Multicenter Clinical Trials
Potential Influence of Consumer Education

EDWARD D. FROHLICH

SUMMARY Multicenter therapeutic trials have demonstrated clearly the efficacy and safety of antihypertensive therapy. Such studies were designed initially to demonstrate the effectiveness of antihypertensive therapy in preventing complications and fatalities from hypertensive disease. Over the three decades since these studies were instituted, succeeding trials have become more sophisticated in design, and those of us who observe and interpret their results have similarly become more sophisticated and more demanding. However, we should not expect more from the studies than their designers intended. Let us neither overinterpret the results nor ascribe failure to studies simply because they do not answer the questions that remain. This discussion concerns primarily three recent multicenter clinical trials: the Hypertension Detection and Follow-up Program (1979), the Australian National Blood Pressure Study (1980), and the Multiple Risk Factor Intervention Trial (1982).

Key Words • Hypertension Detection and Follow-up Program • Australian National Blood Pressure Study • Multiple Risk Factor Intervention Trial • antihypertensive therapy • mild hypertension • myocardial infarction • consumer education • health habits

The program committee requested that I restrict this discussion to my personal interpretations of the implications of the results of three recent multicenter clinical trials. To do so, however, would provide just another editorial viewpoint—something that any interested party can do. Furthermore, as I suggested in a recent communication, a moratorium on such editorials is necessary until new data are provided. Editorials only add to controversy without clarifying issues. Nevertheless, a few specific interpretations are in order, and I shall focus on 1) the specific importance of the assigned studies, 2) their implications for the treatment of patients with mild hypertension, 3) the appropriateness of the widespread general conclusion that multicenter trials have not demonstrated prevention of myocardial infarction, and 4) the influence of consumer education and changing health habits on these multicenter studies.

Three recent multicenter trials were assigned to me for discussion: the Hypertension Detection and Follow-up Program (HDFP; 1979), the Australian National Blood Pressure Study—also known as the Australian Therapeutic Trial in Mild Hypertension (ANBPS; 1980), and the Multiple Risk Factor Intervention Trial (MRFIT; 1982). As my interpretations reflect the influence of other trials not referred to here, I shall also comment briefly on other clinical research and reports.

Hypertension Detection and Follow-up Program

The HDFP was one of the first studies that did not include a placebo group. As such, it should not be faulted for its failure to include what others would have wished to study. In other words, the study was not designed to determine whether antihypertensive therapy was efficacious as compared with a placebo-control study group. This subject was amply studied and reported in two major trials in the United States from the Veterans Administration and the U.S. Public Health Service. Perhaps what was less well demonstrated in the Veterans Administration study were data indicating that patients with mild (essential) hypertension (i.e., diastolic pressures of 90 through 104 mm Hg) should be treated.

The HDFP involved over 10,000 patients who were randomly assigned to two treatment groups in order to determine whether patients in a protocol-designed treatment program of stepped care with pharmacological agents conducted specifically to reduce diastolic pressure below 90 mm Hg (stepped care [SC] group)
would have better morbidity and mortality data than similar patients who were referred to practicing physicians in the same community for medical care (referred care [RC] group). The data clearly demonstrated that overall cardiovascular morbidity and mortality, as well as noncardiovascular mortality, were significantly reduced in the SC group. Further, cardiovascular and noncardiovascular deaths were also significantly reduced in the SC patients with mild hypertension. When the data from these Stratum I patients (those with diastolic pressures between 90 and 104 mm Hg) were analyzed with respect to subgroups (90–94, 95–99, and 100–104 mm Hg) the numbers of deaths and death rates per 1000 patient-years were similarly lower in the SC group (Table 1). As a result, the Joint National Committee of the High Blood Pressure Education Program modified its earlier recommendations to include antihypertensive treatment for all patients with diastolic pressures of 90 mm Hg or more in its 1980 report. Also demonstrated was an unexpected finding in patients with mild hypertension: deaths from myocardial infarction occurred in 30 and 56 patients of the SC and RC groups, respectively. While not statistically significant, in patients with mild hypertension such a finding was impressive.

