine (0.2, 0.4, and 0.6 mg in divided doses given twice daily), captopril (25, 50, and 100 mg in divided doses given twice daily), prazosin (4, 10, and 20 mg in divided doses given twice daily), a sustained-release preparation of diltiazem (120, 240, and 360 mg in divided doses given twice daily), and placebo. Prazosin was started at 1 mg given twice daily for two days to minimize the risk of hypotension with the first dose. All medications were started at the lowest dose, and the dose was increased every two weeks, as required, until a diastolic blood pressure of less than 90 mm Hg was reached without intolerance to the drug on two consecutive visits or until the maximal drug dose was reached. The blood pressure during treatment was taken as the mean of the blood pressures recorded during the last two visits during the titration phase.

Patients whose diastolic blood pressure had reached the goal (a reading of less than 90 mm Hg) on two consecutive visits during the titration phase entered a maintenance phase for at least one year. During this period, interim visits were permitted in order to adjust the dose of drug as needed to maintain the diastolic blood pressure at 99 mm Hg or less and to reduce adverse effects. Control was defined as a diastolic blood pressure of less than 95 mm Hg at one year. Success was defined as attainment of the blood-pressure goal during titration and the maintenance of controlled blood pressure for one year.

After the maintenance phase, each patient entered a four-week placebo washout phase. Patients who had been randomly assigned to clonidine therapy had their doses tapered down over a two-week period to avoid withdrawal symptoms.

The protocol was approved by an institutional review board at each of the 15 participating medical centers and by a central human-studies committee.

Measurement of Blood Pressure

Trained registered nurses or physicians' assistants used standard sphygmomanometers with appropriately sized cuffs to determine blood pressure. The patients were seated with an arm supported at the level of the heart after five minutes of rest. The disappearance of the Korotkoff sounds defined the diastolic blood pressure. The mean of three readings taken one minute apart was used as the blood pressure at that clinic visit.

Adverse Drug Reactions and Termination of Treatment

A 31-item checklist was used to inquire about the patients' symptoms. The patients were encouraged to describe their symptoms at each visit. All withdrawals from the study protocol were evaluated blindly by the study chairman and classified as administrative or medical. Medical withdrawals were further analyzed blindly to determine whether they were due to an adverse drug reaction.

Statistical Analysis

The primary outcome measure was the rate of treatment success (the percentage of randomized patients who reached the blood-pressure goal during the titration phase and maintained control of blood pressure for one year). The rate at which the goal for blood pressure was achieved during the titration phase and the rate of termination due to adverse reactions were secondary outcome measures. The significance of each outcome measure was determined by a chi-square test of homogeneity for a two-by-seven contingency table.

All results are reported according to an intention-to-treat analysis. SAS software⁹ was used for all analyses. Chi-square tests of

homogeneity¹⁰ were performed to compare the proportions for all categorical responses in the seven treatment groups, whereas analysis of variance was used to compare the means for all continuous responses in these groups. When the results were significant at $P \leq 0.05$, differences between pairs of treatments were tested with pairwise contrasts for proportions or Tukey's procedure for means.¹⁰ In these analyses, it is inappropriate to report individual P values for each of the 15 possible pairwise comparisons. Instead, a P value of 0.05 was selected for each group of 15 pairwise comparisons and used to identify the subgroups of treatment pairs that were significantly different. All P values were two-tailed.

RESULTS

Characteristics of the Patients

We randomly assigned 1292 patients to the seven treatment groups. Their base-line characteristics (Table 1) were well balanced across the seven treatment groups. The mean (\pm SD) age of the 546 younger patients (those less than 60 years old) was 50 ± 8 years, and for the 746 older patients (those 60 years old or older) it was 66 ± 4 years. A total of 137 patients withdrew from the study during the titration period, and 410 patients did not qualify for the maintenance phase; the remaining 745 patients entered the maintenance phase. Of these, 145 withdrew from the study during the first year of the maintenance phase, and 65 withdrew thereafter; 535 entered the final placebo period. Thus, 41 percent of the patients initially randomized completed the study.

