Effects of Reduction in Drugs or Dosage After Long-Term Control of Systemic Hypertension

Edward D. Freis, MD, J.R. Thomas, MD, Susan G. Fisher, MS, Robert Hamburger, MD, Richard E. Borreson, MD, Kalman C. Mezey, MD, Bangshi Mukherji, MD, William W. Neal, MD, H. Mitchell Perry, MD, and James T. Taguchi, MD, for the Veterans Administration Cooperative Study Group on Antihypertensive Agents*

The possibility of discontinuing—compared to reducing—antihypertensive drug treatment was investigated in 606 male hypertensive patients with entry diastolic blood pressure (BP) in the range of 90 to 114 mm Hg. Diastolic BP was controlled at <90 mm Hg with 1 of 4 regimens: low dose hydrochlorothiazide (HCTZ), 25 mg twice daily; high dose HCTZ, 50 mg twice daily; or high dose HCTZ plus a low or high dose of a step II drug (propranolol, clonidine or reserpine). After 6 months of treatment that controlled BP, dosages were reduced in two-thirds of the patients. In those patients receiving low dose HCTZ and randomized to dose reduction, antihypertensive drugs were completely discontinued. Although approximately half of these patients remained normotensive for the first 6 months, a significantly greater proportion had elevation of BP compared to the control group, which continued to receive treatment ($p < 0.0001$). In the high dose HCTZ drug group, the proportion of patients remaining normotensive did not differ among those stepped down to low dose HCTZ and the fully treated control group. While not achieving significance the trend was similar with the step II regimens. Although some patients remained normotensive after discontinuation of step II drugs, a greater proportion returned to elevated BP than when step II dosage was unchanged. Therefore, while stopping therapy may be effective in some patients, a decreased dosage is significantly more effective as a method for maintaining an antihypertensive effect. Decreasing drug dosages offers the dual benefit of minimizing side effects and reducing drug costs.

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From the Veterans Administration Medical Center, Washington, DC, Memphis, Tennessee, Hines, Illinois, Boston, Massachusetts, Houston, Texas, East Orange, New Jersey, Oklahoma City, Oklahoma, Dallas, St. Louis, Missouri, and Dayton, Ohio. This study was funded by the Cooperative Studies Program of the Veterans Administration's Medical Research Service. Manuscript received July 19, 1988; revised manuscript received and accepted December 7, 1988.

Address for reprints: Edward D. Freis, MD, Hypertension Research, Veterans Administration Medical Center, 50 Irving Street N.W., Washington, DC 20422.

*See Appendix.

Because antihypertensive drugs are customarily given for life and are often expensive, it is desirable to reduce them if possible. Perry and Schroeder[1] reported in 1956 that the dose requirement of antihypertensive drugs diminished following long-term treatment. Later investigators assessed the effects of complete discontinuation of antihypertensive drugs.[2-6] Unfortunately, hypertension returned in nearly all patients although the return was often delayed for months. Few trials have studied the effects of dosage reduction as an alternative to drug discontinuation.[1,7,8] The present trial was designed to evaluate the effect of dosage reduction compared to complete discontinuation of drugs on blood pressure (BP) control in patients with mild to moderate hypertension.

METHODS

Endpoint measurement: Goal BP was defined as a diastolic BP <90 mm Hg except for newly diagnosed patients with entry diastolic BP between 90 and 94 mm Hg. In them goal BP was defined as diastolic BP at least 5 mm Hg below that at entry. If at any time during the study a patient had 2 consecutive visits with a diastolic BP greater than goal BP and the average was at least 5 mm Hg greater than the baseline level, the BP was considered to be uncontrolled.

Drug regimens: The protocol drug regimens consisted of the following: (1) low dose (25 mg twice daily) hydrochlorothiazide (HCTZ); (2) high dose (50 mg twice daily) HCTZ; (3) high dose HCTZ plus low dose step II drug (low dose step II); and (4) high dose HCTZ plus high dose step II drug (high dose step II). The step II drugs were titrated as necessary. Low dose step II medications were propranolol 40 mg twice daily, clonidine 0.1 mg twice daily or reserpine 0.1 mg once daily. High dose step II medications were propranolol 80 mg increased if necessary to 160 twice daily, clonidine 0.2 mg increased to 0.3 twice daily if needed or reserpine 0.25 mg once daily.

