

Borderline Mild Systemic Hypertension: Should It Be Treated?

EDWARD D. FREIS, MD

Since publication of the Veterans Administration Cooperative Study,¹ it has been generally accepted that antihypertensive drug treatment is effective in preventing cardiovascular complications in severe and moderate hypertension. However, evidence for the effectiveness of treating patients with a diastolic blood pressure (BP) of 90 to 94 mm Hg is controversial.² Some authorities claim that the available data fully justify reducing BP in all patients with diastolic levels of 90 mm Hg or higher.³ Others, including this author,² do not find the evidence to be so convincing. The results of the various therapeutic trials are conflicting with respect to the protection afforded to patients with 90- to 94-mm Hg diastolic hypertension.

Diastolic Blood Pressure Below 100 mm Hg

The most favorable results in treating patients with initial diastolic BP of less than 90 to 94 mm Hg were reported by the Hypertension Detection and Follow-Up Program (HDFP).⁴ Other studies, such as the Veterans Administration trial,¹ U.S. Public Health Service hospitals trial,⁵ Oslo study⁶ and Multiple Risk Factor Intervention Trial (MRFIT),⁷ yielded no significant difference in morbidity or mortality between control and treated patients when the entry diastolic BP was 90 to 94 mm Hg. Significant protection, however, was found when the diastolic BP was approximately 100 mm Hg or higher. Some of these studies were small,^{1,5,6} and significant benefit might have been found in the 90- to 94-mm Hg group if the sample sizes had been larger. The larger Australian trial is not applicable because it did not include patients with borderline levels of BP.⁸

While the HDFP was a large trial, involving over 10,000 patients, the design failed to control variables

other than drug treatment that could have influenced mortality.⁹ The "control" patients were sent out to whatever health care facility was available to them (referred care). They were managed differently from the special treatment (stepped care) patients in most aspects of medical care. The physicians, nurses, clinical facilities and hospital back-up were generally superior in the stepped-care compared with the referred-care group. Education of the patients as to diet, smoking, and so on, also was different. All costs of medical care were provided free to the stepped-care patients, but generally were not so provided to the referred-care or control group. Because of these important differences, HDFP cannot be regarded as a definitive trial of drug treatment per se. The results of such a trial require confirmation from better-controlled studies.

The Australian trial⁸ was not handicapped by the same design problems as HDFP. Control and treated groups were managed similarly except for the administration of active drugs in 1 group and placebos in the other. Although the results indicated that treatment was effective, the range of pretreatment diastolic BPs included in the trial was 95 to 109 mm Hg, excluding patients with borderline levels of 90 to 94 mm Hg. This borderline hypertensive group, however, represents a large population that, according to the National Health Survey, comprises about 25 million patients in the U.S. alone.¹⁰ The decision concerning treatment of this group, therefore, has major medical and economic consequences. Also, because the risk of complications is considerably less than in patients with more severe hypertension, the cost/benefit ratio of treatment at 90- to 94-mm Hg levels of diastolic BP must be carefully evaluated.

Does Treatment Protect Against Coronary Heart Disease?

One of the more important questions in patients with mild hypertension is the effectiveness of treatment in preventing heart attack. Myocardial infarction and sudden death constitute the major complications

From the Veterans Administration and Georgetown University Medical Centers, Washington, D.C. Manuscript received February 26, 1986, accepted April 25, 1986.

Address for reprints: Edward D. Freis, MD, Hypertension Research (151E), Veterans Administration Medical Center, Washington, D.C. 20422.

in these patients, as opposed to stroke and other "hypertensive" complications that occur more frequently in patients with moderate and severe degrees of hypertension. Whether antihypertensive drug treatment is effective in preventing myocardial infarction, however, is highly controversial.

A unique observation of the HDFP was that treatment was as effective in preventing myocardial infarction as it was in preventing stroke. Only when patients with ischemic heart disease were added to those with myocardial infarction did the degree of protection become less than against stroke. Another unusual finding in HDFP was that treatment of borderline hypertension resulted in greater protection against mortality (special-care compared with regular-care patients) than did treatment of moderate hypertension.⁴ The 3 smaller-scale but better-controlled trials^{1,5,6} did not yield a reduction in the incidence of myocardial infarction with treatment; nor was there a significant decrease in all-cause morbidity or mortality when diastolic BP at entry was less than 100 mm Hg.

MRFIT, which was similar in size and design to HDFP, arrived at opposite conclusions.⁷ Unlike HDFP, among the MRFIT patients with an initial diastolic BP of 90 to 94 mm Hg the clinic-treated group experienced more, rather than fewer, cardiovascular deaths than the control group including deaths due to coronary heart disease. In fact, it was only in patients with a diastolic BP of at least 100 mm Hg that the special-intervention group achieved a lower mortality rate than the "control" patients. These contrasting results from MRFIT and HDFP illustrate the problems in interpreting results of unconventionally designed clinical trials.