Australian National Blood Pressure Study

The ANBPS, a multicenter, placebo-controlled trial that involved only patients with mild hypertension, studied almost 3500 people whose entry diastolic pressures were 90 through 109 mm Hg. Patients whose systolic pressures were 200 mm Hg or more or who demonstrated evidence of target-organ involvement were not included. The study was discontinued prematurely for ethical reasons when the supervisory group learned that the actively treated patients demonstrated a decreased cardiovascular mortality. Moreover, all study end points were lower in all three diastolic pressure subgroups (90–99, 100–104, and 105–109 mm Hg). There were 70 events related to ischemic heart disease in the treatment group and 88 events in the placebo group of patients.

A major controversy evolving from this study concerned changes of blood pressure in the placebo-group patients. During the 3-year study, approximately 47% of these patients either achieved diastolic pressures less than 95 mm Hg or were removed from the study for other reasons. Almost 25% of these placebo-treated patients had diastolic pressures that fell below 90 mm Hg. Thus, 25% of patients with mild hypertension attained normal diastolic pressure over a 3-year period without pharmacotherapy. Whether any of these patients subsequently demonstrated pressure elevations is, of course, not known.

The ANBPS did not, however, demonstrate that mild hypertension should not be treated, nor did it show that patients with diastolic pressures between 90 and 95 mm Hg should not be treated; these latter patients were not studied. Nevertheless, the study confirmed the findings of the HDFP study in those patients with mild hypertension whose diastolic pressure was 95 mm Hg or more. One new and fascinating finding relates to the differences between patients who were smokers and those who were nonsmokers. Patients who were cigarette smokers had significantly (and impressively) higher end points at all levels of systolic pressure (Figure 1).

Multiple Risk Factor Intervention Trial

The MRFIT was also faulted for not demonstrating that which it was not designed to demonstrate. This study was designed to determine whether therapeutic interventions in patients with multiple cardiovascular risk factors (i.e., hypertension, obesity, hyperlipidemia, cigarette smoking) would reduce cardiovascular morbidity and mortality. Patients were assigned either to a group that would receive special interventions (SI group) or to physicians practicing in the same community who would give the usually accepted medical care (usual care [UC] group). The study achieved its goal: the patients of the SI group had significantly improved cardiovascular morbidity and mortality. However, an unexpected finding provided grist for much controversy. The study reported that SI patients with mild hyper-

Table 1. Percentage of Reduction in Mortality in HDFP Stratum I Subjects According to Entry Characteristics

<table>
<thead>
<tr>
<th>Entry characteristics</th>
<th>Stepped care</th>
<th>Referred care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of deaths</td>
<td>Rate/1000 patient-years</td>
</tr>
<tr>
<td>Entry diastolic BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90–94 mm Hg</td>
<td>36</td>
<td>7.0</td>
</tr>
<tr>
<td>95–99 mm Hg</td>
<td>39</td>
<td>8.4</td>
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<tr>
<td>100–104 mm Hg</td>
<td>31</td>
<td>9.3</td>
</tr>
<tr>
<td>Range of entry diastolic BP</td>
<td>106</td>
<td>8.0</td>
</tr>
</tbody>
</table>

*Not on antihypertensive treatment and without target-organ damage. Target-organ damage included left ventricular hypertrophy on ECG, history of myocardial infarction, history of stroke, history of intermittent claudication, serum creatinine >1.7 mg/dl.

Tension (diastolic pressures in the 90–94 and 95–99 mm Hg ranges) had more cardiovascular deaths than their UC counterparts. This was the first major multicenter trial in which the more vigorously treated patients had a less satisfactory response than the patients who were treated by the community physicians. Several explanations for this finding are possible: 1) the SI patients with mild hypertension may be different from their counterparts in the UC group; 2) the two groups may have received different treatment; 3) physicians treating the UC group may have provided better therapy; or 4) the SI patients who died may have had more severe hypertension, coronary arterial disease, hypertensive heart disease, or obesity than their UC counterparts.