Prerandomization: Study candidates included previously diagnosed patients whose diastolic BP was <115 mm Hg and newly diagnosed patients with a diastolic BP between 90 and 109 mm Hg on 3 consecutive visits each 2 weeks apart, or between 110 and 114 mg Hg on 2 consecutive visits 1 week apart. Screened patients with malignant hypertension, hemorrhagic stroke, recent myocardial infarction, history of alcoholism or drug abuse, contraindication to study medication or who re-

fused to participate were ineligible. Of the 1,316 patients initially screened for this study 872 met these criteria for entry into the prerandomization drug titration phase.

Depending on the patient's previous treatment, 1 of 3 types of titration procedures was used as follows.

1. Of those patients entering the titration phase, 329 were previously treated with a regimen similar to one of the study regimens; these patients were switched to that study regimen without a washout period. For example, a patient already receiving HCTZ 50 mg plus propranolol 80 mg once daily would be switched to the protocol regimen of HCTZ 50 mg plus propranolol 80 mg twice daily. If BP remained above the goal BP, study medication was titrated upward.

2. Patients previously treated with regimens dissimilar to study regimens (n = 384) had all medications tapered off and withdrawn over a 1- to 2-week period. They were then begun on low dose HCTZ and titrated upward to high dose HCTZ and then to the step II regimens as necessary to achieve goal BP.

3. The 159 previously untreated patients were followed weekly for 2 to 4 weeks to establish that the study criteria for hypertension were met. Those qualifying were then begun on low dose HCTZ and titrated upward as necessary.

During drug titration 147 patients were determined to be ineligible for the study due to failure to meet study criteria for hypertension (n = 27), adverse drug reactions (n = 13), failure to return to clinic (n = 58) and other, nonmedical reasons (n = 49).

Following successful titration to goal BP, the patients entered a 6-month prerandomization baseline phase. Its purpose was to maintain a prolonged period of continuous normotension before medication reduction. Patients excluded during this phase included 6 patients in whom BP rose above goal BP, 29 with medical problems, 33 lost to follow-up and 51 in whom treatment was interrupted for >14 days. Candidates completing this 6-month baseline phase with maintenance of BP control (n = 606) were included in the core study sample.

Randomization and postrandomization phases: Two-thirds of the study patients were randomly assigned to either dose reduction or drug discontinuation depending on drug regimen; the other one-third of the patients continued to receive their unchanged drug regimen as a control group (Figure 1). This 2:1 randomization scheme ensured adequate sample size for a second randomization of the dose reduction group later in the study. Patients in the low dose HCTZ group had the diuretic discontinued while high dose HCTZ patients were switched to low dose HCTZ. Low dose step II patients had the step II drug discontinued but remained on high dose HCTZ and high dose step II patients received a low dose of the step II medication and continued on high dose HCTZ. The appearance of all medications and placebos was kept uniform to maintain the double-blinded design. This first postrandomization lasted 6 months, as did all subsequent study phases.

Patients maintaining goal BP were continuously treated and followed. Patients not maintaining goal BP

