

EFFECT OF ANTIHYPERTENSIVE TREATMENT ON MORBIDITY

EDWARD D. FREIS

Clinical trials evaluating the effects of treatment with antihypertensive drugs on the prevention of the complications of hypertension have been limited almost exclusively to patients with severe hypertension. In malignant hypertension the life expectancy of the untreated patient seldom exceeds one or two years. The prolongation of life of many patients to five years or longer with antihypertensive drug treatment has provided convincing evidence of the benefits of drugs in this condition.¹⁻⁶

The course of the disease, however, is much more variable in the less-severe forms of hypertension. Therefore, the effectiveness of treatment with respect to morbidity and mortality is more difficult to evaluate. In the absence of adequately controlled, prospective trials some authorities have questioned the benefit from antihypertensive drugs on mortality.⁷⁻⁹

Recently, this need for definitive data on the efficacy of treatment in essential hypertension has been partially fulfilled by several prospective controlled clinical trials. The first is a study by Hamilton in England¹⁰ and the second is the Cooperative Study on Antihypertensive Agents carried out by the Veterans Administration.¹¹

In Hamilton's study 61 patients without evidence of prior cardiovascular complications, but with diastolic blood pressures of 110 mm Hg or higher as measured in the clinic, were alternately assigned to antihypertensive drug treatment or placebos. Over an eight-year period of follow-up, 16 of the untreated patients had complications as compared to five of the treated group. Of the latter, the blood pressure was poorly controlled in four patients. Thus, of the treated patients whose

diastolic pressures were reduced to less than 110 by active treatment only one had a severe complication. The most common causes of morbidity in Hamilton's study were strokes and enlargement of the heart usually associated with congestive heart failure.

The Veterans Administration Cooperative Study was unique in several aspects of experimental design. It presents the most convincing evidence for the effectiveness of treatment. The patients were all males with diastolic blood pressures averaging between 90 and 129 mm Hg both in the hospital and in subsequent outpatient follow-up of two to four months when all received only placebos. Thus far, results have been published only on the subgroup whose diastolic pressures were 115 mm Hg or above prior to randomization.

No attempt was made in this study to eliminate patients who had any evidence of prior cardiovascular complications. The exclusions were patients with a prior history of Grade III or IV changes in the optic fundi, cerebral or subarachnoid hemorrhage, acute hypertensive encephalopathy, congestive heart failure uncontrolled by digitalis and mercurials, dissecting aneurysm and uremia. Patients were included in the study who had prior myocardial infarctions or cerebrovascular thrombosis (as opposed to hemorrhage), cardiomegaly as determined by roentgenography or left ventricular hypertrophy as defined by electrocardiography.

A number of problems that are unique to long-term therapeutic trials in outpatients were considered in the design of the study. One of the most important is the problem of dropouts. The larger the number of dropouts the less valid the results. Because it is impossible to determine the reason for defaulting no assumptions can be made as to their outcome. Prior experience of the cooperative study group had indicated the greatest percentage of dropouts occurred in the first several months after the patients entered the trial. To avoid this a prerandomization trial period was instituted in which the patients were required to adhere to regular clinic attendance for a period of two to four months.

A second equally obvious but often overlooked problem in outpatient trials is the failure of the patients to take their medications with sufficient regularity to provide a consistent therapeutic effect. Identification of such patients is often difficult. In the Veterans Administration's trial all patients received known placebos during the prerandomization trial period. Pill counts were carried out at each clinic visit. In addition, riboflavin, which produces fluorescence of the urine in ultraviolet light, was incorporated as a marker in the tablets. A urine sample was exam-

ined under an ultraviolet light at each visit. Only those patients who exhibited both urinary fluorescence and acceptable pill counts during two successive visits of the trial period were accepted into the study.

Another problem was to assure that the treatment and placebo groups of patients were comparable not only with regard to known prognostic criteria but also with respect to presently unknown factors that may influence the risk of developing complications. Standard randomization procedures were used to assure comparability, relying on the laws of chance to provide two groups at equal risk at the time of randomization. The success of this procedure is attested to by the fact that the two groups were practically identical by all known prognostic indices such as age, race, body weight, average blood pressure, fundi grades, electrocardiogram changes, heart size and renal changes.

