Guest Editors’ Summary

Overview of Discussions of the National Institutes of Health Workshop on Antihypertensive Drug Treatment

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The National Heart, Lung, and Blood Institute (NHLBI) Workshop on Antihypertensive Drug Treatment focused on three basic themes: epidemiological, clinical, and economic considerations characterizing hypertension and its treatment. The following article summarizes the workshop’s discussions concerning these themes.

Issues From Epidemiology and Clinical Trials

Although once considered simply as a disease affecting a small number of individuals for whom very little could be done, hypertension is now recognized as a disease and a risk factor. As a disease, there is clearly a profound risk of premature cardiovascular morbidity or mortality associated with severely elevated blood pressure. Intervention to lower blood pressure should be immediate, and there is reasonably common agreement as to how this can best be accomplished.

In addition, blood pressure is a continuously distributed risk variable—the higher the blood pressure, the greater the cardiovascular risk. In the range of mildly elevated diastolic blood pressure (90–104 mm Hg), the risk, although relatively increased, is not large in absolute terms except when projected for many years. However, because there are so many individuals in this category of the diastolic blood pressure distribution, the majority of excess cardiovascular morbidity and mortality is experienced by this group.

Further, some evidence suggests a rather broad prognostic heterogeneity among these subjects. Among the explanatory variables of this prognostic heterogeneity are demographic characteristics like age, race, sex, and socioeconomic status, and other cardiovascular risk factors like hypercholesterolemia, cigarette smoking, and left ventricular hypertrophy. Thus, not all groups at the same level of blood pressure have the same risks for the various adverse cardiovascular sequelae; certain groups are more prone to develop stroke, while others are more prone to develop myocardial infarction, in part because they have additional cardiovascular risk factors. Still other individuals may develop congestive heart failure, and yet others, end-stage renal disease. The workshop participants expressed the need for research to better define cardiovascular renal risks and then to develop interventions that not only lower blood pressure but also confer additional benefits relative to specific disease processes or morbid outcomes.

Participants also discussed other desirable approaches to refining assessments of risk for hypertension-related morbidity and mortality in individuals and in the population. Several of these approaches involve improvements in characterizing the severity of blood pressure elevation itself. The introduction of ambulatory and home blood pressure recording, presently used primarily as a research tool, in time should enable better classification based on true blood pressure for various times and places. In describing populations, as in prevalence studies, data should be reported by severity of hypertension although this objective is difficult to meet for those already receiving drug treatment. The marked upward trend in the prevalence of drug treatment in the United States also raises the question of whether a certain proportion of patients are being treated unnecessarily.

At the individual and population levels, the importance of other major risk factors was noted. Indeed, elevated levels of serum cholesterol contribute significantly to atherosclerotic disease, especially coronary heart disease (CHD), and the threshold is probably well below average levels in Western populations. Although hypertension is clearly the most important risk factor for stroke, the importance of cigarette smoking, alcohol consumption, and probably serum cholesterol to a degree has been increasingly recognized. Thus, the major CHD risk factors are probably predictive of stroke as well, but the different strengths of their relations with stroke have been puzzling because about 70–80% of strokes are thought to be atherothrombotic. Recent observations have indicated that thrombotic stroke in Western populations may not be closely related to extracranial atherosclerosis as previously
thought, but more often, thrombotic stroke may be related to intracranial small-vessel disease.

The evidence that lowering blood pressure reduces stroke morbidity and mortality is clear from clinical trials. The benefits of reducing blood pressure for CHD are less clear. Some investigators have attempted to use observational data analysis from case series, clinical trials, and community studies to elucidate the relation between blood pressure reduction and CHD. Such analyses have suggested that larger degrees of blood pressure lowering are associated with increased risk, including contrasting trends for CHD and stroke end points. However, the characteristics of the populations studied (e.g., presence or absence of electrocardiographic evidence of ischemia), the types and extent of treatment, the specific end points (e.g., sudden death or total CHD), and finally the results have been inconsistent across these studies.

More importantly, such responder-nonresponder analyses are notoriously prone to confounding variables, especially those reflecting severity of disease and thus are difficult to interpret at best.

