Treating High-Risk Hypertensive Patients
Kenneth A. Jamerson

Successful treatment of hypertension entails not only normalizing high blood pressure, but also addressing the associated risk factors that increase the likelihood of cardiovascular morbidity and mortality. Hypertension often occurs in a setting of insulin resistance, hyperinsulinemia, dyslipidemia, and a prothrombotic state. A number of epidemiologic studies have shown that the clustering of these abnormalities is associated with increased risk of cardiovascular morbidity and mortality. Therefore, it is rational to direct therapy at moderating these risk factors as well as at lowering blood pressure in hypertensive patients. This is particularly important in patients with comorbidities such as diabetes, cardiovascular disease, or renal insufficiency. Many physicians prescribe only diuretics and β-blockers, agents that have demonstrated efficacy in long-term randomized controlled trials. However, this approach does not consider the potential benefits of newer agents for which long-term outcome data are not yet available. The ongoing Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, in which the angiotensin II subtype 1 receptor blocker valsartan is compared with the third-generation calcium channel blocker amlodipine, should provide important evidence on the long-term efficacy of these newer agents. A unique feature of VALUE is that it is specifically enrolling into the only current trial, now under way, hypertensive men and women at a relatively high risk for a cardiovascular event to determine the benefits of complete blockade of angiotensin II beyond those of the control of blood pressure.


KEY WORDS: Amlodipine, angiotensin II subtype 1 receptor blocker, cardiovascular risk factors, hypertension, valsartan.

The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) stated that risk for cardiovascular (CV) morbidity and mortality in patients with hypertension is determined not only by blood pressure (BP), but also by the presence or absence of target-organ damage or major independent risk factors such as cigarette smoking, dyslipidemia, and diabetes. As a corollary, treatment of hypertension should address any comorbid conditions and associated risk factors as well as the high BP. This article discusses hypertension in the light of associated risk factors and highlights an ongoing comparative clinical trial of two antihypertensive medications, valsartan, an angiotensin II subtype 1 receptor blocker (ARB), and amlodipine, a third-generation calcium channel blocker (CCB).

THE METABOLIC SYNDROME AND CV RISK

In 1988 Reaven et al described the association of insulin resistance at the cellular level with hypertension and dyslipidemia. This constellation of physiologic abnormalities is referred to variously as “syndrome X,” the “insulin resistance syndrome,” and the “metabolic syndrome.” By 1995, Reaven had hypothesized that a combination of insulin resistance and compensatory hyperinsulinemia are the primary events that
predispose a patient to a cluster of abnormalities consisting of glucose intolerance; hypertriglyceridemia; increased plasminogen activator inhibitor (PAI-1); decreased levels of high-density lipoprotein (HDL) cholesterol; hypertension; hyperuricemia; and smaller, more dense, low-density lipoprotein (LDL) cholesterol particles.\(^3\) One year later, Reaven expanded his model to include the sympathetic nervous system and catecholamines released by the adrenal medulla as effector links between insulin resistance and hypertension and heart disease (Figure 1).\(^4\) Because CV disease (CVD) is the cause of death in two of every three people with diabetes, the clustering of these risk factors increases patients' CV risk.\(^5\)

In agreement with Reaven, Grundy\(^6\) has proposed that insulin resistance lies at the heart of the metabolic syndrome, that central obesity is a clinical marker for insulin resistance, and that hypertriglyceridemia, commonly associated with insulin resistance, is a valuable clinical marker of the metabolic syndrome. According to Grundy, the syndrome manifests as four categories of abnormality: atherogenic dyslipidemia (increased levels of triglycerides, increased small LDL particles, and decreased HDL particles), hypertension, increased plasma glucose levels, and a prothrombotic state.