Another crucial part of the trial was to assure that the blood pressure was reduced to normotensive or nearly normotensive levels in the great majority of the treated patients. Therapy also should be reasonably standardized in the various participating clinics both with regard to drugs and doses. The active drug regimen decided upon was based on experience gained in previous comparative effectiveness drug trials of the Cooperative Study.¹² Results of these trials indicated that additive hypotensive effects were obtained by combining antihypertensive drugs. Diuretic doses of a thiazide plus reserpine plus hydralazine had, on the average, three times the antihypertensive effectiveness of similar doses of each drug used separately.¹² The doses of each drug decided upon were 50 mg hydrochlorothiazide plus 0.25 mg reserpine combined in a single tablet given twice daily. Hydralazine was made up separately in 25 and 50 mg tablets, the smaller dose being given three times daily initially, followed by the 50 mg dose if the diastolic blood pressure did not fall below 90. Further increases in either the hydrochlorothiazide-reserpine tablet or the hydralazine tablets were not permitted. However, the doses could be reduced in the event of an excessive antihypertensive effect; hydralazine could be discontinued and if hypotension persisted the thiazide-reserpine tablet could be reduced.

The placebo and active drugs were made up in identically appearing tablets. Three different code numbers were assigned to each regimen. The code numbers contained four digits to make them more difficult for the participants to remember. Another group of "special" tablets were made up. Some of these contained hydrochlorothiazide without reserpine and the others contained reserpine without the thiazide. When a severe side effect occurred, presumably caused by either drug,

the participant requested the substitute "special" tablets that did not contain the offending agent. Of course, in some cases one placebo was substituted for another, but in other instances the substitution was useful in maintaining the patient on at least two of the three active agents. As in the trial period, riboflavin was added to both the active drugs and placebos used in the treatment period so that regular checks could be made on the patients' adherence to the program. In addition to the fluorescence tests pill counts also were carried out at each clinic visit.

The three-drug regimen proved to be quite successful in controlling the blood pressure in the actively treated group. After four months of active treatment the reduction of blood pressure from prerandomization levels in the 73 patients receiving active drugs averaged 43 mm Hg systolic and 30 mm diastolic. The mean blood pressure for the group was 186/121 mm Hg in the clinic during the prerandomization trial period; it fell to 143/91 mm following the institution of active treatment. In the 70 placebo-treated patients the average prerandomization blood pressure was 187/121 mm Hg and this remained essentially unchanged following randomization.

A significant difference in the rate of organic complications developed within a relatively short period in these "high-risk" patients whose prerandomization clinic blood pressures averaged between 115 and 129 mm Hg. The average period of follow-up of the placebo-treated patients prior to termination of the study was only 15.7 months. During this period morbid events occurred in 27 of the 70 patients. The follow-up period averaged somewhat longer (20.7 months) in the actively treated group. The difference in duration of follow-up in the two groups was because of the termination of many placebo-treated patients at an early period because of serious complications.

Only two morbid events occurred in the actively treated group during this period.

Twenty-one terminating events occurred in the placebo-treated patients. Four of these were deaths caused by dissecting aortic aneurysm in two, ruptured abdominal aortic aneurysm in one and "sudden death" in the fourth. The distribution of deaths is unusual because of the high percentage of aortic catastrophes. In the 17 nonfatal but terminating events the most frequent causes were the development of accelerated hypertension associated with hypertensive neuroretinitis, congestive heart failure that could not be controlled with digitalis, salt restriction and mercurial diuretics, and persistent excessive hypertension. Also, two instances of severe cerebrovascular accidents occurred

and two patients exhibited signs of renal failure. Only one terminating event occurred in the actively treated group. This was a patient who developed hyperglycemia on the thiazide-reserpine combination tablet. The "special" tablet containing only reserpine was substituted, but the patient then developed a depression.

Six events in the placebo-treated patients were nonterminating. These consisted of two patients who developed myocardial infarction, two who exhibited thrombotic cerebrovascular events and one who developed congestive heart failure responding to digitalis. The single nonterminating event in the active treatment group occurred in a 68-year-old man who had hypotensive levels of blood pressure accompanied by a left-sided hemiparesis.

Fortunately, this clearcut result favoring treatment was not obscured by an excessive dropout rate. Of the 143 patients, 12 dropped out, an incidence of less than ten per cent. Further, of this number the distribution was almost equally divided between the two regimens, seven having been assigned to placebos and five to active drugs. If the worst possible assumption is made regarding the dropouts, namely that all of the actively treated patients had developed morbid events as opposed to none in the placebo group—a most unlikely assumption—the result would still be significant at a probability of less than one in 1,000 that the result favoring treatment could have occurred by chance.

