Clinical Overview of Hypertension and Emerging Treatment Considerations

William C. Cushman

Managing hypertension is a complex undertaking, where even the definition of the disorder is subject to discussion. Recently, there has been controversy concerning the most appropriate measure to determine health risks associated with hypertension. In the past, diastolic blood pressure (DBP) was the prime measure for defining hypertension, but currently systolic blood pressure (SBP) and pulse pressure have gained favor. Evidence now suggests that all three measures should be considered as part of the hypertensive profile, with the patient’s age determining the relative importance of each.

Aggressive treatment of hypertension may reduce morbidity and mortality. Data from trials clearly indicate that, for all stages of hypertension, the goal should be a maximum SBP of \(<150\) mm Hg and a DBP of \(<90\) mm Hg, with DBP values as low as 70 mm Hg being safe. For individuals with diabetes mellitus, these target values should be even lower—SBP \(<140\) mm Hg and DBP \(<80\) mm Hg. As a significant number of deaths attributable to hypertension occur in patients who are not diagnosed as hypertensive but whose blood pressure (BP) is above the optimal level of 120/80 mm Hg, lowering BP levels in this group is recommended as well, with lifestyle modification being first-line therapy. Because controlling BP to \(<140/90\) mm Hg often requires the use of two or three agents, the tolerability of the entire regimen must be considered. However, with the multitude of antihypertensive drugs currently available, no patient’s BP should remain above the 150/90 mm Hg level. Am J Hypertens 2001;14:226S–230S © 2001 American Journal of Hypertension, Ltd.

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Hypertension is associated with increased risk of several cardiovascular complications,\(^1\) including stroke, coronary artery disease, and congestive heart failure (CHF). Because 24% of the US adult population currently has hypertension, the scope of this problem is extensive.\(^2\) Fortunately, effective management of hypertension can dramatically lower the incidence of cardiovascular events, morbidity, and mortality: appropriate treatment can reduce the incidence of heart failure by as much as 50% and stroke by as much as 40%.\(^3,4\)

Managing hypertension is a complex undertaking. Even defining the problem has proven difficult. Evidence of risk at lower levels of blood pressure (BP) has accrued during recent years,\(^5\) changing our understanding of what constitutes optimal BP. The importance given to particular BP measures in calculating risk is also subject to controversy; diastolic BP (DBP) has fallen out of favor as the primary determinant of the hypertensive state, to be replaced by systolic BP (SBP) and pulse pressure (PP—the difference between SBP and DBP).

Effective management of hypertension demands that guidelines and thresholds be established and treatment recommendations made for a condition that has demonstrated a consistent and graded correlation to risk of cardiovascular disease (CVD), with no well-defined cut points.\(^5,6\) The classifications and recommendations formulated by the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) serve as a useful guide for managing hypertension and are based in large part on outcomes data from numerous randomized controlled trials.\(^1\)

Relevance of Measures

There has been much controversy recently concerning the most appropriate measure to determine health risks associated with hypertension. Correlation between various measures and risk of CVD has been drawn. For a century, DBP was the prime measure upon which hypertension was defined and on which treatment recommendations were based. Mean arterial pressure has been considered as well, but currently SBP and PP have gained favor as the most relevant measures of BP. However, evidence now suggests

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From University of Tennessee College of Medicine, Memphis, Tennessee.

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that the three measures of DBP, SBP, and PP should be considered as part of the hypertensive profile, with the age of the patient determining the relative importance of each element.

In a recent analysis of the Framingham data, DBP remains the strongest predictor for cardiovascular risk in men and women aged less than 50 years, although SBP is also associated with increased risk. In patients less than 60 years of age, SBP and DBP are equally important in predicting risk. In patients aged 60 years and older, however, SBP and PP become the most important risk factors for morbidity and mortality due to CVD. The PP has the greatest weight in assessing risk in this age group, but it is almost always associated with systolic hypertension. At fixed systolic levels above 120 mm Hg, risk increases with increased PP where DBP is decreasing.

For individuals ≥60 years of age, when SBP and DBP are included in the same model, SBP is positively associated with risk and DBP is inversely related to risk. For any given systolic value, the lower the DBP, the higher the risk of CVD. Thus, in two individuals with identically elevated SBP, the one with isolated systolic hypertension (ISH) would be at greater risk for CHD than the one with combined systolic–diastolic hypertension. Fig. 1 demonstrates the combined influence of SBP and PP on coronary heart disease risk.

