SOUNDING BOARD

SHOULD MILD HYPERTENSION BE TREATED?

THERE is a growing body of opinion that all patients with hypertension — no matter how mild or uncomplicated — should be treated. In a recent report to Congress, the Assistant Secretary for Health, Edward N. Brandt, Jr., stated that the Hypertension Detection and Follow-up Program had demonstrated unequivocally that effective treatment could prolong life in both mild and borderline hypertension.[1] Moser has also claimed that sufficient data have been accumulated to justify reduction of blood pressure in all patients with diastolic pressures above 89 mm Hg.[2]

If put into practice this recommendation will have rather awesome implications. The most recent estimate of the prevalence of hypertension in the United States[3] is 60 million persons, at least 40 million of whom have a diastolic blood pressure of 90 to 99 mm Hg (measured on one visit). Patients with such mild and borderline hypertension, who have generally not been treated in the past, constitute approximately one fifth of the general adult population.

Largely because of poor compliance, the long-term effectiveness of low-sodium or low-calorie diets has not been demonstrated in a general population, and probably the great majority of patients will need drugs to control their hypertension. In considering drug treatment in such a large segment of the population, the disadvantages must be weighed against the possible advantages. Drug treatment may have toxic effects, especially in patients who do not become normotensive with a simple drug regimen but require a combination of drugs. In addition to overt toxicity, most drugs have subjective effects that, though not life-threatening, are disturbing to the person's quality of life. Moreover, there are patients, particularly among the elderly, who do not feel normal or function normally when their blood pressures are reduced.

The problem would be greatly magnified if 40 million or more essentially asymptomatic persons were exposed to drugs. Many patients dislike taking pills or forget to take them. Disturbing also is the financial expense that would be involved in adding 40 million patients to lifelong drug-treatment programs; not only drug costs but also fees for professional services and laboratory tests would be included. With 40 million patients, even a conservative estimate of $500 per patient per year would yield a total cost of $20 billion a year.

If it has been demonstrated, however, beyond reasonable doubt, that drug treatment is highly effective in preventing cardiovascular complications in even the mildest forms of hypertension, these negative considerations are outweighed and universal treatment is indicated. If the evidence is not so conclusive, the possible advantages of treatment must be weighed against the disadvantages, bearing in mind that with so many millions of patients subjected to drugs, the possibility of doing harm is greatly magnified. It is crucial, therefore, to examine the evidence on which the claims of therapeutic benefit are based.

THE HYPERTENSION DETECTION AND FOLLOW-UP PROGRAM

The chief pillar supporting the aggressive treatment of mild hypertension is the Hypertension Detection and Follow-up Program.[4,5] This large multicenter trial involved approximately 11,000 patients, of whom about 8000 had an initial diastolic blood pressure in the range of 90 to 104 mm Hg. The design of the trial was unorthodox. It was not designed to test the effects of drug treatment itself on mortality. Instead, it was supposed to determine whether the availability of complete, intensive, and free medical care in special clinics would be associated with a lower cardiovascular mortality than that associated with the health-care services usually provided in the community. The so-called control patients (the "referred-care" group) were referred to whatever medical care they could find or afford in the community. Thus, general medical care and specific antihypertensive treatment in these "control" patients varied markedly. Some were treated with drugs and others were not. Some had no medical supervision of any kind whereas others did. Many referred-care patients had to pay for their medical care, whereas none of the experimental (step-care) group did. All the patients in the step-care group were followed closely in well-staffed hypertension clinics backed up by large teaching hospitals. The availability, quality, and cost of medical care, therefore, were very different for step-care and referred-care patients and could have accounted for much of the difference in the mortality rates observed.

A major finding of the study was that in borderline and mild hypertension (diastolic pressure, 90 to 104 mm Hg), mortality from cardiovascular causes was 26 per cent lower in the step-care patients than in the referred-care group. However, noncardiovascular mortality, including cancer and accidents, was also reduced (by 14 per cent) in the step-care patients. This result again calls into question the validity of the so-called control group. Medical problems, including cardiovascular complications, would have been more quickly recognized and more promptly and effectively treated under the superior follow-up conditions available to the step-care group. It is not possible, therefore, to determine how much of the improved cardiovascular mortality was due to more effective antihypertensive-drug treatment and how much to better general medical care.

