Ann. Rev. Med. 1979. 30:81–89

VALIDITY OF THERAPY FOR MILD HYPERTENSION

Edward D. Freis, M.D.

Veterans Administration Hospital and Department of Medicine,
Georgetown University School of Medicine, Washington, DC 20422

Hypertension affects at least one in ten adults in nearly every country in the world. It ranks third only to atherosclerosis and cancer as a cause of death. It is also a leading risk factor in atherosclerotic complications such as myocardial infarction, sudden death, and atherothrombotic stroke. Hypertension, therefore, is a double-edged sword. It produces complications specifically related to hypertension per se, such as hemorrhagic stroke, congestive heart failure, and renal failure, and, in addition, it aggravates and accelerates atherosclerosis.

RATIONALE OF TREATMENT

The ultimate cause or causes of essential hypertension are still unknown. Except for rare secondary forms the goal in treating hypertension is not to cure the disorder but to control the blood pressure and, thereby, prevent hypertensive complications. This approach is based on the theory, which we can now regard as established from both animal experiments and clinical trials, that the major cardiovascular complications associated with hypertension are the result of damage produced directly by the elevated blood pressure. It has not been demonstrated, however, that reducing the elevated blood pressure will retard the development of the atherosclerotic complications often associated with hypertension.

The cardiovascular changes that characterize hypertension appear to be secondary to elevated blood pressure (1). Fibrinoid necrosis and hyalinosis of the arterioles probably represent adaptations to the increased blood pressure; cerebral microaneurysms, a frequent source of cerebral hemor-

rhage, may result from yield stresses produced by the hypertension; and left ventricular hypertrophy and dilatation represent adjustment to an increased afterload. The predisposition to atherosclerosis may be due to injury to the arterial intima caused by the hypertension (2). The rationale of antihypertensive treatment, therefore, is to reduce the blood pressure to a level where these damaging effects will not occur.

EVIDENCE IN ANIMALS

The complications of hypertension can be completely prevented by antihypertensive drug treatment in the spontaneously hypertensive rat (3). The Kyoto strain of spontaneously hypertensive rats develop a progressive elevation of blood pressure with increasing age; after one year they begin to die from cardiovascular complications associated with the hypertension. If antihypertensive agents are added to the drinking water their blood pressures remain at low levels and they develop none of the cardiovascular complications associated with hypertension. Furthermore, their life span increases by more than half that of the untreated animals and becomes the same as that of a normal rat (4). The treated animals tolerated the drugs very well; they gain weight normally, bear normal litters, and appear as active and healthy as normotensive untreated rats.

The cardiovascular complications occurring in spontaneously hypertensive rats are in many respects similar to those found in hypertensive patients and include hemorrhagic stroke, congestive heart failure, and renal damage. The rat lesions differ from those in man, however, in one important respect. The rat is resistant to atherosclerosis and seldom exhibits such lesions even when plasma cholesterol levels are increased by diet. The complete protection from cardiovascular lesions provided by treatment in the rat, therefore, applies only to hypertensive complications and not to atherosclerotic lesions, which rarely occur in the spontaneously hypertensive rat.

EARLY CLINICAL TRIALS

The evidence in man is based largely on controlled clinical trials. The first trial was carried out by Hamilton and co-workers (5) in 61 patients of both sexes with severe essential hypertension. Patients were assigned alternately to either active drugs or to no treatment. Over a follow-up period of two to six years, there were significantly fewer complications in the treated patients than in the untreated group. Almost all of the treated patients who developed complications failed to achieve a reduction of diastolic blood

A controlled trial carried out by Wolff & Lindeman (6) in 87 patients with moderate to severe hypertension indicated that over an average follow-up period of two years the incidence of morbid events in the treated patients was one third that observed in the placebo group.

Carter (7) carried out a prospective randomized trial in 97 hypertensive stroke survivors. Over a period of three to five years 46% of the control patients died as compared to 26% of the treated group. Nonfatal strokes occurred in 23% of the control group as compared to 14% of the treated patients. However, in a well-controlled trial in patients with mild hypertension who had survived a single stroke, Hoobler and his associates (8) found no significant protection against subsequent strokes by treatment.

THE VETERANS ADMINISTRATION TRIAL

The largest scale controlled trial was that carried out by the Veterans Administration Cooperative Study Group (9–11). This randomized, double-blind study included 523 male hypertensive patients, average age 49 years, whose initial diastolic blood pressure ranged between 90 and 129 mm Hg (average of two clinic visits immediately preceding randomization). Many of the patients showed evidence of end-organ disease and all maintained a diastolic blood pressure of 90 mm Hg or higher during a week's hospitalization. Patients were randomly assigned, double-blind either to a combination of hydrochlorothiazide, reserpine, and hydralazine or to placebos of these drugs.

The trial was terminated early in the subgroup of 143 patients with initial diastolic blood pressure averaging between 115 and 129 mm Hg (9). Of the 70 patients in the control group 27 developed major cardiovascular complications over an average follow-up period of only 20 months. Most of these complications were of the hypertensive rather than the atherosclerotic type. In the treated group of 73 patients there was only one major cardiovascular event, which was an atherothrombotic stroke. Two others were removed from the study because of side effects of the antihypertensive drugs.

