Alternatives to Traditional Antihypertensive Therapy

Despite the availability of effective antihypertensive therapy for the treatment of patients with mild, moderate, and severe hypertension, and in spite of the clear epidemiologic data confirming a proportional, if not exponential, risk of cardiovascular disease in patients manifesting a wide range of increasing blood pressure values, controversy continues regarding the question of the most appropriate treatment for patients with the mildest form of hypertension, arbitrarily defined as a diastolic blood pressure between 90 and 104 mm Hg.

Numerous, ambitious large-scale trials have been undertaken since the landmark reports of the Veterans Administration on the effects of antihypertensive therapy in the treatment of patients with elevated blood pressure.1 The Hypertension Detection and Follow-up Program2 and the Multiple Risk Factor Intervention Trial3 in the United States as well as the more recently reported studies of the Medical Research Council in England4 and the Therapeutic Trial in Australia5 consistently point to a decreased incidence of cerebrovascular disease in patients in whom antihypertensive therapy reduces the blood pressure below 90 mm Hg. Despite the expectation that antihypertensive therapy will result in a decrease in cardiovascular mortality and in the frequency of myocardial infarction, angina pectoris, and congestive heart failure, extraordinarily large patient populations must be substratified into “special interest” groups so that statistical analyses may confirm what should be obvious benefits to cardiovascular health.

This issue of the journal contains the recently completed guidelines endorsed at a joint meeting sponsored by the World Health Organization (WHO) and the International Society of Hypertension (ISH), establishing a policy for treating patients who have mild hypertension.6 The recommendations of the joint committee of these two distinguished bodies can be divided into a definition of the patient population in question, factors influencing the decision to treat, and, finally, appropriate methods for patient therapy. Depending on one’s definition of hypertension, as many as 60 million Americans and perhaps as many as 500 million to one billion persons throughout the world qualify for consideration for the treatment of elevated blood pressure. The guidelines for the definition of hypertension necessarily must depend on normal values exhibited by otherwise healthy citizens in the country of interest; thus guidelines for the treatment of patients in the industrialized world can differ significantly from those in underdeveloped countries or underdeveloped regions of otherwise “developed” nations. The use of absolute blood pressure values reflects the medical community’s long-standing desire to classify patients on the basis of a numerical, and therefore easily quantifiable, variable. The guidelines reported here suggest that patients with repeatedly demonstrable diastolic blood pressures in excess of 100 mm Hg be treated with pharmacologic therapy while the patient and physician attempt simultaneously to control the blood pressure by nonpharmacologic means. Presumably, the committee members would endorse attempts to decrease or eliminate pharmacologic therapy after blood pressure is controlled in those patients who have changed their life-style in ways likely to result in maintenance of normal blood pressure without drug therapy, that is, patients in whom modifications of diet, nutrition, alcohol intake, tobacco use, and exercise portend an improved cardiovascular status. Indeed, the principle of “step-down” therapy or discontinuation of treatment in patients who have accepted these changes and whose blood pressure has been adequately controlled for prolonged
periods has received inadequate emphasis. All too frequently, physicians maintain patients on unchanging antihypertensive regimens despite decreasing blood pressure levels in these patients. The guidelines reported here suggest a three-month observation period during which appropriate nondrug therapy is initiated in the absence of drug therapy. If the patient’s blood pressure falls below 100 mm Hg during this period, an additional three months are recommended without drug therapy. They recommend continued observation when blood pressure falls below 95 mm Hg and suggest that drug therapy be initiated when values consistently exceed 95 mm Hg during this second observation period. Nondrug therapy clearly is the preferred approach to the treatment of patients with hypertension.

Hazards attend these recommendations. If a patient perceives the physician’s attitude toward the treatment of hypertension as casual, the danger exists that the patient will translate that perception into indifference to an elevation in blood pressure. The potential exists for a loss of physician-patient contact during the critical observation periods. Thus, the first aspect of nonpharmacologic therapy for the treatment of patients with hypertension must be close patient follow-up and adequate patient education about the risks and benefits to be derived from blood pressure control. The physician must emphasize to the patient that not initiating pharmacologic therapy is neither a reflection of disinterest nor a reflection of the lack of significance of the hemodynamic abnormality, but rather a conscious decision to attempt to avoid the potential side effects and risks of drug therapy and to decrease health care costs with interventions having more extensive effects on cardiovascular health.

