Alternatives to Traditional First-Line Antihypertensive Treatment: Unresolved Questions and Therapeutic Dilemmas

A Personal Approach

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The best antihypertensive regimen for use in patients with mild-to-moderate hypertension has not been determined. When nonpharmacological treatment of hypertension fails, initial drug treatment with diuretic drugs, sympatholytic agents (including β-adrenergic receptor blockers), or vasodilators will result in satisfactory blood pressure control. However, each of these therapies has effects that are independent of their antihypertensive activity and that should be considered before a selection is made for initial therapy. The adverse effects of diuretic agents and β-adrenergic receptor-blocking drugs on plasma lipid profiles may diminish the beneficial effects of blood pressure reduction. On the other hand, the hypocholesterolemic effect of α-adrenergic receptor antagonists, the potential cardioprotective effect of angiotensin converting enzyme inhibitors, and the salutary effects of calcium channel blockers on left ventricular function are responses that would support the use of vasodilatory therapy. Vasodilating antihypertensive drugs may be more beneficial than “standard” therapy and should be considered for the initial treatment of newly diagnosed hypertensive patients. (Hypertension 1989;13(suppl I):I-154—I-157)

Although nearly 2 decades have passed since the initiation of the landmark Veterans Administration trials on antihypertensive therapy, controversy still rages with regard to the benefits to be derived from treatment of patients with mild-to-moderate essential hypertension. Although the incidence of myocardial infarction is clearly related to the level of blood pressure as evidenced by the long-term epidemiological studies of the Framingham Heart Study,1 an unequivocally clear and statistically significant reduction in cardiac mortality rates in patients with mild-to-moderate hypertension has not been demonstrated. One may argue that, to demonstrate decreased cardiac mortality rates, it would be necessary to study an extraordinarily large number of patients for an impractically long time. Often, the blood pressure levels of patients in “placebo” treatment groups return to normal, and other risk factors remit during the course of a clinical trial; the expected difference in mortality and morbidity rates between treated and untreated patient populations narrows, so that a clinically significant therapeutic effect cannot be measured with any degree of statistical certainty.

Another factor confounding a conclusive result is the adverse metabolic consequences resulting from “diuretic-based” therapeutic regimens; these regimens have generally formed the foundation of the therapeutic interventions in the large-scale clinical studies reported to date. Although aggressive caloric and fat-intake restriction leading to weight loss may avert drug-induced increases in serum cholesterol levels,2 the administration of thiazide diuretic drugs to patients with mild-to-moderate hypertension often significantly increases plasma lipid levels; this increase can persist beyond the first few months of therapy.3 If one accepts the conclusions of the lipid research clinical trials—that an accelerated decrease in mortality rate results from decreases in total plasma cholesterol concentration4—one can envision a counterproductive and perhaps even an accelerated increase in mortality and morbidity rates resulting from the adverse effects of diuretic agents on lipid metabolism. Thus, one possible explanation for the failure of clinical trials to demonstrate a clearer therapeutic benefit may be the counterproductive effects of diuretic agents under these circumstances.

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Similarly, the use of $\beta$-adrenergic receptor–blocking drugs that are commonly used as initial antihypertensive agents is often associated with adverse metabolic effects. These agents can induce an increase in lipid levels and possibly an associated adverse effect on morbidity and mortality. Yet, the trends in national morbidity and mortality figures suggest a decrease in cardiovascular mortality during the era of aggressive antihypertensive therapy. Despite these equivocal benefits, few physicians are willing to discard the principle that antihypertensive therapy will benefit patients with mildly elevated systemic blood pressures. In view of these uncertainties, one must consider how to best select an antihypertensive agent for the treatment of the enlarging hypertensive-patient population.

An ideal antihypertensive drug would lower blood pressure without producing significant metabolic side effects; this drug would also not require frequent ingestion, would have no adverse effects on quality-of-life considerations, would not impair other organ-system functions, and would be readily available at minimal cost. Currently, however, no antihypertensive agent meets all these requirements. Therefore, we must consider developing a more logical process by which antihypertensive therapy can be initiated.

