Factors That Contribute to Resistant Forms of Hypertension
Pharmacological Considerations

DEARING W. JOHNS AND MICHAEL J. PEACH

SUMMARY Treatment failure may be caused by induction of compensatory mechanisms that compromise effectiveness of the antihypertensive regimen. Antihypertensive agents have been classified according to mechanism of action, and compensatory mechanisms usually evoked by each class of drugs have been reviewed. Host factors may be responsible for the inability to control blood pressure or may predict special sensitivity or contraindication to a particular class of antihypertensive agents. Recommendations have been made for modification of stepped-care regimens and selection of initial antihypertensive agents based on host factors. Experimental evidence suggests the ability to target antihypertensive therapy in a manner that will prevent or reverse specific end-organ damage. Clinical studies are needed to define the long-term benefit derived from aggressive target organ protection. (Hypertension 11 [Suppl H]: II-88-II-95, 1988)

KEY WORDS • refractory hypertension • pharmacology • drug therapy • high blood pressure

THE term resistant hypertension implies that the patient is or has been on pharmacological therapy. The physician must evaluate the "failed" regimen from the standpoint of compensatory mechanisms that might have been induced by antihypertensive agents. Assessment of pharmacological factors contributing to resistant hypertension in a given patient requires a two-pronged approach. The first effort should aim to determine whether the effectiveness of antihypertensive treatment has been compromised iatrogenically by pharmacological induction of new mechanisms that subsequently have become responsible for maintaining elevated blood pressure. The second effort should be to evaluate the antihypertensive regimen according to its appropriateness for the individual patient. Ideally, for each patient, the physician should determine the dominant mechanism responsible for blood pressure control. Practical considerations, however, often require the physician to deduce controlling mechanisms by evaluation of the blood pressure response to manipulation of pharmacological agents. Based on clinical studies, guidelines are emerging that help to predict the response of individual patients to specific medications and that suggest a propensity for certain patients to develop specific target organ damage. Recent experimental evidence reveals regression or prevention of target organ damage by pharmacological agents. Thus, in the future, physicians will also be able to choose antihypertensive treatment based on its ability to reduce or prevent selective end-organ damage.

Before embarking on a discussion of refractory hypertension, it is important to emphasize that true treatment failures do not refer to refractoriness due to 1) failure of patients to take medication; 2) failure of physicians to properly prescribe adequate drug doses; 3) latent secondary hypertension; 4) luxury hypertension; 5) pseudohypertension secondary to noncompliant vessels or widened pulse pressure induced by thyrotoxicosis, aortic insufficiency, or anemia. Having excluded these failures, a variety of other factors affect the control of blood pressure and manifest in patients as true refractory hypertension.

Antihypertensive Agents and Compensatory Mechanisms

When antihypertensive drugs are classified according to mechanisms of action, four broad categories emerge (Table 1): the diuretics, adrenergic blockers, vasodilators, and angiotensin converting enzyme inhibitors.

Diuretics

Diuretics can be divided into three groups: the thiazides, loop diuretics (furosemide, ethacrinic acid, and...
Hypertensive patients will respond to thiazide monotherapy, but many will not achieve adequate chronic blood pressure control on a thiazide diuretic alone. For some, renal insufficiency will explain a poor response as thiazides are ineffective in patients with creatinine clearance less than 30 ml/min (creatinine greater than 2.0 mg/dl). Patients with marginal renal function before therapy may develop diuretic-induced reduction of glomerular filtration rate with renal insufficiency of a magnitude great enough to cause refractoriness to thiazides. In these cases, a loop diuretic will be required to restore responsiveness. Still, in many, the diuretic-induced fall in blood pressure will be incomplete or only temporary despite shrinkage of plasma and extraacellular fluid volume by diuresis and natriuresis (loss of body weight). Compensatory mechanisms (Table 2) induced by diuretics that compromise the antihypertensive efficacy include: 1) activation of the renin-angiotensin system that leads to increased peripheral resistance through a direct action of angiotensin II (Ang II) on arteries and 2) volume and sodium retention, which tends to impair palatability without aggravating blood pressure control.

