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Effects of Treatment on Morbidity in Hypertension

II. Results in Patients With Diastolic Blood Pressure Averaging 90 Through 114 mm Hg

Veterans Administration Cooperative Study Group on Antihypertensive Agents

Three hundred and eighty male hypertensive patients with diastolic blood pressures averaging 90 to 114 mm Hg were randomly assigned to either active antihypertensive agents or placebos. The estimated risk of developing a morbid event over a five-year period was reduced from 55% to 18% by treatment. Terminating morbid events occurred in 35 patients of the control group as compared to 9 patients in the treated group. Nineteen deaths related to hypertension or atherosclerosis occurred in the control group and 8 in the actively treated group. In addition to morbid events, 20 control patients developed persistent diastolic levels of 125 mm Hg or higher. Treatment was more effective in preventing congestive heart failure and stroke than in preventing the complications of coronary artery disease. The degree of benefit was related to the level of prerandomization blood pressure.

In a previous publication in this journal[1] the Veterans Administration Cooperative Study Group on Antihypertensive Agents reported on the beneficial effects of antihypertensive drugs on morbidity in patients with moderately severe hypertension. These were patients with initial diastolic blood pressures averaging 115 through 129 mm Hg who had been randomized into a prospective double-blind trial of active antihypertensive drugs vs placebos. Twenty-seven patients developed assessable events in the control group as compared to two patients in the group receiving active antihypertensive agents. This striking result favoring treatment was in agreement with the results of other prospective trials[2,3] in patients with hypertension of similar severity.

In hypertension of lesser severity, however, there are little or no controlled data available on the value of antihypertensive drug therapy. Resolution of this question is of great importance not only because of the large number of patients with mild hypertension but also because the potential benefits of drug treatment have been questioned especially in this group of hypertensive patients.[4] The present report presents the results of a prospective, controlled trial of drug treatment on morbidity and mortality in a group of 380 patients with mild or moderate hypertension whose initial

For complete list of participants, see page 1152.

Reprint requests to 50 Irving St NW, Washington, DC 20422 (Dr. Freis).

diastolic blood pressure averaged 90 through 114 mm Hg.

Plan of Investigation

The clinical trial included 523 male veterans who, while not receiving antihypertensive treatment, exhibited diastolic blood pressures averaging 90 through 129 mm Hg. Randomization of patients began in April 1964. However, in May 1967, the study was terminated in the subgroup of 143 patients whose diastolic blood pressures averaged 115 through 129 mm Hg prior to randomization. Termination of the study of this group as previously reported[1] was necessitated by the high incidence of morbid events in the control as compared to the treated patients, demonstrating at a relatively early date a highly significant ($P < 0.001$) effect of treatment. Such a significant difference was not evident at the time, however, in the patients whose diastolic blood pressures averaged below 115 mm Hg prior to randomization. These latter patients were continued in the randomized trial until 1969 and are the subject of the present communication.

The experimental design has been described in previous reports.[1,5] Initially all patients were hospitalized for diagnosis and evaluation of the severity of their hypertension. Patients whose diastolic blood pressure averaged 90 through 129 mm Hg during the fourth through sixth hospital day were accepted for further follow-up. Patients whose diastolic averages fell below 90 mm Hg or rose above 129 mm Hg during this period of hospitalization were excluded.

Following hospitalization the patients entered a prerandomization observation period of two to four months' duration during which time they received placebos of antihypertensive agents. The patients whose diastolic blood pressures during the last two clinic visits of the observation period averaged 90 through 129 mm Hg were entered into the trial, providing there were no other reasons for exclusion. Blood pressure was measured by a physician with the patient in a sitting position.

Other reasons for excluding patients from the trial, in addition to diastolic blood pressure, are detailed in other reports.[1,5] Such reasons included a history of a severe hypertensive complication such as a cerebral or subarachnoid hemorrhage, hypertensive neuroretinopathy, dissecting aneurysm, or renal failure, but did not include atherosclerotic complications such as coronary artery disease or cerebrovascular thrombosis. Also excluded were (1) patients with surgically curable hypertension, (2) with unrelated fatal diseases such as malignant tumors, (3) those unwilling or unable to return to clinic, and (4) poorly motivated or otherwise uncooperative or unreliable patients.

The outpatient prerandomization observation period provided a further opportunity to check on the reliability of the patients. Riboflavin, which produces bright yellow fluorescence of the urine, was incorporated in the placebos. At each clinic visit a urine specimen was examined under ultraviolet light. In addition, pill counts were made at each clinic visit. No patient was accepted into the randomized trial unless the urine exhibited fluorescence and the pill counts were within a stipulated range, at each of two successive visits during the prerandomization observation period.

Accepted patients were then randomly assigned double-blind to either active drugs or placebos. Active drugs consisted of two types of tablets, one being a combination tablet containing 50 mg hydrochlorothiazide and 0.1 mg reserpine which was given twice daily. The other was 25 mg of hydralazine hydrochloride given three times daily. The latter medication was raised to 50 mg three times daily if the diastolic blood pressure remained at 90 mm Hg or higher. Obviously, practically all of the patients in the placebo group had their "doses" raised to this level. Provision was made for reduction of doses if hypotensive reactions or other disturbing side effects occurred. Patients in the control group received placebos identical in taste and appearance to the active drugs. Indicated symptomatic treatment, including drugs other than antihypertensive agents, was permitted in all patients.

