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EDITORIALS

Mild Hypertension: To Treat or Not to Treat

EDWARD D. FROHLICH, MD, FACC

New Orleans, Louisiana

Over the past three decades a meaningful sequence of successes was realized in the cardiovascular area, each resulting from the demonstration that antihypertensive agents are effective in reducing cardiovascular morbidity and mortality. In the early 1950s, potent agents were introduced that made malignant hypertension and other severe forms of hypertension amenable to therapy. These results demonstrated clearly the merits of antihypertensive pharmacotherapy. With the series of Veterans Administration multicenter studies, effectiveness of antihypertensive therapy was further demonstrated for patients whose diastolic pressures exceeded 129 mm Hg (1), then 115 through 129 mm Hg (2) and later, 90 through 114 mm Hg (3). These studies may also be credited with a number of secondary accomplishments: 1) they established further credibility that antihypertensive therapy should be advocated at least for all patients whose diastolic pressures exceeded 104 mm Hg; 2) they established the value of prospectively designed multicenter studies dealing with pharmacologic agents; 3) they underscored the necessity for a national education program to ensure that both the medical profession and the lay public would be aware of the disastrous and preventable consequences of untreated hypertension and would know that the clinical problem is eminently treatable; and 4) they provided impetus for the establishment of several new multicenter studies that would later demonstrate the value of the therapeutic approach initially set forth by the Veterans Administration studies (for example, the Hypertension Detection and Follow-Up Program [HDFP] and the Multiple Risk Factor Intervention Trial [MRFIT]). The latter was designed to show that simultaneous reduction of a variety of risk factors will result in reduced cardiovascular death and disability.

To be sure, the bottom-line effect, that is, a reduction in the annual rate of cardiovascular death from 54 to 50% (of total deaths in the United States), was not solely the result of a more vigorous application of antihypertensive therapy over this past decade (Fig. 1). However, antihypertensive therapy was a major factor in addition to the national awareness of the need to consume a more healthful diet, lower excess body weight, discontinue smoking and initiate exercise programs. Other important factors probably included the development of improved modalities of other cardiovascular therapy (pharmacologic and coronary bypass surgery), coronary care units, mobile coronary units, cardiopulmonary resuscitation and electroshock therapy.

Recent Multicenter Trials

Unfortunately, appreciation of the cardiovascular successes emanating from several recent multicenter trials has been clouded by certain reactionary attitudes. Some reflect a belief that only the study treatment centers were able to demonstrate therapeutic success through their vigorous stepped care treatment programs with therapeutic goal pressures. Do we believe that the decade of high blood pressure educational programs was not really that successful? I think not. It is clear that the remarkable reduction of national cardiovascular mortality and the 40% reduction in deaths from stroke were achieved by the practicing physicians throughout our nation (4). These are the physicians who provided the "referred care" or "usual care" for the prospective multicenter studies. It is precisely this group of patients that accounts for the majority of individuals with hypertension and the majority of deaths from hypertension-related diseases. Actually, the average diastolic pressure of the referred care patients of the Hypertension Detection and Follow-up Program (HDFP) study after 5 years of therapy was reduced to less than 90 mm Hg, only a 4 mm Hg difference from that in the group of patients receiving "stepped care" (5). This is a truly remarkable response to a nationwide continuing medical education effort! In contrast, the intensive treatment offered by the stepped care approach effected a lower treatment diastolic pressure after 5 years. This was associated with a significantly greater reduction not only in cardiovascular deaths but also in total (or overall) death rates (5). Negative statements to the contrary, the patients with mild hypertension who were treated by the stepped care approach did, in fact, demonstrate a reduction in deaths from myocardial infarction. This was observed in the stratum I patients with mild hypertension.

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Address for reprints: Edward D. Frohlich, MD, Alton Ochsner Medical Foundation, 1516 Jefferson Highway, New Orleans, Louisiana 70121.