From an endocrinologic perspective, the primary culprit is the tissue's decreased sensitivity to insulin, which results in hyperinsulinemia. Hyperinsulinemia is thought to have direct toxic effects on cells as well as to stimulate vascular hypertrophy. The pathophysiologic results have an alternative interpretation, however. As a result of demonstrations of reduced blood flow and glucose uptake in skeletal muscles in diabetic subjects, studies at the University of Michigan have examined the effect of reflex-induced sympathetic nervous system activation on the peripheral utilization of skeletal muscles in healthy volunteers (Figure 2).\(^7\) Locally infused norepinephrine, the major neurotransmitter of the sympathetic nervous system, induced vasoconstriction and, ultimately, insulin resistance in these healthy subjects. The results of these studies suggested that the increased sympathetic tone and vasoconstriction associated with longstanding hypertension can impair the delivery and use of glucose. Thus, although endocrinologists may be correct in maintaining that insulin resistance may lead to hypertension, high BP may lead to metabolic abnormalities. Furthermore, the activity of the sympathetic nervous system (and perhaps other currently undefined components of the insulin-resistant state) may antagonize the normal vasodilative effects of insulin in obese patients and those with hypertension.\(^4\)

**CLUSTERING OF RISK FACTORS IN EPIDEMIOLOGIC STUDIES**

An ongoing epidemiologic study being conducted in Tecumseh, Michigan, the residents of which are all of virtually 100% European ancestry, is providing information on the CV health of an entire community.\(^8\) Not only does this lack of diversity in Tecumseh make it a nearly ideal control group for comparison with various ethnic populations, it also serves as a laboratory in which to test hypotheses about the clustering of CV risk factors. For example, in individuals as young as 18 years old, borderline increases in BP are associated with increased cholesterol, triglyceride, and insulin levels, a slightly high hematocrit value, a fast heart rate, and 22 pounds of extra weight.
In 1995, the National Institutes of Health convened investigators from various trials conducted by the National Heart, Lung, and Blood Institute (NHLBI) in diverse ethnic populations to determine whether the insulin resistance syndrome existed across populations and to determine the essential features of the syndrome. These populations included those from the Atherosclerosis Risk in Communities (ARIC) study in North Carolina, Mississippi, Minnesota, and Maryland; the Strong Heart study in 13 Native American communities; the Coronary Artery Risk Development in Young Adults (CARDIA) study in Birmingham, Alabama, and Oakland, California; a study in Cuban Americans and blacks from Miami, Florida; and the Framingham Heart Study among the largely European American residents of Framingham, Massachusetts, to determine the essential features of the syndrome. This convention of investigators reached a consensus that increased levels of triglycerides, low levels of HDL cholesterol, central obesity, and hyperinsulinemia have a definite statistical association with each other, constituting a syndrome. Other risk factors that were identified as contributors to the syndrome, although not at a level of statistical significance, were hyperuricemia, increased levels of PAI-1, hypertension, hyperdynamic circulation, increased levels of apolipoprotein B, and the presence of smaller, more dense LDL particles. Thus, consistent evidence from population-based epidemiologic studies exists for the presence of these clusters of major atherogenic risk factors in both genders and across all ages and ethnic groups examined.

**CV Risk Is Amplified in Diabetic Patients**

The long-term Multiple Risk Factor Intervention Trial (MRFIT) assessed the efficacy of a multifactorial intervention program in reducing CV mortality in hypertensive men 35 to 57 years old with no history of CVD at baseline.\(^9\) When the data from MRFIT were stratified by the number of additional major risk factors (increased systolic BP, elevated serum total cholesterol level, and cigarette smoking), CV mortality was seen to increase linearly over a 12-year period. Men with diabetes, however, were at much higher risk for CV mortality than were men without diabetes, despite any given number of additional risk factors (Figure 3).\(^10\)

Another interesting comparison emerged from a subgroup analysis of the MRFIT study. It is well known that blacks have higher rates of morbidity and mortality from diabetes and CVD than do European Americans. This difference held true, as expected, when data from nondiabetic enrollees of MRFIT were compared. However, the addition of diabetes to the clinical picture eradicated the differences between the ethnic groups.\(^10\)