Postrandomization clinic visits were at monthly intervals for the first two months and at bimonthly intervals thereafter. Annual examinations included taking a history and a physical examination, roentgenogram of the chest, electrocardiogram, pertinent chemical analyses of the blood, and renal function tests. Additional interim visits could be scheduled when indicated.

Characteristics of Patients

Three hundred and eighty patients with diastolic blood pressures averaging 90 through 114 mm Hg were randomized into the trial. Of this number, 186 received active drugs while 194 were given placebos. Tables 1 and 2 indicate that the two groups were comparable according to the indicated variables. The median ages were 49.2 and 48.1 years and the average ages were 52.0 and 50.5 years in the control and treatment groups, respectively. Negro patients comprised 42% of the control group and 41% of the treated group. Blood pressure as measured in the clinic during the posthospitalization observation period prior to randomization averaged 165.1/104.7 mm Hg in the control group and 162.1/103.8 mm Hg in the treated patients. There were no significant differences between the control and treated pa-

tients with regard to findings from renal function tests, fasting blood sugar value, serum cholesterol value, uric acid level, and left ventricular enlargement as assessed by x-ray films and electrocardiography. By all factors measured the two groups were comparable.

Duration of Observation

Patients were entered into the trial from April 1964 to September 1968, and the study was terminated in October 1969. Thus, the earliest entrants were observed for 5.5 years and the latest entrants for a minimum of 1 year. The average potential duration of observation, disregarding losses and terminations, was 3.9 years for the control group and 3.7 years for the treated patients. However, because of the losses and terminations due to elevated diastolic blood pressure described below, the actual duration of postrandomization observation was 3.3 years for the control group and 3.2 years for the treated patients.

Changes in Blood Pressure

Systolic and diastolic blood pressure fell promptly and significantly in the treated patients and remained at reduced levels throughout the trial. The changes in blood pressure at the fourth month of observation in the treated and control patients are depicted in Fig 1. The mean change in systolic blood pressure was an increase of 4.2 mm Hg in the control group and a fall of 27.2 mm Hg in the treated patients from the levels recorded during the prerandomization observation period. The mean change in diastolic blood pressure was a rise of 1.2 mm Hg in the control patients and a fall of 17.4 mm Hg in the treated group during this same interval. The distribution of the changes in blood pressure as shown in Fig 1 indicates a marked shift to the left into the "decrease" zone for the treated patients as compared to the control group. Also apparent is the wide variation in individual responses particularly with regard to systolic blood pressure.

Table 1.—Background of Randomized Patients: Numeration Data

Characteristic	Control Group No.	Control Group %	Treatment Group No.	Treatment Group %	Total
Total randomized	194		186		380
Negro	81	42	76	41	157
Other*	114	58	109	59	223
Heart size by roentgenogram					
Ungerleider enlarged	42	22	53	29	95
Electrocardiogram					
Left ventricular hypertrophy	32	16	30	16	62

*In addition to whites, this group includes four patients of Asiatic extraction, two in the control group and two in the treated group.