The inverse relationship between DBP and CVD risk is a result of physiologic changes that occur in the cardiovascular system with advancing age. Starting at middle age, the large arteries begin to stiffen, SBP increases, and DBP decreases. Parallel increases in SBP and DBP reflect an increase in peripheral vascular resistance.

**Treatment Goals**

**Prevention**

Prevention is the most effective method of managing hypertension. Overall, 41% of men and women with high-normal BP (SBP 130 to 139 mm Hg or DBP 85 to 89 mm Hg) will go on to develop sustained hypertension (SBP ≥140 mm Hg and DBP ≥90 mm Hg) within just 4 years. Equally important to consider is the fact that a significant number of deaths attributable to hypertension occur in patients who are not diagnosed as hypertensive but whose BP is above the optimal level of 120/80 mm Hg. Therefore, lowering BP levels even in the high-normal range is recommended.

In the population with high-normal BP, lifestyle modification is the appropriate method to reduce the risk of hypertension-associated cardiovascular events. Regular physical exercise—at least 30 min of activity three times per week—and a low-fat, high-fiber diet with an emphasis on fruits and vegetables can decrease SBP by 5 mm Hg and DBP by 3 mm Hg. Weight reduction can lower BP, and reduction of sodium intake by 44 mmol/24 h can reduce DBP by 0.9 mm Hg and SBP by 1.7 mm Hg. In heavy drinkers, SBP or DBP can be affected by reducing alcohol consumption. For every one less drink per day consumed, a drop of 1 mm Hg can be achieved.

![FIG. 1. Joint influences of systolic blood pressure (SBP) and pulse pressure (PP) on coronary heart disease (CHD) risk (Framingham Heart Study). Participants >50 years old. Adapted with permission from Franklin SS, et al: Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. Circulation 1999;100:354–360.](image1)

![FIG. 2. Four-year progression to hypertension by age (Framingham Heart Study). 95% confidence interval; optimal blood pressure (BP) <120/<80 mm Hg; normal BP <130/<85 mm Hg; high normal BP, systolic 130 to 139 mm Hg or diastolic 85 to 89 mm Hg. Data from Vasan RS, et al. J Am Coll Cardiol 2000;35(suppl A):291.](image2)
end-organ damage, or other risk factors.\textsuperscript{1} In addition, JNC VI recommends drug therapy for most individuals with stage 1 systolic hypertension if lifestyle changes are not successful in achieving SBP <140 mm Hg.\textsuperscript{1}

In stage 2 and stage 3 hypertension, immediate initiation of therapy with antihypertensive medication is recommended, even in the absence of other risk factors. Again, the goal is to bring BP to <150/90 mm Hg. The JNC VI recommendations are somewhat more rigorous, with the goal of maintaining SBP <140 mm Hg and DBP <90 mm Hg.\textsuperscript{1} This is certainly a reasonable goal, but at the very least, BP should be brought to <150/90 mm Hg.

**Hypertensive Patients With Diabetes**

Patients with comorbid diabetes and hypertension are at increased risk for CHD compared with those who have either risk factor alone.\textsuperscript{18} Therefore, recommendations for this group call for more stringent BP control. Data from the United Kingdom Prospective Diabetes Study (UKPDS) and the HOT study indicate that target BP should be SBP 140 mm Hg and DBP 80 mm Hg.\textsuperscript{14,18} Tight control of BP in this trial resulted in a 24% reduction of all diabetes-related end points, a 37% reduction in microvascular complications, a 44% reduction in stroke, and a 32% reduction in diabetes-related death.\textsuperscript{18} However, the smaller Appropriate Blood Pressure Control and Diabetes (ABCD) trial did not show that a greater reduction in BP further decreased the incidence of microvascular or macrovascular events.\textsuperscript{19} More research is needed on whether lower BP goals are appropriate for patients with type 2 diabetes.