Traditional first-line therapy, the so-called “stepped-care approach” for the treatment of hypertension, has contributed greatly to public awareness of the dangers of high blood pressure. One cannot dismiss the benefits derived from the approaches recommended by the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Perhaps the greatest lesson from our experience of the last decade is that well-designed programs in patient education elucidating the dangers associated with high blood pressure, increased plasma cholesterol, and tobacco abuse has had substantial impact on patients’ lifestyles. Therapeutic changes in lifestyle are a critical component in the initial treatment of patients with hypertension. In patients with mildly elevated blood pressures, one cannot emphasize too strongly the benefits derived from elimination of tobacco use; limitation or elimination of alcohol intake; and changes in dietary intake (designed to reduce plasma cholesterol and triglycerides), weight loss, and regular physical exercise. Less clear are the benefits that accrue from the restriction or supplementation of monovalent and divalent cations. The newly reported guidelines for the levels of acceptable plasma total cholesterol from the National Institutes of Health suggest that an ever-increasing patient population will require pharmacological therapy to reduce this significant risk factor. No antihypertensive regimen should complicate the treatment of this risk factor, especially because the plasma total cholesterol level is abnormal in an extraordinarily high percentage of hypertensive patients.

If, however, nonpharmacological therapy alone is unsuccessful in adequately controlling blood pressure, how might we best initiate therapy in the mildly hypertensive patient? A strong argument can be made for the use of vasodilating agents as initial therapy for the treatment of patients with hypertension. Vasodilating agents—$\alpha$-adrenergic antagonists, angiotensin converting enzyme inhibitors, and calcium channel blockers—share a number of desirable characteristics. First, these agents specifically correct the principal pathophysiological abnormality associated with an elevation of blood pressure; that is, these agents decrease systemic vascular resistance. In contrast, however, $\beta$-adrenergic receptor–blocking drugs increase systemic vascular resistance. It is paradoxical that a clinical disorder characterized by peripheral vasoconstriction can be treated effectively with an agent that, among other actions, exacerbates this underlying abnormality, and that such an approach would be recommended for large numbers of newly diagnosed patients. A second advantage of the vasodilating drugs is that they do not have adverse effects on cardiac performance during physical activity. If one of the mainstays of nonpharmacological therapy is regular exercise with a goal of decreasing weight and lipid values, then the use of agents that interfere with muscle function, either directly through their physiological mechanisms or indirectly through changes in serum electrolyte levels, would be counterproductive. Third, increasing evidence suggests that left ventricular hypertrophy in patients with hypertension is an independent and significant risk factor for subsequent cardiovascular mortality and morbidity. The $\alpha$-adrenergic receptor blockers, converting enzyme inhibitors, and calcium channel blockers reduce left ventricular mass in therapeutically effective doses. $\beta$-Adrenergic receptor blockers also reduce left ventricular mass, but the effects of diuretic agents are less consistent. Fourth, it is possible to demonstrate subtle but significant abnormalities in left ventricular function, primarily during the diastolic phase of the cardiac cycle, in patients with mild hypertension who might not demonstrate left ventricular hypertrophy (R.M. Zusman, unpublished observations). These patients respond well to calcium channel antagonists, which act in part by improving left ventricular diastolic performance. This attribute may be particularly important in the treatment of some patients who develop clinically significant dyspnea on exertion because of abnormalities in ventricular compliance. As blood pressure levels rise, ventricular systolic function becomes impaired as well; this impairment appears to be more directly related to the level of systemic vascular resistance. In these patients, vasodilation results in improved left ventricular systolic performance and an increase in cardiac output (R.M. Zusman, unpublished observations).

Other potential benefits to be derived from the vasodilating agents include 1) the potential hypcholesterolemic effect associated with $\alpha$-adrenergic...
blockade\textsuperscript{11} and 2) the stimulation of endogenous prostaglandin E and prostacyclin biosynthesis by vascular endothelial and smooth muscle cells and by renal tissue in response to sulfhydryl-containing converting enzyme inhibitors like captopril.\textsuperscript{12} A clinically significant inhibition of platelet aggregation has been demonstrated in patients receiving captopril, which may contribute to a possible cardioprotective effect associated with this medication.\textsuperscript{13} This concept of cardioprotection resulting from captopril use is theoretical at present but may be a factor to consider in the selection of vasodilating agents and, in particular, in the selection of an angiotensin converting enzyme inhibitor.

Additional modifications may be needed in the way that practitioners prescribe antihypertensive drugs. The concept of "step-down" therapy involves a reduction in the dosage of antihypertensive medication after initial adequate control of the blood pressure. Many clinicians have observed, in "uncontrolled" clinical experiences, that once a patient's blood pressure is lowered, it is possible to reduce the dosage of medication without compromising adequate blood pressure regulation. This phenomenon may reflect the influence of factors like the patient's reduction in weight, dietary modification (including caloric restriction and changes in cation intake), discontinuation of tobacco and alcohol use, increased physical activity, or perhaps a more important physiological response involving the "resetting" of the blood pressure regulating mechanisms. This issue requires more extensive formal investigation. It may be profitably included, in future clinical trials, to address the antihypertensive efficacy and safety of newly developed therapeutic agents.