Although essential hypertension is generally regarded as a slowly progressive disorder, such was not the case in these male patients with clinic diastolic blood pressures of 115 mm Hg or higher. A surprising number of placebo-treated patients showed evidence of progression to the accelerated phase of hypertension and probably would have gone on to develop fatal malignant hypertension if known active treatment had not been started. The combined results of the VA and Hamilton's study also indicate significant protection against vascular catastrophes such as dissecting aortic aneurysm and cerebrovascular hemorrhage. It also was apparent that congestive heart failure was prevented by the antihypertensive regimen.

On the other hand the incidence of atherosclerotic events such as myocardial infarction and cerebrovascular thrombosis did not occur in sufficiently high incidence in either group to make an informed judgment regarding the possible protective effect of antihypertensive drug treatment. In treated patients, myocardial infarction including "sudden death" has become the leading cause of mortality according to Hodge and Smirk,¹³ far exceeding congestive heart failure, cerebro-

vascular hemorrhage and uremia, which formerly were the leading causes of death. Whether the *total* incidence of atherosclerotic events has been reduced by antihypertensive treatment cannot be deduced from such uncontrolled observations. It seems likely, however, that the effect of antihypertensive treatment, if any, on the prevention of accelerated atherosclerosis is not as great as the prevention of purely hypertensive complications.

In view of the high risk associated with diastolic elevations in the 110–120 mm Hg range and the conclusive evidence favoring treatment in this group it would appear that the early identification and treatment of such patients is an important and immediate public health problem.

The evidence demonstrating the benefits of treatment is more soundly based than it is in most other chronic diseases. In addition, hypertension of this degree of severity is not uncommon. The justification and need for a more positive approach to this problem should be apparent to all physicians and agencies concerned with national health.

REFERENCES

- ¹ Perry, H. M., Jr. and Schroeder, H. A., The Effect of Treatment on Mortality Rates in Severe Hypertension: A Comparison of Medical and Surgical Regimens, *Archives of Internal Medicine*, 102, 418–425, 1958.
- ² Dustan, H. P., *et al.*, The Effectiveness of Long-Term Treatment of Malignant Hypertension, *Circulation*, 18, 644–651, 1958.
- ³ Harrington, M., Kincaid-Smith, P. and McMichael, J., Results of Treatment in Malignant Hypertension, *British Medical Journal*, 2, 969–980, 1959.
- ⁴ Sokolow, M. and Perloff, D., Five-Year Survival of Consecutive Patients with Malignant Hypertension Treated with Antihypertensive Agents, *American Journal of Cardiology*, 6, 858–863, 1960.
- ⁵ Björk, S., *et al.*, The Effect of Active Drug Treatment in Severe Hypertensive Disease, *Acta Medica Scandinavica*, 169, 673–689, 1961.
- ⁶ Mohler, E. R. and Freis, E. D., Five-Year Survival of Patients with Malignant Hypertension Treated with Antihypertensive Agents, *American Heart Journal*, 60, 329–335, 1960.
- ⁷ Perera, G. A., Antihypertensive Drug Versus Symptomatic Treatment in Primary Hypertension: Effect on Survival, *Journal of the American Medical Association*, 173, 11–13, 1960.
- ⁸ Goldring, W. and Chasis, H., Antihypertensive Drug Therapy: An Appraisal, *Archives of Internal Medicine*, 115, 523–525, 1965.
- ⁹ Relman, A. S., *in* Ingelfinger, F. J. and Relman, A. S., *CONTROVERSY IN INTERNAL MEDICINE*, Philadelphia, W. B. Saunders Company, 1966, pp. 101–102.

¹⁰ Hamilton, M. in Gross, F., *Antihypertensive Therapy: Principles and Practice*, an International Symposium, New York, Springer-Verlag New York, Inc., 1966, pp. 196-211.

¹¹ Veterans Administration Cooperative Study Group on Antihypertensive Agents, Effects of Treatment on Morbidity in Hypertension: Results in Patients with Diastolic Blood Pressures Averaging 115 Through 129 mm Hg, *Journal of the American Medical Association*, 202, 1028-1034, 1967.

¹² ———, Double Blind Control Study of Antihypertensive Agents: III. Chlorothiazide Alone and in Combination with Other Agents, *Archives of Internal Medicine*, 110, 230-236, 1962.

¹³ Hodge, J. V. and Smirk, F. H., The Effect of Drug Treatment of Hypertension on the Distribution of Various Causes: A Study of 173 Deaths among Hypertensive Patients in the Years 1959 to 1964 Inclusive, *American Heart Journal*, 73, 441, 1967.