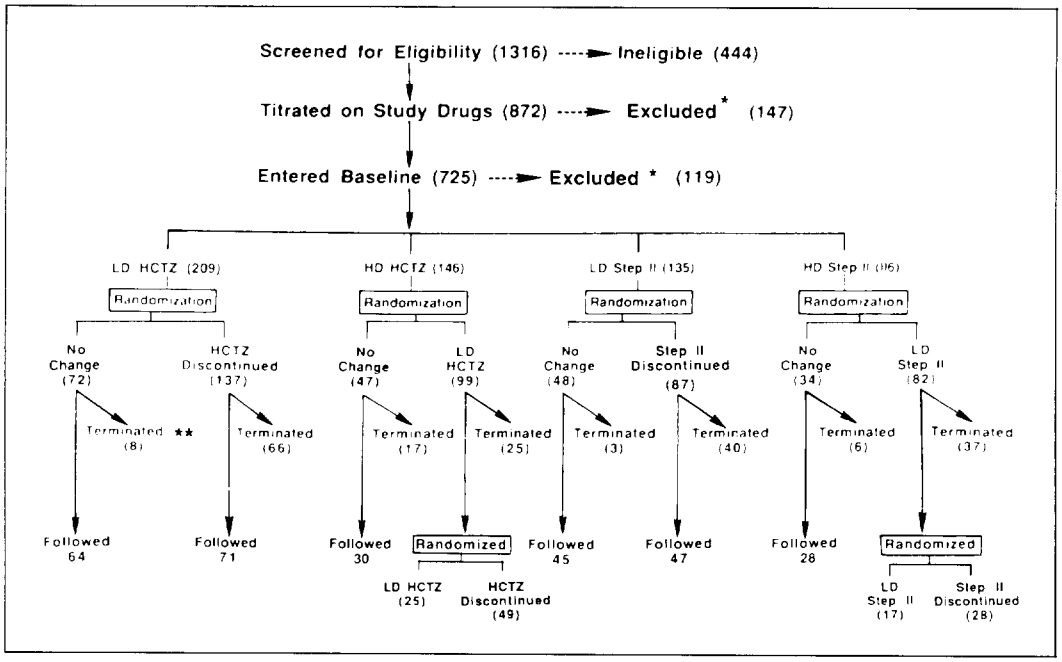

FIGURE 1. Flow sheet showing the prerandomization drug titration phase using the 4 step regimens as needed to control diastolic blood pressure to <90 mm Hg followed by 6-month treatment maintenance phase. Eligible patients then entered the postrandomization period where drugs were reduced in two-thirds of patients and remained unchanged in one-third. After 6 months, two-thirds of eligible patients underwent a second medication reduction. *Excluded patients include those in whom blood pressure was not controlled within study limits and patients with other medical or nonmedical problems. **Reasons for postrandomization terminations are similar to prerandomization reasons with the addition of patients being unable to complete the 6-month phase because the study ended (see text). LD = low dose.

TABLE I Background Characteristics of Randomized Patients

	Pts (n)	Mean Age (yrs)	Race			Before Randomization BP* (mm Hg)	Prior Rx	
			White	Black	Other		Yes	No
Low dose HCTZ								
No change	72	58 ± 8	31	38	3	126/80 ± 13/6	67	5
Dose reduced	137	57 ± 9	60	75	2	129/82 ± 13/6	124	13
High dose HCTZ								
No change	47	56 ± 9	22	25	0	128/84 ± 13/5	45	2
Dose reduced	99	59 ± 8	44	54	1	129/82 ± 15/5	88	11
Low dose step II								
No change	48	56 ± 10	24	22	2	126/82 ± 10/6	44	4
Dose reduced	87	56 ± 10	40	47	0	126/83 ± 13/5	84	3
High dose step II								
No change	34	56 ± 9	19	15	0	125/84 ± 11/5	32	2
Dose reduced	82	55 ± 10	43	38	1	128/84 ± 14/5	81	1
All treatment arms	606	57 ± 9	283	314	9	127/83 ± 136	565	41

* During treatment to lower BP.
All ± values are mean ± standard deviation.
No significant differences in background characteristics between treatment groups.
BP = blood pressure; HCTZ = hydrochlorothiazide.

TABLE II Percent of Patients Remaining Under Blood Pressure Control at Various Times During 30 Months After Randomization

Group	Percent Controlled After Randomization (months)		
	6	18	30
Low dose HCTZ unchanged	94 ± 3	89 ± 4	86 ± 4
Low dose HCTZ discontinued	55 ± 4	35 ± 4	23 ± 5
High dose HCTZ unchanged	79 ± 7	55 ± 9	†
High dose HCTZ reduced to LD	84 ± 4	58 ± 9	†
High dose HCTZ second stepdown	*	20 ± 6	12 ± 7
Low dose STEP II unchanged	96 ± 3	84 ± 6	84 ± 6
Low dose STEP II discontinued	56 ± 5	37 ± 6	16 ± 8
High dose STEP II unchanged	85 ± 6	70 ± 11	70 ± 11
High dose STEP II reduced to LD	62 ± 6	47 ± 9	47 ± 9
High dose STEP II second stepdown	*	17 ± 6	†

* Patients were randomized to initial drug reduction for first 6 months after randomization. Second reduction began after this period.
† Some data were omitted at the 30-month follow-up because the number of patients were too few to provide a reliable statement.

were considered to have reached a study endpoint; their drugs were unblinded and appropriate increases were made in study medication to achieve control of BP. Patients unable to maintain goal BP on the maximum study regimen were treated in hypertension clinics on nonprotocol regimens.

