Antihypertensive Therapy and Cardiovascular Disease
Impact of Effective Therapy on Disease Progression

Henry R. Black

Hypertension is the most ubiquitous risk factor for developing cardiovascular disease, which is the leading cause of death in the United States. Results from clinical trials have established the benefit of antihypertensive therapy in preventing the morbidity and mortality associated with high blood pressure, including stroke, coronary heart disease, and heart failure. Treatment is effective in the elderly, a significant consideration because the percentage of the elderly population is growing rapidly. This article reviews the impact of antihypertensive treatment on cardiovascular disease and treatment endpoints. Am J Hypertens 1998;11:3S–8S © 1998 American Journal of Hypertension, Ltd.

KEY WORDS: β-Blocker, blood pressure, cardiovascular disease, hypertension, J-curve.

According to results from the Third National Health and Nutrition Examination Survey, an estimated 43 to 50 million adults in the United States have elevated blood pressure, defined as systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg.1 The prevalence of hypertension increases with age, is higher in blacks than in whites, and is higher in men until approximately 60 years of age, when the prevalence of hypertension becomes higher in women (Figure 1).1,2 Patients with hypertension experience more strokes, myocardial infarctions, renal insufficiency, and episodes of heart failure than do those with normal blood pressure.

Numerous studies have examined whether blood pressure reduction with antihypertensive therapy can prevent cardiovascular disease progression. Antihypertensive therapy has clearly prevented strokes and coronary heart disease events.3 Until recently, the effectiveness of treatment in elderly patients has been questioned. These concerns have directed research to determine the benefit of antihypertensive therapy in the elderly, the role of antihypertensive therapy in prevention of coronary heart disease, appropriate treatment, and the endpoints of therapy.

ANTIHYPERTENSIVE THERAPY IN THE ELDERLY

More than 60% of the American population aged 60 years or older have hypertension.2,4 Because of the lack of controlled large-scale trials, there had been some reluctance to treat hypertension in elderly patients.5 However, trials conducted in the last decade have now confirmed that the risk of cardiovascular disease can be significantly reduced in this population with antihypertensive therapy.

Overview of Trials Evidence supporting the use of antihypertensive therapy in the elderly can be found in the results from the European Working Party on High Blood Pressure in the Elderly Trial (EWPHE),6 the Hypertension Detection and Follow-up Program...
(HDFP), the Medical Research Council (MRC) Trial of treatment of hypertension in older adults, the Systolic Hypertension in the Elderly Program (SHEP), and the Swedish Trial in Old Patients with Hypertension (STOP) (Table 1). With the exception of EWPHE, studies in the elderly demonstrate significant reduction in the incidence of stroke with antihypertensive therapy ($P < .05$). The EWPHE study was stopped early as there was a reduction in overall cardiovascular events and a clear trend toward fewer strokes in the actively treated group was noted. In addition, all studies indicate that treatment significantly reduces the relative risk for developing all cardiovascular diseases. In all studies prior to 1997, diuretics, β-blockers, or a combination of diuretics plus β-blockers were the only antihypertensive therapies used in elderly indi-

**TABLE 1. RESULTS OF ANTIHYPERTENSIVE TRIALS IN THE ELDERLY**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EWPHE</th>
<th>HDFP</th>
<th>MRC</th>
<th>SHEP</th>
<th>STOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
<td>840</td>
<td>2376</td>
<td>4396</td>
<td>4736</td>
<td>1627</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>&gt;60</td>
<td>60–69</td>
<td>65–74</td>
<td>60–80+</td>
<td>70–84</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>182/101</td>
<td>170/101</td>
<td>185/91</td>
<td>170/77</td>
<td>195/102</td>
</tr>
<tr>
<td>Relative risk (treated vs control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>0.64</td>
<td>0.56*</td>
<td>0.75*</td>
<td>0.67*</td>
<td>0.53*</td>
</tr>
<tr>
<td>CAD</td>
<td>0.80</td>
<td>0.85</td>
<td>0.81</td>
<td>0.73*</td>
<td>0.87†</td>
</tr>
<tr>
<td>CHF</td>
<td>0.78</td>
<td>NR</td>
<td>NR</td>
<td>0.45*</td>
<td>0.49*</td>
</tr>
<tr>
<td>All CVD</td>
<td>0.71*</td>
<td>0.84*</td>
<td>0.83*</td>
<td>0.68*</td>
<td>0.60*</td>
</tr>
</tbody>
</table>

BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cardiovascular disease; EWPHE, European Working Party on High Blood Pressure in the Elderly; HDFP, Hypertension Detection and Follow-Up Program; MRC, Medical Research Council; NR, not reported; SHEP, Systolic Hypertension in the Elderly Program; STOP, Swedish Trial in Old Patients With Hypertension.

* $P < .05$.

† Myocardial infarction only.

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ANTIHYPERTENSIVE THERAPY AND CARDIOVASCULAR DISEASE

vinduals. A recent trial in elderly subjects with isolated systolic hypertension (Syst-Eur) reported that the risk for strokes was reduced with the calcium channel blocker nitrendipine and enalapril and a diuretic, if necessary, to achieve goal blood pressures. Treatment Effects on Stroke and Myocardial Infarction Elevated blood pressure contributes to the occurrence of more than 500,000 strokes and 1 million myocardial infarctions annually. Elderly individuals are at increased risk because of the high prevalence of hypertension as well as other cardiovascular risk factors in this segment of the population. Four recently published clinical trials have clearly shown the benefits of therapy in older hypertensives.

In the Medical Research Council Trial, subjects with hypertension were randomized to placebo or treatment with either atenolol or hydrochlorothiazide and amiloride. At the end of the study, the active treatment group experienced a 25% reduction in stroke (P = .04) and a 19% reduction in coronary events compared with the placebo group. Further analysis showed that patients who received diuretic therapy had a significantly reduced risk of stroke (P = .04), coronary events (P = .0009), and all cardiovascular events (P = .0005), whereas patients who received β-blockers did not show significant risk reductions for these endpoints.

The Systolic Hypertension in the Elderly Program (SHEP) was the first study to establish that antihypertensive treatment can prevent stroke and myocardial infarction in elderly patients with isolated systolic hypertension. The prevalence of isolated systolic hypertension, defined as systolic blood pressure >160 mm Hg and diastolic blood pressure <90 mm Hg, is known to increase with age. Isolated systolic hypertension may cause greater risk for cardiovascular disease than either elevated diastolic blood pressure or elevated diastolic and systolic blood pressures combined. In SHEP, patients were treated with chlorthalidone and atenolol or reserpine, if needed, or placebo for an average of 4.5 years. Those receiving drug treatment experienced a highly and statistically significant 36% reduction in incidence of stroke and, similarly, a significant 27% reduction in incidence of nonfatal and fatal myocardial infarction. In addition, there was a favorable trend with lower all-cause mortality, but SHEP was not statistically powered (neither large nor long enough) to prove that active treatment reduced all-cause mortality. Syst-Eur confirmed the benefit of treating older hypertensives with isolated systolic hypertension.

The Swedish Trial in Old Patients With Hypertension (STOP) confirmed that antihypertensive therapy can also benefit “older” elderly patients. Patients aged 70 to 84 years with diastolic hypertension were randomized to receive either placebo or active treatment consisting of a β-blocker or a diuretic. Patients on active treatment experienced fewer strokes and stroke-related deaths (P = .0081) as well as a lower incidence of the treatment endpoints (eg, myocardial infarction, stroke, or other cardiovascular-related death) (P = .0079).

ANTIHYPERTENSIVE THERAPY IN YOUNGER PATIENTS

The risk of cardiovascular disease at any blood pressure level is greater in the elderly than in a younger population, and antihypertensive therapy in the elderly produces a more pronounced effect on the reduction in incidence of cardiovascular events than it does in those under 60 years of age. Nevertheless, the benefit of antihypertensive therapy is clear in younger subjects, but because the absolute risk of cardiovascular events is lower, the benefit of treatment in younger patients requires a larger sample size to demonstrate.

