Rationalizing the Treatment of Hypertension

Michael A. Weber

Management of hypertension in this country is confounded by continual changes in recommended target blood pressure (BP) goals and a nonhomogeneous patient population who have a variety of demographic and clinical characteristics that influence treatment. This paper focuses on three major elements in managing hypertension: BP and the importance of reducing it to acceptably low levels; concomitant risk factors or cardiovascular and renal target involvement; and drug therapy that may confer prognostic advantages beyond those predicted by BP effects. Am J Hypertens 2001;14:3S–7S © 2001 American Journal of Hypertension, Ltd.

Key Words: Hypertensive control, combination antihypertensive therapy, angiotensin converting enzyme inhibitors, calcium channel blockers.

It is important to determine the most logical approaches to the treatment of hypertension, particularly as it remains the most common condition that clinicians are called on to manage. But, as demonstrated by the length and complexity of the official published guidelines on this subject,1 devising a simple and consistent approach is far easier said than done. Practitioners are confronted by continuing changes in the recommended target blood pressure (BP) goals of treatment, and by the special requirements of numerous concomitant clinical conditions associated with hypertension. Newly developed drugs with innovative and exciting properties, albeit of uncertain clinical value, create further complexity. Add to this debates over such issues as the relevance and practicality of nonpharmacologic therapies, the costs of treatment, and the maze of arbitrarily restricted formularies from which clinicians must choose their treatments, and it becomes easier to understand why the management of hypertension in this country appears to fall far short of the ideal.2

Partly because of these problems it has become clear that hypertension is truly a more complicated and difficult condition than has been traditionally supposed. As evidence of this, the American Society of Hypertension recently set in motion the process by which appropriately qualified experts in this field will be formally designated as Hypertension Specialists. It is inevitable, none the less, that the majority of patients with hypertension will continue to receive their management from primary care physicians. Therefore, any attempts that are made to restructure our knowledge and understanding of hypertension into more logical headings can only be of value in improving treatment outcomes. This brief paper looks at one such classification. There are three major elements: first, the issues of BP itself and the importance of reducing it to acceptably low levels; next, the question of patient characteristics, which encompasses demographic factors such as age or race, and also the presence and influence of concomitant risk factors or cardiovascular and renal target organ involvement; and, finally, the properties of drugs, particularly those actions that might confer prognostic advantages beyond those predicted simply by BP effects.

Need to Achieve Blood Pressure Goals

The current Joint National Committee report (JNC-VI) recommends that BP in hypertensive patients should be reduced below 140/90 mm Hg.1 By the same token, any previously undiagnosed patient whose BPs are consistently above this level, and who does not respond to lifestyle modification, should be given drug treatment to achieve this goal. Patients with meaningful concomitant conditions or evidence for target organ damage probably should be treated to lower targets. For example, clinical trials in which hypertensives with diabetes were included have shown that optimal protection against major cardiovascular or renal end points is achieved when BP are driven to levels even lower than 140/90 mm Hg.3,4 Patients with evidence for renal disease, regardless of whether or not they are diabetic, also have better outcomes with lower BP.5 For diabetic patients, therefore, it is generally recommended that BP be reduced below 130/85 mm Hg, and for those with renal impairment evidenced by...
proteinuria, pressures should be reduced below 125/75 mm Hg.

**Combination Therapy Required to Achieve Blood Pressure Goals**

Unfortunately, practitioners with experience in managing these more complex patients will readily acknowledge that it is particularly difficult to effectively control their BP. Except for those relatively few patients whose pretreatment BP are already close to the target zone, monotherapy will rarely be adequate. Indeed, the clinical trials that demonstrated the outcomes benefits of aggressive BP control used anywhere between two and four drugs, typically in full doses, to achieve the full benefits of therapy.\(^3\)\(^-\)\(^5\) Specific drug classes that might be best in these various circumstances will be discussed later; but although angiotensin converting enzyme (ACE) inhibitors will generally be regarded as the cornerstone of such regimens, it is critical to remember that these difficult patients will almost invariably require addition of another agent, such as a calcium channel blocker (CCB) or a diuretic, to have a good chance of achieving BP targets. Moreover, for many patients with diabetes and renal insufficiency, thiazide diuretics may not be adequate and it might be necessary to use loop diuretics.

We have not been particularly successful in achieving adequate treatment goals and we do not have ready explanations for this disappointment. The National Health and Nutrition Examination Survey (NHANES)\(^2\) has shown that only one-quarter of hypertensive people in the United States have a BP below 140/90 mm Hg. Interestingly, the failure in about three-quarters of these individual cases lies with reducing the systolic blood pressure (SBP) below 140 mm Hg. This is a serious issue, especially as it is now so clear that the risk of cardiovascular end points in hypertension is tied up far more closely with increased SBP than with increased diastolic blood pressure.\(^6\) A study performed in Veterans Affairs (VA) Medical Centers in New England casts another light on this issue.\(^7\) It demonstrated that poor results could not be explained by high drug costs (the patients in that healthcare system received their medications free), nor by a lack of interest or availability of physicians (patients were seen an average of more than six times each year). What is noteworthy about both these findings is that almost half the hypertensive patients involved had SBP of 160 mm Hg or above, a level that triples the risk of cardiovascular events. These observations indicate either a lack of willingness by clinicians to use the strategies necessary to achieve reasonable BP control, or perhaps the true difficulty of getting BP down to acceptable levels in a large proportion of patients.

