Implications for Research

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Selected portions of the workshop's closing discussion are summarized. Major ongoing clinical trials of antihypertensive drug treatment are described. Some recommendations offered by workshop participants for future research directions are summarized. (Hypertension 1989; 13(suppl I):I-171–I-172)

One of the important objectives of this conference was to identify areas for future research. As background for such recommendations, ongoing major trials are described. Four major trials are currently underway in the United States. The Trial of Antihypertensive Intervention and Management (TAIM) is a multicenter study of approximately 880 mild hypertensive subjects. In a factorial design, two traditional classes of drugs, chlorthalidone as a diuretic agent and atenolol as a β-blocker, are compared with placebo. The other comparison incorporates two forms of nutritional treatment, weight reduction versus modification of sodium and potassium intake. The main outcome measure is a diastolic blood pressure change at 6 months, although several other important outcomes are also examined, including treatment effect on left ventricular mass (echocardiography), serum lipid and lipoprotein levels, and indices of quality of life. The intervention and follow-up phase was completed in 1988 with a mean follow-up period of about 18 months.

The Treatment of Mild Hypertension Study (TOMHS) is also a multicenter placebo-controlled trial in mild hypertensive subjects. The main focus of this trial, in approximately 900 subjects, is the comparison of five classes of drugs: a diuretic agent (chlorthalidone), a β-blocker (acebutolol), an angiotensin converting enzyme inhibitor (enalapril), an α-adrenergic blocker (doxazosin), and a calcium entry blocker (amlodipine). All subjects are also receiving nonpharmacological therapy. The end points are similar to those investigated in TAIM but also include an assessment of treatment effect on ventricular arrhythmias by Holter monitoring.

The effects of various diuretic drugs on the frequency and severity of ventricular arrhythmias are being evaluated in the Hypertension Arrhythmia Reduction Trial (HART). Five active interventions—hydrochlorothiazide (HCT) alone, HCT in combination with oral potassium, HCT with oral potassium and magnesium, HCT plus triamterene, and chlorthalidone alone—are compared with placebo in 400 previously treated hypertensive men with resting electrocardiographic abnormalities.

The fourth trial, the Systolic Hypertension in the Elderly Project (SHEP), has completed enrollment of 4,736 participants. The primary objective of SHEP is to determine whether antihypertensive therapy—chlorthalidone (12.5–25 mg/day) followed by atenolol (25–50 mg/day) or reserpine (0.05–0.10 mg/day)—when compared with placebo will reduce the combined incidence of fatal and nonfatal stroke in individuals 60 years of age or older with isolated systolic hypertension (systolic blood pressure ≥160 mm Hg and diastolic blood pressure <90 mm Hg).

A study of hypertensive men and women 70–84 years of age, the STOP Hypertension trial, is being planned in Sweden. A total of 2,000 subjects will be enrolled in this 3-year multicenter study, which has stroke, myocardial infarction, and sudden death as end points. A combination of a diuretic drug and a β-blocker will be compared with placebo.

The Medical Research Council (MRC) Elderly Trial has recruited its 4,400 participants from 230 family practitioners. The trial is placebo controlled and single-blind with two treatment regimens, one of which is atenolol, 50–100 mg/day, and the other of which is a combination of 25–50 mg hydrochlorothiazide and 2.5–5.0 mg amiloride. If the duration of the trial is as long as planned, it will end in early 1990.

Recommendations for Future Research

It was recommended that two issues be considered for the fourth report of the Joint National Committee (JNC). First, in its third report, the JNC
made reference to the importance of considering coronary disease risk factor levels in deciding whether to treat subjects with a diastolic blood pressure between 90 and 94 mm Hg. It seems prudent to extend this consideration to the importance of taking action against these risk factors. The MRC in the United Kingdom has been approached about the need for studies of smoking cessation in hypertensive subjects. The potential impact on the risk of stroke and coronary diseases is enormous. Second, with the emergence of newer classes of effective antihypertensive agents, more attention could and should be placed on the cost of drugs. Thus, cost considerations were recommended as part of the new JNC guidelines.

One of the real problems related to the treatment of hypertension is the fact that we really do not know the mechanism(s) behind hypertension. We are probably treating the chain of events too late. Thus, more laboratory research should be encouraged.

Because antihypertensive treatment conveys a multitude of effects, favorable and unfavorable, there is a need for developing combined end points, particularly in trials involving mild hypertensive subjects. Low event rates and small treatment effects have implications for statistical power. Reasonable algorithms for combined end points are also important for trials comparing equipotent antihypertensive agents.

The available information on hypertension and renal disease is limited, and it was suggested that more could be learned by taking advantage of existing hypertension data sets and linking them with end-stage renal disease registries. There is also a need to evaluate new tools, for example, ambulatory blood pressure monitoring, to determine whether they help predict risk more accurately, particularly as we focus increasingly on mild hypertension.

Several classes of antihypertensive agents are available to physicians, and these agents vary, as discussed at the conference, in mechanisms of action, antihypertensive potential, undesirable side effects, cost, and so forth. Comparative studies with disease end points are urgently needed. Due to the sample size requirements, large multicenter and possibly multinational trials are needed. Because the use of angiotensin converting enzyme inhibitors is increasing, one such priority would be a comparison of these inhibitors with a β-blocker, preferably with as few subject exclusions as possible.

References

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The National Heart, Lung, and Blood Institute Workshop on antihypertensive drug treatment. The benefits, costs, and choices. Implications for research.
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