There remained in the trial 380 patients with mild to moderate elevations of blood pressure prior to randomization averaging between 90 and 114 mm Hg (10). These patients were followed for an average period of 3.3 years and some were followed for more than five years. Nineteen of the control patients died of cardiovascular complications as compared to eight in the treated group, a ratio of more than two to one in favor of treatment. All of the deaths occurring in the treated group of patients were related to atherosclerotic complications whereas the deaths in the control group were due to either hypertensive or atherosclerotic events. Since many of the

patients had hypertension of long duration, it would be expected that they already had extensive atherosclerosis at the time of entry.

The incidence of all morbid events both nonfatal as well as fatal was assessed by the life-table method of analysis (Figure 1). This indicated that over a five-year period the risk of developing a major cardiovascular complication was reduced from 55% in the control group to 18% in the treated patients, a ratio of approximately three to one in favor of treatment. In addition to these morbid events there were 20 patients, all in the control group, who exhibited progression of their hypertension to above 120 mm Hg diastolic blood pressure and who were removed from the trial before they developed a major complication.

The effectiveness of treatment was definitely related to the initial height of the blood pressure (10, 11). The striking effect of treatment in the group

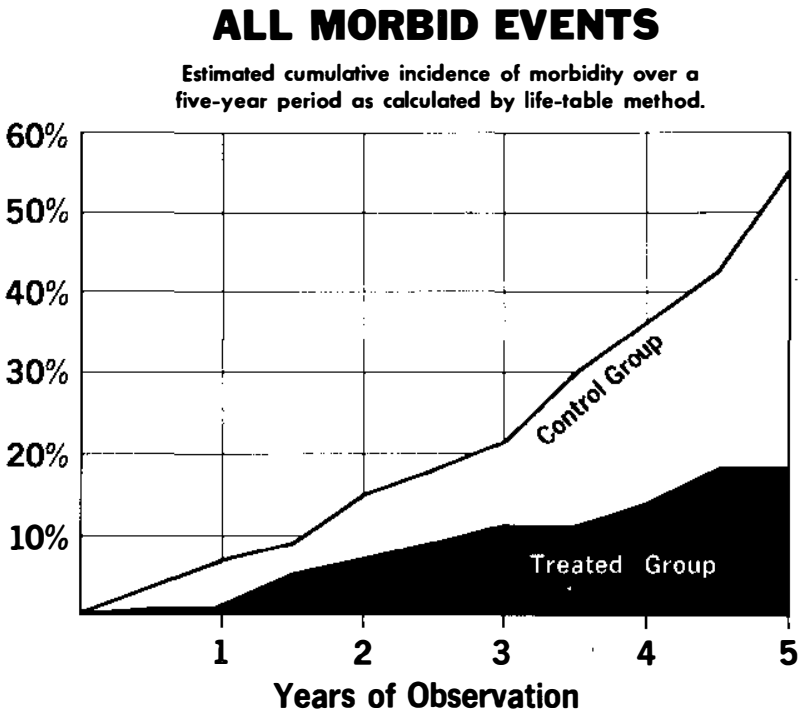

Figure 1 Graph of estimated five year morbidity in the control vs the treated group of 380

with severe hypertension has already been described. The patients with mild to moderate hypertension were subdivided into two groups, those with initial diastolic levels of 90–104 mm Hg and the group with diastolic blood pressures of 105–114 mm Hg at entrance into the study. Treatment was considerably more effective in the latter than in the former or mild group. In the patients with moderate hypertension cardiovascular complications were four times higher in the control than in the treated patients. But, in the mild group the difference was less than two to one in favor of treatment. Because of this minor difference in incidence of complications and also because of the relatively small size of the mild subsample, the effectiveness of treatment for mild hypertension was left in doubt. It is worth noting, however, that progression to a more severe stage of hypertension and the development of left ventricular hypertrophy were not included as assessable morbid events. If they had been included the results would have indicated a greater effectiveness of treatment.

US PUBLIC HEALTH SERVICE HOSPITALS TRIAL

There are, as yet, no other controlled trials on mild hypertension in which the data have been published in full. The results of the study in the United States Public Health Service Hospitals conducted by Dr. W. McFate Smith have been published only in preliminary form (12). Their patients numbered 389 and were followed for as long as seven years. In contrast to the Veterans Administration study, none of their patients exhibited evidence of end-organ disease at the time of entry into the study. Furthermore, they tended to be younger with an average age of 44 years as opposed to 49 years in the Veterans trial. The trial also included females as well as male patients. While they admitted patients with diastolic levels ranging between 90 and 115 mm Hg, the majority of the patients had rather mild hypertension as indicated by the average admission blood pressure of 148/99 mm Hg.

Over the seven-year period of follow-up, hypertensive complications occurred more than twice as frequently in the control as in the treated group. Most of the preventable complications appeared to be related to electrocardiographic manifestations of left ventricular hypertrophy. The incidence of atherosclerotic events, however, including those related to coronary artery disease, was essentially the same in the treated and control patients.

CORONARY ARTERY DISEASE

Hypertension even of mild degree aggravates and accelerates atherosclerosis (13). Atherosclerosis appears to be a response to injury to the arterial

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.