Issues, Goals, and Guidelines in Selecting First-Line Drug Therapy for Hypertension

John H. Laragh

Modern antihypertensive therapy is enriched by an explosion in drug development that makes available increasingly specific agents whose effects have advanced our understanding of pressor mechanisms. This and other research into hypertensive mechanisms has defined the clinical, pharmacological, and endocrinologic heterogeneity of human hypertension. The sum of these developments is a greatly enhanced ability to identify curable and definable causes of hypertension and to pathophysiologically stratify the remaining cases of essential hypertension. Modern treatment can be much more specific than before. When long-term drug therapy is indicated, the regimen is more likely to achieve a primary goal for each patient, that is, the fewest possible drugs in the smallest amount and in lowest frequency. Two clinically quantifiable mechanisms for long-term arteriolar vasoconstriction can be identified within the spectrum of human hypertension. The first, renin-mediated vasoconstriction, is directly related to the plasma renin level. The second, sodium-volume-related vasoconstriction, is marked by a reciprocally subnormal renin level and involves abnormal sodium retention and calcium transport. A baseline renin-sodium profile can identify the pressure of one of these two forms of vasoconstriction and therefore is the key for the diagnosis of the two curable disorders that fully express one of the two pressor mechanisms—renovascular hypertension and primary aldosteronism. Renovascular hypertension, more common than once thought, is often cured by angioplasty. It is important to diagnose these curable forms before beginning long-term drug therapy. The renin-sodium profile, used in conjunction with serum potassium and creatinine measurements, is valuable not only in screening patients for curable forms, but also for stratifying the remainder according to the pathophysiological vasoconstrictor mechanism that underlies the hypertension. Converting enzyme inhibitors or β-blockers are, by themselves, often effective in correcting the hypertension of high- or medium-renin patients, whereas calcium antagonists, diuretic agents, or α-blockers alone are most effective against the low-renin form of vasoconstriction. In the large midzone of renin values, if monotherapy fails, a rational basis for combined antirenin-antisodium volume therapies can be developed. (Hypertension 1989;13[suppl I]:I-103–I-112)

By now, it should be clear that hypertension includes a heterogeneity of causes and effects and that the level of hypertension appears largely irrelevant to this heterogeneity. The evidence for this finding has been compiled in the clinic, where it is abundantly evident that patients with comparable degrees of hypertension may differ significantly in their endocrinological profiles, in their response or lack of it to particular drug types, and in their prognosis and outcome. Confirming this evidence—indeed, making some of it possible—is a battery of new and exciting antihypertensive drugs targeted against specific hypertensive mechanisms. Sustained arteriolar vasoconstriction is the basis for all diastolic hypertension. Two long-term mechanisms have been identified to account for major portions of this vasoconstriction.1 One is due to an excess of the vasoconstrictive hormone angiotensin II, generated by plasma renin consequent to excessive renal secretion of renin; this problem can be addressed by antirenin-system agents. The other long-term mechanism is marked by a low plasma renin value. Because low plasma renin is a uniform response to sodium administration in normal and hypertensive people, and because the blood pressure of such hypertensive people is often normalized by diuretic or dietary sodium depletion, it is reasonable to assume that this form of arteriolar vasoconstriction is related somehow to antecedent

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TABLE 1. Overall Goals for Evaluating and Treating Hypertensive Patients

<table>
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<th>Goals of evaluation</th>
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<tr>
<td>To identify all curable and definable forms of hypertension</td>
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<tr>
<td>To stratify all other forms of hypertension based on their underlying pathophysiological mechanisms</td>
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<td>Goals of long-term drug therapy</td>
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<td>To give the minimum number of drugs, in the minimum effective amounts, with the minimum frequency possible,</td>
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<td>thus minimizing both short- and long-term side effects</td>
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excessive renal sodium retention. The vasoconstrictive pathway of this sodium-related mechanism is not entirely clear, but it may be associated, at least partly, with an imbalance between intracellular and extracellular calcium. Accordingly, this form of vasoconstriction is correctable by diuretic agents or by calcium channel or α-adrenergic receptor blockade.

The implications of all this is that we are at last able to mount a rational diagnostic and management program for hypertensive patients that is several important steps removed from the blind empiricism of the past.

