Translating Data on Antihypertensive Drugs Into Clinical Practice

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Two problems in the treatment of hypertension continue to be largely unsolved. The first, and more simple, is our inability to adequately control blood pressure in the majority of hypertensive patients. This not only reflects the difficulty of retaining patients in effective treatment programs, but also of convincing physicians to strive for optimal blood pressure levels. There is a continuing need for new antihypertensive drugs and combinations to help accomplish these goals.

The second major problem is that the major clinical endpoints, including coronary events and renal failure, have not been adequately reduced by traditional therapies. Standard regimens, particularly those including diuretics, have protected against strokes and heart failure. Our improved understanding of vascular biology in hypertension has directed interest to the mechanisms in hypertensive patients that might accelerate atherosclerosis and vascular events in these individuals. This involves addressing the concomitant metabolic risk factors that comprise the “Hypertension Syndrome,” and, perhaps of equal importance, finding therapies that directly inhibit unwanted types of growth and proliferative activities within the walls of critical arteries. Many substances within the endothelium and the vascular wall may participate as initiators or mediators of patholty, but most information thus far has focused on the renin-angiotensin system. Angiotensin converting enzyme inhibitors (and potentially angiotensin receptor blockers) have provided coronary and renal protection in various cardiovascular conditions, though not yet in formal hypertension trials. Calcium channel blockers have also shown promise, including recent stroke and cardiovascular benefits in patients with isolated systolic hypertension, but, again, definitive coronary data in hypertension are awaited.

Unless concomitant conditions mandate the selection of a particular antihypertensive drug class, physicians currently have a dilemma: should they choose drugs from older classes that have not provided full protection? Or, should they prescribe newer agents with exciting potential but with, as yet, unproved endpoint benefits in hypertension? Until currently ongoing prospective trials of antihypertensive therapy are completed, physicians must be guided by their own interpretations of the available data. Am J Hypertens 1998;11:89S–94S © 1998 American Journal of Hypertension, Ltd.

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physicians in this matter for over 20 years. The earlier reports tended to favor diuretics as the first step of antihypertensive therapy, but by the fourth report, published in 1988, the JNC had recognized that there were at least four classes of drugs that appeared appropriate for initiating therapy: diuretics, \( \beta \)-blockers, calcium channel blockers, and angiotensin converting enzyme (ACE) inhibitors. The JNC at that time suggested that doctors, bearing in mind the different characteristics of these drug groups, aim to select the most appropriate agent for each individual patient.

The JNC V Report\(^1\) appeared to take a step backward when it indicated that diuretics and \( \beta \)-blockers should be “preferred” first-line agents. The chief spur to this was a randomized clinical trial, the Systolic Hypertension in the Elderly Program (SHEP),\(^2\) which had shown that the diuretic chlorthalidone in conjunction with the \( \beta \)-blocker atenolol (though the \( \beta \)-blocker did not appear to influence the clinical endpoints) was significantly more effective than placebo in decreasing strokes and congestive heart failure in elderly patients with isolated systolic hypertension. Other hypertension experts questioned whether this highly selective study (only about 1% of elderly patients evaluated for enrollment into the SHEP study actually met its rigorous entry criteria) could be the basis for providing advice concerning the whole gamut of hypertensive patients. Other hypertension experts questioned whether this highly selective study (only about 1% of elderly patients evaluated for enrollment into the SHEP study actually met its rigorous entry criteria) could be the basis for providing advice concerning the whole gamut of hypertensive patients. Other hypertension experts questioned whether this highly selective study (only about 1% of elderly patients evaluated for enrollment into the SHEP study actually met its rigorous entry criteria) could be the basis for providing advice concerning the whole gamut of hypertensive patients. Other hypertension experts questioned whether this highly selective study (only about 1% of elderly patients evaluated for enrollment into the SHEP study actually met its rigorous entry criteria) could be the basis for providing advice concerning the whole gamut of hypertensive patients.

**BLOOD PRESSURE**

Despite our growing interest in the potentially important nonhemodynamic actions of antihypertensive drugs, it is still necessary to find agents with strong blood pressure-lowering properties. Even modest elevations of blood pressure appear to confer risk. Analysis of longitudinal data from the Multiple Risk Factor Intervention Trial (MRFIT),\(^3\) as shown in Figure 1, has helped to stimulate the recommendation of the JNC that hypertension be diagnosed with diastolic blood pressure values as low as 90 mm Hg or systolic values of only 140 mm Hg. The diagnostic recommendations have been modified in JNC VI, which is basing its diagnostic criteria on the concept of total cardiovascular risk, thus, the presence or absence of such factors as diabetes mellitus, lipid disorders, or left ventricular hypertrophy—in addition to the blood pressure values—will determine whether or not lifestyle modifications or drug therapy should be started.