When physicians are asked to explain poor treatment results they generally refer to poor patient compliance. A recent scholarly review of this subject\(^8\) has cited evidence that patients themselves tend to blame forgetfulness and adverse drug effects as the main reasons for poor adherence to their treatment.\(^9\) In a further study it was noted that, whereas physicians believed that they had given patients comprehensive and compelling explanations of their hypertension and its need for treatment, the patients themselves in many instances appeared to have an incomplete understanding of what was being done for them.\(^10\)

Contrary to widely held beliefs, there is now some evidence that aggressive control of BP, even if it requires multiple antihypertensive agents, actually appears to improve quality of life.\(^11\) Some investigators have interpreted this finding as showing that hypertension per se may be symptomatic, and that reduction of BP with modern agents that do not produce meaningful side effects can, therefore, produce a net improvement in how patients feel. Another possibility is that once patients know that their BP have been effectively reduced, their satisfaction with the good results may give them a greater sense of confidence.\(^12\)

**Patient Characteristics Often Require Dual Mechanisms of Action**

Hypertension typically exists as a syndrome of cardiovascular risk factors, of which high BP is only one. Lipid abnormalities, insulin resistance, and changes in thrombotic factors are some examples of the risk factors. Cardiovascular changes that appear to be part of this syndrome are increases in left ventricular muscle mass, reduced endothelial function, reduced arterial compliance, and tendencies to hyperfiltration in the kidney.\(^13\) Moreover, these findings tend to cluster in families, suggesting a genetic or inherited factor that might underlie several or all of these findings.\(^13\) Partly for these reasons, drugs that are known to correct some of these changes, or at least not adversely affect them, have grown in popularity. The ACE inhibitors, angiotensin receptor blockers, and CCB may be examples of such drugs.

The JNC-VI report has gone to great lengths to identify those comitant conditions associated with hypertension that require the use of specific antihypertensive agents. These so-called compelling indications include diabetes mellitus, for which ACE inhibitors are the treatment of choice, and also congestive heart failure, again for which ACE inhibitors should be prescribed. Patients with clinical ischemic heart disease are good candidates for treatment with b-blockers or possibly CCB. These recommendations are based on evidence that these particular drugs offer benefits beyond their antihypertensive properties and thereby, are of value in managing the full clinical picture.

Other patient characteristics can also influence the approach to treatment. African American patients, for instance, appear to have better BP responses to such agents as diuretics and CCB than to ACE inhibitors or b-blockers. But there may be caveats to this simple approach, for recent evidence suggests that for African American pa-
tients with renal insufficiency and proteinuria, ACE inhibitors and β-blockers may be associated with improved clinical outcomes (unpublished data [presented at Annual Scientific Sessions, American Society of Nephrology, Toronto, 2000]). Large-scale clinical trials in elderly patients with isolated or predominant systolic hypertension have shown that diuretics and dihydropyridine CCB significantly reduce stroke and other major cardiovascular events.

Even body weight may be a determinant of drug choice. A recent reanalysis of data from the Systolic Hypertension in the Elderly Program (SHEP) has shown that the diuretic chlorthalidone was particularly beneficial in reducing mortality and major clinical events in overweight and obese patients, but was ineffective in conferring such benefits in lean hypertensives.14 This may help explain the apparently paradoxical observation that lean hypertensives in general have a poorer cardiovascular prognosis than obese hypertensives,15,16 and so raises the likelihood that obese and lean hypertensives have different underlying mechanisms that require different therapeutic approaches for optimal results.

**Drug Characteristics**

Debates over which class of drug should be used to initiate treatment in hypertensive patients is often irrelevant, for in the majority of patients it will be necessary to use a combination of agents to achieve BP goals. Even so, properties of the various drug classes may be of particular value in certain settings. A detailed discussion of drug properties is beyond the scope of this brief paper, but the following issues should be taken into account.

**Diuretics**

These agents are still widely used and form part of many effective drug combinations. In low doses the metabolic problems that traditionally were associated with these drugs tend to disappear or be only minimal. The best credentials for these agents lie in the elderly with systolic hypertension, for such pivotal trials as SHEP have shown that these agents have survival and clinical end point benefits in these patients.16 Diuretics are also inexpensive, another factor to be considered.

**β-Blockers**

These agents, like the diuretics, have been suggested by the JNC as good first-line choices for patients with uncomplicated hypertension. This is an interesting recommendation, based more on the ability of these agents to prevent strokes than to prevent coronary events in hypertension. In fact, it is interesting to consider that β-blockers are particularly valuable in the postmyocardial infarction setting and in congestive heart failure, conditions in which they have been shown to improve survival and reduce further coronary and other cardiovascular events. It is not entirely clear why these agents appear to be more effective at secondary prevention than primary prevention in hypertension.