Overall Goals of Evaluation and Treatment

A rational method for selecting drugs for the individual hypertensive patient must be based on an individual pathophysiological evaluation. The basic diagnostic work-up, aside from the routine blood count and urinalysis, includes serum potassium, blood urea nitrogen, serum creatinine, a baseline electrocardiogram, an echocardiogram for evaluation of left ventricular mass, and the renin-sodium profile described in the next section. The first goal of this process (Table 1, upper panel) is to identify or exclude definable and curable causes for the hypertensive disorder. To do so may spare many patients a lifetime of needless, costly, and intrusive drug therapy, for often a cure can be effected by relatively simple nonsurgical techniques.

The remaining 85% or so of patients, for whom no definable cause for the hypertension can be found but who can be stratified pathophysiologically by the same renin-sodium test, are candidates for long-term drug therapy. This assumes, of course, that their hypertension is significant (>150/95 mm Hg) and sustained, is possibly causing target-organ strain, and is not responsive to nonpharmacological therapies (weight reduction, low-salt diet, or alcohol withdrawal). For these patients, the baseline evaluation process helps determine the selection of the most effective and least counterproductive drug or drug regimen from the diversity of modern antihypertensive agents available.

With the initial work-up in hand, today's practitioner can arrive more directly at the basic primary goal in applying any long-term drug therapy: to give each patient the fewest number of drugs in the smallest effective amounts and with the lowest possible frequency (Table 1, lower panel). This goal is particularly important in hypertension, considering that every antihypertensive drug presents a problem of toxicity of one degree or another and that the commitment to such a drug is sure to be long-term and possibly lifelong. Effective monotherapy of hypertension is now more possible than many physicians are aware. This is a real advance in a field that, in the past, has been characterized by additive and multiple-drug therapy.

Identifying the Curable Forms of Hypertension: The Captopril Test

Curable and definable forms of hypertension should be identified before contemplating long-term drug therapy. Rarer causes of chronic hypertension aside, the baseline evaluation has much to offer in detecting the presence or absence of parenchymal kidney disease and of such angioplastically or surgically curable forms of hypertension as renovascular hypertension, coarctation, pheochromocytoma, and primary aldosteronism.

The renin-sodium profile, which shows increased renin levels in curable renovascular disease and suppressed levels in primary aldosteronism, is a valuable primary screen. It is not much more expensive or complicated than the cholesterol assays so common nowadays, and it is potentially far more relevant not only because it can absolutely diagnose the curable forms of hypertension but also because, in the remainder, it can be used for evaluating pathophysiology and planning treatment. The test involves the collection of a 24-hour urine for sodium measurement and a venous blood sample for renin measurement, the latter collected while the patient is seated quietly in the office. The plasma renin activity level is plotted against the 24-hour urinary sodium level, thereby allowing for the fact that renin, as a regulatory hormone, is normally increased in response to a low-salt diet and is reduced in response to a high-salt diet.

As with most laboratory tests, the renin-sodium profile is most powerful when its deviations from normal are great. Thus, very low or very high values lead one to suspect, respectively, adrenocortical or curable renovascular disease. The baseline plasma renin and serum potassium measurements are essential tools for the exclusion or diagnosis of these types of hypertension.

Excluding curable hypertension has special meaning and urgency these days, for the possibilities of curing renovascular disease have multiplied dramatically with the advent of balloon angioplasty. The number of cases being detected by renin profiling after the simple and inexpensive captopril test (described later) has increased dramatically. In the last 3 years at The New York Hospital-Cornell Medical Center, we have successfully used balloon dilatation in treating more than 400 hypertensive patients. More than one half these patients are now
fully corrected and are not taking any medications. We have learned that these patients often have milder forms of hypertension.\(^3\) If not for today’s advanced testing protocols, a very large proportion of these patients would still be on a lifetime regimen of drugs, having been incorrectly diagnosed as having “essential hypertension.”