Table 2.—Measurement Data Prior to Randomization

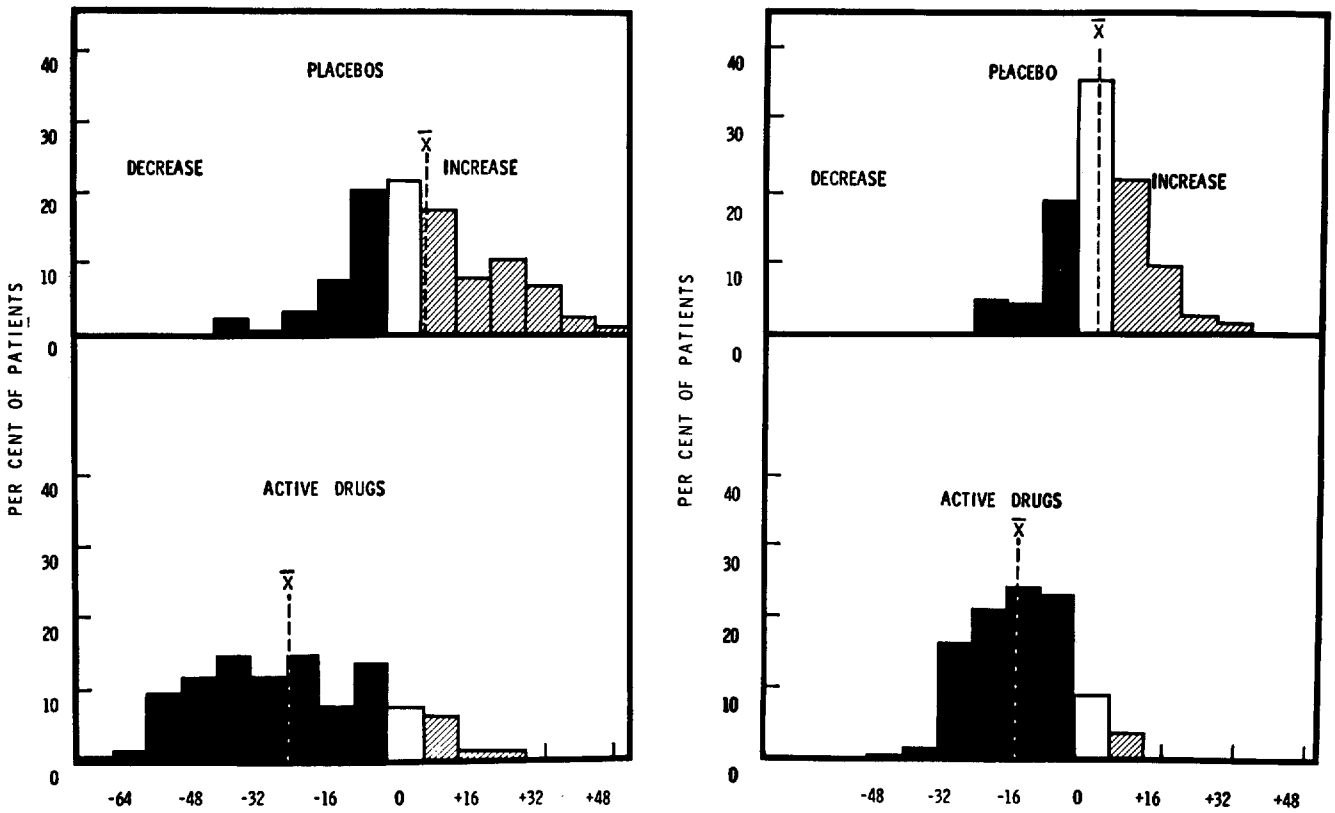
Characteristic	Control Group Mean	Treatment Group Mean
Age (yr)	52.0	50.5
Age (median, yr)	49.2	48.1
Height, cm (ft, in)	175.3 (5, 9)	172.7 (5, 8)
Weight, kg (lb)	82.0 (180.9)	79.8 (176.1)
Duration known hypertension (yr)	4.4	4.6
Average hospital diastolic pressure (mm Hg)	101.3	100.2
Average hospital systolic pressure (mm Hg)	157.5	154.0
Average clinic diastolic pressure (mm Hg)	104.7	103.8
Average clinic systolic pressure (mm Hg)	165.1	162.1
Total severity score*	6.7	6.8
Renal score (0-4)	0.2	0.2
Cardiac score (0-4)	0.8	0.9
CNS† score (0-4)	0.3	0.3
Serum creatinine (mg/100 cc)	1.26	1.24
BUN (mg/100 cc)	15.6	16.2
Serum potassium (mEq/liter)	4.4	4.4
PSP‡ excretion (% in 2 hr)	58.8	60.0
Fasting blood glucose (mg/100 cc)	96.5	100.4
Cholesterol (mg/100 cc)	250.1	245.0
Uric acid (mg/100 cc)	6.3	6.0

*Detailed criteria for grades 0 through 4 given in reference 6.
†CNS signifies central nervous system.
‡PSP signifies phenolsulfonphthalein.

Losses Other Than Assessable Events

Deaths Due to Unrelated Conditions.—Four patients died of disorders unrelated to hypertension. Two of the patients were in the control group. One died of generalized carcinomatosis demonstrated at autopsy and the other of uremia secondary to carcinoma of the urinary bladder. One patient in the treated group died of a subdural hematoma following a skull fracture and another of penicillin anaphylaxis. Postmortem examination was carried out in both of these patients.

Losses Due to Drug Toxicity.—Two patients in the treatment group developed reactions thought to be due to drug toxicity. The first patient developed orbital edema with fever and malaise. Roentgenogram of the chest revealed infiltrates in the lungs. There was no dermatitis or arthritis. Lupus cells were not found in the blood although the antinuclear antibody test was positive. Protocol drugs were discontinued because of the possibility of lupus syndrome associated with hydralazine. The second patient developed purpura one month after beginning active drug treatment. Findings from examination in the hospital, including biopsy, were con-



1. Changes in systolic (left) *and diastolic blood pressure* (right) *after four months of treatment in patients given placebos* (top) *and in patients treated with active drugs* (bottom). *Mean of changes* ($\bar{X}$).

sistent with anaphylactoid purpura. The purpuric lesions cleared two weeks after protocol treatment was discontinued and reappeared within three days after administration of active drugs began again. Protocol treatment was, therefore, discontinued.

Drop-Outs.—Fifty-six or 15% of the 380 randomized patients were classified as drop-outs during the course of the trial. Of this number 27 had been randomized to receive placebos and 29 to receive active drugs. The average period of follow-up prior to dropping out was 17.6 months with a range from less than 1 month to 49 months. Six patients moved away from the area of the clinic. Two were lost from follow-up because of closure of one participating clinic. Four returned to the care of their private physicians. Fifteen complained of side effects prior to dropping out. Nine of these patients had been receiving drugs, and six were taking placebos. Five patients had psychiatric or alcoholic problems of such severity as to make continued protocol treatment impractical. In the remaining patients the reason for drop-out could not be determined. It should be noted that three of the patients taking placebos sustained nonterminating morbid events prior to their dropping out.