Getting the blood pressure down is not easy. The third National Health and Nutrition Examination Survey (NHANES 3), performed in the early 1990s, indicated that barely one-quarter of hypertensive patients in the United States had blood pressure values <140/90 mm Hg. Even among those patients known to have hypertension and considered to be receiving active treatment the control rate was <50%. It is not clear why achieving this relatively modest therapeutic target is so elusive. Among other explanations, it is likely that physicians are not being sufficiently aggressive in pursuing goal blood pressure responses, nor are they being successful in persuading their patients to adhere closely to prescribed therapies. But, to be fair, it is also likely that bringing blood pressure down to an acceptable range is truly a challenging task that requires innovative medications and the creative use of combination therapy. There is clearly a need for continuing development of new pharmacologic products to help in this work.

**Do Demographics Help?** There has been a widely accepted belief that various population groups are best served by particular agents. It has been suggested that such agents as \( \beta \)-blockers, ACE inhibitors, and
angiotensin receptor blockers may work best in white or Asian patients and in the young, whereas such classes as diuretics and calcium channel blockers might be more efficacious in black patients and in the elderly. These ideas were tested in a Veterans Affairs cooperative study that examined a variety of drug classes in patients of different ages and ethnic backgrounds. Indeed, at the extremes, it was confirmed that young white patients responded best to an ACE inhibitor or a β-blocker, whereas the efficacy of a diuretic was not different from that of placebo in this group. In contrast, the experience in older black patients indicated that a calcium channel blocker was best and that a diuretic was also effective; the β-blocker and ACE inhibitor were not significantly different from placebo. This information can be helpful in selecting a first agent, but this study also pointed out that even optimal drug selection produced meaningful blood pressure responses in barely half the patients. This emphasizes that the very simple approaches are not sufficient; much of the time it will be necessary to test differing drugs in a search for the best single monotherapy, and it is likely—especially when the goal of bringing blood pressure below 140/90 mm Hg is pursued—that thoughtfully selected drug combinations will be required.

THE CORONARY HYPOTHESIS

What are the mechanisms that lead to vascular disease and clinical events—particularly coronary disease—in hypertensive patients? The so-called coronary hypothesis, which has been discussed in more detail elsewhere, is based on three principal facets. As shown in Figure 2, it is believed that vascular disease begins very early in the lives of most hypertensive patients. This has been demonstrated in animal models of genetic hypertension, and can be at least partly confirmed by demonstrations of reduced arterial compliance and endothelial dysfunction in the young offspring of hypertensive patients. Genetic changes in key components of the renin system, the sympathetic nervous system, and endothelial factors are among the possible explanations. These early changes are exaggerated by the concomitant risk factors that typically accompany hypertension. For example, lipid abnormalities and insulin resistance are frequently components of the hypertension syndrome and work together with high blood pressure to accelerate the already existing vascular wall abnormalities in hypertensive patients. Finally, with aging, the developing atherosclerosis and stiffening of the arterial circulation further increase systolic blood pressure and contribute to the high pulse pressure and lability that characterize elderly hypertensives.

For these reasons, effective care of hypertension requires a three-pronged attack. Specifically, we should be choosing therapy, usually drugs, that potentially exhibit antiproliferative vascular properties that can limit atherosclerosis. We should select drugs that—if not actually metabolically beneficial—are at least neutral; and we should select drugs that effectively reduce blood pressure. In older patients, in whom vascular disease may be well advanced, this last hemodynamic action of antihypertensive drugs may be the most important factor in achieving clinical benefits. But in younger patients where the goal is to minimize or prevent ongoing vascular damage, the vascular and metabolic properties of drugs become very important. The question arises: how do the newer drugs measure up to these requirements?

THE NEWER DRUG CLASSES

There are a variety of drug classes currently under development, but for this discussion we will focus on the three groups that currently are the focus of interest: the ACE inhibitors, the angiotensin II receptor antagonists, and the calcium channel blockers.