The effects of antihypertensive therapy on all-cause mortality in more than 10,000 patients with hypertension were evaluated in HDFP. Patients were randomized to receive either a rigorous special care regimen (SC or stepped-care) or routine care in the community (RC or referred-care). Those randomized to stepped care received antihypertensive medication to decrease diastolic blood pressure to a predetermined goal, whereas those randomized to referred care received whatever treatment to whatever goal their community medical practitioners felt was most appropriate.

At the end of the formal trial (5-year follow-up), there was an overall lower incidence of all-cause mortality in patients between 30 and 59 years of age than in older patients (60 to 69 years) for both the stepped-care and referred-care groups (Table 2). The benefit of stepped care was apparent in patients >50 years of age at both follow-up points, but in patients between 30 and 49 years of age the benefit of stepped care was observed only after an 8.3-year follow-up. Younger individuals with hypertension are at a lower immediate risk of mortality and the benefit of antihypertensive therapy takes longer to become apparent. Nevertheless, treatment of hypertension in the young may prevent disease progression and reduce cardiovascular mortality in the future.

ANTIHYPERTENSIVE THERAPY AND HEART FAILURE

According to the National Heart, Lung and Blood Institute, more than 4.7 million Americans have heart failure, and approximately 465,000 new cases are estimated to occur each year. The prevalence of heart failure increases with age and doubles each decade after 50 years of age. The 5-year survival rate in a recent study from Framingham was 24% for men and
was greatest in those who were randomized to chlorthalidone. Patients who received pharmacologic treatment obtained significantly lower blood pressures and lower rates of cardiovascular events.

### TREATMENT ENDPOINTS FOR ANTIHYPERTENSIVE THERAPY

Whether there is a specific limit to the benefit from reducing diastolic blood pressure is a controversial issue. Past studies support a linear relationship between systolic blood pressure and cardiovascular morbidity and mortality. The greater the blood pressure reduction, the lower the risk for cardiovascular events in patients with hypertension. However, there may be a point at which the rates of coronary disease rise. This hypothesis has been called the J-curve.\(^{22}\)

#### J-Curve Hypothesis

The J-curve hypothesis proposes that the risk of coronary heart disease events increases if treatment reduces the diastolic blood pressure below a critical threshold value, usually estimated to be 85 mm Hg. Although randomized controlled trials have not yet been completed to confirm or refute this hypothesis, a metaanalysis has examined 13 studies and suggests that the J-curve hypothesis could be valid.\(^{22}\) This metaanalysis included more than 48,000 patients with diastolic blood pressures between 90 and 124 mm Hg at entry. The follow-up duration ranged from 4 to 12 years. Results were not significant for a J-curve relationship between diastolic blood pressure and stroke, but in 10 of the 13 studies there was a significant J-curve relationship between diastolic blood pressure and coronary heart disease.

The authors could not identify whether the J-curve hypothesis was specific to any subgroup, such as gender, race, or smokers. Nevertheless, continuing antihypertensive treatment to a target below 85 mm Hg was found to increase the risk of cardiovascular disease. The J-curve hypothesis is physiologically plausible; coronary arteries are perfused during diastole, and low flow could lead to thrombosis.

There is another way to interpret the data showing increased risk in those with diastolic blood pressure <85 mm Hg. Evaluation of a large cohort of men with hypertension confirmed many earlier observations that systolic blood pressure is a stronger predictor of risk for coronary heart disease and stroke than is diastolic blood pressure.\(^{23}\) Relative risk in this cohort was proportionately higher at every level of increase in systolic blood pressure than for diastolic blood pressure. The Third National Health and Nutrition Examination Survey reports that the average diastolic blood pressure in the United States population increases until approximately 55 years of age and then begins to decrease.\(^{1}\) However, systolic blood pressure rises throughout as the population ages. With this trend, the gap between diastolic blood pressure and

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### TABLE 2. RESULTS OF ALL-CAUSE MORTALITY FOR STEPPED-CARE AND REFERRED-CARE PATIENTS, STRATIFIED BY AGE AT ENTRY, AT 5 AND 8.3 YEARS OF FOLLOW-UP