### Adrenergic Blockade

All drugs that interfere with sympathetic function, with the possible exception of ß-blockers, promote sodium and water retention, which tends to impair their antihypertensive effectiveness. ß-Adrenergic inhibitors, in addition to exerting negative ionotropic and chronotropic effects, suppress plasma renin activ-

### Table 1. Classification of Antihypertensive Agents

<table>
<thead>
<tr>
<th>I. Diuretics</th>
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<tr>
<td>A. Thiazides:</td>
<td>hydrochlorothiazide</td>
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<td>B. Loop diuretics:</td>
<td>furosemide, ethacrynic acid</td>
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<tr>
<td>C. Potassium-sparing:</td>
<td>spironolactone, triamterene, amiloride</td>
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<th>II. Adrenergic blockade</th>
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<tr>
<td>A. ß-Blockers:</td>
<td>nonselective vs ß₁ selective</td>
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<tr>
<td>B. ß₂-Antagonist:</td>
<td>prazosin</td>
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<tr>
<td>C. ß₂-Agonists:</td>
<td>clonidine, guanabenz, methyldopa</td>
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<tr>
<td>D. Combined ß- and ß-blocker:</td>
<td>labetolol</td>
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<tr>
<td>E. Neuronal blockers:</td>
<td>reserpine, guanethidine, guanadrel</td>
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<th>III. Vasodilators</th>
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<tbody>
<tr>
<td>A. Predominantly arterial:</td>
<td>hydralazine, minoxidil</td>
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<tr>
<td>B. Calcium entry blockers:</td>
<td>verapamil, diltiazem, nifedipine</td>
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<th>IV. Converting enzyme inhibitors</th>
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<tr>
<td>A. Captopril</td>
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<td>B. Enalapril</td>
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<th>TABLE 2. Reasons for Poor Response</th>
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<tr>
<td>I. Diuretics</td>
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<tr>
<td>A. &quot;Overdiuresis&quot; leading to activation of sympathetic nervous system and renin-angiotensin-aldosterone system</td>
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<tr>
<td>B. Impaired renal function (CrCl&lt;30 ml/min), need loop diuretic</td>
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<tr>
<td>C. Hypokalemia or hypomagnesemia</td>
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<td>D. Extravagant salt intake</td>
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<table>
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<tr>
<th>II. Adrenergic blockers</th>
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<tbody>
<tr>
<td>A. General (except ß-blockers):</td>
<td>sodium and water retention</td>
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<tr>
<td>B. ß-Blockers: increased peripheral resistance (α activity unopposed), ß₁ selectivity may minimize undesirable α influence</td>
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<tr>
<td>C. ß₂-Agonists: rebound hypertension with abrupt discontinuation</td>
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<td>D. Neuronal blockers: guanethidine-induced rise in peripheral resistance (denervation supersensitivity), impairment of guanethidine uptake by concomitant use of sympathomimetics, tricyclic antidepressants, or phenothiazines</td>
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<th>III. Vasodilators</th>
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<tr>
<td>A. Arterial: reflex tachycardia, fluid retention</td>
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<tr>
<td>B. EDRF-mediated: absence of endothelium perhaps with atherosclerosis or hypertension-induced functional impairment of endothelial cells</td>
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ity (except pindolol) and perhaps also tyrosine hydroxylase and dopamine \( \beta \)-hydroxylase activities. They do not cause hypokalemia. The nonselective \( \beta \)-blockers (propranolol, nadolol, pindolol, alpenrolol, and timolol) are associated with a greater hypertensive response to isometric exercise and hypoglycemia than are cardioselective (\( \beta_{1} \)-blockers) blocking agents (atenolol, metoprolol, and acebutelol) presumably because of induction of a state of relatively increased or unopposed \( \alpha \)-adrenergic activity. Drayer et al. have reported a hypertensive response to propranolol in one patient due to an \( \alpha \)-adrenergic-mediated increase in peripheral resistance. A hypertensive response to propranolol has been reported in a patient treated with methyldopa (presumably due to blockade of the \( \beta \)-adrenergic effects of \( \alpha \)-methylnorepinephrine). \( \beta \)-Blockers usually are not associated with postural hypotension perhaps because of this mild increased sympathetic activity. In the resting state and in doses usually used to treat hypertension, there is little difference in efficacy between the \( \beta_{1} \) selective and the nonselective blocking agents.