Risk Versus Benefit

The results of the trials dealing with treatment of borderline hypertension are often contradictory. The evidence from the HDFP that treatment had a greater protective effect in borderline-mild than in moderate-severe hypertension has not been confirmed by other trials. Furthermore, the reduction of 45% in fatal myocardial infarction reported by HDFP is not supported by results of other trials. Neither HDFP nor any other trial published provides a mandate for indiscriminate drug treatment of borderline hypertension. The question cannot be answered on the basis of the available evidence.

While we have reason to suspect the efficacy of treating borderline hypertension, there is no doubt that long-term drug treatment can cause side effects and toxicity. Although serious reactions may be uncommon, they can add up to a considerable number when the drugs are administered, as they are now, to many millions of patients for very long periods. For example, β -blocking drugs can precipitate severe and even fatal attacks of bronchial asthma. They also may aggravate cardiac failure and produce other side effects. The thiazides have been accused, probably unjustly, of increased risk associated with hypokalemia

and hypercholesterolemia. Nevertheless, they have other side effects, including hyperglycemia, hyperuricemia with or without gout, and skin rashes. Prazosin causes orthostatic hypotension, particularly after the first dose of the drug. Reserpine can cause depression; captopril may induce taste disturbance and, in high doses, neutropenia. Therefore, no drug for reducing blood pressure is innocuous. All of them can produce severe and even fatal reactions. Other disadvantages of drug treatment include the inconvenience of taking medications every day, and the expense of medications can also be considerable. Patients are often given the newest and most expensive of the current wonder drugs, even though a much less costly tried-and-true regimen may do as well.

Results of Treatment of Diastolic Blood Pressure of 95 to 99 mm Hg

The evidence favoring drug treatment of patients with a diastolic BP of 95 to 99 mm Hg is clearer than it is in the patients with a diastolic BP 90 to 94 mm Hg. In the Australian study, treated patients with initial diastolic levels of 95 to 99 mm Hg had 30% fewer complications than patients who received placebo.⁸ HDFP reported a 23% reduction in mortality in stepped-care as compared with referred-care patients with a diastolic BP 95 to 99 mm Hg at entry. On the other hand, the somewhat similarly designed MRFIT⁷ yielded no difference in mortality between the special-intervention and referred-care or usual-care patients. The Oslo trial⁶ also yielded no benefit from treatment in patients with entry diastolic BPs of less than 100 mm Hg. Thus, while the evidence for the effectiveness of treating patients with diastolic BPs of 95 to 99 mm Hg is somewhat stronger than in patients with borderline hypertension it is by no means unanimous.

HDFP indicates that the decreased mortality in the stepped-care patients was associated with an average diastolic BP reduction to 83.4 mm Hg, compared with 87.8 mm Hg in the referred-care group. However, neither the Australian Hypertension Trial¹¹ nor the Veterans Cooperative Study¹² yielded a correlation between BP level and the incidence of complications when the diastolic BP was 95 mm Hg or less during treatment.

Recent Therapeutic Trials

The Medical Research Council (MRC) of Great Britain has conducted the largest trial, with 17,354 patients.¹³ Baseline diastolic BP ranged from 90 to 109 mm Hg. The study was carried out in family practices. Patients were randomized either to bendroflumethiazide, propranolol (40 to 240 mg/day) or placebo. The number of total cardiovascular events was 352 in the placebo group and 286 in the treated patients ($p < 0.05$ on sequential analysis). There was no difference, however in coronary events, the greatest reduction being in the incidence of strokes, which was 109 in the control group and 60 in the treated group ($p < 0.01$). Retrospective subgroup analysis, a technique of questionable validity, indicated that nonsmokers who took

propranolol had a significant reduction in cardiovascular complications ($p < 0.01$), whereas the reduction in stroke rate was significantly greater in those receiving the diuretic ($p = 0.002$). Subgroup analysis by entry diastolic BP has not been published for this study, and it is therefore not possible to determine the effectiveness of treatment in patients with diastolic BPs of less than 95 or less than 100 mm Hg.

The principal conclusion of the MRC trial is that the major effect of treatment was prevention of stroke. This result was similar to that of most other trials, including the original Veterans Administration trial¹ and the Australian trial.⁸ However, the degree of protection afforded against stroke in the MRC trial was low, probably because the risk was low. Their results indicated that it would be necessary to treat 850 mildly hypertensive patients to prevent a single stroke over 1 year. To accomplish this a substantial percentage of patients were subjected to chronic side effects, some of which were more than minor. It is also of interest that all-cause mortality was the same in the treated and control groups.

The European Working Party of High Blood Pressure in the Elderly (EWPHE) was a smaller but well controlled trial that included 840 patients older than 60 years with entry BP of 160 to 239/90 to 119 mm Hg.¹⁴ Therefore, the study included patients with moderately severe as well as mild hypertension. Total cardiovascular mortality rate was lower in the treated than in the placebo group. The results differed, however, from most other trials in that the effectiveness of treatment was greater in prevention of cardiac mortality than of cerebrovascular mortality, although there was an impressive reduction in both groups. However, with respect to nonterminating morbid events the situation was reversed, with a greater reduction in cerebrovascular events than of cardiac events. While EWPHE provides evidence for the effectiveness of treatment, it must be recognized that this trial is not limited to patients with mild hypertension, but includes patients with baseline diastolic levels as high as 119 mm Hg. Until more information is published by the European Working Party on the relation between entry BP strata and morbid events, the results of the trial cannot be applied to patients with borderline-mild hypertension.