Following the first 6-month postrandomization phase, patients maintaining BP control in whom medication was originally reduced but not discontinued—i.e., the high dose HCTZ and the high dose step II regimens—were randomized a second time. Thus, two-thirds received a second dose reduction/drug discontinuation while one-third remained on the same dosage. In that way, two-thirds of the high dose HCTZ patients initially reduced to low dose HCTZ now had it discontinued. High dose step II patients, in whom the step II medication had been previously reduced, now had the step II medication discontinued although these patients continued to receive high dose HCTZ. After this second randomization no further changes in medication were made unless a study endpoint was reached. Patients who maintained control BP were followed for up to 30 months after randomization.

Throughout the study medication compliance was measured. Patients had to return their medication bottles containing the remaining unused tablets (we deliberately provided a small excess of tablets). Patients were considered compliant if they returned <30% of the number of tablets that should have been taken without exceeding 110% of the number to be taken. The return of an empty bottle was considered a violation. Tablet counts were done on every visit throughout the trial.

In cases in which therapy was stopped because of illness, surgery, trauma, etc., the code-labeled medications could be reinstituted if the interruption was ≤7 days during the prerandomization phases or ≤14 days during the postrandomization period. Otherwise, patients were terminated from the trial.

Data analysis: Descriptive statistics including 95% confidence intervals were used to describe the percentage of patients maintaining BP control in each study phase. Long-term maintenance of BP was estimated using Kaplan-Meier techniques. Differences between background characteristics, laboratory values and side effects were examined by the chi-square test of homogeneity and the Student *t* test. Logistic regression procedures were used to identify variables as potential predictors of a patient's ability to maintain BP control. In all cases a 2-tailed p value of 0.05 was considered statistically significant. All patients entering the trial signed an informed consent statement after the procedure had been fully explained.

RESULTS

After the 6-month baseline treatment period 606 patients maintained BP control and were therefore eligible for randomization. Of these, 209 were receiving the low dose HCTZ, 146 the high dose HCTZ, 135 the low dose step II regimen and 116 the high dose step II regimen.

The major characteristics of randomized patients are listed in Table I. There were no significant differences

between treatment groups. The mean age of the sample was 56.9 years. The racial distribution was 52% black and 47% white. There was no significant difference in pretreatment BP between the control group and the drug reduction group within each drug regimen category. Ninety-three percent of the patients entering the trial had been receiving antihypertensive therapy previously.

First six-month postrandomization phase: Depending on the therapeutic regimen 55 to 84% of patients on reduced dosage remained within the acceptable levels of diastolic BP during the first 6 months (Table II). Low dose HCTZ was the only regimen in which all antihypertensive drug therapy had been discontinued. Although 55% of these patients maintained goal BP throughout this treatment phase (Figure 2), this proportion was significantly less than the fully treated low dose HCTZ control patients ($p < 0.0001$). The high dose HCTZ patients who were reduced to low dose HCTZ had the greatest percentage remaining controlled at or below goal BP (84%) after 6 months (Figure 3). At the end of 6 months, 56% of the low dose step II patients in whom step II medication was discontinued maintained BP control (Figure 4). Among the high dose step II patients in whom the step II drug was reduced, 62% remained controlled during the 6-month period (Figure 5). Both low and high dose step II groups were significantly different from their unchanged dose controls. There was no significant difference, either before or after dose reduction, among any of the 3 antihypertensive drugs used in the step II regimens.

Among patients remaining within goal BP criteria, the greatest average increase in BP occurred among those in whom medication was reduced from low dose HCTZ to no active treatment. Six months after randomization these patients increased BP by 13.9 mm Hg systolic and 3.6 mm Hg diastolic. The 2 treatment groups who were stepped down to a lower dose and remained controlled exhibited only small increases in BP (approximately 5/2 mm Hg).