According to the guidelines, the presence of additional factors, such as a concomitantly elevated systolic blood pressure, evidence of cardiac disease (e.g., left ventricular hypertrophy, dyspnea, or symptoms suggestive of myocardial ischemia), the presence of renal disease, or a strong family history of vascular disease, is a good basis for deciding to initiate pharmacologic antihypertensive therapy without an extended observation period. The joint committee finds no evidence that antihypertensive treatment is of benefit in persons 80 years and older. Hypertension in the elderly, however, often can be controlled with lower doses of medications than are required in younger patients with similar blood pressure values. The development of agents with beneficial hemodynamic characteristics suggests the need for a reassessment of this blanket disregard of benefits in patients entering their ninth decade. In addition, the qualitative assessment that patients who are frail or who have advanced cardiovascular disease, dementia, or other debilitating illnesses should not be given antihypertensive drug therapy unless the diastolic blood pressure consistently exceeds 110 mm Hg may be too broad—that is, this pronouncement might affect a patient population whose quality of life could in some instances be significantly improved by adequate blood pressure control. The elderly might gain benefit from medications having favorable effects on cerebral perfusion, coronary artery blood flow, and glomerular filtration rate. When we dismiss so many patients with such brief consideration, we deny a large portion of a progressively aging world population the individual attention and care that these people deserve.

The recommendations of the subcommittee for a limited investigation of patients with newly discovered increased blood pressure reflects an appropriate approach to investigational procedures in patients of whom the overwhelming number eventually will be found to have essential hypertension. Indeed, the absence of physical signs suggestive of secondary forms of hypertension, the presence of a family history, and the absence of the sudden onset of hypertension might be the most appropriate screening tests to exclude secondary hypertension. Except in patients in whom we strongly suspect secondary hypertension (because of prior data or because they are resistant to otherwise reasonable multidrug antihypertensive regimens), the routine use of intravenous pyelography, radionuclide renal imaging, or digital subtraction angiography for the examination of renal artery anatomy can no longer be justified. Nor should we rely on expensive biochemical screening tests of the status of the renin-angiotensin-aldosterone axis as affected by dietary intake or manipulations of position.

In initiating nonpharmacologic therapy for elevations in blood pressure, we must aggressively emphasize the obvious benefits from regular exercise, weight loss, the elimination of tobacco use, and the cessation of heavy alcohol consumption. The expected associated salutary changes in glucose tolerance, plasma cholesterol concentrations, and plasma triglycerides should be emphasized to this extensive patient
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population. The development of organized, prospective, cardiovascular risk reduction programs often provide the framework in which patients who are motivated but otherwise undisciplined can obtain the reinforcement and instruction necessary to provide them with the "fortitude" to sustain these often difficult-to-maintain modifications in life-style.

To this point in the recommendations, little controversy exists as to the potential benefits to be derived, although some physicians might disagree with the exact goal blood pressure value, the nature of the recommendations for nonpharmacologic therapy, and the emphasis on the various aspects of such therapy, particularly the institution of salt restriction and/or calcium, magnesium, and potassium supplementation. However, in ignoring the development of newer antihypertensive agents, the recommendations of the WHO/ISH Committee are all too reminiscent of previous recommendations by similar organizations. Using a measurement of blood pressure at a given point in time, we can consider patients as mildly, moderately, or severely hypertensive. An alternative method of assessment might consider functional cardiovascular status, either as evidenced by left ventricular mass or functional performance of the ventricle under conditions of rest and peak exercise. When such assessments are made, even in patients with mild elevations of blood pressure, it is possible to discern abnormalities of left ventricular function during both the diastolic and systolic portions of the cardiac cycle. These abnormalities may reflect the functional impairment induced by elevations in systemic vascular resistance that characterize the progressive development of hypertensive cardiovascular disease. Whether modifications in these functional characteristics of left ventricular performance will affect cardiovascular morbidity and mortality more predictably than simply basing therapeutic decisions on an arbitrary blood pressure measurement will require even more extensive clinical investigational trials than have been reported to date. Yet if we believe that hypertension is a progressive disorder, perhaps with risks proportionately related to the absolute value of blood pressure elevation but clearly not limited solely to effects dependent on the absolute value of diastolic blood pressure elevation, then current recommendations for the initial treatment of patients with hypertension can no longer be accepted as appropriate.