The concern of producing congestive heart failure with \( \beta \)-blockers in patients with cardiac hypertrophy and strain is often overemphasized. As long as the blood pressure is lowered, the reduction in afterload will usually compensate for the reduction in cardiac output. Caution also must be used in prescribing \( \beta \)-blockers in diabetic patients prone to hypoglycemia for two reasons: 1) \( \beta \)-blockade impairs insulin release, and nonselective agents prolong insulin-induced hypoglycemia; 2) \( \beta \)-blockade masks symptoms of hypoglycemia and potentiates hypoglycemia-induced blood pressure elevation.

Prazosin selectively inhibits \( \alpha_{1} \)-receptors and effectively reduces peripheral resistance without altering cardiac output. Its ability to lower blood pressure in hypertensive patients is modest, and few side effects accompany its use. One of the major impediments to its usefulness as a chronic antihypertensive medication is the pseudotolerance or volume retention often associated with long-term therapy.

Unlike many vasodilating agents, chronic prazosin treatment usually does not lead to tachycardia perhaps because selective blockade of \( \alpha_{1} \)-receptors does not impair presynaptic \( \alpha_{1} \)-receptor-mediated inhibition of norepinephrine release. Prazosin tends also to dilate visceral, more than acral, blood vessels, which leads to central pooling of blood and may explain the first-dose hypotension that has been reported. Nonselective \( \alpha \)-receptor inhibitors phenoxybenzamine and phentolamine are mainly for treatment of hypertension due to pheochromocytoma and autonomic hyperactivity that is associated with Laundy-Guillain-Barré disease, spinal cord injury, and posterior fossa tumors. More recently, labetolol, an inhibitor of \( \alpha \)- and \( \beta \)- (with slight emphasis on \( \beta_{1} \) inhibition) receptors has been used for these special cases of hyperadrenergic activity. Labetolol also has been associated with mild fluid retention but antihypertensive effectiveness is restored rapidly with addition of appropriate diuretic agents.

The centrally acting \( \alpha_{1} \)-agonists clonidine, guanabenz, and the active metabolites of methyldopa (e.g., \( \alpha \)-methylnorepinephrine) are potent antihypertensive agents but also can cause significant postural hypotension. Chronic use is accompanied by volume retention, thus limiting long-term monotherapeutic usefulness for hypertension. Rebound hypertension has been reported following sudden cessation of these agents probably because of denervation supersensitivity. The new transdermal clonidine preparation was developed to maintain therapeutic levels by slow, maintained absorption. Discontinuation of the clonidine patch is associated with a plasma elimination half-life of approximately 20 hours, which may aid in modulation of the rebound phenomenon. However, there has been a report of blood pressure overshoot upon discontinuation of the clonidine patch to levels above pretreatment value. Rebound hypertension with methyldopa is less frequent probably because its active metabolite, \( \alpha \)-methylnorepinephrine (or \( \alpha \)-methylphenylpseudoephedrine), acts as a false transmitter that turns over in the body more slowly than the parent compound.

The neuronal blockers reserpine, guanethidine, and guanadrel deplete intracellular storage granules of noradrenaline. Guanethidine and guanadrel eventually, themselves, become false transmitters. The initial displacement of norepinephrine and competition with norepinephrine for uptake with these two agents can cause a rise in blood pressure when administered intravenously. Chronic use of these agents will lead to a reduction in peripheral resistance, heart rate, cardiac output, and marked inhibition of the vasoconstrictive baroreceptor reflex. Thus, severe, orthostatic hypotension can ensue. Resistance to these agents also may result from concomitant use of indirectly acting sympathomimetic agents such as ephedrine and pseudoephedrine or the tricyclic antidepressants as well as the substituted phenothiazines that block uptake of guanethidine into nerve terminals.