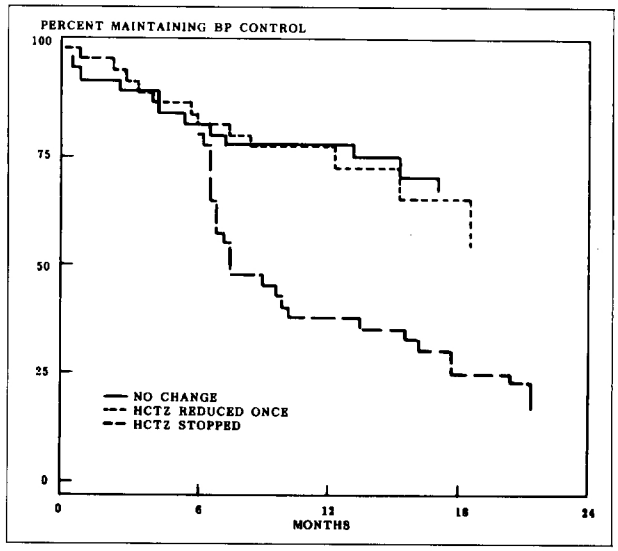

FIGURE 3. Percent of high dose HCTZ patients remaining under diastolic BP control during 20 months after randomization. The *solid line* represents the patients whose dose of 50 mg HCTZ twice daily remained unchanged. The *broken line with frequent interruptions* indicates the patients whose HCTZ was reduced from 50 to 25 mg twice daily but was not discontinued. The *broken line with few interruptions* represents the patients who, after 6 months of initial dose reduction, had active medication discontinued. Blood pressure control is well maintained in the dose reduced group but not in the drug discontinued patients, i.e., after the first but not the second reduction.

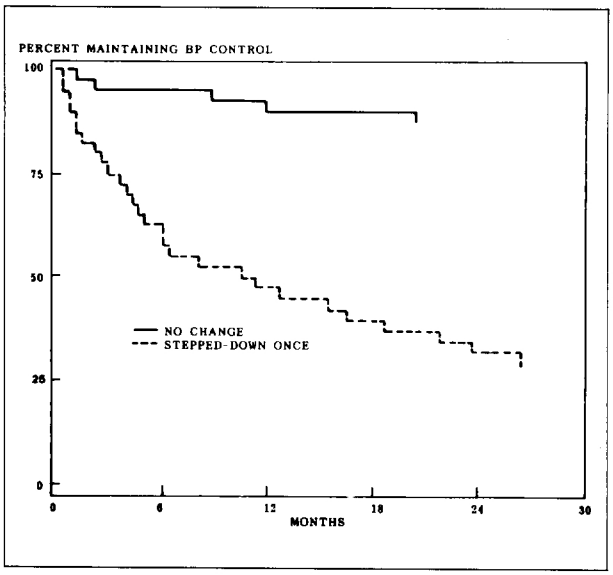

FIGURE 2. Percent of low dose HCTZ patients maintaining diastolic BP control during 24 months of follow-up. The *solid line* indicates the patients remaining on 25 mg HCTZ twice daily. The *broken line* indicates the patients whose HCTZ was discontinued. A high rate of loss of blood pressure control occurred when HCTZ was discontinued.

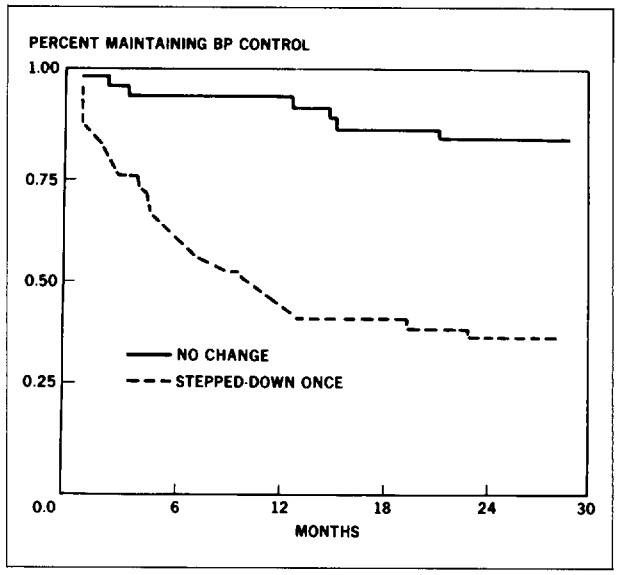

FIGURE 4. Percent of patients on low dose step II drugs remaining under diastolic BP control during 30 months following randomization. The *solid line* represents the patients remaining on HCTZ 50 mg twice daily plus step II drug. The *broken line* indicates patients whose step II drug, but not HCTZ, was discontinued.