The WHO/ISH Committee as well as the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure of the National Institutes of Health have consistently recommended that initial therapy in hypertensive patients comprise diuretic or \( \beta \)-adrenergic receptor blocking agents. The practice of routinely using these agents ignores the significant adverse metabolic and hemodynamic effects of such drugs. The diuretic agents, which traditionally have been used as the initial step in treatment, induce significant abnormalities of metabolism even when employed in low dosages (equivalent to 25–50 mg of hydrochlorothiazide). The adverse effects on uric acid metabolism, plasma cholesterol, and triglyceride concentrations, as well as the decreases in serum potassium might in fact increase cardiovascular risk in patients whose blood pressures have fallen; in these patients, diuretics affect these well-recognized (cardiovascular) risk factors in a negative way and may contribute to increases in the incidence of coronary artery disease, angina pectoris, myocardial infarction, and congestive heart failure. Similarly, the \( \beta \)-adrenergic receptor blocking agents adversely affect total plasma cholesterol and triglycerides while reducing the high density lipoprotein fraction of cholesterol. Such changes in cholesterol levels may increase cardiovascular mortality. The recently reported lipid research trials confirmed that decreasing plasma cholesterol concentrations produces an accelerated benefit in cardiovascular mortality. Thus, a drug-induced increase in plasma cholesterol concentrations may be associated with an accelerated cardiovascular risk. In addition, the suppression of cardiac performance, as evidenced by decreases in cardiac output in patients receiving \( \beta \)-adrenergic receptor blocking drugs, and the limited peak exercise performance of these patients indicate that the reduction in blood pressure is associated not with improvements in cardiovascular physiologic parameters but rather with a suppression of cardiac function.

If the currently recommended drugs for the initial treatment of mild hypertension carry with them unacceptable adverse metabolic and physiologic side effects, the failure of the large-scale clinical trials to show significant improvements in cardiovascular morbidity and mortality might be interpreted as the result of the conflicting effects of diuretics and \( \beta \)-adrenergic blocking drugs, which were used uniformly in
each of these investigations on blood pressure, with other risk factors (glucose, potassium, cholesterol, triglycerides, cardiovascular function). Adverse effects on these latter variables may have canceled out the benefits to be derived from reductions in blood pressure. Fortunately, the development of newer antihypertensive agents that do not have these adverse effects on metabolic and physiologic functions offers an alternative to previously recommended and currently endorsed initial treatments for hypertension.

The α-adrenergic receptor blocking drugs, by virtue of their prevention of norepinephrine-mediated systemic vasoconstriction, reduce systemic vascular resistance, thereby decreasing blood pressure and sustaining — if not increasing — cardiac output at rest and at peak exercise. Treatment with prazosin (as an example of this class of drugs) also reduces total plasma cholesterol concentrations, thus decreasing this all-important risk factor while simultaneously controlling blood pressure. The mechanism by which plasma cholesterol concentrations fall remains unclear but might relate to the interrelationship between the adrenergic nervous system and plasma lipoprotein metabolism.