Assessable Morbid Events

The records of the patients reported as having assessable morbid events were reviewed by two consulting physicians who had not participated in the trial. All assessable events were reviewed except those related to the development of electrocardiographic signs of left ventricular hypertrophy or of roentgenographic evidence of cardiac enlargement, which will be reported in a subsequent communication. All available data pertaining to each organic complication, except the type of protocol treatment and the level of blood pressure, were presented to the reviewers and their decisions regarding the occurrence and classification of an event according to the definitions given in the protocol (see list of assessable events at the end of the communication) were accepted as final.

Table 3 summarizes the assessable events by major categories. Such events occurred in 98 of the 380 randomized patients, 76 in the control group and 22 in the treated patients. Of this number 20 control patients developed an increase in

diastolic blood pressure to levels exceeding 124 mm Hg on three separate clinic visits and persisting for 3 weeks or longer. Since these patients were removed from the trial only because of persistent blood pressure elevations and not for an organic complication, they will not be included in the subsequent assessment of effectiveness of treatment in preventing morbid events.

The remaining 78 patients had organic complications subdivided as follows: 56 of 194 or 28.9% of the control group and 22 of 186 or 11.8% of the treated patients. The most striking evidence of benefit of treatment was manifested in the count of class A events (hypertensive complications defined in the protocol which required removal of the patient from the study.[1] There were none among the treated patients but 14 among the controls. These included five class A deaths (Table 4) plus nine other class A events (Table 5). When other cardiovascular (class B) deaths and treatment failures were added, the comparisons were still impressive, 35 of 194 patients or 18.0% amongst the controls and only 9 of 186 or 4.8% in the treated group (Table 3). The effectiveness of treatment (difference in percent incidence of complications between control and treated groups divided by the percent incidence in the control group) in preventing terminating organic complications was 73% (Table 3). The decision to discontinue the trial was based on this favorable evidence supplemented by the life-table analyses described below which suggested that the benefit of treatment was continuing through time and was not solely concentrated in the first year or two of treatment.

Terminating Events. — DEATHS RELATED TO CARDIOVASCULAR DISEASE.—Twenty-seven patients died of hypertensive or atherosclerotic complications, 19 occurring in the control group and 8 in the treated patients (Table 4). Five deaths associated with class A or hypertensive events (see list of assessable events at the end of the communication) were cerebral hemorrhage in four and dissecting aortic aneurysm in one, all occurring in the control group of patients. Deaths resulting from class B events were associated predominantly with coronary artery disease. Eleven patients in the placebo group and 6 in the treated group had either a documented myocardial infarction or a "sudden death." Cerebrovascular thrombosis as opposed to hemorrhage was the cause of death in three control patients and in one treated patient. The remaining

Table 3.—Summary of Assessable Events

	Control Group		Treated Group		
	No.	%	No.	%	% Effectiveness*
Terminating morbid events†	35	18.0	9	4.8	73
Nonterminating B events	21		13		
Total morbid events	56	28.9	22	11.8	59
Terminated on account of elevated blood pressure	20		0		
Total assessable events	76	39.2	22	11.8	70
No. patients randomized	194	100.0	186	100.0	

*See text.
†Includes cardiovascular deaths, class A events, and treatment failures except those due to diastolic levels >124 mm Hg.

Table 4.—Causes of Death

Cause	Control Group	Treated Group
Deaths due to class A events		
Cerebrovascular hemorrhage	3	0
Subarachnoid hemorrhage	1	0
Dissecting aneurysm	1	0
Deaths due to class B events		
Myocardial infarction	3	2
Sudden death	8	4
Cerebrovascular thrombosis	3	1
Ruptured atherosclerotic aneurysm	0	1
Total related deaths*	19	8

*Does not include four unrelated deaths, two in the control group and two in the treated group (see text).

Table 5.—Terminating Morbid Events Other Than Death

Type of Event	Control Group	Treated Group
Class A events		
Uncontrolled cardiac failure	5	0
Dissecting aortic aneurysm	1	0
Subarachnoid hemorrhage	1	0
Fundi, striate hemorrhages	1	0
Acute hypertensive encephalopathy	1	0
Subtotal	9	0
Treatment failures		
Cerebrovascular thrombosis, severe	4	0
Progressive azotemia	1	0
Fundi, one striate hemorrhage and ? early papilledema	1	0
Fundi, one striate hemorrhage and ? encephalopathy	1	0
Hypotension	0	1
Subtotal	7	1
Total	16	1

Table 6.—Nonterminating Class B Events

Type	Control Group	Treated Group
CVA, thrombosis or TIA*	8	4
Congestive heart failure†	6	0
Myocardial infarction	2	5
Atrial fibrillation	2	3
Heart-block	1	1
Serum creatinine, persistent, >2.0 mg/100 cc	1	0
Proteinuria, persistent, >1+	1	0
Total	21	13

*Cerebrovascular accident, either a thrombosis (clinical diagnosis) or transient ischemic attack with objective neurological signs.
†Controlled by administration of digitalis and short-term diuretics.