The presence of diabetes also removes the differences between the genders in the prevalence of CVD.\(^11\) Because diabetic men and women are at similarly high risk for CV morbidity and mortality, women as well as men should be treated aggressively for all risk factors.\(^12\)

**Pharmacologic Therapy for High-Risk Hypertensive Patients**

Although all available antihypertensive medications effectively lower BP, effects on morbidity and mortality in long-term randomized controlled trials have been recorded for only two classes of drugs, diuretics and \(\beta\)-blockers. For this reason, the JNC VI recommended these agents as initial therapy for uncomplicated hypertension if no specific indications exist for the use of other classes of drugs.\(^1\) However, the JNC VI also stated that a patient’s risk profile and comorbid conditions should be considered when choosing an antihypertensive medication, even if the use of that medication is not yet supported by data from studies on long-term outcomes. For example, the use of angiotensin-converting enzyme (ACE) inhibitors is preferred for diabetic patients with proteinuria because members of this drug class moderate proteinuria and delay the progression of nephropathy.\(^1\) Recent studies also have suggested the advantages of ACE inhibitors over CCB in diabetic patients.\(^13,14\)

The Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial (FACET) compared the effects of the ACE inhibitor fosinopril with those of the CCB amlodipine on serum lipid levels and control of diabetes in hypertensive type 2 diabetic patients.\(^13\) The occurrences of major CV events were evaluated as...
secondary end points. No significant differences were found between the two treatments in terms of lipid profile or glucose control, although the fosinopril-treated patients had a lower risk of acute myocardial infarction (MI), stroke, or angina than did the amloidipine-treated patients.

In the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, the ACE inhibitor enalapril and the CCB nisoldipine were used to compare the effects of intensive versus moderate control of BP on the incidence and progression of diabetic vascular complications.\textsuperscript{14} In this trial, as in FACET, the ACE inhibitor was more beneficial than the CCB at reducing the number of CV events. In fact, after 67 months, the study’s Data Safety Monitoring Committee decided to switch the nisoldipine-treated hypertensive patients to open-label treatment with enalapril. These results support the hypothesis that blockade of the renin-angiotensin system provides a significant advantage in diabetic hypertensive patients.

Although the aforementioned smaller studies have suggested a benefit of ACE inhibitors in diabetics, the large-scale United Kingdom Prospective Diabetes Study Group (UKPDS)\textsuperscript{15} and the Hypertension Optimal Treatment (HOT) study\textsuperscript{16} both found that aggressive BP control in hypertensive diabetics, rather than any specific drug class, is essential to reducing CVD risk. The HOT study suggests a combination of medications (approximately three) is necessary to achieve the desired target of 80 mm Hg. Similarly, the UKPDS found that multiple antihypertensive medications are necessary to achieve aggressive BP targets. Further, there was equal benefit whether an ACE inhibitor or a \(\beta\)-blocker was used. Therefore, the benefits of specific antihypertensive medications conferring benefits other than lowering BP requires further elucidation.\textsuperscript{17}

**THE ARB**

It is tempting to extrapolate the benefits of the ACE inhibitors to the ARB, as both of these classes block the deleterious effects of angiotensin II. ACE inhibitors have been shown to reduce left ventricular hypertrophy in hypertensive patients\textsuperscript{18} and, more recently, so have ARB.\textsuperscript{19,20} Additionally, ACE inhibitors clearly have demonstrated favorable effects when used in patients after an MI\textsuperscript{21–23} and in the setting of congestive heart failure (CHF).\textsuperscript{24,25} Currently, three trials are investigating the advantages of ARBs in patients with CHF. The initial optimism from the Evaluation of Losartan in the Elderly (ELITE) study, that ARBs may be more useful in reducing morbidity and mortality than ACE inhibitors,\textsuperscript{26} has not been supported by the recent, larger ELITE II trial.\textsuperscript{27} Whereas the ELITE II trial compared an ACE inhibitor with an ARB, the Valsartan in Heart Failure Trial (ValHeFt)\textsuperscript{28} compares the effectiveness of a large dose of valsartan given to patients who, in most cases, are already receiving an ACE inhibitor. The Candesartan in Heart Failure (CHARM) study\textsuperscript{29} investigates the use of candesartan in different types of CHF either alone or in combination with ACE inhibitors. Results of these trials will more fully elucidate the value of ARB in treating CHF.