One of the most striking results of the study was the 45 per cent reduction in fatal myocardial infarction found in the step-care patients with mild hypertension. Unfortunately, the causes of death were determined by death certificates, which are notoriously unreliable. An additional large number of cardiovascular deaths were reported under the classification of "other ischemic heart disease," which would still represent deaths

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thought to be associated with coronary heart disease. In this category there were 10 per cent *more* deaths in the step-care than in the referred-care group. When the two diagnostic categories are combined they indicate a 20 per cent, rather than a 45 per cent, reduction for all deaths related to coronary heart disease, including those labeled as myocardial infarction.

A further difficulty lies in the handling of referred-care patients whose hypertension progressed to a more severe stage. In other controlled trials approximately 2 to 3 per cent of untreated patients per year had progression from mild hypertension to a more severe stage.[6,7] Since in these other trials the control patients were followed as closely as the treated patients, the increased severity of the hypertension was promptly recognized, and the patient was removed from the trial to be treated openly. Such a procedure tends to cause an underestimate of the effectiveness of treatment, since the patients at high risk because of increased blood pressure are selectively removed from the control group before a morbid event occurs. In the Hypertension Detection and Follow-up Program, however, the patients in the referred-care group who may have received inadequate medical care or no care and who progressed to more severe hypertension may not have been seen for a period of months to more than a year. If so, the number of patients who died in the control group with mild hypertension was inflated by patients whose hypertension had in reality progressed from a mild stage to a more severe stage. In contrast to management in conventionally designed trials, this type of management would result in overstating the effectiveness of treatment, since these control patients would still be counted as mild hypertensives.

Diastolic blood pressure was reduced from an average of 96.4 to 87.8 mm Hg in the referred-care patients, many of whom received some treatment in the community.[4] Diastolic pressure was reduced from an average of 96.3 to 83.4 mm Hg in the step-care patients. Because of this difference it has been suggested that a reduction in diastolic pressure to below 90 mm Hg is not enough, and that it should be reduced to below 85 mm Hg. It is interesting to speculate on the frequency and severity of the side effects that would result if this advice were implemented. The 4.4-mm Hg difference in diastolic pressure after treatment was only one of many differences between the step-care and referred-care groups. Hence, it is not justifiable to ascribe the difference in mortality to this one factor.

If it is true that the greater the reduction of blood pressure, the fewer the complications, there should be a correlation between the degree of blood-pressure lowering and the reduction of morbid events in similarly treated patients. Unfortunately, a correlation between blood-pressure reduction and death rates was not reported in the step-care group. Such an analysis would have had the advantage of minimizing extraneous therapeutic influences, since all the step-care patients were treated more or less similarly. This type of analysis was carried out in the Veterans Administration study, and it failed to show an influence of different degrees of blood-pressure reduction on morbidity.[8] Moreover, in the Australian trial, as pointed out by Kaplan[9] and others,[10,11] treated patients whose diastolic pressure was lowered had more trial end points than control patients at the same level of blood pressure — that is, lowering the blood pressure with drug treatment did not confer the same degree of protection against complications that occurred in untreated patients at similar levels. Unlike the Hypertension Detection and Follow-up Program, the Australian study also found that in patients with diastolic pressures averaging <95 mm Hg during the trial, there was no relation between the level of diastolic pressure and the incidence of cardiovascular complications[11] — that is, a reduction to 80 mm Hg was no more effective than a reduction to 90 mm Hg.

The Australian National Blood Pressure Study

The Australian trial is generally regarded as confirming the Hypertension Detection and Follow-up Program with respect to the treatment of patients with mild hypertension. The design of the Australian trial is acceptable in that, except for antihypertensive treatment, the conditions of follow-up care were similar in the control and treatment groups. Furthermore, no one in the control group received antihypertensive-drug treatment. Approximately 3500 patients were randomized into the trial.