Blood-Pressure Response during the Titration Phase

During the titration phase, there were significant ($P < 0.001$) differences between treatments in the mean decrements in diastolic and systolic blood pressure

Table 1. Characteristics of the Randomized Patients as a Whole and According to Age and Race.*

CHARACTERISTIC	ALL PATIENTS	YOUNGER WHITES	YOUNGER BLACKS	OLDER WHITES	OLDER BLACKS
No. of patients	1292 (100)	246 (19)	291 (22)	408 (32)	330 (26)
Age (yr)	59 \pm 10	51 \pm 7	49 \pm 9	66 \pm 4	66 \pm 4
Systolic blood pressure					
Mean (mm Hg)	152 \pm 14	149 \pm 13	147 \pm 13	154 \pm 13	157 \pm 13
≥ 160 mm Hg	367 (28)	54 (22)	49 (17)	135 (33)	126 (38)
140–159 mm Hg	691 (54)	133 (54)	151 (52)	220 (54)	179 (54)
Diastolic blood pressure					
Mean (mm Hg)	99 \pm 3	99 \pm 3	100 \pm 4	98 \pm 3	100 \pm 3
100–109 mm Hg	456 (35)	89 (36)	125 (43)	102 (25)	133 (40)
95–99 mm Hg	836 (65)	157 (64)	166 (57)	306 (75)	197 (60)
Heart rate (beats/min)	74 \pm 11	75 \pm 11	76 \pm 11	73 \pm 11	74 \pm 11
Body-mass index [†]	29 \pm 5	29 \pm 5	29 \pm 5	29 \pm 4	28 \pm 5
Cigarette smoking					
Current	412 (32)	69 (28)	139 (48)	84 (21)	118 (36)
Former	557 (43)	103 (42)	87 (30)	229 (56)	134 (41)
Never	323 (25)	74 (30)	65 (22)	95 (23)	78 (24)
Ethanol consumption (drinks/day)					
0 or <1	987 (76)	168 (68)	217 (75)	310 (76)	278 (84)
1–3	241 (19)	53 (22)	61 (21)	83 (20)	42 (13)
>3	64 (5)	25 (10)	13 (4)	15 (4)	10 (3)
Antihypertensive treatment at screening	916 (71)	164 (67)	196 (67)	303 (74)	241 (73)

*Patients less than 60 years of age were considered "younger," and those 60 or older were considered "older." Plus-minus values are means \pm SD. Numbers followed by a number in parentheses are numbers of patients and percentages of the group total.

[†]Calculated as the weight in kilograms divided by the square of the height in meters.

(Table 2), the proportion of patients reaching the goal for diastolic blood pressure (<90 mm Hg), and the proportion of patients with systolic blood pressure below 140 mm Hg.

The pairwise comparisons indicated that the mean decrement in diastolic blood pressure was greater with diltiazem than with all the other active drugs except clonidine; clonidine and atenolol were more effective than captopril. The proportion of patients reaching the goal for diastolic pressure was higher with diltiazem than with hydrochlorothiazide, prazosin, or captopril; patients taking clonidine or atenolol reached this goal at a rate similar to that of patients taking the other drugs (Fig. 1). In the case of systolic pressure, the proportion of patients with readings below 140 mm Hg was higher with clonidine and hydrochlorothiazide than with prazosin, captopril, or placebo (Fig. 1). The effects of diltiazem and atenolol were not significantly different from those of the other active agents. The effects of prazosin and captopril were not significantly different from those of placebo.

The response profile for each dosage of medication during the titration phase (Table 3) showed that a high proportion of patients with a response reached the goal for that phase at the lowest dosage: 12.5 mg of hydrochlorothiazide once a day (45 percent), 25 mg of atenolol once a day (49 percent), 0.1 mg of clonidine twice a day (48 percent), and 2 mg of prazosin twice a day (48 percent). The group assigned to diltiazem had the highest proportion of responses, but many of these patients required the higher dosage.