The ACE Inhibitors The basis for this class of drug lies in the discovery, approximately 25 years ago, that the renin-angiotensin system is closely involved in the cardiovascular prognosis of hypertensive patients. In essence, when hypertensive patients were subdivided into high, medium, and low renin subgroups (with comparable blood pressure values), long-term follow-up revealed that the high renin patients were clearly more likely to experience myocardial infarctions. Although the vasoconstrictor actions of angiotensin II might contribute to the hemodynamic component of hypertension, the key claim in Laragh’s original hypothesis was that angiotensin II might have direct pathophysiologic vascular actions—indeed of its blood pressure effects—that could explain its adverse impact on prognosis.

More recent studies in the laboratory have helped to clarify the molecular biology of this action of angiotensin II. In vitro studies have demonstrated, for example, that angiotensin II promotes hypertrophy of vascular smooth muscle cells, stimulates the connec-
tive tissue matrix growth within the vascular wall, and has a disruptive and inhibitory effect on the endothelium. At the same time, studies in atherogenic animal models have demonstrated that the ACE inhibitors, independent of their blood pressure effects, can inhibit the development of atherosclerotic disease.

What data do we have in humans? Although we are still awaiting the result of prospective randomized clinical endpoints trials in hypertension, we have some useful preliminary lines of evidence. In patients with congestive heart failure, for example, it has been well established that ACE inhibitors improve symptoms, reduce hospitalization, and—most importantly—improve survival. But, in addition, they also decrease the incidence of acute myocardial infarction and other coronary events in these patients. Another source of evidence comes from the experience with ACE inhibitors in patients who have suffered an initial myocardial infarction with compromised left ventricular systolic function: in addition to decreasing the likelihood of these patients developing clinical congestive heart failure, the ACE inhibitors also appeared to reduce the probability of new myocardial infarctions. And in patients with diabetic or nondiabetic nephropathy, ACE inhibitors have not only provided renal protection but also have tended to reduce other cardiovascular events and improve survival.

This constellation of evidence, although not originating primarily from studies in hypertensive patients, provides strong encouragement that the ACE inhibitors should be regarded as drugs with good potential for protecting against coronary events in hypertension. Some interesting supporting data come from a recent paper based on clinical events in a large cohort of hypertensive patients being followed in the greater New York area. While this study, strictly speaking, could be described as “observational”—a somewhat disparaging term used to describe retrospective case control studies—this report has the virtue of originating from a project in which the patients and their clinical progress and outcomes were monitored from the very outset with the intention that clinical events would be analyzed. It was discovered that the incidence of serious cardiovascular episodes in patients treated with ACE inhibitors was slightly less than 40% of that with diuretics and about half that observed with β-blockers. Prospective studies would be helpful in completing this chain of evidence.

Angiotensin Receptor Blockers This is the newest of the antihypertensive drug classes to be approved; currently there has been limited clinical experience. The antihypertensive efficacy of these agents is comparable to that of the other drug classes, but they seem to have the advantage of being exceptionally well tolerated. Indeed, the incidence of adverse events or complaints with these drugs does not appear to differ from that of placebo.

It is still too early to report any clinical endpoint data. Preliminary work from the laboratory confirms that these blockers of the renin-angiotensin system, as with the ACE inhibitors, have clearly beneficial effects on vascular structures. Of particular note, however, the manufacturers of these new drugs have decided, right at the time of launching them, to undertake long-term studies of their effects on myocardial infarction, stroke, and other vital cardiovascular endpoints. Recently, clinicians have been tantalized by the Evaluation of Losartan in the Elderly (ELITE) study in which the angiotensin receptor blocker losartan was significantly more effective than the ACE inhibitor captopril in reducing mortality in patients with congestive heart failure. Again, this was not a hypertension study; the patient numbers were small and there were aspects of the study design that would compel caution in interpreting this finding. Moreover, similar results have not been replicated in other clinical studies with other drugs in this class.

Calcium Channel Blockers These drugs have perhaps created more controversy than any of the other antihypertensive classes. Studies in animal models of atherosclerosis have demonstrated that these agents are effective in preventing or minimizing vascular disease. Moreover, because they frequently are indicated for the treatment of angina pectoris, many physicians have come to believe that they are a treatment of choice in hypertensives with concomitant coronary artery disease.