One can no longer excuse committing a new patient to long-term drug therapy before the diagnosis of curable renovascular disease has been considered and excluded. We no longer need to wait for the autopsy, which historically has shown that structural renovascular disease is even more common than coronary artery disease. Thus, moderate or severe renal artery stenosis was found to have occurred in 53% of 295 unselected autopsies and in 77% of those known to be hypertensive.\(^4\) The steps necessary to clinically identify this disorder are now simple and precise. Previously, the intravenous pyelogram involved proved neither sensitive nor specific, and renin assays frequently were technically inadequate. Today, however, peripheral blood renin assays are uncomplicated and dependable, and we have the captopril test and reliable angiography to guide us further.

We consider that any untreated hypertensive patient with an ambulatory plasma renin value of 2.5 ng/ml/hr is a candidate for further evaluation for unilateral renal artery stenosis.\(^5\) So far, in 32 consecutive patients, we have not seen a patient with proven unilateral renovascular disease whose renin level was below that value. Any patient with an abnormal serum creatinine value (>2.0 mg%), regardless of plasma renin values, is also a candidate for further work-up because plasma renin is not always elevated in bilateral renal artery stenosis. In fact, renin levels may be reduced in reaction to impaired sodium excretion and volume expansion. Even in this subgroup, however, a renin value less than 1 ng/ml/hr is unusual.

Patients with ambulatory plasma renin values greater than 2.5 ng/ml/hr or with an abnormal serum creatinine are given the diagnostically powerful captopril test. This test is best performed in untreated patients, but our data indicate that patients receiving only a \(\beta\)-blocker can also be tested. The test is based on the remarkable specificity of captopril to erase the underlying effect of angiotensin II and thereby induce a reactive increase in renin secretion from the ischemic kidney. Patients who are salt depleted because of either a low-salt diet or a diuretic regimen are ineligible for the test because they start with iatrogenically high renin levels and may show a false-positive further increase.\(^6\) However, while false-positives may occur for this and other reasons (i.e., malignant hypertension, scleroderma, and other types of renal diseases), such false-positive results can help uncover an unsuspected secondary hypertension besides that caused by an obstruction of the renal artery. Thus, the captopril test is extremely valuable as a screening test for finding renovascular disease and for establishing the diagnosis of essential hypertension because false-negative tests from the latter category are extremely rare.

In this test,\(^7\) a single dose of 25 mg captopril is given orally to a quietly seated patient (Figure 1). Captopril is rapidly absorbed, producing blockade of the renin system within 1 hour. Patients with renovascular hypertension react to this blockade with an unusually vigorous rise in renin secretion from the ischemic kidney, whereas those hypertensive patients without renal artery obstruction show little or no plasma renin response (Figure 1). With the angiotensin effect erased by the captopril, the ischemic kidney with renovascular disease abruptly loses its intense efferent constriction, and its filtration is threatened. In prompt reaction, renin secretion from the stenotic kidney soars in a failed attempt to restore the situation.

Table 2 lists the procedures for performing the captopril test, and Table 3 displays criteria for

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**Table 2. Instructions for Performing a Captopril Test**

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<th>Procedure</th>
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<tr>
<td>Maintain the patient on normal salt intake and give no diuretic agents</td>
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<tr>
<td>If possible, withdraw all antihypertensive medications 3 weeks before the test</td>
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<tr>
<td>Allow the patient to sit quietly for at least 30 minutes</td>
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<tr>
<td>Measure blood pressure at 20, 25, and 30 minutes (average the three readings to obtain baseline)</td>
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<tr>
<td>Draw a venous blood sample for measurement of baseline renin activity</td>
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<tr>
<td>Administer 25 mg captopril orally</td>
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<tr>
<td>Measure blood pressure at 15, 30, 40, 45, 50, 55, and 60 minutes after captopril administration</td>
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<tr>
<td>At 60 minutes, draw a second venous blood sample for measurement of stimulated plasma renin activity</td>
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interpreting the test. It must be emphasized that the 60-minute plasma-renin response rather than the blood pressure response is the discriminator for the diagnosis of renovascular hypertension. Although a substantial blood pressure decline may often accompany the abnormal reactive rise in plasma renin, this phenomenon is not an altogether reliable indicator either of renin dependency or of renovascular hypertension because, acutely, other transient defenses of the blood pressure level may be operative. Nevertheless, a dramatic decrease in blood pressure is certain confirmation of renin dependency, and a total lack of response generally indicates a nonrenin vasoconstrictor mechanism.5