Blood-Pressure Response during the Maintenance Phase

The 745 patients who reached the goal for diastolic blood pressure without intolerable side effects entered a maintenance phase of at least one year and continued to receive blinded therapy. During this phase

there were small increases in systolic and diastolic blood pressure (4 ± 11 and 2 ± 6 mm Hg, respectively). The percentage of patients with initial control of blood pressure in whom the diastolic blood pressure remained below 95 mm Hg at one year was similar for all treatment groups ($P = 0.926$), ranging from 82 percent (for hydrochlorothiazide) to 75 percent (for prazosin).

For the primary study end point, the proportion of patients initially randomized who responded to therapy and maintained a diastolic pressure below 95 mm Hg after one year of treatment, there were significant ($P < 0.001$) differences between treatments (Fig. 2). This rate of treatment success reflects the initial blood-pressure response, the number of patients who did not withdraw because of side effects or other causes, and the degree to which control was maintained. The pairwise comparisons show that diltiazem was more effective than captopril or prazosin. All the treatments were superior to placebo.

Blood-Pressure Response According to Age and Race

Race and, to a somewhat lesser extent, age were powerful influences on the response of blood pressure to individual drugs. Data obtained at the end of the titration phase (Table 2) indicate statistically significant differences between drugs. Figure 3 shows the criterion of a 15 percent difference in efficacy between two or more drugs, the difference specified in the study design to be clinically important.

There were no statistically significant differences according to age and race with respect to mean changes in either systolic or diastolic blood pressure from base line to the end of the titration phase (Table 2). Blood pressure was reduced by $11 \pm 10/10 \pm 7$ mm Hg for 243 younger whites, by $9 \pm 11/9 \pm 8$ mm Hg for 288 younger blacks, by $12 \pm 12/12 \pm 6$ mm Hg for 405 older whites, and by $11 \pm 12/11 \pm 7$ mm Hg for 330 older blacks. There were significant differences be-

Table 2. Average Reductions in Blood Pressure from Base Line to the End of the Titration Phase.*

VARIABLE AND SUBGROUP	HYDROCHLOROTHIAZIDE	ATENOLOL	CAPTAPRIL	CLONIDINE	DILTIAZEM	PRAZOSIN	PLACEBO
<i>no. of patients, reduction in pressure, statistical difference</i>							
Diastolic pressure (mm Hg)							
All patients	188 10±6 BC	176 12±6 B	188 10±7 C	177 12±6 AB	182 14±5 A	186 11±7 BC	186 5±7 D
Younger whites	34 7±6 BC	37 13±6 A	39 10±7 AB	32 13±5 A	38 13±5 A	32 10±6 AB	31 4±7 C
Younger blacks	48 10±6 AB	34 11±9 AB	44 9±7 B	39 10±7 B	37 14±5 A	42 8±8 BC	44 4±6 C
Older whites	60 11±6 A	57 13±6 A	55 11±5 A	60 14±5 A	52 14±5 A	58 14±6 A	63 6±7 B
Older blacks	44 12±6 AB	47 11±5 BC	48 7±7 CD	45 12±7 AB	53 15±5 A	49 11±6 BC	44 5±7 D
Systolic pressure (mm Hg)							
All patients	188 14±11 AB	176 11±12 BC	188 9±10 C	177 16±13 A	182 13±9 AB	186 12±12 BC	186 3±10 D
Younger whites	34 12±11 AB	37 14±11 AB	39 11±9 ABC	32 16±12 A	38 11±9 ABC	32 8±9 BC	31 5±10 C
Younger blacks	48 14±9 A	34 7±11 BC	44 8±11 AB	39 13±10 AB	37 14±10 A	42 8±12 AB	44 0.5±10 C
Older whites	60 13±12 A	57 12±14 A	55 11±9 A	60 17±13 A	52 12±9 A	58 17±12 A	63 3±10 B
Older blacks	44 16±11 A	47 9±11 BCD	48 7±12 CD	45 17±15 A	53 15±7 AB	49 13±13 ABC	44 3±11 D

*On each line, pairs of treatments that are not assigned at least one letter in common are statistically different; e.g., for diastolic blood pressure in all patients, hydrochlorothiazide (BC) is different from placebo (D) and diltiazem (A), but not from atenolol (B), captopril (C), clonidine (AB), or prazosin (BC). The letters progress from the highest (A) to the lowest (D) magnitude of difference. The one-way analysis of variance must be statistically significant ($P \leq 0.05$) in order to justify this pairwise analysis. The numbers of patients in the subgroups do not total the numbers shown for all patients because 17 patients were studied who were neither black nor white. Reductions in blood pressure are reported as means \pm SD.