It came as a surprise, therefore, when a paper presented at a clinical meeting—but given wide prominence by a skillful public relations and media campaign—asserted that calcium channel blockers, when compared with diuretics, were associated with a 60% increase in the likelihood of myocardial infarctions in hypertensive patients. This work, later published, was based on a retrospective evaluation of patients treated by physicians other than the authors in a large health maintenance organization (HMO) in Seattle. Subsequent evaluations of this surprising finding, including a special meeting of the Cardiovascular and Renal Drugs Advisory Committee of the US Food and Drug Administration (FDA), found that these concerns were not justified when applied to approved antihypertensive agents of this class. Two principal problems arose with this study. First, that the retrospective nature of the data gathering did not allow investigators to determine the basis on which the prescribing physicians in the HMO had originally selected drugs; it was not possible to refute the probability that calcium channel blockers were preferentially given to patients already known to have
coronary disease. Second, the cost-conscious formulation of the HMO did not include any of the contemporary FDA-approved antihypertensive channel blockers; rather, the physicians were compelled to prescribe nonapproved short-acting agents to their hypertensive patients. These formulations evoke marked hemodynamic and neuroendocrine responses and are inappropriate for the treatment of hypertension.

The importance of this issue is highlighted by the New York experience discussed earlier. The short-acting calcium channel blockers were almost three times as likely as diuretics to be associated with major cardiovascular events. In contrast, the approved long-acting calcium channel blockers were actually about 40% less likely than diuretics (though this difference was not statistically significant) to be associated with major adverse events. Other experiences with the long-acting calcium channel blockers have confirmed the safety of these agents.

Two recent trials appear to have provided an even more positive basis for the use of calcium channel blockers in hypertension. In one, Chinese hypertensive patients treated with a long-acting dihydropyridine experienced significantly fewer strokes and other cardiovascular events than those receiving placebo. Admittedly, this trial did not randomize patients to treatment groups but used sequential allocation and it also deviated in other ways from an ideal prospective double-blind trial. A far more powerful study, the Syst-Eur Trial, also compared a long-acting dihydropyridine with placebo in elderly patients with systolic hypertension. Again, there was a clear benefit in terms of reduced strokes and other clinical events with the calcium channel blocker. It is noteworthy that although the JNC VI report is recommending diuretics as preferred therapy in elderly patients with isolated systolic hypertension, it has listed the use of long-acting dihydropyridine calcium channel blockers as a possible alternative treatment.

Other Drug Classes The beneficial attributes of diuretics and β-blockers should not be underestimated. Diuretics certainly have proved effective in protecting against stroke and congestive heart failure in elderly patients and have also been part of antihypertensive regimens that have improved outcomes in younger individuals with severe forms of hypertension. From a practical point of view, low-dose diuretics are effective as adjuncts to other drug classes in optimizing blood pressure reduction. β-Blockers have been less effective in reducing clinical events when used as monotherapy. In fact, this has created a fascinating question: why has it been so difficult for β-blockers to document coronary protection or other cardiovascular benefits in hypertension when they have been so uniformly effective in providing secondary prevention in patients who have experienced an initial heart attack? Carvedilol, a newly available agent with α- as well as β-blocking properties, recently has been shown to reduce mortality and other major events in patients with congestive heart failure. It would be interesting to learn whether this agent might have similar benefits in a hypertensive population.

COMBINATION THERAPY

Because single agent therapy normalizes blood pressure in fewer than half of all hypertensive patients, there has been a long-standing interest in combination therapy. There is now renewed interest in this approach, particularly with the availability of some innovative fixed-dose combinations. One such approach has been to bring together very small doses of a diuretic and a β-blocker. Each of these doses, by itself, does not confer meaningful antihypertensive efficacy, but in combination there is a strong antihypertensive effect. The virtue of this low-dose strategy is that this is not bought at the expense of untoward side effects. A product with this formulation has actually been approved by the FDA as first-line therapy for hypertension and is acknowledged in JNC VI.

Another new approach is to combine an ACE inhibitor with a calcium channel blocker. The efficacy of this combination, which is well tolerated, is greater than its individual components; it represents a convenient and efficacious approach to treatment. Because each of the components of this combination might have cardiovascular protective effects (see above), it could be conjectured that the combination might be beneficial in preventing clinical endpoints. At this time, however, there are no clinical endpoint data with this type of therapeutic approach.

FINAL COMMENT

Treating hypertension is demanding. To grant one class of drugs a favored status over others is unwise; in reality each of the antihypertensive classes has an important part to play in allowing us to reduce blood pressure to acceptable levels and, we hope, in protecting against clinical cardiovascular events. A host of large-scale clinical trials is now underway to determine the prognostic impact of treatment with such drug classes as angiotensin antagonists, ACE inhibitors, and calcium channel blockers. Until the results of this work become available—and it may take another 2 to 4 years before this happens—we should thoughtfully use these drugs and stay alert to any new evidence that gives us further direction in their optimal use.
REFERENCES