**Antihypertensive Drugs**

Early trials of diuretic or \(\beta\)-blocker therapy in the treatment of diastolic hypertension demonstrated reduced rates

### Table 1. Placebo-controlled systolic hypertension trials in the elderly

<table>
<thead>
<tr>
<th>Event</th>
<th>SHEP ((n = 4,736))</th>
<th>STOP ((n = 1,627))</th>
<th>MRC Elderly ((n = 4,396))</th>
<th>Syst-Eur ((n = 4,695))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial active drug</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>36*</td>
<td>47*</td>
<td>31*</td>
<td>42*</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>27*</td>
<td>13</td>
<td>44*</td>
<td>30</td>
</tr>
<tr>
<td>Heart failure</td>
<td>49*</td>
<td>51 (NR)</td>
<td>NR</td>
<td>29</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>32*</td>
<td>40*</td>
<td>35*</td>
<td>31</td>
</tr>
<tr>
<td>Mortality</td>
<td>13</td>
<td>43*</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td><strong>Event Reduced (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCTZ/Amiloride or (\beta)-blocker</td>
<td></td>
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</tbody>
</table>

HCTZ = hydrochlorothiazide; MRC Elderly = Medical Research Council trial of treatment of hypertension in older adults; NR = not reported; SHEP = Systolic Hypertension in the Elderly Program; STOP = Swedish Trial in Older Persons with Hypertension; Syst-Eur = Systolic Hypertension in Europe Trial. Reprinted with permission from Cushman WC: Geriatric hypertension, in Massry SG, Glassock RJ (eds): Massry & Glassock’s Textbook of Nephrology, ed 4. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 1190–1191.\textsuperscript{20}

* Significant reduction.
of cardiovascular events and mortality with these agents (Table 1). Although effective in younger patients, β-blockers have not been as consistently effective as diuretics in the elderly. This finding is the basis for the JNC VI recommendation that β-blockers not be used as monotherapy in the elderly, except in cases of comorbid conditions necessitating their use. Diuretics are preferred initial therapy in the elderly, and dihydropyridine calcium channel blockers (CCB) are an alternative in ISH.

In the first of the large studies comparing newer with older classes of antihypertensive agents, the Captopril Prevention Program (CAPP), captopril appeared as effective as conventional therapy with diuretics or β-blockers in reducing cardiovascular events. However, captopril therapy was associated with a possible increased risk of stroke in this study. This increased risk of stroke with angiotensin converting enzyme (ACE) inhibitors has not been reported in any other trial.

Another trial, the Swedish Trial in Old Patients with Hypertension-2 (STOP-2), compared ACE inhibitors with CCB, diuretics, or β-blockers. The ACE inhibitors and CCB appeared to be as effective as conventional therapy. Differences were noted, however, between the ACE inhibitors and the CCB for the end points of myocardial infarction and incidence of heart failure, with frequencies lower for both in the patients receiving ACE inhibitors. Given that this was not the primary analysis and there were multiple comparisons involved, a definitive conclusion cannot be made about this comparison. However, the results raise some concerns about CCB that bear watching.

With approximately 42,000 patients enrolled, the Antihypertensive Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) currently under way promises to provide a large amount of relevant data on the use of CCB, α-adrenergic blockers, ACE inhibitors, and diuretics in the treatment of hypertension. The α-blocker arm of the trial has been discontinued because of a significantly higher (25%) incidence of combined CVD events and twice as much CHF in the doxazosin group than in the chlorthalidone group (Fig. 3). The study design does not permit a conclusion of whether this difference is the result of chlorthalidone’s being more effective or doxazosin’s being less effective. A statistically significant difference was seen in the incidence of CVD events.

Final Considerations—Therapeutic Differences

Data from the major clinical trials suggest that there are differences in efficacy and safety between the various classes of antihypertensive drugs. The benefits of these agents must be carefully weighed against their contraindications. In the case of the α-blockers, for example, their use in patients with benign prostatic hyperplasia (BPH) is supported by clinical data from the large-scale Hypertension and BPH Intervention Trial (HABIT), however, α-blockers should not be used as monotherapy in hypertension in view of the recent ALLHAT findings.

Dosing convenience and cost must be considered in any treatment regimen. Because controlling BP to <140/90 mm Hg requires the use of two or three agents on average, the tolerability of the entire regimen, as well as the individual drugs involved, must also be considered. Perhaps equally important in controlling BP is educating the patient about the risks associated with hypertension, the importance of reaching the lower BP goal, and the likelihood that multiple medications may be required. Patients who are well informed are much more likely to adhere to treatment regimens. Achieving the recommended BP goals is critical in reducing the health risks associated with hypertension. With the multitude of antihypertensive drugs currently available, no patient’s BP should remain above the 150/90 mm Hg level.

References