Table 7.—Classification of Morbid Events by Diagnostic Categories

Diagnosis	Total Events		Terminating Events	
	Control	Treated	Control	Treated
Cerebrovascular accident	20	5	12	1
Coronary artery disease	13	11	11	6
Congestive heart failure	11	0	5	0
"Accelerated" hypertension	4	0	4	0
Renal damage	3	0	1	0
Other	5	6	2	2
Total	56	22	35	9

death in the treated group was caused by a rupture of an atherosclerotic aneurysm of the aorta.

OTHER CLASS A EVENTS.—Nine patients in the control group as opposed to none in the treated group developed nonfatal class A events (Table 5). Five of the patients had congestive heart failure which could not be controlled by administration of digitalis, sodium restriction, and the intermittent administration of diuretics. In the four remaining patients there was one instance of each of the following complications: dissecting aortic aneurysm, subarachnoid hemorrhage, multiple striate retinal hemorrhages, and acute hypertensive encephalopathy with accompanying neurological signs.

OTHER TERMINATING EVENTS.—Additional organic complications, which did not fulfill the criteria for class A events but which were nevertheless of sufficient severity to require terminating protocol treatment occurred in eight patients of which seven were in the control group. These are listed in Table 5 under the subtitle "treatment failure." Four were associated with cerebrovascular accidents diagnosed clinically as thrombosis rather than hemorrhage but which resulted in such severe incapacity that the patients were unable to attend the clinic. Two additional control patients were removed from the study because of the appearance of a single striate retinal hemorrhage associated in one with symptoms suggesting acute hypertensive encephalopathy, and, in the other, with questionable early papilledema. The remaining control patient exhibited increasing azotemia. One patient in the treated group was removed from the study because of hypotension following a myocardial infarction which resulted in his inability to tolerate the antihypertensive regimen. It is noteworthy that of the 17 nonfatal terminating events (class A and others) 16 occurred in the control group and only one in the treated patient (Table 5).

Nonterminating (Class B) Events.—Class B events include organic complications which require no or only temporary suspension of protocol treatment (see list of assessable events listed at the end of the communication). Objectively demonstrable atherosclerotic complications predominate as class B events, but the category also includes congestive heart failure responsive to routine therapy other than administration of antihypertensive drugs and certain less severe manifestations of renal disease.

Nonfatal class B events occurred in 21 of the control patients and in 13 of the treated patients (Table 6). Six patients developed congestive heart failure controllable by digitalis and short-term administration of diuretics. It is noteworthy that all six of these patients were in the control group. Also, the incidence of nonterminating cerebrovascular accidents was twice as great in the control as in the treated patients. However, nonfatal myocardial infarction occurred in five of the treated patients as opposed to two of the control group. The incidence of atrial fibrillation and conduction defects was essentially the same in the two groups.

Life-Table Analysis.—The benefit of treatment is more precisely analyzed using life-table methods (Fig 2). This method has the following advantages: (1) it adjusts for the fact that patients enter the study at different times and thus are observed for varying lengths of time; (2) the method adjusts for any differences in losses to observation between the control and treated groups; and (3) most important, it determines whether the benefit of treatment occurs early or late or is continuing through time. The distance separating the control and treatment lines is a measure of the degree of benefit.

It is clear from Fig 2 that the benefit of treatment manifested itself early and continued throughout the entire five years of follow-up. The life-table analysis of either terminating or all morbid events indi-

Table 8.—Incidence of Morbid Events With Respect to Level of Prerandomization Blood Pressure

Prerandomization Blood Pressure, mm Hg	Control Group			Treated Group			% Effectiveness
	Patients Randomized	Patients With "Morbid Event"		Patients Randomized	Patients With "Morbid Event"		
		No.	%		No.	%	
Systolic <165	98	15	15.3	108	10	9.3	40
Systolic 165+	96	41	42.7	78	12	15.4	64
Total	**194**	**56**		**186**	**22**		
Diastolic 90-104	84	21	25.0	86	14	16.3	35
Diastolic 105-114	110	35	31.8	100	8	8.0	75
Total	**194**	**56**		**186**	**22**		

Table 9.—Incidence of Morbid Events With Respect to Age and Race

	Control Group			Treated Group			
	Patients Randomized	Patients With "Morbid Event"		Patients Randomized	Patients With "Morbid Event"		% Effectiveness
Age (on admission)		No.	%		No.	%	
<50 yr	99	15	15.2	102	7	6.9	55
50 & over	95	41	43.2	84	15	17.9	59
Total	**194**	**56**		**186**	**22**		
Race							
Negro	81	21	25.9	76	8	10.5	54
Other	113	35	31.0	110	14	12.7	59
Total	**194**	**56**		**186**	**22**		