TABLE III Patients Entering and Patient Attrition on Each Regimen During the First 18 Months After Randomization

Time from Randomization (months)	No. of Pts Entered			Patient Attrition During Study Phase								
				Elevated BP			Other Causes			End of Study*		
	0–6	6–12	12–18	0–6	6–12	12–18	0–6	6–12	12–18	0–6	6–12	12–18
Low dose HCTZ	209	135	110	63	15	10	10	5	11	1	5	11
High dose HCTZ	146	103	52	23	31	9	15	10	5	5	10	16
Low dose step II	135	91	62	39	11	4	2	5	4	3	13	18
High dose step II	116	72	40	33	23	2	7	3	2	4	6	17
Total	606	401	264	158	80	25	34	23	22	13	34	62

* Patients entering late who were unable to complete all phases of the study before the termination date.

For causes other than an increase above goal BP, terminations from the study were uncommon: 6% of the control patients and 5% of the reduced dosage group had to be terminated. The most frequent reason was failure to return to the clinic. Other terminations included major cardiovascular complications (5) of which 4 were in patients receiving HCTZ at the time; adverse drug reactions (2) both in patients receiving only placebo; and BP >114 mm Hg on 2 visits or >119 mm Hg on 1 visit (2).

Long-term follow-up: Patients were followed for a maximum of 30 months after randomization. Table III lists the number of patients available for entry into the first 3 postrandomization phases by regimen. Patient attrition during these phases is also shown. The 3 main reasons for a constantly decreasing pool of patients are elevated BP, which was the major study endpoint; terminations for other causes including medical problems such as cardiovascular complications, or administrative reasons such as refusal to return to clinic; and inability to complete all phases before the end of the study because of sequential enrollment. Although 30-month results are listed in Table II, it should be recognized that due to attrition these results are based on a very small sample of patients.

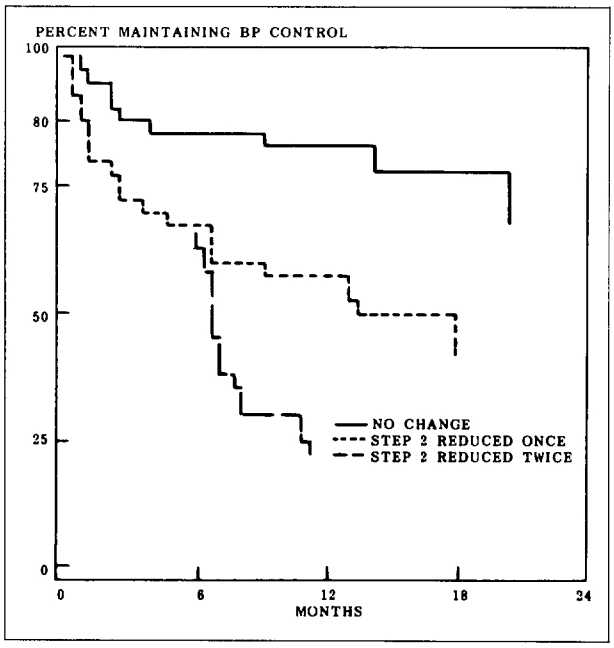

FIGURE 5. Percent of patients on high dose step II regimens remaining under diastolic BP control during 20 months after randomization. During the first reduction (*line with frequent interruptions*) the step II drugs were reduced but not discontinued. HCTZ dosage remained unchanged. At 6 months some of the patients were subjected to a second reduction in which the step II drug was discontinued. Discontinuation of step II drug, despite continuation of HCTZ, was followed by a steep decline of patients remaining under diastolic BP control.

Table II lists the decreasing percent of patients remaining under BP control at 6-month intervals up to 30 months from the time of randomization. Among the low and high dose HCTZ groups the patients most effectively maintaining their BP over time were those in whom doses were reduced rather than discontinued. In fact, up to 18 months after randomization, the percent of high dose HCTZ patients remaining normotensive was essentially the same between the dose reduction and the dose unchanged control groups. Also, among the step II patients in whom dosage was reduced but not discontinued, nearly half maintained BP control up to 30 months.

The long-term results in the patients whose drug was discontinued were not as favorable. Among patients having low dose HCTZ discontinued 23% were able to maintain BP control as long as 30 months (Table II). The patients originally given high dose HCTZ and who after 2 dose reductions were receiving no active drug fared worse: the percentage with BP control decreased to 12% after 30 months of follow-up (Table II, Figure 3). Results of discontinuation of low dose step II drug were also poor (Table II), even though patients continued to take HCTZ. Some of these patients had begun prerandomization treatment with step II regimens. Many others who had begun with HCTZ failed to show BP control on the single drug and were, therefore, advanced to step II. Over 30 months, major complications averaged 3% (n = 6) in the control group and 2% (n = 8) in the reduced dosage group. Thus, dose reduction did not appear to increase the risk of major complications over the period of the study.