The data of the first MRFTT report confirms the first possibility (Table 2): more patients randomly assigned to the SI group had abnormal electrocardiograms, and there were more coronary heart disease deaths and total deaths in that group of SI patients with abnormal electrocardiograms. The detailed report concerning the specific electrocardiographic abnormalities is not yet available, but dysrhythmias, left ventricular hypertrophy, and pre-existing coronary arterial disease increase the risk of sudden death. 14 Although serum potassium levels in the two groups have been reported to be the same, these levels were not measured immediately preceding the deaths. Editorial statements have repeatedly indicated that the diuretic therapy of the two groups cannot account for the deaths on the basis of hypokalemia, but, again, the data have not been published by the study group. However, untreated patients with essential hypertension and left ventricular hypertrophy have more ectopic ventricular beats than those patients without left ventricular hypertrophy. 15 Therefore, it seems reasonable to assume that in the presence of some degree of hypokalemia and ventricular hypertrophy there is a possibility of arrhythmias favoring sudden death. Further, with coexistent obesity, excess use of tobacco, otherwise unrecognized coronary arterial disease, and so on (all features of the MRFTT patients), the risk would be that much greater. Hopefully, forthcoming reports from the MRFTT study group will clarify the issue.

It is also possible that the physicians treating the UC group did provide different, or even more effective, care. At the time of the HDFP study, the physicians providing care for the RC patients were advised to "individualize" their care of the Stratum I (mildly hypertensive) patients. 10 But during the MRFTT study, β-blocking therapy for patients with hypertension was accepted practice in the general medical community. Investigators of the MRFTT study suggest that no disparity occurred between β-blocker therapy for the SI and UC patients. Following the same line of reasoning, pharmaceutical sales records of the National Prescription Audit indicate that combination therapy of a thiazide diuretic with a potassium-sparing agent was the number one drug regimen prescribed in this country at the time of the MRFTT study. Perhaps this phenomenon in treatment practice could also explain this difference in the results of the two studies. However, the answers at this time remain pure conjecture—arguments to the contrary notwithstanding.

### Myocardial Infarction

As a result of the many multicenter studies conducted, the efficacy and safety of antihypertensive drug therapy have been established and cardiovascular mortality and morbidity have diminished with treatment. All observers agree that deaths and morbid events relating to congestive heart failure, stroke, dissecting aortic aneurysm, and progression of hypertensive vascular disease have decreased. Indeed, according to the 1985 data from the National Center for Health Statistics, deaths resulting from stroke have diminished by 49% in the United States, and deaths from myocardial infarction have been reduced by 35% (Figure 2). It is difficult, however, to ascribe the 35% reduction in deaths from myocardial infarction to antihypertensive therapy with great certainty.

Rather than leave this question as it is, many have been more direct in their conclusions. They have indicated that no multicenter study has demonstrated that deaths from myocardial infarction are reduced by antihypertensive drugs. This conclusion is not valid. The HDFP indicated that patients with mild hypertension...
hypertensive therapy failed to prevent myocardial infarction in middle-aged men. This question is raised because autopsies have shown that 18- to 5-year-old American soldiers who died of war injuries already demonstrated pathological evidence of early coronary arterial lesions. Thus, it is my personal opinion that it is inappropriate to suggest that antihypertensive therapy failed to prevent myocardial infarction.

Influence of Consumer Education on Health Habits

A number of factors have come into play in our society that may have influenced the overall reduction of cardiovascular mortality from more than 54% to less than 50% (see Figure 2). These factors, like the pathological factors associated with hypertension, can be expressed as a mosaic (Figure 3).

Since 1963, we have seen our consumer society become more health conscious and more sophisticated in matters of disease prevention. Data from the U.S. Department of Agriculture have demonstrated a 27% reduction in cigarette consumption, a similar decrease in consumption of animal fat, and an increase in consumption of vegetable fats and fish. Data from the National High Blood Pressure Education Program have documented a 36% reduction in food-grade salt sales in the United States, from 2.25 to 1.44 lb per capita between 1972 and 1985. With these major changes in health habits occurring in the background of these so-called controlled multicenter trials, we can appreciate this variety (or mosaic) of factors (shown in Figure 3) interacting with and affecting the results of antihypertensive drug trials. Therefore, we might ask if there is not a possible explanation at hand for the disparity between cardiovascular mortality rates in the United States and those in other countries. Clearly, in a more sophisticated society, scientific answers will become more difficult to obtain in controlled multicenter studies.

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