**ACE Inhibitors**

These agents have now become the most popular class for the management of hypertension. Strangely, there is still no definitive clinical trial in hypertension in which these agents have been shown to have outcomes benefits. On the other hand, in every other cardiovascular indication in which they have been tested, notably congestive heart failure, the postmyocardial infarction setting, diabetic nephropathy, and in patients with any previous history of significant vascular events, there have been powerful cardiovascular and renal protective effects.17–20 The recent Heart Outcomes Prevention Trial (HOPE) has drawn particular attention to the ACE inhibitors, as it established their protective effects in patients with evidence for a wide range of previous cardiovascular events but without congestive heart failure or other conditions requiring ACE inhibitors by traditional criteria.20 The totality of the cardiovascular experiences with the ACE inhibitors, together with retrospective evidence of their value in hypertension, have combined to persuade most experts and clinicians that these drugs should be regarded as a good starting point for most patients with hypertension.

**Angiotensin Receptor Blockers**

These newer agents are designed to selectively block the AT₁ angiotensin II receptors, and have been shown to be efficacious in reducing BP. Moreover, they do not cause the problem of cough seen in up to 20% of patients taking ACE inhibitor, and thus have developed a deserved reputation for excellent tolerability. This probably explains the high persistency rates—in essence, the desire of patients to refill their prescriptions—that may contribute usefully to improving treatment compliance. Clinical end point trials with the angiotensin receptor blockers in hypertension are already underway, and results are expected by 2002. Already there is evidence that these agents are probably comparable to ACE inhibitors in their end point effects in patients with congestive heart failure, and soon there will be data on the effects of these agents in a broad array of cardiovascular conditions. If these clinical trials are positive, there will be a strong impetus to elevate the angiotensin receptor blockers to a prominent role in the management of hypertension.

**Calcium Channel Blockers**

These agents continue to be used widely for treating hypertension. The older very short-acting agents have now been discredited, chiefly because their acute but short-lived hemodynamic effects may create a situation in which heart attacks and strokes could actually be precipitated. However, the approved once-daily antihypertensive agents of this class have been shown to confer clear benefits. The
Systolic Hypertension in Europe (Syst-Eur) trial, performed in older patients with predominantly systolic hypertension, demonstrated that dihydropyridines reduce strokes and appear to reduce other cardiovascular end points as well. In addition, two recent hypertension clinical trials, using either a dihydropyridine or diltiazem, have shown that these agents are at least as effective as previously recommended conventional therapies (diuretics and β-blockers) in preventing clinical events. Because these drugs are effective in reducing BP in the elderly and in African Americans as well as in other groups of hypertensives, they remain an important part of the hypertension armamentarium.

**ACE Inhibitors/CCB—Newest Combination Treatment**

Combining agents from different pharmacologic classes results in additive hypertensive effects that are more effective than those observed with monotherapy. In addition to better BP control, use of these agents also results in a lower prevalence of dose-dependent side effects. This benefit occurs not only because these combinations use each of the agents in lower dosages (eg, amlodipine/benazepril), but also because the ACE inhibitor is able to prevent the edema that can be associated with CCB use. Moreover, because these agents provide BP control for 24 h, they may be given once daily, improving compliance. Another advantage to a fixed-dose combination is their cost, as the combination typically costs less than if each agent was prescribed separately. The Fosinopril Versus Amlodipine Cardiovascular Events Trial (FACET) trial demonstrated fewer cardiovascular events in patients with diabetic nephropathy receiving the ACE inhibitor fosinopril, compared to those receiving a dihydropyridine CCB, but the patients who received a combination of both agents demonstrated the best overall survival percentages after 30 months of therapy. Although these results are highly promising, there is a need for long-term trials to assess this combination’s effects on cardiovascular outcomes.

It is evident that treating hypertension is not a simple task and there is clearly a need for ongoing research to better define optimal strategies (eg, combination therapy) and perhaps develop newer antihypertensives agents that could allow us to improve our performance. The complexity of treating hypertension arises from the fact that patients with this condition are far from homogeneous and have a wide variety of demographic and clinical characteristics that must influence the approach to their therapy. Likewise, we have available a broad constellation of antihypertensive drugs with differing properties and attributes that, again, create difficulties in selecting a treatment regimen. It is worth noting that the recently completed Swedish Trial in Old Patients with Hypertension (STOP-2) trial compared the clinical end point effects of ACE inhibitors, CCB, diuretics, and β-blockers, and concluded that, overall, these four major classes were similarly effective.27

**Strategy to Better Blood Pressure Control**

Beyond these issues remains the fact that reducing BP still continues to be a primary part of antihypertensive therapy and continues to represent one of the major challenges in this field. It is necessary in most patients to use combination treatment, for our ability to find the perfect one drug to match an individual patient’s needs is rarely achieved.

**References**