Reestablishment of blood pressure control: During the course of the study there were 202 patients on reduced drug dosages whose BP increased above the permissible limits of goal BP and at least 5 mm Hg above the prerandomization level. These patients had their dosages retitrated. Of these 202 patients, 172 were recontrolled on their prerandomization medication and dosage. Thus, the great majority of the patients re-

TABLE IV Biochemical Changes After Six Months of Study Treatment

	Low Dose HCTZ		High Dose HCTZ		Low Dose Step II		High Dose Step II	
	No Change	Reduction	No Change	Reduction	No Change	Reduction	No Change	Reduction
Glucose (mg/dl) (× 0.05551 mmol/liter)	−3.7	−7.7	3.8	2.5	−7.0	3.4	−1.9	0.5
Potassium (mEq/L) × 1.0 mmol/liter)	−0.1	0.6†	0.2	0.2	0.1	−0.1	0.1	−0.1
Cholesterol (mg/dl) (× 0.02586 mmol/liter)	−15.4	−19.9	−2.0	0.3	−18.9	−3.0*	−21.9	1.3
Triglycerides (mg/dl) (× 3.397 mmol/liter)	−35.2	−43.1	14.0	1.0	−1.2	32.7	31.2	−54.6
Uric Acid (mg/dl) (× 59.48 μmol/liter)	−0.2	−0.9†	−0.2	−0.6	−0.1	−0.0	0	−0.2
Alkaline phosphatase (units/liter) (× 7.1 U/liter)	−1.1	7.5*	2.1	2.4	−2.2	1.8	−2.1	−3.0

* $p < 0.05$; † $p < 0.001$.
To obtain the results in SI units multiply the values shown by the appropriate factor in parentheses.

gained BP control on the same dosage they required during initial titration.

Biochemical changes: Table IV lists the mean changes in biochemical serum levels from the time of randomization to 6 months after. Significant differences between treatment groups most frequently occurred in the low dose HCTZ patients in whom all medication was withdrawn. In these patients there was a significant increase in serum potassium levels, a decrease in serum uric acid and an increase in alkaline phosphatase. These changes were not seen in the high dose HCTZ patients possibly because their dosage was only reduced rather than discontinued during the first 6-month postrandomization phase. Serum cholesterol decreased with some regimens and not with others. The reason for the decreases was not apparent. There was considerable variation within groups since only the difference between the control and reduced low dose step II patients was significant ($p < 0.05$). There were no significant changes in fasting blood glucose. Changes in biochemical levels during later postrandomization phases were similar to those in Table IV.

Side effects and compliance: Patient-reported side effects were minimal. Headache was reported on ≥1 visit by 4% of patients. Gout and dizziness occurred intermittently in 3% and 2% of the patients, respectively. There were no significant differences in the incidence of side effects between the drug reduction and the control groups or between the different regimens. No particular side effect was associated with any specific drug or regimen. As estimated by pill counts there was no difference in the level of compliance between the various treatment groups.

Factors predictive of successful dose reduction: Characteristics predictive of successful reduction in medication were investigated using univariate and multivariate analyses. Characteristics differing ($p < 0.20$) between patients in whom medication was successfully reduced or discontinued and those with unsuccessful drug reduction were selected for inclusion in a logistic regression analysis. These characteristics included mean diastolic BP during baseline, variability of BP during baseline, patient compliance, time since diagnosis, hemoglobin, hematocrit, alkaline phosphatase, potassium, white blood cell count and pulse rate. Other factors considered as potential covariates included in the statistical model were race, age, each drug regimen and treatment assignment, i.e., reduction of drug dosage or discontinuation. Variables that contributed significantly to the model included treatment assignment ($p < 0.0001$), baseline diastolic BP ($p = 0.003$) and compliance ($p = 0.0528$). The statistical significance of the randomization treatment assignment rather than the specific drug regimen suggested that drug dosage reduction was more successful than drug discontinuation, regardless of drug regimen group. Patients with a lower diastolic BP during baseline were more likely to maintain BP control, as were compliant patients.