Another major advantage of the ARB, including valsartan, is their excellent safety and tolerability profile,\textsuperscript{30} which is comparable to that of placebo. In particular, the ARB do not produce dry cough, a bothersome side effect reported by 5% to 20% of patients who take ACE inhibitors.\textsuperscript{31}

Prospective outcome trials in which ARB are compared with ACE inhibitors or CCB in hypertensive patients are needed to demonstrate whether differences exist between these classes of agents in terms of morbidity and mortality.

**THE LOSARTAN INTERVENTION FOR ENDPOINT REDUCTION (LIFE) IN HYPTERTENSION STUDY**

LIFE compares the effects of the ARB losartan with the \(\beta_1\)-selective adrenergic blocker atenolol on CV morbidity and mortality in approximately 8300 patients with hypertension (defined as systolic BP of 160 to 200 mm Hg, diastolic BP of 95 to 115 mm Hg) and left ventricular hypertrophy. LIFE will continue until at least 2001. It is designed to have sufficient statistical power to detect differences of 15% in the incidence of combined CV morbidity and mortality. LIFE is also the first prospective study that has been designed with enough power to link the reversal of left ventricular hypertrophy with a reduction of major CV events.\textsuperscript{32}

**THE VALUE STUDY**

Approximately a quarter of a million patients are currently enrolled in hypertension clinical trials. One large trial currently under way is the Valsartan Antihypertensive Long-term Use Trial (VALUE). VALUE is a prospective, randomized, multinational trial to evaluate the effectiveness of the ARB valsartan and the third-generation CCB amlopidine\textsuperscript{33} in decreasing the incidence rates of acute MI, CHF, and sudden cardiac death in high-risk hypertensive patients. The primary end point of the study is time to the first event of cardiac morbidity or mortality. VALUE will include some 14,400 patients in more than 30 countries. The inclusion and exclusion criteria of VALUE are summarized in Table 1.\textsuperscript{33} The study will continue until 1450 of the enrolled patients die.\textsuperscript{33}

VALUE is specifically designed to enroll patients with a high-risk profile or predisposing factors, a feature that distinguishes it from virtually every other randomized controlled trial (RCT) conducted in hypertension. The JNC VI pointed out that most RCT are not true representations of clinical practice because
they typically exclude high-risk patients and enroll a study cohort that has a lower level of risk than that of the general population. Moreover, RCT focus primarily on prior end points, perhaps disregarding the other benefits of therapy, such as progression to disease end points, improved quality of life, reduced effect of comorbid conditions, and fewer lost workdays for illness.

VALUE is unique in that it will not only shed light on the potential protective value of the ARB valsartan and the third-generation CCB amlodipine in hypertensive patients, it will also assess the predictive power of the CV risk profile in a large population of treated hypertensive patients. This is an urgent need because high BP is a major public health issue, and the benefits of treating it have been proved. Only 27% of hypertensive Americans have their BP levels adequately controlled and rates of CV morbidity and mortality in hypertensive patients are still unacceptably high.

This review converges to an essential theme in treating high-risk hypertensive patients: aggressive control of BP is essential to reduce risk. This will likely be accomplished with a multidrug regimen. The attenuation of the deleterious effects of angiotensin II and excellent tolerability of the ARB class confer a distinct advantage for achieving aggressive BP goals. The results of the VALUE trial will determine whether valsartan has the ability to lower CVD risk through mechanisms other than lowering BP. The results of the VALUE study are anxiously anticipated in 2005.

REFERENCES