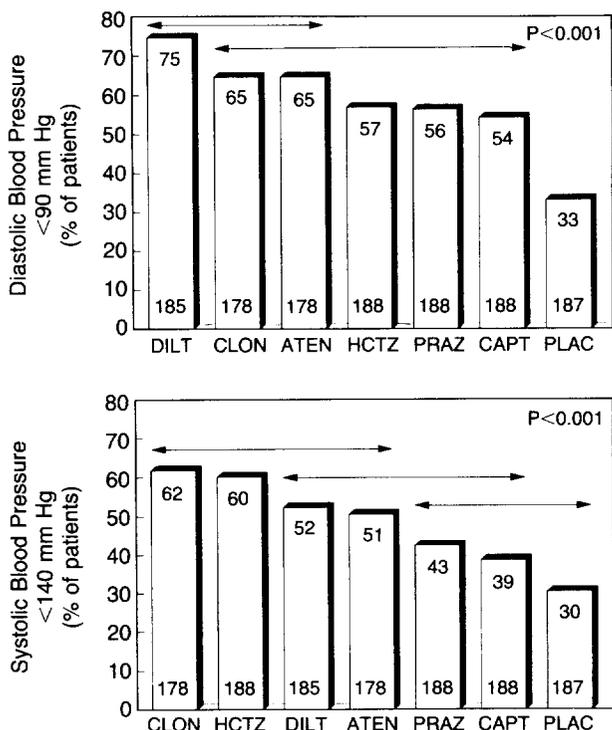


Figure 1. Patients with a Diastolic Blood Pressure of Less Than 90 mm Hg or a Systolic Blood Pressure of Less Than 140 mm Hg at the End of the Titration Phase.

The P values were derived by a chi-square test comparing the treatments. On the basis of pairwise comparisons, the horizontal arrows group drugs the effects of which were not significantly different from one another, but that were significantly different from the drugs not included under the arrow. ATEN denotes atenolol, CAPT captopril, CLON clonidine, DILT diltiazem, HCTZ hydrochlorothiazide, PRAZ prazosin, and PLAC placebo. The numbers at the top of the bars indicate the percentage of patients with the response shown, and the numbers at the bottom of the bars indicate the number of patients in each group.

tween drugs according to age and race. Clonidine, atenolol, and diltiazem were the most effective in reducing the diastolic blood pressure of younger whites; hydrochlorothiazide was the least effective. Diltiazem was most effective for younger blacks, and prazosin least effective. All the drugs were similarly effective for older whites; diltiazem was most effective for older blacks, and captopril least effective.

Rates of treatment success were different for the different drugs in each of the four groups defined according to age and race (Fig. 3). Younger black patients responded best to diltiazem; older blacks to diltiazem or hydrochlorothiazide; younger whites to captopril, atenolol, or clonidine; and older whites to atenolol, diltiazem, captopril, clonidine, hydrochlorothiazide, or prazosin (listed in descending order).

Final Placebo Phase

At the end of the final placebo phase, the diastolic blood pressure remained at least 6 mm Hg below the base-line level in all the treatment groups except the clonidine group, in which it returned to 1 mm Hg

below the base-line value. In the case of systolic blood pressure, all treatment groups except the clonidine group had values at least 1 mm Hg below base line after the final placebo phase, but the values for the clonidine group were 8 mm Hg above base line. Similar results were obtained for the difference between the final visit in the maintenance phase and that in the final phase: blood pressure increased by 22/13 mm Hg after the withdrawal of clonidine, a larger increase than was found with any other drug. The pairwise comparisons showed that clonidine was significantly different in this regard from all other drugs and placebo.