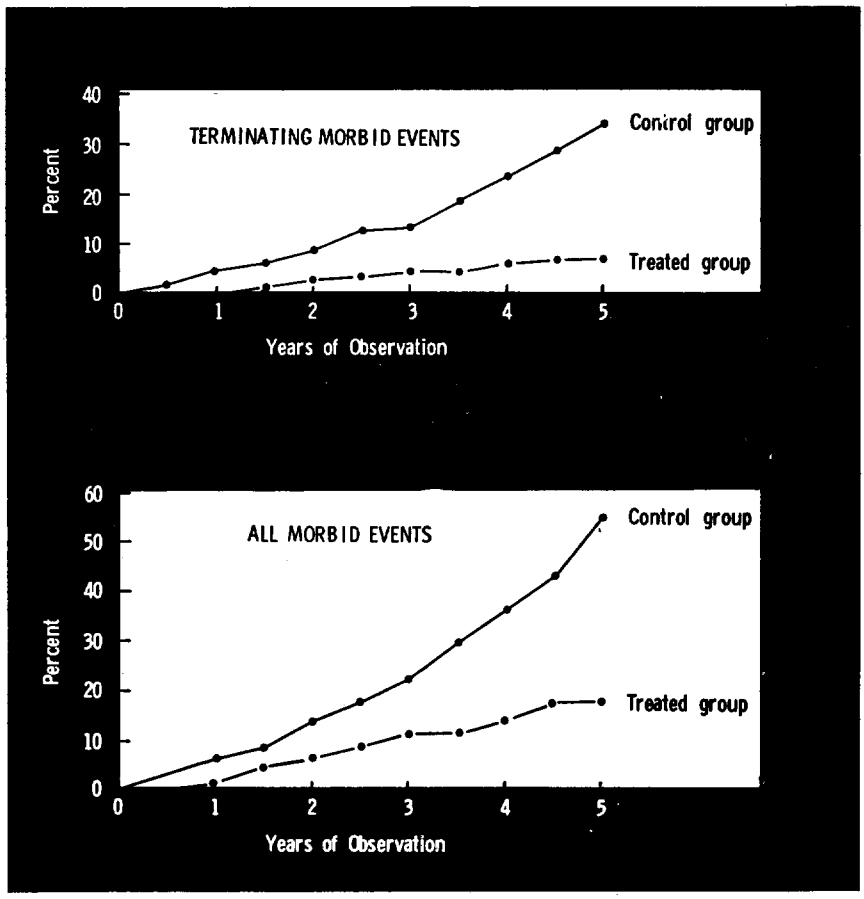
cates that the benefit increased with time. For example, with respect to "all morbid events" it may be seen that at three years the estimated cumulative incidence of morbidity in the control group is twice as great as in the treated patients. This suggests that treatment was about 50% effective at three years. At five years the spread between the two curves was substantially greater indicating an increasing degree of benefit with the passage of time. Specifically, at five years the cumulative incidence rate of events for the control group rises to 55%. By contrast, for the treated group the indicated incidence of events at five years is only 18%. It can be estimated, therefore, that over a five-year period treatment prevented 37% morbidity (55% minus 18%), and this represents a 67% effectiveness (37/55).

The standard errors at five years were 6.3% for the control patients and 4.0% for the treated group. The significance of the difference between the two rates of 55% and 18% yielded a *t*-value of 5.0 which is highly significant. A crude estimate gave confidence limits of 49% to 81% for the observed 67% effectiveness.

Relationship of Treatment to Other Factors.—Relationship to Diagnostic Categories.—It is revealing to examine the incidence of morbid events as related to treatment when the events are classified according to diagnostic categories (Table 7). Thus, in the control vs the treated groups, the prevalence of congestive heart failure was 11:0, of renal deterioration 3:0, and of "accelerated" hypertension (hypertensive neuroretinopathy or encephalopathy) 4:0. The number of cerebrovascular complications also seemed to be considerably influenced by treatment since the ratio of cerebrovascular events in the control vs treated patients was 20:5, and, of the more severe or terminating cerebrovascular events, it was 12:1. On the other hand, assessable events caused by coronary artery disease (myocardial infarction or sudden death) were nearly the same in the two groups, 13 in the control and 11 in the treated, although fatal coronary events were somewhat greater in the control group.

Relationship to Prerandomization Blood Pressure.—The beneficial effect of treatment was most evident in the patients with higher initial levels of blood pressure. With respect to diastolic blood pressure the effectiveness of treatment was 75% in the patients with prerandomization diastolic blood pressure averaging 105 through 114 mm Hg as opposed to only 35% in the group averaging 90 through 104 mm Hg (Table 8). A similar although somewhat less striking trend was noted with respect to systolic blood pressure, the effectiveness of treatment being 64% in patients with initial systolic levels averaging 165 mm Hg and above as opposed to 40% in the group with lower initial systolic blood pressure.

Relationship to Age.—The majority of the patients developing



2. Estimated cumulative incidence of morbidity over a five-year period as calculated by life-table method. Terminating morbid events (top) *and all morbid events* (bottom).

morbid events were in the older age group. Of the 56 control patients developing morbid events 41 were 50 years of age or older at the time of admission to the study, while only 15 were below age 50. A similar distribution was found with respect to the treated patients. The percent effectiveness of treatment was approximately the same in the younger and older groups (Table 9). However, because of the lower number of events in the patients below age 50 the estimated effectiveness of treatment cannot be accepted with the same degree of confidence as in the older patients.

RELATIONSHIP TO RACE.—The incidence of morbid events was no greater in Negro patients. In fact, in the control group the incidence of events was slightly lower in Negroes, 25.9% as opposed to 31.0% of the other patients. A similar relationship was noted in the treated patients (Table 9). The percent effectiveness of treatment was essentially the same in the two racial groups.