DISCUSSION

There were no significant differences in major patient characteristics between the various treatment groups. Sample sizes were adequate in all groups and remained adequate up to 18 months after randomization. Black patients equalled 52% of the total. The study was limited to men. After randomization the patients whose drugs were reduced but not entirely discontinued maintained more effective BP control than those whose drugs were completely discontinued. The latter group included patients whose sole medication of HCTZ 25 mg twice daily was suddenly discontinued. The second most frequent group to develop BP elevation was patients receiving the low dose step II regimens. These patients continued to take HCTZ (only the step II drug was discontinued). The failure of HCTZ alone to control BP in these patients may have been due, at least in part, to their more resistant hypertension. They had failed to achieve normalization of BP with HCTZ alone during titration of dosage. The percent of step II patients maintaining BP control was slightly greater among the high dose step II patients in whom step II medication was reduced rather than discontinued. After 6 months, however, the difference was not significant. The greatest percent of patients maintaining control BP despite dose reduction was achieved in the high dose HCTZ group. Their dose was reduced from 50 to 25 mg twice daily. These patients maintained levels of BP that closely approximated the control group whose dosage was not reduced.

The highest percentage of patients whose BP increased to hypertensive levels was those whose medication was completely discontinued. Within each treatment regimen, the patients most likely to increase diastolic BP to >89 mm Hg were those with higher levels

of diastolic BP at randomization. By the time of the second dose reduction most patients were receiving minimal or no therapy. In the patients receiving HCTZ alone and randomized to medication reduction, HCTZ had been stopped, while in the patients on step II treatment only HCTZ was maintained. No further reductions in dosage were made after the second randomization. Despite minimal or no medication the rate at which patients exhibited return of hypertension diminished after the first 12 months following randomization. This was probably because no further dosage reductions occurred during that period and also because patients most susceptible to lose BP control had experienced BP elevations during their first year in the trial. However, following the second reduction, at 6 months many of the patients failed to maintain normal BP when most antihypertensive drugs were discontinued (Figures 3 and 5). The critical factor, therefore, seemed to be whether the medication was reduced or completely discontinued.

It is possible that after the first 6 months following the initial reduction, the patients remaining in the trial represented a population that for various reasons were better able to maintain their BP within normal limits following treatment discontinuation. Although not instituted in this study, weight reduction and sodium restriction have been used with some success in preventing the return of elevated blood pressure after drug withdrawal.[11]

The relative lack of purely drug-related side effects in this study applied to all drug regimens including reserpine plus HCTZ. However, more than half of the patients received only 0.1 mg reserpine daily. These results confirm our former study of small doses of reserpine with HCTZ.[10]

The present results suggest that degree of elevation of the prerandomization diastolic BP was significantly related to the return of hypertension. The patient's BP variability before randomization also directly correlated with return of hypertension. It is also possible that some of the mildly hypertensive patients had only temporary elevations of BP when admitted to the trial and they returned spontaneously to normal after repeated visits.[12] The present results suggest that after long-term treatment, dosage reduction is more effective in preserving antihypertensive control than is discontinuation of medications. Dose reduction should be advantageous over the long term because smaller doses reduce the risk of adverse effects and decrease the cost of treatment.

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APPENDIX

The following persons participated in the study.

Chairman's Office: Barbara Gregory, BSN, Washington, DC.

Consultant: Barry J. Materson, MD, Miami, Florida.

Clinic Associates: Debbie Ohlen, PA, Patricia Kershen, PA, Dallas, Texas; Ruth Collins, RN, Houston; Phyllis Mangas, FNP, Dayton, Ohio; Lorretta Hoerman, PA, St. Louis, Missouri; Mary Jo Barsotti-Tracey, MS, Barbara Lesniak, East Orange, New Jersey; Anne M. Faiella, BSN, Catherine Cummings, RN, Boston, Massachusetts.

Cooperative Studies Program Coordinating Center: William G. Henderson, PhD, Jean Rowe, Laura Weber, MS, Mary Ellen Vitek, Hines, Illinois.

Cooperative Studies Program Clinical Research Pharmacy: Larry M. Young. RPh, Jane Weber-San-Hamel, PharmD, Dennis Toussaint, RPh, Mike Sather, RPh, Albuquerque, New Mexico.

Operations Committee: Morten H. Maxwell, MD, Chairman, Walter M. Kirkendall, MD, Theodore Colton, ScD.

Cooperative Studies Program Central Administration: Daniel Deykin, MD, Janet Gold, Boston; James A. Hagans, MD, PhD, Ping Huang, PhD, Washington, DC.

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