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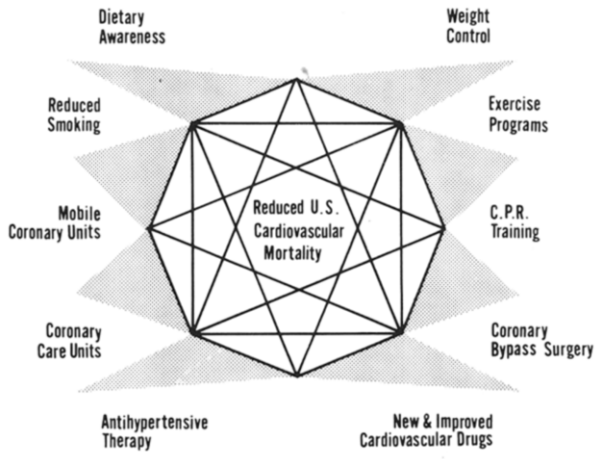

Figure 1. Mosaic of factors associated with reduced cardiovascular mortality in the United States (with thanks to I. H. Page).

Pharmacotherapeutic Approach to Mild Hypertension?

Recently, the Multiple Risk Factor Intervention Trial (MRFIT) program reported the first results of its aggressive therapeutic approach to reduce cardiovascular risk factors (6). These results indicated that there were *more* cardiovascular deaths among patients with mild hypertension who were treated intensively by the treatment centers (the "special intervention" group) than in the community (usual care) group. The response to these results was amazing. First, authorities, and even the lay press, concluded that perhaps we should "throw the baby out with the bath water." After all, if the special intervention or stepped care approach produced this, antihypertensive therapy may not be as sound as we had initially thought. Unfortunately, there was no immediate response from those with greater expertise to ask: what might have accounted for these differences; could the referred care and usual care groups have been doing something better; and could alternative forms of therapy have prevented these deaths?

Role of diuretic-induced hypokalemia and arrhythmias. Results showed that the increased deaths of the special intervention group of patients with mild hypertension (in the MRFIT study) occurred in those patients who had a greater incidence of abnormal electrocardiograms before the initiation of the study than the patients of the usual care group. Of these patients with abnormal electrocardiograms, over half demonstrated voltage changes compatible with left ventricular hypertrophy; almost an additional one-third had either conduction defects or rhythm disturbances (7). We now learn from the National Heart, Lung, and Blood Institute that hypokalemia associated with the diuretic therapy in those patients most likely accounted for these deaths. Thus, it is reasoned that the diuretic-induced hypokalemia predisposed the already abnormal heart to arrhythmias and, therefore, sudden death. Several reports (8–10) already have indicated that patients treated with diuretic drugs—particularly with higher doses—demonstrated hypokalemia that was associated with a greater frequency of cardiac arrhythmias. Moreover, a recent report from our laboratory (11) indicated that even untreated patients with hypertension and left ventricular hypertrophy demonstrated a greater frequency of ventricular ectopic activity over a 24 hour period. These findings should be more reason for the practicing physician to be aware of a greater frequency of ventricular arrhythmias in the hypertensive patient with cardiac enlargement who develops diuretic-induced hypokalemia.

Coincident with these developments, there has been a major change in the pharmaceutical-prescribing practice of physicians. No longer are the major tranquilizing agents the most frequently prescribed drugs; they have been surpassed by cardiovascular agents (agents used for the treatment of hypertension, diuretics with potassium-retaining agents and the beta-adrenergic receptor blocking drugs) (12). Although the data detailing use of these agents by the referred care or usual care physicians (of the Hypertension Detection and Follow-Up Program [HDFP] and Multiple Risk Factor Intervention Trial [MRFIT] studies, respectively) are not yet published, their wide use by the nationwide community of practicing physicians is a matter of record (12).