A great deal is known about the benefits of antihypertensive drug treatment for most vascular complications, but it is apparent that reliable data about the effects on the incidence of renal disease in nonmalignant hypertension are quite sparse. Another disease offering great potential benefit from treatment, but with information currently limited, is diabetic microangiopathy. Further clinical and epidemiological research in these areas would be most valuable.

An important risk factor that could influence treatment decisions is gender: women with few or no other risk factors have low absolute risk if blood pressure is only mildly elevated. From the Medical Research Council (MRC) trial data, women also appear to have somewhat higher side-effect rates with propranolol than do men. Thus, even if the relative benefit for women is concluded to be equal to that for men, at least for stroke (which seems reasonable), the absolute benefit-harm ratio is likely to be considerably less; this reasoning suggests that a higher blood pressure threshold for initiating treatment or higher treatment goals for women may be justified.

Differences exist in the interpretation of apparent subgroup effects on stroke, CHD, or both in the major trials. These interpretations include the differential effects of diuretic-based stepped care on CHD according to the presence or absence of resting electrocardiographic abnormalities in the Multiple Risk Factor Intervention Trial (MRFIT), and of propranolol on stroke and CHD according to cigarette smoking status in the MRC Trial. The reasons for the controversy are that these effects were observed in the absence of clearly stated prior hypotheses, and appropriate sample sizes were neither computed nor obtained. In other instances, the subgroups did not result from random assignment, and therefore, differences in outcomes may very well not be attributable to the intervention.

Occasionally, support for the results of subgroup analyses is sought by examining data from other trials although consistency of results across multiple studies is not always found. For example, the MRC finding regarding the ineffectiveness of β-blocker treatment, particularly for stroke prevention in smokers, was not confirmed in the International Prospective Primary Prevention Study in Hypertension (IPPSPH) or in the Heart Attack Primary Prevention in Hypertension Trial (HAPPHY). The β-Blocker Heart Attack Trial and the Timolol Trial also did not show any significant differential therapeutic effectiveness based on smoking status. The type of β-blocker used (nonselective vs. cardioselective) does not appear to be a factor in explaining the differential results in these trials. It would seem, therefore, that subgroup analyses should be used mainly for hypothesis generation, and the overall results of trials should be used for providing guidance for treatment decisions.

Regarding specification of end points, mortality is obviously a good end point when it can be anticipated that a sufficient number of deaths will occur to permit inferences to be made about the effects of an intervention. Recently, however, the focus has intensified on patients with mild hypertension (diastolic blood pressure 90–104 mm Hg) for whom the short-term risk of mortality is rather low. Therefore, there is a need for more creative thinking about what events may be characterized as intermediate end points, including the development of asymptomatic complications like left ventricular hypertrophy, reduced glomerular filtration in the kidney, or simply a progressive rise in blood pressure. Therefore, there is also a need for easily obtainable measurements for these intermediate end points. Echocardiography and quantitative microalbuminuria assays are examples of newer sensitive measurement methods for such intermediate outcomes.

With regard to secular trends from the early 1970s to the present and their influence on health, it was speculated that the improvement in social and economic conditions for some portions of the population, especially black women, could have contributed to improvement of their health status. In the past 15 years, black women have experienced the greatest relative declines in all-cause mortality, especially that from cardiovascular disease. Cardiovascular disease mortality trends are partially a function of socioeconomic conditions like diet, smoking, and alcohol consumption; the degree of patient compliance; and general educational levels. Therefore, while the benefits of treatment may seem clear, they may be influenced by a variety of other factors. The possibility of diverging trends in cardiovascular mortality among race-sex groups during the 1980s needs further study.

Finally, because blood pressure is a continuously distributed risk variable, there is at least the concep-
tual possibility of primary prevention of hypertension by environmental manipulations that are designed to shift the entire blood pressure distribution toward the lower end with the expectation of reducing hypertension-related morbidity and mortality. Such interventions are currently being tested and include maintenance of ideal body weight and reduced sodium consumption. Other therapies undergoing further research include dietary supplementation with potassium, calcium, or magnesium; restriction of alcohol intake; and changes in the distribution of dietary fats. If and when the scientific evidence is satisfactory, changing these lifestyle factors could involve such societal institutions as schools, food producers and distributors, and other community institutions.