Adverse Drug Effects

During the titration phase, there were significant differences between groups in the percentage of patients requiring withdrawal from the study drug or a reduction in dosage because of side effects. Patients treated with clonidine or prazosin were intolerant of the study drug more often (14 and 12 percent of the respective treatment groups) than patients given captopril (7 percent), placebo (6 percent), atenolol (5 percent), diltiazem (4 percent), or hydrochlorothiazide (3 percent).

Only patients receiving clonidine or prazosin had significantly more side effects during the titration phase than patients receiving placebo. In the case of the clonidine group, these side effects were fatigue (17 percent of patients vs. 8 percent for placebo), sleepiness (30 percent vs. 6 percent), nonpostural dizziness (8 percent vs. 5 percent), and dry mouth (37 percent vs. 6 percent). In the case of the prazosin group, the side effects were fatigue (13 percent of patients vs. 8 percent for placebo), sleepiness (12 percent vs. 6 percent), and nonpostural dizziness (12 percent vs. 5 percent). No drug was associated with a significant increase in the frequency of impotence or edema.

Termination of Treatment

Of the 1292 randomized patients, 137 (10.6 percent) were withdrawn from the trial during the titration phase (Table 3). Of the 745 patients who entered the maintenance phase, 145 (19.5 percent) were withdrawn within one year. In the case of 194 patients treatment was terminated for medical reasons, including loss of blood-pressure control in 44 patients and adverse drug reactions in 84 (Table 3). Most adverse drug reactions were those known to be associated with the specific drugs. In the placebo group, they included dizziness (three patients), sleep disturbances (two patients), severe dry mouth, acute gout, and proteinuria (one patient each). There was one termination of treatment due to proteinuria in each drug group except the clonidine group. Three patients died during the study from causes unrelated to the study drug.

Prazosin had the highest rate of adverse effects leading to the termination of treatment (13.8 percent),

which was significantly higher than the rate for captopril (4.8 percent), atenolol (2.2 percent), or hydrochlorothiazide (1.1 percent). The rate for clonidine (10.1 percent) was significantly different from the rates for hydrochlorothiazide and atenolol. The rate for diltiazem was 6.5 percent, and for placebo 6.4 percent.

There were no significant differences between drug

Table 3. Responses to Treatment at the End of the Titration Phase and Withdrawals at Each Dose Level during the Titration and Maintenance Phases.*

DRUG AND RESPONSE TO MEDICATION	DOSE LEVEL			
	LOW	MEDIUM	HIGH	ALL
	<i>no. of patients</i>			
Hydrochlorothiazide				
Response/no response	48/138	25/108	34/66	107/66
Withdrawals (titration/maintenance)				
Adverse drug reaction	0/1	0/1	1/0	1/2
Loss of BP control	1/1	1/0	4/1	6/2
Other medical reason	0/2	0/1	0/2	0/5
Nonmedical reason	1/7	4/2	3/1	8/10
Atenolol				
Response/no response	56/115	33/80	26/48	115/48
Withdrawals (titration/maintenance)				
Adverse drug reaction	1/2	0/1	0/0	1/3
Loss of BP control	1/1	1/1	1/1	3/3
Other medical reason	2/2	0/2	2/0	4/4
Nonmedical reason	4/3	1/0	3/3	8/6
Captopril				
Response/no response	38/142	26/110	38/63	102/63
Withdrawals (titration/maintenance)				
Adverse drug reaction	4/1	1/1	2/0	7/2
Loss of BP control	0/0	2/1	5/2	7/3
Other medical reason	1/2	2/3	0/3	3/8
Nonmedical reason	3/2	1/2	2/2	6/6
Clonidine				
Response/no response	55/118	31/84	29/51	115/51
Withdrawals (titration/maintenance)				
Adverse drug reaction	3/4	2/2	2/5	7/11
Loss of BP control	1/0	1/1	2/0	4/1
Other medical reason	2/3	0/2	0/4	2/9
Nonmedical reason	0/2	0/0	0/1	0/3
Diltiazem				
Response/no response	43/136	45/88	50/38	138/38
Withdrawals (titration/maintenance)				
Adverse drug reaction	2/2	1/2	0/5	3/9
Loss of BP control	0/0	0/0	0/0	0/0
Other medical reason	3/3	0/0	0/4	3/7
Nonmedical reason	4/1	2/6	0/3	6/10
Prazosin				
Response/no response	51/119	33/80	22/55	106/55
Withdrawals (titration/maintenance)				
Adverse drug reaction	13/6	2/2	1/2	16/10
Loss of BP control	0/0	1/0	1/1	2/1
Other medical reason	3/5	0/6	0/1	3/12
Nonmedical reason	4/3	3/0	1/0	8/3
Placebo				
Response/no response	24/154	11/138	27/97	62/97
Withdrawals (titration/maintenance)				
Adverse drug reaction	4/2	3/0	1/2	8/4
Loss of BP control	2/0	0/0	6/4	8/4
Other medical reason	1/1	1/0	2/1	4/2
Nonmedical reason	3/1	1/1	5/3	9/5