A positive test that meets the criteria listed in Table 3 strongly implicates renovascular disease. In a series comparing 56 patients with proven renovascular disease with 54 with essential hypertension established arteriographically, the test was found to be 95% sensitive and 95% specific for renin-dependent hypertension related to renal artery stenosis.5

A positive captopril test establishes renin dependency, but the test does not discriminate between unilateral or bilateral kidney disease nor among parenchymal, arteriolar, or vascular lesions. In patients with a positive captopril test, these questions can be definitively resolved by digital subtraction angiography, arteriography of the renal vessels, or by a renal vein renin study. In typical renovascular disease, renin is secreted from only one kidney; a simple arithmetic analysis of the renin concentration in each renal vein can identify the renin-secreting kidney and assess its degree of ischemia. At the same time, the peripheral blood level reflects the renin secretion rate from that kidney.6-7

Bilateral parenchymal renal disease or bilateral renal artery stenosis is possible when the creatinine value is more than 2.0 mg%, or when the creatinine value is between 1.5 and 2.0 mg% and the blood urea nitrogen exceeds 25 mg%. In such hypertensive conditions, renin is often suppressed by impaired sodium excretion and volume expansion. The captopril test can be misleading in this situation,5 and definitive distinction between the two entities requires renal arteriography.

Curable primary aldosteronism is characterized by the diagnostic triad of 1) hyperaldosteronism, revealed by a 24-hour urine or a plasma aldosterone measurement, causing 2) sodium-volume expansion and a markedly suppressed plasma renin activity, and 3) serum potassium values below 3.5 meq/l. Plasma renin levels are typically below 0.5 ng/ml/hr but occasionally can be as high as 1.3 ng/ml/hr. The aldosterone values may not be very high but should be assessed in relation to the degree of hypokalemia, which markedly suppresses aldosterone secretion even in primary aldosteronism. The response of plasma aldosterone to upright posture, a computer-assisted tomography scan, or special radiographic studies, in some instances combined with adrenal vein hormone measurements, then enables definitive diagnosis of either adenoma or bilateral hyperplasia.

To complete the pretreatment evaluation, special tests for other uncommon curable forms of hypertension like pheochromocytoma, Cushing's syndrome, and thyroid disease should also be performed whenever the clinical picture is suggestive.

Applying Drug Therapy in Essential Hypertension

After the initial evaluation in which the diagnosis or exclusion of curable hypertensive disease has been accomplished, the clinician will find the same baseline renin data of additional use for deciding which drug treatment to give to the patients whose hypertension is not curable but rather "essential." With the renin participation in blood pressure maintenance already defined, the pathway to simpler and more specific drug treatments can be considerably clearer for patients without renovascular disease, and especially for those in whom balloon dilatation or surgery are either impractical or technically unsuccessful.

Renin System Patterns Reveal Vasoconstrictor Mechanisms

The renin-sodium profile test allows the clinician to exploit knowledge of renin-system behavior to analyze and treat high blood pressure in individual patients. From numerous studies, we know that renin secretion from a normal kidney approaches zero with either high blood pressure or a high-salt diet. Thus, any renal renin secretion in the face of high arterial pressure is probably abnormal.8 Accordingly, whenever plasma renin is medium or high in a hypertensive person, it implies that a subpopulation of nephrons is inappropriately secreting renin and the remainder are turned off, or there is a uniform diffuse lesion of all nephrons.8

From the responses to renin system–blocking drugs, we also know that low plasma renin levels probably do not contribute to the arteriolar vasoconstriction, whereas those patients with medium or high renin values, to a commensurate degree, use renin to constrict their blood vessels. Accordingly, low-renin volume-expanded patients respond best to dietary or diuretic-induced sodium depletion9 or to calcium antagonists.10-12 Thus, two different long-term mechanisms of vasoconstriction appear to be operating in hypertensive patients. One is caused by and related to the plasma renin level, and the
other is related to sodium retention and is characterized by a low plasma renin value. We can often selectively treat these two vasoconstrictor mechanisms by choosing the right pharmacological agent.2