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>N</th>
<th>5 Years</th>
<th>8.3 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SC</td>
<td>2427</td>
<td>81</td>
<td>152</td>
</tr>
<tr>
<td>RC</td>
<td>2371</td>
<td>82</td>
<td>173</td>
</tr>
<tr>
<td>50–59*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SC</td>
<td>1856</td>
<td>116</td>
<td>220</td>
</tr>
<tr>
<td>RC</td>
<td>1912</td>
<td>160</td>
<td>300</td>
</tr>
<tr>
<td>60–69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SC</td>
<td>1202</td>
<td>153</td>
<td>302</td>
</tr>
<tr>
<td>RC</td>
<td>1172</td>
<td>179</td>
<td>312</td>
</tr>
</tbody>
</table>

RC, referred-care patients; SC, stepped-care patients.

* \(P < .01.\)

(Modified from Hypertension Detection and Follow-up Program Cooperative Group,\(^{15}\) with permission. © 1988 American Medical Association.)
systolic blood pressure, or the pulse pressure, steadily increases, such that older individuals have wider pulse pressures than do younger individuals. Diastolic blood pressure falls because of progressive stiffening and loss of compliance of large arteries due to worsening atherosclerosis. The risk of a lower diastolic blood pressure noted in the aforementioned trials may not, in fact, be a result of excessive therapy but rather of the problems associated with worsening atherosclerosis that are manifested clinically by a widened pulse pressure.

Widened Pulse Pressure A study by Madhavan and colleagues24 showed that the incidence of cardiovascular disease was higher in patients who had wide pulse pressures. In this study, more than 2,000 patients, all of whom received similar antihypertensive treatment, were stratified into one of three tertiles based on posttreatment pulse pressure: tertile I, ≤46 mm Hg; tertile II, 47 to 62 mm Hg; and tertile III, ≥63 mm Hg. After an average follow-up of 5 years, cardiovascular events occurred most frequently in patients with the widest pulse pressures or, in this case, tertile III. In fact, 56% of all myocardial infarctions, 48% of all strokes, and 57% of all deaths due to cardiovascular disease occurred in patients in tertile III. When the diastolic blood pressure was compared specifically to the incidence of myocardial infarction at both the lower and higher levels of the fall in diastolic blood pressure (Figure 2). A further analysis that replaced diastolic blood pressure by tertiles of relative falls in systolic blood pressure revealed no significant differences in the incidence of myocardial infarctions. These data suggest that a wide pulse pressure is independently associated with cardiovascular complications.

Results from a study by Perry and colleagues25 provide additional insight concerning widened pulse pressure by comparing its significance to the incidence of end-stage renal disease. Blood pressure is itself an important predictor of end-stage renal disease, and elevated pressures have been associated with even subclinical renal dysfunction. In this analysis of almost 12,000 male veterans who were followed for approximately 14 years, wider pulse pressures significantly correlated with increasing risk for end-stage renal disease. In my view, the “J-curve” is a clinical marker of individuals who have more severe atherosclerosis and are at greater risk of cardiovascular disease. When complete in late 1997, the Hypertension Optimum Treatment (HOT) Study will tell us definitively if outcome can be improved by reducing diastolic blood pressure to <90 mm Hg, <85 mm Hg, or <80 mm Hg.

CONCLUSION Hypertension is an early, modifiable, risk factor for cardiovascular disease. By aggressively controlling

![Figure 2. Incidence of myocardial infarction by tertile of pretreatment pulse pressure and in-treatment diastolic blood pressure fall (reproduced from Madhavan et al,24 with permission. © 1994 American Heart Association.).](https://academic.oup.com/ajh/article-abstract/11/S1/3S/145184/15843158)
and maintaining blood pressure at normal levels in patients with hypertension, the incidence of cardiovascular morbidity and mortality can be decreased. Studies have demonstrated that antihypertensive therapy in patients with elevated blood pressure (regardless of age) is also significant in reducing the risk of cardiovascular complications. Furthermore, the earlier hypertension is detected and treated, the lower the risk for potential cardiovascular complications. Therapy should be individualized in each patient based on overall risks and benefits. This suggests that even normotensive individuals with other risk factors, such as individuals with diabetes mellitus or smokers with unfavorable family histories, may be candidates for antihypertensive treatment.

REFERENCES