*Patients who had a diastolic blood pressure of less than 90 mm Hg without drug intolerance were considered to have responded to treatment. BP denotes blood pressure.

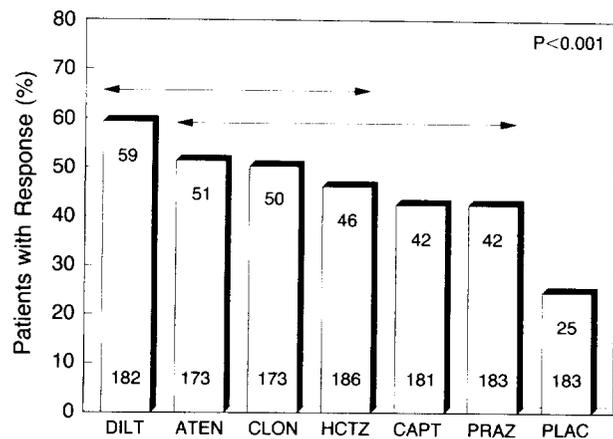


Figure 2. Patients with Responses in Each of the Study Groups. A response was defined as a diastolic blood pressure of less than 90 mm Hg at the end of the titration period and less than 95 mm Hg at the end of one year of treatment. The abbreviations and arrows are explained in the legend to Figure 1.

groups with respect to the rates of adverse effects that caused the termination of treatment among younger blacks (0 to 6.8 percent). Among younger whites, the comparison of prazosin (15.2 percent) with both hydrochlorothiazide (2.9 percent) and captopril (2.6 percent) approached statistical significance. Among older whites, the rates for prazosin (19.0 percent) and clonidine (16.7 percent) were higher than the rates for atenolol (1.7 percent) and hydrochlorothiazide (1.7 percent). The rates for the other three treatment groups ranged from 5.7 to 9.1 percent. For older blacks, the comparison of both diltiazem (12.2 percent) and prazosin (11.3 percent) with placebo (0 percent) approached statistical significance.

Laboratory Data

In the hydrochlorothiazide-treated patients, pairwise comparisons showed that the increase in serum cholesterol of 3.3 mg per deciliter (0.086 mmol per liter) was significantly different from the decrease of 9.3 mg per deciliter (0.24 mmol per liter) in the prazosin group, but was not different from the changes in the placebo group or the other groups, and it did not persist at one year. Fasting blood glucose increased significantly by 6.7 mg per deciliter (0.37 mmol per liter) in the hydrochlorothiazide group as compared with the placebo, captopril, and atenolol groups, and it remained elevated at two years.