Side Effects

In the treated group of patients dosage adjustments frequently were required because of hypotensive and other symptoms. A complete analysis of these and other side effects will be made in a subsequent communication. The two patients lost to protocol because of drug toxicity have been described above. In addition, in the present report only those side effects requiring removal of either reserpine or hydrochlorothiazide from the treatment regimen will be considered.

Administration of either reserpine or hydrochlorothiazide or their placebos was withdrawn because of side effect in 29 patients. Reserpine and hydrochlorothiazide were administered combined in a single tablet. In order to avoid losses to protocol because of side effects presumably caused by one or the other of the two agents, provision was made to permit substitution of a tablet which contained either reserpine or hydrochlorothiazide alone and omitted the offending medication. These special tablets were made available on request of a participating physician. Similar-appearing placebo tablets were made available for the control patients and the physician did not know whether the substitution represented active drugs or placebos.

In the majority of the 29 patients substitution of the special tablet was necessitated by presumed reserpine-induced side effects. Mental depression occurred in 12 patients. However, only seven of these patients had been receiving active drugs while the remaining five had been randomly selected to receive placebos. Ten patients developed peptic ulcer of which six had been taking active drugs and four placebos. In two patients substitution was made because of impotence; one of these two had been randomly selected to receive the placebo regimen. The remaining six patients all were receiving active treatment. Their side effects included sleepiness, severe nasal stuffiness, gout, seizures presumably caused by hypotension, and abnormal results from the glucose tolerance test.

Comment

The effectiveness of treatment was clearly demonstrated in the patients with prerandomization systolic blood pressures above 164 or diastolic pressure above 104 mm Hg. The difference in the incidence of morbid events between control and treated patients was less clear cut in the patients with blood pressures below these levels. This may be due to the fact that organic complications appear slowly in mild hypertension as indicated by the considerably lower incidence of such events in patients with blood pressures below 165/105 mm Hg.

As would be expected, a greater incidence of organic complications occurred in the older than in the younger patients. Of considerable importance is the observation that treatment was found to be effective in reducing the number of such complications in these older patients. Although the indicated effectiveness of treatment was essentially the same in patients above and below age 50 years, the results were not as convincing in the younger group because of the low incidence of morbid events in both the control and treated patients. It should be mentioned, however, that in the group of 20 control patients, not counted as having morbid events but who were removed from the study because of persistent elevation of diastolic blood pressure greater than 124 mm Hg, 14 so removed were below 50 years of age.

Treatment was most effective in preventing hypertensive complications and least effective in preventing atherosclerotic complications, particularly those associated with coronary artery disease. Complications such as congestive heart failure, renal damage, cerebrovascular hemorrhage, and accelerated hypertension occurred only in the control group. On the other hand, the incidence of complications associated with coronary artery disease was essentially the same in the control and treated patients.

Because of the gradual progression of atherosclerosis, the negative result with regard to prevention of myocardial infarction and sudden death cannot be taken as evidence that treatment is ineffective. Continuation of the present study was not justified because of the favorable evidence with regard to prevention of hypertensive complications. If follow-up had been longer, and if administration of antihypertensive drugs had been started at an earlier age, a significant difference might have been demonstrated. The average age of the patients was 51 years and hypertension could have been present for many years prior to randomization. Atherosclerosis of the coronary arteries, therefore, may have been well established at the time of entrance into the study. Further trials are needed in a more selected population to determine whether antihypertensive treatment helps prevent coronary artery disease.

It is of interest to compare the results of the present series of patients whose initial diastolic blood pressures averaged 90 through 114 mm Hg with the results previously reported in the patients whose diastolic blood pressures at the beginning of study averaged 115 through 129 mm Hg.[1] The benefit of treatment was quickly manifested in the latter series. Thirty-eight percent of the control patients in that series developed assessable events over an average period of only 15.7 months of postrandomization follow-up, whereas such events occurred in only 3% of the treated patients. A considerably longer period of follow-up was required to demonstrate a significant benefit of treatment in the presently reported series of patients with lower levels of diastolic blood pressure.

The distribution as to type of events also was different in the two groups of patients divided according to level of initial diastolic blood pressure. In the control patients with initial diastolic levels of 115 through 129 mm Hg accelerated hypertension with hypertensive neuroretinopathy was the most frequent complication. In the present series cerebrovascular disease, congestive heart failure, and coronary artery disease were the most frequent morbid events occurring in the control group. Of the four control patients who died in the previously reported series of patients with high diastolic pressures, three deaths were caused by dissecting or ruptured aortic aneurysm whereas the most common causes of death in the series of patients with lower diastolic pressures were strokes, myocardial infarcts, and sudden death.