Clinical Considerations

Quality-of-life issues have recently emerged as important considerations in the selection of therapy for hypertensive patients. It is not that quality of life was formerly an unimportant issue, but in the past, the primary goal was to reduce mortality and morbidity by reducing blood pressure. This goal could only be accomplished, in most instances, by a limited number of drugs whose blood pressure-lowering efficacy was well established, but whose side effects were often quite troublesome. With the advent of new drugs, we are witnessing not only continued efficacy in the reduction of blood pressure but also more specific pharmacological action and fewer side effects. Because of this present situation, survey instruments are now being developed that can provide a reasonable and reliable measure of the quality of life, and thus, it can be anticipated that these instruments will be used in establishing benchmarks for ensuring that future antihypertensive therapy is not only efficacious but also safe and associated with an absolute minimum of side effects.

Sexual dysfunction, a potential side effect of virtually any antihypertensive drug, encompasses a variety of sexually related disorders ranging from erectile dysfunction to loss of libido. From a pathophysiological standpoint, one line of reasoning suggests that, in some cases, sexual dysfunction appears to be directly related to the blood pressure reduction associated with antihypertensive drug therapy. However, there is also reason to believe that some contributions to sexual dysfunction may be drug-specific and unrelated to the absolute decrease in blood pressure. For those clinicians whose experience supports the latter view, it has been found that sexual dysfunction can sometimes be overcome by simply switching to an agent from a different class or to a different agent within the same class.

Much controversy has centered around the use of newer antihypertensive agents (e.g., angiotensin converting enzyme inhibitors and calcium entry blockers) as first-line drug treatment for hypertension. Because these newer agents have been shown to be relatively safe and efficacious in lowering blood pressure, there is a temptation to equate these short-term attributes with long-term benefit, specifically with reduction in cardiovascular morbidity and mortality. However, one discussant warned about premature enthusiastic endorsement for the calcium entry blockers. The basis for concern is a meta-analysis of several secondary prevention trials involving 12,000 patients who were placed on calcium entry blocker therapy (primarily nifedipine and verapamil) for unstable angina, myocardial infarction, and postmyocardial infarction management. This meta-analysis suggested a trend toward a higher mortality associated with use of the calcium entry blockers although the trend was not statistically significant. This example, however, was used as a caveat to guard against premature extrapolation of short-term blood pressure-lowering effects to long-term benefits of reduced morbidity and mortality for drugs that have not been specifically tested for these long-term effects.

Economic Considerations

Addressing the issues of cost, cost-benefit, and cost-effectiveness in the treatment of hypertension is fraught with the same multiple hazards associated with determining the costs and benefits of any health intervention. These problems center primarily on the difficulty in making assumptions about the value of human life, how to assign benefit to reduced mortality and morbidity, and computation of costs that are indirectly related to hypertension like days lost from work. Other cost issues are a little easier to resolve, like the differential costs of therapy in the drug treatment of hypertension. However, in developing national policy, it is difficult to know to what extent the cost of different therapies should influence recommendations. For example, calcium entry blockers have been found to reduce blood pressure in patients with sodium-sensitive hypertension. In other words, these agents may be as useful as diuretic drugs, and moreover, they seem to be associated with fewer side effects, including the adverse metabolic side effects of the diuretic agents like modification of lipid metabolism, hyperglycemia, and hypokalemia. However, the calcium entry blockers lack data supporting long-term risk reduction, and the costs of these drugs are substantially higher than the costs of diuretic drugs. This situation compounds the difficulty of making policy recommendations for the use of drugs for millions of Americans whose abilities to pay for therapy are quite variable. As a related point, several participants remarked on the unjustified neglect of low-dose reserpine as a low-cost and effective second-step drug.

In summary, that the benefits, costs, and choices in the selection of antihypertensive drug treatment are complex issues was well reflected in the breadth and intensity of the discussion between the oral presentations of the scientific papers. For detailed presentations of the issues alluded to in this over-
view, the reader is referred to the remainder of these proceedings; regarding the implications for research and policy, the reader is directed to the last two articles of this supplement by Harlan\textsuperscript{15} and Horan\textsuperscript{16} and to the concluding discussion.

References

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