The Australian trial, however, provided no information on the important group of patients with borderline hypertension — diastolic blood pressures of 90 to 94 mm Hg. Diastolic pressure on entry ranged between 95 and 109 mm Hg only. It is more or less generally agreed that treatment is effective in patients with diastolic pressures averaging 100 mm Hg or above. The controversy is with respect to treating patients with diastolic levels below 100 mm Hg. Therefore, the most important aspect of the Australian trial is the subgroup with pressures of 95 to 99 mm Hg on entry.

The Australian study led to two reports — one on the results at three years and eight months of follow-up,[12] and another on the findings at four years.[7] In the first report treatment was effective only in the patients with initial diastolic pressures of 100 mm Hg or higher. The difference in trial end points between control and treated patients in the group entering with diastolic pressures of 95 to 99 mm Hg was not significant. However, after four more months of follow-up the difference became significant. Would the result have reversed again if the study had been continued for another four months? In this regard it is noteworthy that between 3⅔ and four years the incidence of trial end points in the treated group *decreased* from 16.5 to 15.6 per thousand person-years of risk. It would seem important to know why patients with trial end points were removed from the treated group between the first and the second publication, since this decision could be crucial in determining whether the effectiveness of treatment

achieved significance in the group with pressures of 95 to 99 mm Hg. Thus, for patients with diastolic pressures below 100 mm Hg the confirmatory evidence supplied by the Australian trial is open to question, because the important group with borderline hypertension (diastolic pressures of 90 to 94 mm Hg) were not included, and because in the 95-to-99 group the significance of the result does not stand up convincingly when subjected to close analysis.

Other Trials

The most recent trial is the Oslo study.[13] This investigation included 785 men with systolic pressures between 150 and 179 mm Hg and diastolic pressures below 110 mm Hg. The design of the trial was orthodox in that patients were randomly assigned either to active drugs or to a control group and both groups were followed for five years. In contrast to the Hypertension Detection and Follow-up Program, the Oslo study found that treatment had no effect on cardiovascular morbidity or mortality, although blood pressure was reduced by an average of 17/10 mm Hg in the treated, as compared with the control, group — considerably more than the difference observed in the Hypertension Detection and Follow-up Program.

The evidence supporting the value of treating borderline and mild hypertension with antihypertensive drugs, therefore, is not as clearly established as many believe. The most favorable results come from the study of most questionable design, in which interpretation is difficult because the trial was not planned to test drug treatment but rather global medical care. The better-controlled trials aimed specifically at drug treatment in mild hypertension either obtained results that fluctuated from insignificant to significant or found no indication of benefit at any time. In this connection two earlier and smaller controlled trials — the Veterans Administration Study[6] and the U.S. Public Health Service Hospitals trial[14] — also found no significant difference in cardiovascular morbidity or mortality between actively treated patients and patients receiving placebo for mild or borderline hypertension.

Effect of Treatment on Coronary Heart Disease in Mild Hypertension

There is a tendency to assume that because the risk of cardiovascular complications is related to the height of the blood pressure in untreated patients,[15] the increased risk in mild hypertension, which is due primarily to coronary heart disease, can be reversed to normal by lowering the blood pressure. For example, according to this assumption the cardiovascular risk of a patient with a diastolic pressure of 99 mm Hg will be reduced to that of a normal person if the diastolic pressure is lowered to 85 mm Hg or less. However, as noted above, a correlation between blood-pressure reduction and morbid events has not been demonstrated in similarly treated patients,[8] and reduction to a given level with treatment does not confer the same protection observed in untreated patients with the same diastolic pressures.[11]

What can the physician hope to achieve by prescribing drugs for any and all patients with diastolic blood pressures above 89 mm Hg? Will the benefits, if any, in mild hypertension outweigh the disadvantages of medical treatment? The Veterans Administration controlled trial indicated that the benefits of antihypertensive drugs are much reduced in patients with mild hypertension, as compared with those with higher blood pressures.[6] Antihypertensive-drug treatment is most effective in preventing complications of hypertension such as hemorrhagic stroke, renal failure, congestive heart failure, and aortic dissection, and it is least effective in preventing atherosclerotic complications, including coronary heart disease,[6] the major complication in mild hypertension.