Similarly, the concept of progressive or stepped-care therapy involving the addition of a second agent in the treatment of patients who are unresponsive to an initial therapeutic regimen has been challenged, and the possibility of "replacement" rather than stepped-care therapy has been suggested.\textsuperscript{14} Undoubtedly, there are patients who are responsive to one class of medication but who are incompletely or not adequately responsive to another. One can envision a therapeutic algorithm in which agents are added sequentially and their dosages are subsequently reduced or eliminated until the more effective agents, given in the lowest dosages, have been identified.

Finally, one cannot help but express concern for the total financial burden that the treatment of millions of hypertensive patients will place on the health care economy. Arguments have been made for the use of the least expensive therapeutic regimen possible. However, how do we define least expensive? The true cost of antihypertensive care involves not only the cost of the drug itself but also involves the costs of ancillary tests, the treatment of diseases that are direct complications of the therapy, the potential economic cost of premature coronary artery disease resulting from hypercholes-terolemic effects of an antihypertensive agent, and considerations of the quantity and quality of extended life derived from effective antihypertensive therapy.\textsuperscript{15,16}

An analysis of trends in antihypertensive therapy in this country during the last few years shows the continued predominant use of diuretic agents and \textbeta-adrenergic receptor antagonists in the treatment of hypertensive patients rather than an expanding use of the vasodilating converting enzyme inhibitors, calcium channel blockers, or \textalpha-adrenergic antagonists.\textsuperscript{17} Indeed, there has recently been a dramatic increase in the use of \beta-adrenergic receptor antagonists and of other adrenergic inhibitors, despite the introduction of numerous vasodilating agents to the therapeutic armamentarium. These data demonstrate the power of the National High Blood Pressure Education Program and the recommendations of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. If alternative approaches to the treatment of mild-to-moderate hypertensive patients are to achieve widespread understanding and possibly even acceptance, they will require a commitment from national health organizations (the American Heart Association and the National Institutes of Health) to programs of patient and physician education. Unwavering commitment to a rigid stepped-care approach in the treatment of hypertension in light of the many controversies regarding such therapeutic regimens and of the introduction of new physiologically specific antihypertensive agents is neither appropriate nor acceptable. The treatment of this patient population should be individualized and should take into consideration the patient's blood pressure level, concomitant risk factors, and the potential benefits derived from individual classes of antihypertensive agents.

**Addendum**

A number of important and relevant articles have been published since this workshop was held. First, Hebert et al\textsuperscript{18} have reviewed the combined results of eight randomized trials of antihypertensive therapy involving more than 34,000 patients. This review confirms the statistically significant reduction in "all-cause mortality" associated with antihypertensive therapy. Nonvascular mortality was not affected by treatment, and vascular mortality was reduced, but this entire benefit was derived from a reduction in fatal strokes. Neither fatal nor total myocardial infarctions were reduced in these diuretic-based clinical studies. The results of the Metoprolol Atherosclerosis Prevention in Hypertension\textsuperscript{19} study indicated a statistically significant reduction in mortality from coronary heart disease in patients treated with metoprolol as opposed to those treated with thiazide diuretic agents. The reason for the reduced rate of fatal myocardial infarction in the patients treated with the \beta-adrenergic receptor blocker is unknown, but this group did have a lower total...
plasma cholesterol concentration than did those treated with diuretic drugs. The importance of lowering plasma cholesterol levels was reemphasized by the publication of the report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Their suggestions for the aggressive treatment of hypercholesterolemia and the setting of 200 mg/dl as the ceiling for a “desirable” cholesterol concentration for most hypertensive patients has underscored the problems associated with the use of antihypertensive drugs that raise cholesterol concentration. These new guidelines have important implications for the selection of initial therapy for hypertensive patients.21

Finally, the 1988 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure22 has endorsed the use of calcium channel blockers or angiotensin converting enzyme inhibitors, as well as diuretic agents and β-blockers, as initial therapy for newly diagnosed hypertensive patients. In doing so, the committee acknowledged the lack of clinical trials demonstrating the protective effects of these newer agents, but it also recognized the postulated drawbacks associated with the more “traditional agents.” Until one course of treatment is acknowledged as a superior treatment regimen based on definitive clinical trials, each clinician must resolve to his/her own satisfaction the dilemmas associated with the selection of any therapeutic regimen.

References

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