Vasodilators

The vasodilators lower peripheral resistance. The more selective the action on vascular smooth muscle (the more it spares other systems related to cardiovascular control), the greater the likelihood of a reflex increase in heart rate and cardiac output and the greater the volume retention that will accompany its use. Thus, hydralazine and minoxidil, which primarily dilate arterial blood vessels, will require sympathetic inhibition to suppress reflex tachycardia and often a loop diuretic to counteract volume retention.

Calcium channel (entry) blockers, on the other hand, also decrease peripheral resistance, but the degree of reflex sympathetic stimulation varies depending on which calcium channel inhibitor is used. The order of potency for reflex stimulation of sympathetic activity is nifedipine > diltiazem > verapamil. Although nifedipine (and other dihydropyridines) causes peripheral edema, it fails to cause volume retention. In fact, diltiazem actively promotes natriuresis. The natriuretic effect of calcium channel blockers is greater in
low renin hypertensive patients than in other types of hypertension.

Verapamil's effectiveness is frequency dependent (use dependent).

With aging, there is a relative increase in fat metabolism and plasma levels of kinins. Thus, actions other than suppression of angiotensin

Converting enzyme inhibitors are often effective antihypertensive agents in patients with nonrenin-dependent forms of hypertension. Thus, actions other than suppression of angiotensin I conversion have been invoked. For instance, converting enzyme (kininase II) also is the enzyme responsible for bradykinin degradation, and converting enzyme inhibition may result in an increase in the plasma levels of kinins. Thus, the converting enzyme inhibitors are nearly ideal antihypertensive drugs, for they lower blood pressure without causing a reflex increase in vasoconstrictor systems or volume retention.

Host Factors and Specific Antihypertensive Agents

A decade ago treatment resistant hypertension was nearly synonymous with severe hypertension. In recent years, the profile of patients with refractory hypertension has changed. We are now beginning to recognize specific groups of patients who may have only modest blood pressure elevation yet who fail to achieve normal blood pressure despite moderate to large amounts of antihypertensive medication. Contributing factors for the shift in patient profile include the tremendous influence of mass media campaigns for better public health and the emphasis of health care providers on preventive medicine (reduction of cardiac risks). These factors have led to a greater public awareness of the beneficial effect of lifestyle alteration and hypertension control in reducing future morbidity. Concomitantly, there has been an increase in the number of patients who know they have high blood pressure and who are now seeking and accepting treatment. Also, major responsibility for the changing profile resides with the increase in the number of potent drugs available with selective action and, therefore, fewer side effects. With expansion of the antihypertensive armamentarium to include potent drugs with selective action, physicians now are able to maintain the patient as symptom-free with treatment-controlled blood pressure as the individual was in the untreated, hypertensive state.

The effectiveness of the stepped-care treatment plan for control of blood pressure has been documented amply and also has had an impact on redefining the treatment resistant population. But, just as there has been a shift in profile of treatment resistant patients, so should we modify our stepped-care approach by choosing initial therapy aimed at the predominant pathophysiological mechanism that controls blood pressure in each patient as well as any specific contraindications (Table 3). Subsequent combinations of drugs should then be responsive to expected drug-induced counterregulatory mechanisms, that is, mechanisms caused by antihypertensive treatment that thwart effectiveness.