It should be emphasized that the present study dealt with a selected population. Many uncooperative and unreliable patients were identified and eliminated from the trial on the basis of pill counts, urine fluorescence test results, and irregularity of clinic attendance during a prerandomization observation period. Treatment obviously would not have been as effective in a group of patients less carefully selected with regard to their desire to cooperate. The population was further limited in that it excluded female patients and patients with labile hypertension whose diastolic blood pressures averaged lower than 90 mm Hg during the fourth through the sixth day of hospitalization. Finally, the incidence of morbid events in the group below age 50 was relatively low. Further studies are needed to evaluate the effectiveness of treatment in labile hypertension and in the prevention of atherosclerotic complications, particularly coronary artery disease. Such studies would seem to require larger numbers of younger patients

who can be followed up for long periods of time.

Within the limits defined by this study, however, the present results leave little doubt that antihypertensive drug treatment is beneficial. The present results together with those previously reported in patients with initial diastolic blood pressures of 115 through 129 mm Hg[1] indicate clearly that the higher the level of blood pressure the greater the degree of benefit of such therapy. Certain complications such as congestive heart failure, hypertensive neuroretinopathy,[1] strokes, and renal deterioration were reduced or essentially eliminated in the treated patients. In addition, treatment prevented elevation of diastolic blood pressure to levels where the risk of developing hypertensive complications is greatly increased. The effectiveness of the treatment in preventing such progression is indicated by the fact that while persistent elevation of diastolic blood pressure exceeding 124 mm Hg occurred in approximately 10% of the control patients, they were completely absent in the treated group.

Participants

Permanent Members of the Study Group: Massimo Calabresi, MD; C. Hilmon Castle, MD; Leo Elson, MD; Edward D. Freis, MD, *Chairman*; Rudolph E. Fremont, MD; Michael A. Harris, MD; David Littman, MD; Eli A. Ramirez, MD; and J. R. Thomas, MD.

Other Members: Luis A. Arias, MD; Mark L. Armstrong, MD; Alston W. Blount, MD; Thomas A. Bruce, MD; Ovid B. Bush, Jr., MD, *deceased;* Eugene C. Clark, MD; Annette Fitz, MD, R. M. Freeman, MD; Edward D. Frohlich, MD; Arthur Gear, MD; John D. Kyriacopoulos, MD; Alan F. Lyon, MD; Gloria D. Massaro, MD; Donald McCaughan, MD; Jean Morgan, MD; Henry W. Overbeck, MD; Eliseo C. Perez-Stable, MD; Mitchell Perry, MD; Roger Sutton, MD; and James Taguchi, MD.

Participating Veterans Administration Hospitals: Allen Park, Michigan; Birmingham, Ala; Brooklyn, NY; Dayton, Ohio; Iowa City; Jackson, Miss; Memphis; Nashville, Tenn; Oklahoma City; Pittsburgh; Richmond, Va; Salt Lake City; St. Louis; San Juan, PR; Washington, DC; West Haven, Conn; and West Roxbury, Mass.

Biostatisticians: Russell B. Tewksbury, ScD, and Lawrence W. Shaw.

Central Office Coordinator: Harold W. Schnaper, MD.

Consultants: Jacques Genest, MD; Ray W. Gifford, Jr., MD; Walter M. Kirkendall, MD; Louis Lasagna, MD; David W. Richardson, MD; and Robert W. Wilkins, MD.

The special medications used in this investigation were prepared by William E. Wagner, MD, of Ciba Pharmaceutical Co., Summit, NJ.

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Assessable Events

Abbreviated definitions of terminating events (class A and treatment failures) and nonterminating (class B) events.

Class A Events

1. Striate hemorrhages in more than one retinal quadrant or cotton wool exudates or papilledema.
2. Cerebral or subarachnoid hemorrhage.
3. Dissecting aortic aneurysm.
4. Inability to control congestive heart failure without using antihypertensive agents.
5. Elevation of blood urea nitrogen level (BUN) by more than 50% of previous level and exceeding 59 mg/100 cc.
6. Acute hypertensive encephalopathy requiring hospitalization.

Treatment Failures

1. Diastolic blood pressure exceeding 124 mm Hg on each of three successive visits and persisting for three weeks or longer.
2. Assessable organic complications not fulfilling criteria for class A events but of sufficient severity to require discontinuation of protocol regimen.

Class B Events

Cardiac

1. Myocardial infarction documented by characteristic electrocardiogram or serum enzyme changes.
2. Congestive heart failure controllable by routine therapy other than antihypertensive agents including digitalis, restricted activity, low salt diet, and intermittent diuretics.
3. Atrial fibrillation or flutter or ventricular tachycardia without evidence of quinidine or digitalis intoxication.
4. Heart-block such as bundle-branch block, second or third degree heart-block or first degree heart-block with P-R interval of 0.28 seconds or more.
5. Left ventricular enlargement by ECG or roentgenogram.
6. Pulmonary embolism or infarction.

Central Nervous System

1. Cerebrovascular thrombosis or embolism.
2. Transient ischemic attacks with objective neurological changes during the attack.

Aorta

1. Arteriosclerotic aneurysm.

Renal

1. Doubling of BUN (but to below 60 mg/100 cc) or creatinine levels to values above normal limits not due to primary renal disease.
2. Proteinuria (2+ or more in three or more specimens) in absence of congestive heart failure, primary renal disease, or lower urinary tract disease.
3. Persistent hematuria (> 5 cells per high power field centrifuged sediment) not due to primary renal or lower urinary tract diseases.

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