Inhibitors of the angiotensin converting enzyme (captopril, enalapril) constitute a second important group of agents for use in initial treatment of patients with all degrees of hypertension. With the recognition that these agents produce minimal side effects when used in patients with normal renal function and without collagen vascular disease, these drugs exhibit the ideal characteristics for the treatment of patients with mild hypertension. The reduction in the contribution of the renin-angiotensin-aldosterone system to systemic vasoconstriction and sodium retention results in a decrease in systemic vascular resistance as well as a decrease in plasma volume because these indirect vasodilators increase urinary sodium excretion. The resultant balanced systemic vasodilation decreases systemic vascular resistance and is associated with maintenance of, or a slight increase in, cardiac output at both rest and peak exercise. In addition, the angiotensin converting enzyme inhibitors have neutral effects on cholesterol and triglyceride metabolism and have no adverse effects on plasma uric acid levels. Indeed, because of the fall in plasma aldosterone concentrations, plasma potassium concentration may rise slightly and thus prevent cardiac irritability and ventricular ectopic activity. The combination of converting enzyme inhibitors with diuretic agents produces additive antihypertensive activity and prevents many of the adverse metabolic effects of the diuretics when used alone. The mechanism of this blunting of the adverse metabolic effects of the diuretics is unknown, but again might reflect changes in adrenergic nervous system effects as well as potential effects associated with an increase in plasma potassium concentration and its regulation of lipolysis, insulin release, and gluconeogenesis. In addition, the recently reported improvement in the quality of life of patients receiving captopril, as opposed to the effects of propranolol and α-methyldopa, suggests that previously recognized clinical changes in patient attitude can now be quantified. The improvement in the quality of life of patients receiving captopril, as opposed to those receiving β-adrenergic blocking agents and centrally acting sympatholytic drugs, is clinically significant. Such a change in psychologic parameters may play an important role in limiting the number of patients who discontinue taking antihypertensive therapy because of the disruption of either psychologic or physiologic function during antihypertensive care for what is an otherwise asymptomatic disease.

The calcium channel antagonists (diltiazem, nifedipine, verapamil) are the most recently introduced class of drugs potentially useful for the treatment of patients with hypertension. These agents, which are already used extensively outside the United States, have characteristics that might recommend them for use in mildly hypertensive patients. Because of the importance of calcium in vascular smooth muscle contraction, these agents reduce systemic vascular resistance. In addition, the calcium channel blockers have been associated with an improvement in cardiovascular function both during systole and diastole and thus may deal specifically with the abnormalities of cardiac function produced by untreated elevations in blood pressure.

Traditional approaches to the treatment of hypertension continue to involve initial therapy with diuretics or β-adrenergic blocking drugs and the subsequent combination of these agents in those patients unresponsive to monotherapy. A consideration of the physiologic, metabolic, and psychologic effects of these drugs leads us to the conclusion that their use might not allow the optimal reduction in cardiovascular mortality,
and suggests that traditional approaches to antihypertensive care should be discarded in favor of a more physiologic approach to blood pressure control. An alternative approach in patients with mild hypertension would be "first-step" therapy with a vasodilating agent (i.e., an α-adrenergic receptor blocker, angiotensin converting enzyme inhibitor, or calcium channel blocker) because of the desirable physiologic and metabolic effects of these agents. In patients not responsive to monotherapy, the combination of two vasodilating agents acting through different mechanisms of actions, such as the combination of an converting enzyme inhibitor and a calcium channel antagonist (which have been shown to result in an additive antihypertensive effect), might produce appropriate blood pressure control without causing adverse metabolic and physiologic effects. Only in the absence of adequate blood pressure control would one prescribe a diuretic, which enhances the antihypertensive activity of vasodilating agents. Finally, a β-adrenergic receptor blocker could be added for blood pressure control in the hypertensive patient resistant to triple-drug therapy.

Such an approach to blood pressure regulation would significantly change the way physicians prescribe medication to treat hypertension. The majority of patients with mild hypertension would no longer receive diuretics and β-adrenergic receptor blocking drugs but rather would be given vasodilators to be used alone or in combination with one another. Whether such a change in our approach to the treatment of patients with mild to moderate hypertension would be associated with a greater reduction in cardiovascular morbidity and mortality than has been observed with the traditional methods of therapy can only be assessed through additional, large-scale therapeutic trials. Although few would relish the obligation to initiate such studies, the development of newer, more physiologic antihypertensive drugs will necessitate such an endeavor in view of the expanding patient population qualifying for such therapy and the inevitable public and governmental demands for documentation of the benefits to be derived from the expenditure of large sums of health care dollars for the treatment of this asymptomatic population.

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