Community treatment versus special intervention. From this information it is clear that we should derive more from the Multiple Risk Factor Intervention Trial study than the disconcerting information that treatment of mild hypertension may increase cardiovascular deaths. We must also realize that these deaths were found primarily in the patients with mild hypertension of the special intervention group who had an abnormal electrocardiogram before initiation of therapy. We should realize that patients with an abnormal electrocardiogram were not allocated in equal numbers by randomization into two groups. In other words, we should know that the treated (usual care) patients treated by their personal physicians did not have as many deaths or as many pretreatment abnormal electrocardiograms. We should also consider that the physicians in the community just might have been doing something better than the therapists of the special intervention centers. We should also realize that the patients in the community also were concerned about risk factors other than hypertension and they did something about them.

Nonetheless, these preliminary reports have prompted a series of editorial comments that could be most damaging to the overall concept of pharmacotherapy of hypertension. To be sure, the authors (13–16) cautioned that their advice concerns the treatment of only mild hypertension. However, their cautions are easy to carry over to other circumstances—guilt by association is a common failing.

Benefits of Pharmacotherapy in Mild Hypertension

Let us remember that the strongest prospectively collected epidemiologic data indicate no specific level of pressure that defines increased cardiovascular risk. The higher the pressure—systolic or diastolic—the greater is the risk (17). The data from the Veterans Administration and U.S. Public Health Service (few as they are concerning patients whose diastolic pressures decreased to between 90 and 104 mm Hg) (3,18), the Hypertension Detection and Follow-Up Program (4), Multiple Risk Factor Intervention Trial (5) and Australia study (19) did demonstrate the efficacy of pressure reduction in patients with mild hypertension.

Let us not confuse the issue with statements that in no study did antihypertensive treatment prevent deaths from myocardial infarction. This is truly another question which to some extent is answerable. First, we must recall that the average age of patients at entrance to the Veterans Administration studies was the late 40s, an age when coronary artery lesions already occur in male Americans. Autopsy reports of teenaged American soldiers, killed in Korea or Vietnam, demonstrated the presence of atherosclerotic lesions (20,21). Second, fatal myocardial infarction was reduced by 46% in the stratum I stepped care patients of the Hypertension Detection and Follow-Up Program study (5). There were 30 stepped care patients with mild hypertension having myocardial infarction and 56 referred care patients. These data were even more impressive than for the total experience of the Hypertension Detection and Follow-Up Program. In addition, there was a 45% reduction in deaths from cerebrovascular disease in the stepped care group with mild hypertension (5). Another study, from Sweden (22), demonstrated significant reduction in fatal and nonfatal myocardial infarctions. In addition, clinicians from the Mayo Clinic (23,24) recently reported the benefit of antihypertensive therapy for survival of patients with atherosclerotic heart disease.

Recommendations

Therefore, in these times when it is popular to discredit established practice and belief (a characteristic not exclusive to the field of medicine), let us maintain reason and not be too quick to destroy well conceived and validly demonstrated practices. We should still consider that all individuals whose diastolic pressure exceeds 90 mm Hg are at increased cardiovascular risk. Moreover, we must still recognize that in these individuals pressure should be reduced in order to minimize that risk. It is not unreasonable to pursue nonpharmacologic means to control pressure, but, in any case, at the least these patients should remain under continuous and close clinical observation and management. Should restriction of dietary sodium or reduction in body weight not be feasible or effective for a specific patient in a reasonable time period, there is no reason why drug treatment should not be prescribed. With the availability of several therapeutic alternatives including once-daily administration of beta-receptor blocking agents or diuretics with potassium-retaining agents, danger of hypokalemia is not the necessary alternative or consequence. Moreover, we have also come to realize that there is little necessity to prescribe 100 mg daily of hydrochlorothiazide; initiation of therapy at 25 mg (and later, 50 mg) doses may be adequate.

Let us not reverse the remarkable downturn in cardiovascular and stroke mortality solely through the weight of editorial comment. The supportive well established data were long and hard to come by and were costly in human contribution and dollars. Ethical practice (and our material resources) will not permit a more ideal reexamination of this problem. Finally, let us not impugn the results of these studies by implying that the investigators resorted to biostatistical game-playing. At best, these comments directed toward reputable professionals who were not playing games are unfair and unfounded; and their peer-reviewed statistical analyses may be subjected to professional questioning but not discredit.

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