In the elderly with true systolic hypertension, diuretics and sympatholytic agents have been effective in lowering blood pressure. There are several excellent reviews of the features special to the geriatric population that must be considered when treating hypertension. With aging, there is a relative increase in fat metabolism.
stores and a decrease in total body water, plasma volume, and lean body mass. Thus, the volume of distribution of water-soluble drugs tends to decrease while that of lipid-soluble drugs increases. Glomerular filtration rate and hepatic function are decreased, which can lead to reduction of metabolic clearance. Baroreceptor reflexes are often blunt and, plasma renin activity tends to be lower (unless congestive heart failure is present) than in younger patients with comparable mean arterial pressure. Thus, hypertension in the elderly tends to be less volume dependent than in the young hypertensive patient despite a low plasma renin activity. In response to hypovolemia, there is often an exaggerated increase in release of antidiuretic hormone and a defect in conservation of renal sodium while on a low salt intake. These abnormalities tend to make the geriatric patient more sensitive to diuretic-induced water intoxication with accompanying hyponatremia. Thus, to avoid serious hypotension and other untoward effects, all drugs must be given with extreme caution (e.g., begin with one half of the usual initial dose, double the usual interval for dose increase). The ideal antihypertensive agent for the elderly patient with hypertension would be one that selectively increases blood vessel compliance. To date, no antihypertensive agent has been shown to restore elasticity. However, calcium channel antagonists lower peripheral resistance without causing glucose intolerance, hyperuricemia, hyponatremia, hypokalemia, or orthostatic hypotension. Experimental evidence reveals inhibition by verapamil of age-induced accumulation of arterial calcium as well as inhibition of platelet aggregation. These data suggest a role for calcium channel blockers in the treatment of hypertension in the elderly.

Systolic hypertension increases the risk of stroke. Clinical trials have shown that lowering mean blood pressure does reduce the frequency and severity of stroke. Sadoshima et al. showed an increase in frequency of stroke (cerebral hemorrhage and ischemia) ipsilateral to sympathectomy in stroke-prone hypertensive rats. This intriguing experimental evidence suggests protection from stroke damage by maintenance of intact sympathetic innervation to cerebral blood vessels. Further investigation is needed to determine whether the ability to protect against stroke is the same regardless of which antihypertensive agent is used to lower blood pressure.

Low renin hypertensive patients tend to be extremely responsive to diuretics and most will achieve normal blood pressure on a single diuretic, for they lack one of the mechanisms responsible for diuretic refractoriness — a rise in plasma renin activity following diuresis. However, a small percentage of these patients deserve the label "low renin—diuretic resistant." In this group, blood pressure control is best achieved by choosing a regimen composed of several diuretics such that each acts at a different anatomic site along the nephron or acts by a different physiological mechanism to promote natriuresis and diuresis (hydrochlorothiazide, furosemide, amiloride, or metolozane). Recently, it has been shown that calcium channel inhibitors also promote natriuresis and are especially effective in low renin patients.

Williams and Hollenberg have identified a group of sodium-sensitive hypertensive patients, termed nonmodulators, who have a defective ability to suppress renin and aldosterone in response to Ang II. In this group, sodium does not modulate renal and adrenal responsiveness to Ang II. Characteristically, the nonmodulators exhibit a rise in blood pressure after an acute sodium load, whereas normotensive and hypertensive controls do not. The sodium load does not cause an increase in renal blood flow in the nonmodulators, and their ability to excrete the sodium load is blunted. Moreover, the nonmodulators fail to suppress renin activity when they are given a saline infusion or Ang II. Converting enzyme inhibition corrects all of these abnormalities except the last. Thus, these hypertensive patients are readily controlled with converting enzyme inhibitors but may appear resistant to treatment when an inappropriate antihypertensive regimen is selected.

Patients with end-stage renal disease and those with connective tissue disease, such as scleroderma, constitute two groups of patients noted for frequent occurrence of severe resistant hypertension. The converting enzyme inhibitors have been lifesaving in the treatment of the malignant hypertension associated with scleroderma and have been helpful in preventing the inexorable progression to irreversible renal failure. This has led to the recommendation for captopril as early therapy for renal scleroderma. Enalapril (which lacks the sulfhydryl moiety found in captopril) may be associated with a lower incidence of granulocytopenia in this high-risk population of patients with autoimmune disease.

