The Burden of Cardiovascular Disease: Following the Link From Hypertension to Myocardial Infarction and Heart Failure

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Cardiovascular disease (CVD) is an enormous health care burden in the United States (US) and is responsible for approximately 40% of all US deaths annually. Heart failure (HF) represents the final stage of the continuum of CVD and is increasing in incidence. Between 1970 and 2000, hospital discharges for HF in the US increased 145%. This trend appears to be related to rising life expectancy and the aging of the population. Once HF develops, the long-term prognosis continues to be dismal.

Hypertension is a major risk factor for CVD and the most common risk factor for the development of HF. The results of clinical trials such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) have helped to clarify the importance of optimizing antihypertensive therapy to reduce CVD risks and development of HF. The trial also confirmed the need for multiple antihypertensive medications to reach recommended blood pressure (BP) goals in most patients. Aggressive lowering of BP is critical to help reduce the risk of CVD and help prevent the development of HF.

Key Words: Hypertension, heart failure, antihypertensive therapy, β-blockers.
The prevalence of heart failure (HF) rises with increasing age. Before age 65 years, rates of HF in men are roughly twice those in women, but these rates are approximately equal in both sexes after the age of 65 years.1

- Prehypertension: SBP of 120 to 139 mm Hg or DBP of 80 to 89 mm Hg
- Hypertension: Stage 1: SBP 140 to 159 mm Hg or DBP 90 to 99 mm Hg; Stage 2: SBP ≥160 mm Hg or ≤100 mm Hg

These classifications are based on the mean of two seated BP readings on each of two or more office visits.

The JNC 7 classifications reflect recent data showing that hypertension plays a central role in the progression of CVD. A recent study in the Framingham Heart Study population of men and women aged 55 to 65 years who were free of hypertension at baseline (n = 1298) found that the residual lifetime risk of developing hypertension was 90%.4 The high lifetime risk for hypertension was similar for men and women. More than one half of the 55-year-old participants and approximately two thirds of the 65-year-old participants developed hypertension within 10 years of follow-up, indicating the importance of adopting lifestyle changes for maintaining optimal BP and preventing the development of hypertension.

Hypertension is the most common risk factor for the development of HF, the final stage in the continuum of CVD.2 Uncontrolled high BP, as well as other closely associated CV risk factors such as obesity, diabetes, smoking, and dyslipidemia, can lead to left ventricular hypertrophy (LVH) and/or MI, progressive diastolic and/or systolic dysfunction, and eventually to HF and death. Treatment of hypertension has been shown to reduce the risk of developing HF. The Systolic Hypertension in the Elderly Program (SHEP) study, for example, showed that antihypertensive therapy in elderly subjects with isolated systolic hypertension decreased HF rates by 49%.5

Issues in Antihypertensive Therapy

Antihypertensive therapy is well established to reduce the risk of CV morbidity and mortality. However, the optimal choice for initial pharmacotherapy for hypertension is uncertain. Earlier clinical trials documented the benefit of lowering BP using primarily thiazide diuretics or β-blockers (BB). After these studies, several newer classes of antihypertensive agents such as angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers (CCB), α-adrenergic blockers (α-blockers), and more recently, angiotensin II receptor blockers (ARB) became available. Over the past decade, major placebo-controlled trials have documented that ACE inhibitors and CCB reduce CV events in hypertensive individuals. However, their relative effectiveness compared with older, less expensive agents remained unclear.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was conducted to investigate the comparative effects of various antihypertensive therapies on CV morbidity and mortality.6 The main objective of this randomized, double-blind study was to compare the effects on outcomes of antihypertensive therapy initiated with the thiazide diuretic chlorthalidone, the CCB amlodipine, the ACE inhibitor lisinopril, or the α-blocker doxazosin (the doxazosin arm was discontinued early because of a higher incidence of new-onset HF).6 The primary outcome was the combined incidence of fatal CHD and nonfatal MI. Secondary outcomes were all-cause mortality, stroke, combined CHD (CHD, coronary revascularization, or hospitalized angina), combined CVD (CHD, stroke, angina, HF, or peripheral arterial disease), LVH, renal disease, improved health-related quality of life, and reduced major costs of medical care.

Data from ALLHAT included the 33,357 hypertensive patients who received chlorthalidone, amlodipine, or lisinopril and who were treated to a BP goal of <140/90 mm Hg and followed for an average of 4.9 years.6,7 All participants were aged ≥55 years (mean, 67 years) and had hypertension and at least one other CV risk factor. For patients who did not attain goal BP with the starting drug, the study investigator could add the step 2 agents atenolol, clonidine, or reserpine. The step 3 agent provided by the study was hydralazine, to be added if BP was still not at goal early because of a higher incidence of new-onset HF).6 The primary outcome was the combined incidence of fatal CHD and nonfatal MI. Secondary outcomes were all-cause mortality, stroke, combined CHD (CHD, coronary revascularization, or hospitalized angina), combined CVD (CHD, stroke, angina, HF, or peripheral arterial disease), LVH, renal disease, improved health-related quality of life, and reduced major costs of medical care.

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Results for the primary outcome were similar in all three treatment groups. In secondary outcomes, however, subjects treated with a chlorthalidone-based regimen had a 38% lower risk of HF compared with the amlodipine group, and a 19% lower risk of HF compared with the lisinopril arm. Treatment with doxazosin doubled the risk of HF, compared with chlorthalidone (P < .0001), resulting in the early termination of the doxazosin arm. Risks of
cumulative event rates for HF hospitalization and fatal HF in subjects in the chlorthalidone group were lower by 69%, 35%, and 11% compared with patients in the doxazosin, amlodipine, and lisinopril groups, respectively (Fig. 2). These HF outcomes in favor of chlorthalidone were consistent across all subgroups, including age <65 or ≥65 years, men and women, African American and non-African American, and diabetic and nondiabetic groups.

The lower risk for HF with chlorthalidone-based therapy may be explained by differences in BP reductions. Compared with the chlorthalidone group, mean SBP was significantly higher in the amlodipine arm (1 mm Hg; \( P = .03 \)) and in the lisinopril group (2 mm Hg; \( P < .001 \)), after 4.9 years (Fig. 3). Mean SBP was also higher in the doxazosin arm compared with the chlorthalidone group (2 mm Hg) after 4 years.\(^6\) Moreover, reductions in BP occurred more quickly in the chlorthalidone arm than in the other arms, and the differences observed in the development of HF began early as well.

Conclusions

Optimizing control of hypertension is critical to help reduce the associated risks of CVD and the development of HF. Reflecting the findings of ALLHAT and other large-scale hypertension studies, the JNC 7 appropriately emphasizes the importance of achieving BP control quickly, which often requires the use of multiple antihypertensive agents.\(^3\)

References