**Plasma Renin as a Guide to Drug Selection**

When plasma renin values are clearly low (<1.0 ng/ml/hr), converting enzyme inhibitors usually are ineffective or produce very little depressor effect.5,8,13-15 When plasma renin values are very high (>10 ng/ml/hr), converting enzyme inhibitors are almost always effective in lowering pressure. However, baseline renin measurements in the middle ranges are less consistently predictive for choosing first-drug therapy for patients in whom curable disease has been excluded. As shown in Figure 2, this effect is due to the considerable overlap of blood pressure responses in the middle region (1–10 ng/ml/hr) of the plasma renin spectrum. Some patients in this range will exhibit little or no depressor response to antirenin system agents, whereas others will respond impressively. In this middle region, the renin test resembles many other common and valuable tests like the electrocardiogram and blood sugar assay. For all these tests, normal or near-normal values may not be helpful or conclusive, but as deviations from normal become more extreme, they can often redirect therapeutic strategy. Possibly, those hypertensive patients with mid-zone plasma renin values have a mixed vasoconstrictive signal involving renin and sodium factors. In some patients, for reasons still unclear, the sodium-related vasoconstriction mechanism may have displaced the renin mechanism. In either case, the frequent success of antirenin, antivolume, or a combination of the two therapies indicates that one or both mechanisms are still involved in some reciprocal manner.

In any event, the renin test’s lack of predictive power in the middle ranges should not detract from its usefulness in the high and low regions of the spectrum, where, in most cases, the test clearly identifies two different vasoconstrictive mechanisms.

**Drug Therapy for the High-Renin Patient**

For those patients with a medium-to-high renin profile (plasma renin activity >2.5 ng/ml/hr) and in whom the captopril test confirms renin dependency but who do not have a curable renovascular disease, the modern choice for first-line therapy is a converting enzyme inhibitor, presently captopril, enalapril, or lysinopril. This choice results from the specificity of these drugs: there is no longer any doubt that the overwhelming portion of their depressor effect is due to inhibition of angiotensin II formation.13-15 The effectiveness of converting enzyme inhibition is well illustrated in Figure 2, which depicts the relation of intravenous teprotide, the first converting enzyme inhibitor, and teprotide’s oral analogue, captopril, to the pretreatment plasma renin level. The higher the baseline renin, of course, the more dramatic is the blood pressure correction and vice versa. Not illustrated by this plot of the acute response to the drugs is the additional long-term effect achieved by the accompanying blockade of aldosterone’s sodium retention.

A reasonable alternative for first-drug choice in the medium-to-high renin group is a β-blocker. Although not as potent as converting enzyme inhibitors, β-blockers are extremely effective in lowering renal renin secretion.16 and in certain subgroups (e.g., those with tachycardia or coronary disease), β-blockers have the added value of reducing cardiac work and perhaps protecting from future coronary events. Furthermore, unlike therapy with diuretic agents, β-blocker monotherapy has been shown, in controlled trials, to protect from coronary events, the major sequelae of hypertension.17,18
Drug Therapy for the Low-Renin Patient

A low-renin profile suggests a nonrenin sodium-related factor in diastolic hypertension. Here, the choice of first-line therapy is somewhat broader. Historically, the first choice for this group is a diuretic agent, the cornerstone of the old-fashioned stepped-care empirical approach to treating all essential hypertension. In the past, all other drugs were then added on in “steps.” The diuretic agent was needed because all of the other older drugs caused reactive fluid retention. However, with modern agents, reactive fluid retention generally is not a problem. Now, even in low-renin patients, the predominant use of diuretic agents is under sharp challenge by the newer calcium antagonists and by \( \alpha_1 \)-adrenergic receptor blockers.\(^{19,20}\) Calcium antagonists are especially effective in low-renin patients,\(^{10-12}\) many of whom have sodium-dependent vasoconstriction.