A third, recently published trial, the International Prospective Primary Prevention Study in Hypertension,¹⁵ did not include patients with diastolic BPs of less than 100 mm Hg. Therefore, the results are not germane to the present discussion because patients with diastolic BPs of 90 to 99 mm Hg were excluded.

Choosing Patients for Treatment

In view of these conflicting reports, what is the most reasonable course to take in the management of patients with a diastolic BP of less than 100 mm Hg? The 1984 report of the Joint National Committee¹⁶ states that the benefit of treatment outweighs the risk in patients with a diastolic BP consistently elevated at or above 95 mm Hg and also for those with lesser eleva-

tions who have risk factors such as target organ damage, diabetes mellitus or other major risk factors for coronary heart disease. The report states that "Opinion varies as to the need for treatment in the 90 to 94 mm Hg range but if not treated they should be closely followed to detect any signs of progression." These guidelines probably represent the most reasonable recommendations that can be made on the basis of the current evidence. The World Health Organization also recommends drug treatment only when the diastolic BP is at least 95 mm Hg.¹⁷

The Joint National Committee also stresses the importance of recording BP during at least 3, and preferably more, visits before making a therapeutic decision. The exceptions, of course, are in patients with a diastolic BP of 110 mm Hg or more, in whom early treatment is mandatory, although if at all possible, it is desirable even to have the patient return within a few days of the initial visit for a second reading before treatment. Even some of these patients may exhibit sharp drops of BP sometimes to the normal range, thereby calling for a longer period of pretreatment observation.

Conclusions

Recommendations regarding selection of patients for treatment have been liberalized greatly in recent years. This has been the result of favorable evidence accumulated by various intervention trials. However, with respect to treatment of borderline hypertension—a diastolic BP 90 to 94 mm Hg—the evidence for benefit resulting from treatment is neither consistent nor convincing. Patients with borderline hypertension should be observed periodically for evidence of progression of hypertension. However, until more definitive evidence of benefit becomes available, there is no need to treat everyone in this population, especially those without other risk factors. By using discretion, millions of patients who are not likely to achieve much if any benefit can be spared the potential adverse effects, inconvenience and expense of life-long drug treatment.

References

1. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA* 1970;213:1143-1152.
2. Freis ED. Sounding board. Should mild hypertension be treated? *N Engl J Med* 1982;307:306-309.
3. Moser M. "Less severe" hypertension. Should it be treated? *Am Heart J* 1982;101:465-472.
4. Hypertension Detection and Follow-up Program Cooperative Group. The effect of treatment on mortality in "mild" hypertension. Results of the Hypertension Detection and Follow-up Program. *N Engl J Med* 1982;307:976-980.
5. Smith WM. United States Public Health Service Hospitals Cooperative Study Group. Treatment of mild hypertension. Results of a ten-year intervention trial. *Circ Res* 1977;40:suppl 1:1-98-1-105.
6. Helgeland A. Treatment of mild hypertension: a five year controlled drug trial. The Oslo Study. *Am J Med* 1968;69:725-732.
7. Multiple Risk Factor Intervention Trial Research Group. Multiple Risk Factor Intervention Trial: risk factor changes and mortality results. *JAMA* 1982;248:1465-1477.
8. Management Committee of the Australian Hypertension Trial. The Australian therapeutic trial in mild hypertension. *Lancet* 1980;1261-1266.
9. Hypertension Detection and Follow-up Program Cooperative Group. Five

- year findings of the hypertension detection and follow-up program. I. Reduction in mortality of persons with high blood pressure including mild hypertension. *JAMA* 1979;242:2562-2571.
10. U.S. Department of Health and Human Services, Public Health Service. *Health, United States, 1980 with Prevention Profile*. Washington, D.C.: U.S. Govt. Print. Off., 1981:35. [DHHS Publ No. (PHS) 81-1232].
11. Management Committee of the Australian Hypertension Trial. Untreated mild hypertension. *Lancet* 1982;1:185-191.
12. Taguchi J, Freis ED. Partial reduction of blood pressure and prevention of complications in hypertension. *N Engl J Med* 1974;291:329-331.
13. Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *Br Med J* 1985;291:97-104.
14. European Working Party on High Blood Pressure in the Elderly. Mortality and morbidity results from European Working Party on High Blood Pressure in Elderly trial. *Lancet* 1985;1:1349-1354.
15. IPPPSH Collaborative Group. Cardiovascular risk and risk factors in a randomized trial of treatment based on the beta-blocker oxprenolol: the International Prospective Primary Prevention Study in Hypertension (IPPPSH). *J Hypertension* 1985;3:379-392.
16. The Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure: the 1984 report of the Joint National Committee on Detection, Evaluation, and Treatment of high blood pressure. *Arch Intern Med* 1984;144:1045-1057.
17. World Health Organization/International Society of Hypertension. Guidelines for the treatment of mild hypertension: memorandum from a WHO/ISH Meeting. *Lancet* 1983;1:457-458.