DISCUSSION

Although it was limited to male veterans, this study provides new information about the comparative efficacy of six commonly used drugs for the initial therapy of mild-to-moderately-severe hypertension. The inclusion of a placebo group allowed a true estimate of the active drug effects, and the large study population — nearly 200 patients per treatment group — provided adequate power to detect differences between drugs. Furthermore, the population was large and het-

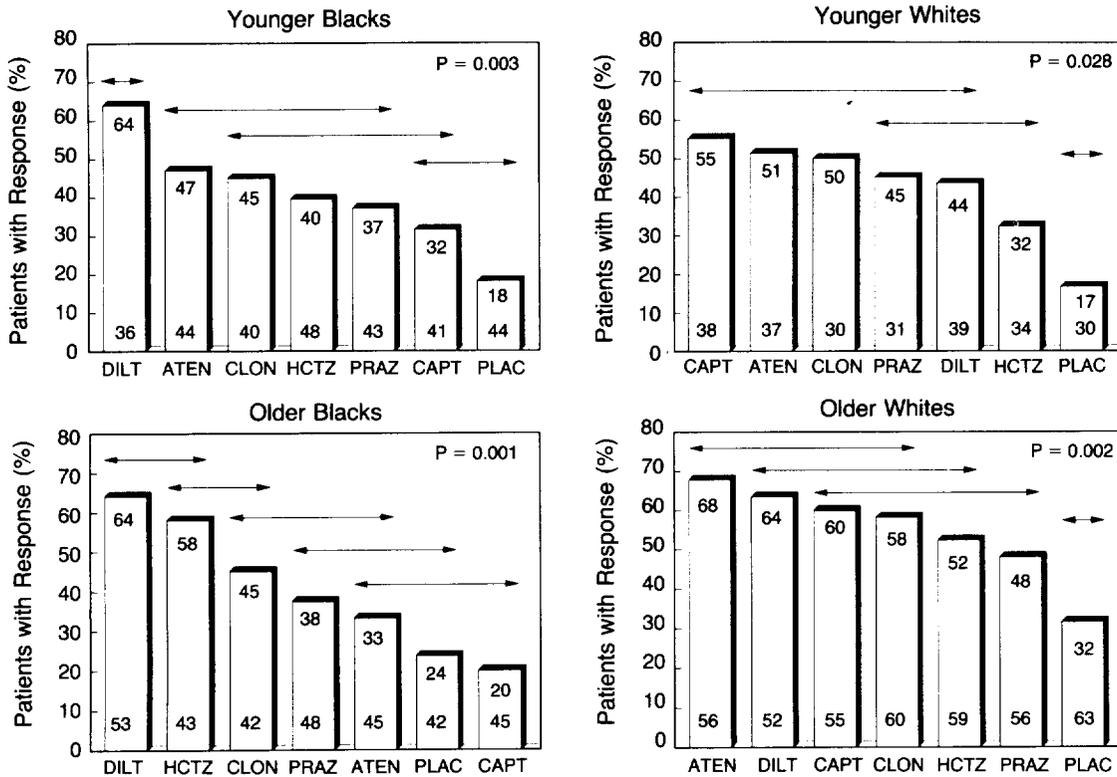


Figure 3. Younger Black Patients, Younger White Patients, Older Black Patients, and Older White Patients with Responses in Each of the Study Groups.

The abbreviations are explained in the legend to Figure 1. The arrows group the drugs whose effects do not differ from each other by more than 15 percent.

erogeneous enough for differences in treatment responses to be examined according to age and race. Our conclusions about the comparative efficacy of the six study drugs are influenced by the doses selected. Different results might have been obtained if different doses had been chosen.

This study differed from other comparative studies of single-drug therapy for hypertension^{8,11,12} in that it prospectively compared representatives of six classes of drugs with each other and with placebo. A sufficient number of patients were randomly assigned to the drug groups for valid conclusions to be drawn from the data.

We demonstrated that the response to single-drug therapy in this group of hypertensive patients was quite high, although there were significant differences among drugs in achieving that response. The blood-pressure decrement achieved by placebo (3 mm Hg systolic and 5 mm Hg diastolic) and the response rate are similar to those of previous studies. Overall, the most consistent response of diastolic blood pressure was to diltiazem. There were no significant differences in the response rates of white patients to the various drugs, although atenolol and captopril had the highest response rates at one year. Systolic blood pressure was most responsive to hydrochlorothiazide and clonidine. Captopril was the least effective in black patients, a subgroup in whom angiotensin-converting-enzyme

inhibitors and beta-blockers are known to be less effective. However, the magnitude of the change in blood pressure, the percentage of patients who reached the goal for blood pressure, and the 58 percent response rate at one year for white patients are all consistent with the results of our previous study of captopril.⁴ Furthermore, in the present study captopril ranked first in younger whites and third (after atenolol and diltiazem) in older whites. In general, prazosin was less effective than the other drugs; it and clonidine were the least well tolerated of the six.