The specificity of calcium antagonists for this group of patients is by no means absolute; these drugs may also produce significant depressor responses in medium- and even high-renin patients, possibly because increased cytokastic calcium may be a final pathway for sustaining all forms of vasoconstriction. However, their selective effectiveness in low-renin hypertension is also supported by work showing that a calcium antagonist fails to block the pressor action of angiotensin II while readily blocking norepinephrine action.\(^{21}\)

The calcium blockers’ greater effectiveness against low-renin hypertension may be exploited in an interesting way. We have shown that concurrent sodium administration does not oppose and even may enhance the antihypertensive action of these agents.\(^{22}\) Allowing salt in the diet reduces renin and shifts the patient to sodium-dependent vasoconstriction, constriction against which the calcium antagonists are most effective. On the other hand, sodium depletion and high-renin secretion induced by diet or diuretic therapy may rob these agents of their depressor power while enhancing the antihypertensive effect of converting enzyme inhibitors. These relations agree with several reports that indicate greater effectiveness of calcium antagonists in low-renin forms of hypertension\(^{16-18}\) and with other reports indicating little or no added benefit from combining these agents with a diuretic agent.\(^{23-25}\) The results are of practical interest because patients given calcium antagonists can liberalize their sodium intake and thereby improve volume and flow without adverse effect on blood pressure.

Calcium channel blockers are theoretically more attractive than diuretic agents because, like the converting enzyme inhibitors, as the calcium channel blockers reduce blood pressure, they actually improve blood flow to the heart, brain, and kidneys. Calcium channel blockers are not associated, as the diuretics are, with dehydration, hemococoncentration, impotence, abnormal lipid profiles, hyperuricemia, and azotemia. Indeed, the fact that long-term clinical trials with a diuretic-based regimen have failed to show protection against coronary artery disease may be attributable to some of these very problems.\(^{26}\) Quite possibly, as preliminary evidence suggests, converting enzyme inhibitors and calcium channel blockers\(^{27}\) may demonstrate cardioprotection in long-term controlled trials.

Another class of agents that maintain tissue flow as they lower pressure are the \( \alpha \)-blockers like prazosin. The best responders to \( \alpha \)-blockers, like the best responders to calcium antagonists, are those patients with low-renin hypertension.\(^{19,20}\) These \( \alpha_1 \)-receptor blockers are less potent than the calcium channel blockers, but the former appear to affect the same vasoconstrictor mechanism, perhaps because of the close proximity of \( \alpha \) and calcium receptors on the cell wall.\(^{28}\) Combining \( \alpha \)-blockers and calcium channel blockers can produce additive effects.\(^{28,29}\)

Therapy for the Medium-Renin or Unprofiled Patient

As shown in Figure 2, plasma renin activity values of about 8–10 ng/ml/hr or under 1.0 ng/ml/hr point reliably to selective and effective antirenin or antischodium monotherapy, but intermediate-range values show far less effect. In this range of values, it is possible that renin-mediated and sodium-mediated mechanisms of vasoconstriction overlap or function reciprocally. Unfortunately, the majority of patients with essential hypertension have these intermediate-range values, and the clinician must use the all-too-familiar technique diagnosis ex juvantibus, the empirical process of seeing what works.\(^{30}\) Five major drug types (Figure 3) are now available for this exercise.

The empirical process of seeing what works need not be as blind as formerly, however, and the process most surely is not as limited in its alternatives. First, the renin profile may be available to add valuable information to that derived from other tests in the baseline evaluation: values on the high side (as opposed to values on the low side) are suggestive of which type of drug should be tried first. Figure 3 presents an idealized schematic representation of the probable effectiveness or lack of the five major drug types, depending on the renin profile of the patient. The diagram suggests that, in general, unless the renin profile is low, it is best to begin the trial-and-error strategy with a converting enzyme inhibitor.

The rationale for this choice is that the converting enzyme inhibitor, of all available medications, is the most specific agent, so that a negative result is as informative as a positive one. The strongest immediate effect of converting enzyme inhibition is directed against angiotensin’s vasoconstriction. During a longer term (2–3 weeks), however, the impact of converting enzyme inhibitors in blocking aldosterone secretion is also expressed; thus, these
agents work on the sodium-related aspect as well. If, after a few weeks, a converting enzyme inhibitor has failed to produce an acceptable response, the next alternative is to choose an agent to oppose the sodium-related vasoconstriction, that is, in sequence, calcium channel blockers, $\alpha_1$-adrenergic blockers, and diuretic agents. The reason for this ranking is that the first two agents, when they induce a successful depressor result, do so without reducing the blood flow that could be so vital to cardiovascular health and that may be compromised by diuretic drugs. There are, of course, exceptions to this sequence. Diuretic drugs may be the first choice in patients with overt hemodilution or fluid retention, phenomena that are often present in obese and low-renin hypertensive subjects.