The Hypertension Detection and Follow-up Program found the opposite result — that treatment was more effective in mild hypertension than in moderate or severe hypertension. This finding was attributed to the more aggressive treatment by outside physicians of referred-care patients with moderate and severe hypertension. Although this may be true, it demonstrates again that the results of this study cannot be accepted at face value but must be interpreted in the light of the unusual design of the trial.

The most controversial question about antihypertensive-drug treatment is whether it significantly reduces the incidence of coronary-artery disease. Of the various trials, only the Hypertension Detection and Follow-up Program, as noted above, showed a significant reduction of fatal coronary-artery disease with treatment. The investigators did not report their experience with nonfatal myocardial infarction. In the Oslo trial more myocardial infarction occurred in the treated patients.[13] Some of the other trials, such as the Veterans Administration study[6] and the Australian trial,[7] showed a reduction in fatal coronary-artery events with treatment, but the number of events was small and did not reach the level of significance. On the other hand, nonfatal myocardial infarction occurred more frequently in treated than in control patients in both the Veterans Administration and the Australian trials, so that combined morbidity plus mortality due to coronary-artery disease was about the same in the treated and control patients. It is possible that the more favorable effects of treatment on fatal myocardial infarction were due to drug-induced hemodynamic changes, such as a reduction in myocardial oxygen demand as a result of a lowered afterload, the effects of diuretics in preventing congestive heart failure, and the influence of beta-adrenergic blocking drugs in reducing serious cardiac arrhythmias.

Recommendations

Epidemiologic investigations, such as the Framingham Study,[15] indicate that the risk of myocardial

infarction, the most frequent complication in mild hypertension, varies markedly, depending on the number of other risk factors present. For example, the risk that a myocardial infarction will occur over a six-year period in a 45-year-old man with a systolic pressure of 165 mm Hg (equivalent in risk to a diastolic pressure of 95 mm Hg) is 3.1 per cent if no other risk factors are present. With a systolic pressure of 135 mm Hg the risk is 2.1 per cent. The most that one could expect from antihypertensive-drug treatment in such a patient would be to reduce the risk by 1 per cent. On the other hand, with multiple risk factors present (such as cigarette smoking, electrocardiographic evidence of left ventricular hypertrophy, hypercholesterolemia, and glucose intolerance) the risk in men increases to 26.6 per cent with a systolic pressure of 165 mm Hg and to 20.0 per cent with a systolic pressure of 135 mm Hg. The risk is now considerable, and the increment in risk due to hypertension alone is 6.6 per cent. Therefore, if antihypertensive treatment is beneficial in reducing the risk of myocardial infarction, it is most beneficial in patients with multiple risk factors. Parenthetically, it is worth noting that stopping cigarette smoking will have nearly as great an effect on reducing the risk as lifelong drug treatment. The National Health Interview Survey showed that only one in three hypertensive smokers had been advised by a doctor to stop smoking.[3]

In view of the uncertainties, we may be doing more harm than good by giving lifelong drug treatment to patients with borderline or mild hypertension. However, because of the possibility of benefit, even though it is unproved, a compromise position, as suggested by others, may be most appropriate.[10,17] Patients with diastolic pressures of 90 to 99 mm Hg (average of at least three visits) are treated or not, according to the number of risk factors present. Patients with few other risk factors are given reducing or low-sodium diets but not drugs. The Australian study found a gradual fall in blood pressure in many of their placebo control patients.[11] By the third year of follow-up, 48 per cent of the patients who began with diastolic pressures ≥95 mm Hg had pressures below this level, 12 per cent had progressed to a more severe stage, and only 32 per cent remained in their initial range of 95 to 109 mm Hg. This experience demonstrates the wisdom of waiting for an extended period before initiating antihypertensive-drug treatment in mild hypertension. Patients with many risk factors may have their blood pressure reduced with drugs if necessary. If drugs are used they should be given by the step-care method, beginning with a diuretic alone and avoiding complicated multiple-drug regimens. All patients with elevated blood pressures should be followed periodically to detect any evidences of progression to a more severe stage of hypertension. By such a discriminative approach, many millions of people could be spared needless lifelong exposure to drugs.

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