The mechanisms underlying the varying responses among the classes of agents remain unclear. It has been proposed that blacks and older patients may be less responsive to angiotensin-converting-enzyme inhibitors and more responsive to diuretics and calcium-channel blockers because these groups of patients tend to have low-renin hypertension.^{13,14} Although the current data are consistent with these hypotheses, they do not establish a mechanism for this pattern of responses. In any case, in several demographic groups the differences between drugs are substantial enough to guide the initial choice of a drug.

Few studies have evaluated more than two antihypertensive agents prospectively in placebo-controlled trials. The Treatment of Mild Hypertension Study¹¹ was a randomized, parallel, placebo-controlled study of antihypertensive agents similar to those used in

our trial. All the patients participated in a diet for weight and sodium reduction and a program of increased physical activity that reduced blood pressure by 10.6/8.1 mm Hg. No differences in efficacy were observed among drugs.

The Trial of Antihypertensive Interventions and Management¹² tested various diets plus antihypertensive drug therapy with either chlorthalidone or atenolol. Black patients responded better to chlorthalidone plus dietary sodium restriction, whereas white patients responded better to atenolol plus diet. Saunders and collaborators⁸ studied atenolol, captopril, and sustained-release verapamil in 394 black patients. They observed short-term decreases in diastolic blood pressure similar to those in our study.

Diuretics (both hydrochlorothiazide and chlorthalidone) have had impressive efficacy in treating isolated systolic hypertension in the elderly.¹⁵⁻¹⁷ Our study did not include subjects with isolated systolic hypertension, but hydrochlorothiazide was somewhat more effective in reducing systolic blood pressure in older patients of both races. Three cooperative studies by the Department of Veterans Affairs showed that thiazide diuretics were more effective in older patients than in younger ones and had a greater effect on the reduction of systolic pressure in the older patients.¹⁸

Low-dose hydrochlorothiazide (12.5 mg per day) and atenolol (25 mg per day) produced significant responses; 12.5 mg of hydrochlorothiazide was associated with only minimal biochemical perturbations. Hydrochlorothiazide-treated patients in this study had the lowest rate of drug intolerance and the fewest terminations of treatment for adverse drug reactions, but hydrochlorothiazide was less effective in younger patients. Conversely, although diltiazem was highly effective, a high proportion of patients had adequate blood-pressure control only at the highest dose. The doses of captopril employed in this study were those usually used in clinical practice. It is not known whether the use of a higher or more frequent dose would have improved the results with this drug, although other studies have shown the dose-response curve to be flat from 75 to 150 mg.^{4,5,19}

The subjects in this study were not characteristic of the general population with hypertension. They were older and more likely to be black, and there were no women. We are not aware of valid data that demonstrate a meaningful difference in drug response according to sex.²⁰ Nevertheless, we cannot generalize our results to women. Our study does not pertain to important factors, such as the effect of racial identity and socioeconomic status in the causation or prevalence of hypertension,²¹ nor do we address specific mechanisms of hypertension. We believe that our data do demonstrate the power of the patient's race and age as determinants of the response to various antihypertensive drugs and that racial identification is important for that specific purpose.

Antihypertensive treatment must be tailored to the individual patient. Small differences in efficacy may

be less important than differences in quality of life or cost. This study provides some guidelines for the practicing physician about which drugs to try initially to control patients' blood pressure, taking into consideration the characteristics of the patient. When they are subsequently combined with data on costs and quality of life, the results of this study may clarify recommendations on the preferred single-drug therapy for specific groups of patients. A long-term study that includes women is needed to identify the possible advantages of one or more of these classes of drugs in reducing morbidity and mortality from cardiovascular causes.

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APPENDIX

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