**Combining First-Line Drugs**

With some notable exceptions, any two of the five major drug types ($\beta$-blockers, angiotensin converting enzyme inhibitors, calcium antagonists, diuretic drugs, $\alpha$-blockers) can rationally be com-
bined to gain added antihypertensive action when desired. The first two operate primarily against renin vasoconstriction, whereas the last three oppose sodium-volume (calcium-linked) vasoconstriction.

Perhaps the most efficient and conceptually attractive approach in treating patients in whom converting enzyme or calcium antagonist monotherapy fails is to combine the two agents, thereby blocking both major vasoconstrictive mechanisms. With a moderate or even liberalized salt intake, this strategy can maintain or improve tissue blood flow as blood pressure is reduced. The additive effects of such a combination have been verified.31

There is also a rational basis for combining an antirenin-system drug with a diuretic agent to block both vasoconstrictor mechanisms. In low-renin and some medium-renin patients with an underlying sodium excess and in whom converting enzyme inhibitors alone are ineffective, diuretic therapy arouses a reactive renin release, thereby iatrogenically introducing renin-dependent vasoconstriction and thus enabling the converting enzyme inhibitor to work more effectively.32,33 However, it would be prudent to add some general cautionary considerations. When combination therapy is indicated, the foregoing discussion supports the logic of combining antirenin and antisodium agents. However, the data that provide the rational basis for such combinations also indicate that hypotension and possible renal failure may occur when full-dosage antirenin therapy is given in cases where there is already excessive sodium depletion. In fact, in animal models and humans, prior sodium depletion with attendant high-renin activity sets the stage for converting enzyme inhibitors alone to be ineffective, diuretic therapy preventing a reactive renin release, thereby iatrogenically introducing renin-dependent vasoconstriction and thus enabling the converting enzyme inhibitor to work more effectively.32,33 For this reason, converting enzyme inhibitors should probably always be commenced in sodium-replete patients, and sodium depletion should be superimposed only gradually in resistant patients. Such precautionary guidelines are not applicable when β-blockers are used as the antirenin agent because their antirenin effect is less total.

Two important caveats should be observed in applying the empirical evaluation-treatment process to patients with medium-range renin values. First, the clinician should resist the temptation to begin adding other drugs when converting enzyme monotherapy seems inadequate at first. Converting enzyme inhibitors also suppress aldosterone secretion, but because the effect of this action only reaches its full expression slowly (endogenous aldosterone activity accounts for 1–2% at most of daily renal sodium reabsorption), several weeks may pass before the full benefits of converting enzyme inhibitors are seen in patients in whom sodium dependency shares culpability with renin dependency. This component of the converting enzyme inhibitor’s antihypertensive action resembles that of spironolactone in the delayed onset of what eventually can be a considerable depressor effect, an effect often greater than that of full-dose thiazide diuretic agents.

Second, the clinician must be willing to pursue monotherapy and try only one drug at a time. Unless a rigorous systematic trial of monotherapies makes additive therapy the last resort, it is no trial at all. Additive therapy provides few clues to the nature of the basic hypertensive lesion, little advance in understanding the pathophysiology of hypertension, and less-than-optimal service to the patient. Superimposing one drug on another, as in the stepped-care regimen, makes the entire pursuit impossible to analyze and allows many patients to take nontherapeutic and possibly detrimental drug agents for life. A recent review of 1,486 clinical trials shows that many patients whose blood pressures were controlled by combination therapy rather than by monotherapy most likely represent a summing of patients, not of drug effectiveness.30 These patients, responding separately and specifically to the effective components in their antihypertensive recipe, would have been better served had there been an orderly effort to discover to which component of the combination they were responding. Therefore, one must be wary of these older reports, which focus primarily on the mean responses for groups. Often hidden by this analysis is the fact that, within such a group, very good responders may be averaged with nonresponders and with those who actually exhibit pressor response.30 This point is well illustrated by the recent reports of Ménard et al35 and Bidiville et al.36