The management of target organ damage, including structural vascular changes, represents a particularly difficult challenge in long-standing hypertension. End-organ damage, especially advancing renal disease, can increase the severity of the hypertension and reduce its susceptibility to treatment. In patients such as these, three or four drugs may be required to achieve blood pressure control. It is particularly important to proceed cautiously and with patience, for the body requires time to adjust to hemodynamic manipulation. Also, care must be taken to choose drugs so as to suppress sequentially those mechanisms leading to maintenance
of hypertension by choosing agents with different mechanisms or sites of action. A recent survey revealed most physicians are using a stepped-care approach. That is, most physicians would add a second drug when the first drug has failed. Hydrochlorothiazide was used alone by 56% and a β-blocker alone by 23% of physicians. The same survey reported less than 40% of patients under treatment for hypertension achieved goal blood pressures. Thus, somehow current management is falling far short of treatment aim. Therefore, physicians need not feel bound to use diuretics as initial antihypertensive medication. In general, the younger the patient, the more likely that blood pressure control will be achieved with sympathetic or angiotensin converting enzyme inhibitors alone. The older the patient, the more likely that the calcium channel blockers or diuretics will be effective monotherapeutic agents. Regardless of which antihypertensive drug is selected for initial therapy, if blood pressure control is not achieved, a second agent may be substituted from another category of antihypertensive agents. Therapy may be guided by the captopril stimulation test to identify renin-dependent forms of hypertension and assessment of urinary sodium excretion to suggest sodium- or volume-dependent hypertension. If, however, after appropriate trials with two different classes of antihypertensive agents (monotherapies) blood pressure is still not controlled, then the addition of a second concomitant drug therapy is indicated. Side effects can often be minimized or avoided by using lower doses of two medications, rather than raising each agent to maximal levels. The choice of a second additional agent should be dictated by counterregulatory mechanisms set in motion by the initial therapeutic choice. The same guideline should apply if a third agent is required.

Once blood pressure control is achieved and the patient has been stable for several months, it is reasonable to reduce dosages or discontinue therapeutic agents instituted earlier. But it is important to remember that monotherapy rarely is achieved by the rapid substitution of one antihypertensive agent for another. Random substitution (without attention to specific host mechanisms) has too often led to erroneous classification of treatment resistant hypertension. Greater efforts are needed to determine how host factors might dictate appropriate initial therapy.

**End-Organ Damage and Specific Antihypertensive Agents**

In addition to choosing an antihypertensive regimen aimed at mechanisms that initiate and maintain the hypertensive state, prevention or reduction of hypertension-induced end-organ damage is now possible (Table 4). For instance, regression of cardiac hypertrophy has been seen with sympathetic inhibition, calcium channel blockade, and converting enzyme inhibition, but it has not been seen by treatment with hydralazine despite an equivalent lowering of blood pressure. Calcium channel blockers and some β-blockers may prevent or cause regression of atherosclerosis. There is experimental evidence that potassium supplementation protects against hypertensive agent-induced glomerular damage and reduces the frequency of stroke. Also, the frequency and severity of stroke has been indirectly correlated with potassium intake in an elderly patient population. using the remnant kidney model have shown protection against hypertension-induced renal pathology with enalaprilat but not with standard triple drug therapy despite similar blood pressure control. Similarly, prevention of diabetic glomerulopathy has been seen by converting enzyme inhibition in diabetic (Munich-Wistar) rats despite hyperglycemia and elevated levels of glycosylated hemoglobin. More experimental evidence, corroborated by properly conducted clinical trials, is needed to determine the degree of end-organ protection afforded by each specific antihypertensive agent or combination despite similar antihypertensive effectiveness.

The ideal or perfect antihypertensive agent does not yet exist, but looming on the horizon may be one calculated to approach the ideal or will lead to the development of such an agent. Atrial natriuretic hormone lowers blood pressure and decreases peripheral resistance while promoting natriuresis and diuresis. Plasma renin activity is suppressed as are basal and stimulated aldosterone secretion. Arginine vasopressin also is inhibited by atrial natriuretic peptide. Thus, these atrial peptides lower blood pressure in several types of hypertension without causing reflex stimulation of vasoconstrictor systems or volume retention, which are the two mechanisms most often responsible for failure of chronic antihypertensive therapy.

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