Other Guidelines for Choosing Drugs

A few other general rules for selecting drugs—some so well known or obvious that they appear trivial—should be mentioned again because of their practical value. By statistical measurement, because elderly, black, or obese patients are more prone to lower renin levels, individuals in these categories are more likely to respond to diuretic drugs or calcium antagonists. Thiazide diuretic agents, which interfere with insulin secretion, or β-blockers, which mask hypoglycemia, are relatively to absolutely contraindicated in diabetic patients, and β-blockers should be avoided in patients with bradycardia, airway disease, or peripheral vascular disease. β-Blockers and calcium antagonists are preferred in patients with coronary insufficiency. However, converting enzyme inhibitors or calcium antagonists, because of their putative positive effects on renal circulation, may be preferred in hypertensive patients with diabetic or parenchymal renal disease.

A word of caution should also be said about other possible combinations of the five major drug types that work primarily against either the renin- or sodium-related type of vasoconstriction. The addition of a β-blocker effectively counters the reflex tachycardia and headache that sometimes accompanies the use of the dihydropyridine types of calcium antagonists and α-blockers, and it can add
to the hypotensive action as well. Caution should be exercised, however, in combining β-blockade with verapamil or diltiazem, drugs that slow atrioventricular nodal conduction; converting enzyme inhibition is the safer antirenin additive in this case.

More on Combination Therapy

In fact, the combination of a converting enzyme inhibitor with a calcium antagonist might provide other special values. There is evidence that the reflex tachycardia and peripheral edema associated with the dihydropyridine group is blunted or corrected. The reflex tachycardia is corrected by a parasympathomimetic influence and the peripheral edema by a postcapillary or venodilating effect of the added converting enzyme inhibitor.

As indicated already, superimposed diuretic therapy may actually impair the effectiveness of calcium antagonist therapy, as it modifies the renin level and hemodynamic profile adversely. Theoretically, adding a diuretic agent to an α-blocker–treated patient might produce a similar negative interaction, but this has not yet been critically examined. However, this combination is not associated with untoward side effects.

α-Blocker therapy can potentiate the antihypertensive effectiveness of a calcium antagonist. The combination of an α-blocker with a converting enzyme inhibitor also could be synergistic by blocking two different vasoconstrictor pathways.

It has long been recognized that α-blockers can be combined with β-blockers to achieve better blood pressure control by blocking the unopposed other limb of the sympathetic system. This still-promising approach has been exploited with the development of compounds that possess both α- and β-blocking properties such as labetolol.

Recently, strong new support has been provided for the treatment algorithms developed herein. A study by Niutta et al. has evaluated separately in each subject the effectiveness of a β-blocker, a converting enzyme inhibitor, and a diuretic agent in randomized, 4-month, change-over sequence. All three drugs had equal mean effectiveness; however, each agent was effective in different particular groups of patients, and this selective effectiveness or lack of it was predictable by renin profiling. This study verifies an earlier crossover design study reported by Bühler et al. Moreover, there is statistical validity and considerable potential for reexamining single antihypertensive agents in a double crossover factorial design to reveal differences in individual responses. Altogether, applications and new studies built on this new information promise to bring us closer to achieving the basic goals of long-term antihypertensive drug therapy.

Older Agents

What is the role of older antihypertensive agents like hydralazine, minoxidil, and guanethidine? These agents can often be very effective. However, the reflex tachycardia and reactive fluid retention of the first two make it almost impossible to use them except in combination with two other types of drugs—a β-blocker and a diuretic agent. Today, this type of triple-drug therapy is rarely needed because converting enzyme inhibitors or calcium blockers even as monotherapy are usually simpler alternatives. Similarly, guanethidine is a very potent agent but too often is associated with unpleasant side effects consequent to broad autonomic blockade. Accordingly, this group of agents now serves only in a backup role.

Furthermore, drugs that lower pressure by acting on the brain should be the last choice for treating hypertension, because these drug types (e.g., reserpine, methyldopa, clonidine, and guanabenz) interfere with mood, mentation, and sexual function. In some situations, however, these side effects do not occur, nor are they an issue. Indeed, there are special but unusual situations in which these drugs can be useful as primary agents or adjuvants.

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