Hypertension Grand Rounds

Management of Hypertension in the Very Elderly Patient

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Abstract—This Hypertension Grand Rounds discusses pharmacological treatment of hypertension in individuals who have survived 9 decades on earth. This rapidly growing group of relatively active and healthy elderly people is at high risk for hypertension, its treatment, and its adverse consequences, including stroke and heart failure. In this age group, the most common abnormality is elevated systolic blood pressure, which is much more predictive of stroke and heart disease death after 53 years of age. With the possible exception of the Antihypertensive and Lipid Lowering to prevent Heart Attack Trial (ALLHAT), recent clinical trials have emphasized the overriding importance of lowering blood pressure rather than the specific agent chosen to begin therapy. In 1999, a metaanalysis of 7 clinical trials that enrolled 1670 subjects >80 years of age indicated that active antihypertensive drug therapy significantly reduced stroke by 34% and heart failure by 39% but was associated with a nonsignificant 6% increase in mortality. The HYpertension in the Very Elderly Trial (HYVET) will enroll 2100 patients >80 years of age and will compare 2 groups randomized to indapamide±perindopril versus placebo±placebo for incident stroke during 5 years of follow-up. This study should answer lingering questions about whether active antihypertensive therapy is associated with a major and significant reduction in cardiovascular morbidity and mortality in this age group as it clearly does in younger hypertensives. Its choice of a diuretic as initial therapy is consistent with other trials, but chlorthalidone is the drug with the most compelling evidence in large US trials that included very elderly patients. (Hypertension. 2004;44:800-804.)

Key Words: antihypertensive therapy ■ clinical trials ■ elderly ■ population

Hypertension is the most common chronic condition for which Americans see a health care provider and is increasing in prevalence as Americans age and grow larger (in waist circumference and body mass index). The World Health Organization recently concluded that hypertension is the most common attributable cause of preventable death in developed nations and is increasing in importance in developing countries. The most powerful risk factor for death, cardiovascular death, and hypertension in large populations is age. Therefore, it is not surprising that the lifetime risk of developing hypertension among 55- and 65-year-old individuals in the Framingham Heart Study is >90%. Current demographic trends in the United States highlight the growth and importance of the demographic subgroup of very elderly people (defined for this purpose as those >80 years of age). According to the US Census Bureau, from 1990 to 2000, the number of Americans >80 years of age increased by 31%. During the next 20 years, greater expected longevity among “baby boomers” will result in ≈15 million people >80 years of age, or 4.5% of the population (from its current 1.5%).

The impending “explosion” of growth in the population most at risk for hypertension and its sequelae has positive and negative aspects. Because more people are diagnosed and treated for hypertension during their working years, the number of strokes, myocardial infarctions, and heart failure hospitalizations should be significantly decreased. However, postponement of these hypertension-related adverse events after age 65 could have major adverse negative consequences for vastly increased health care expenditures and disability payments to Medicare beneficiaries. Since 1972, the federal government has been a willing partner in the successful effort to improve hypertension control in the United States. The federal treasury benefits from prevention of cardiovascular events in working people because they continue to pay income taxes and do not require death or disability payments. Treatment of hypertension and prevention of cardiovascular events in retired people may have the opposite effects. The recent upward revision of the age at which one can become eligible for entitlement programs for retirees may have resulted from these sorts of considerations.

On a population basis, and most especially economically, there is therefore concern about devoting scarce health care resources to any condition, including treatment of hypertension, for individuals in whom it has not proven to be beneficial. Most early clinical trials in hypertension enrolled very few individuals >80 years of age because of concerns about their relatively short life expectancy and high risk of death from causes not hypertension related. However, there are at least 2 reasons why information about antihypertensive therapy on the basis of clinical trial results would be most relevant and applicable to people in this age group. First,
older individuals are, by definition, at higher absolute risk of all cardiovascular events and death; therefore, treatment is more cost-effective for them (assuming they have a similar relative risk reduction with therapy as do younger individuals). Secondly, the short duration of most clinical trials (4 to 5 years on average) is more relevant to those >80 years of age because this time period represents a greater proportion of their remaining life expectancy (which was nearly 9 years at age 80 in 200213) than it would for a younger person.

Case Summary
An 86-year-old “semiretired” physician sought advice after a Grand Rounds presentation about the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7). He indicated that his blood pressure (BP) had always been <“100 plus his then-current age/90” mm Hg, which he believed was acceptable. He was disturbed that the new guidelines made no exceptions to the target of <140/90 mm Hg for individuals his age and older. He asked what would be the expected benefits and risks for beginning appropriate drug therapy for hypertension at his age.

He was otherwise healthy and very active, spending an equal number of hours per week at his medical practice and golfing. His only medication was low-dose aspirin. He had no surgical history and only presbyacusic and mild symptoms consistent with benign prostatic hypertrophy. His wife died ~2 years earlier; he took most of his meals either at the country club or at the hospital.

BP s were 176/78 and 174/80 mm Hg supine, standard adult-sized cuff in the right arm and about the same on the left. Standing BP was 162/62 mm Hg. Resting pulse was 68 and regular. Weight was 72 kg (158 pounds); height was 167 cm (5 feet, 6 inches); body mass index was 25.6 kg/m2. Direct ophthalmoscopy showed Grade II Keith-Wagener-Barker retinopathy, but the physical examination was otherwise unremarkable. All of his laboratory tests done the previous day were within the reference ranges, including a serum creatinine of 1.4 mg/dL (and eGFR of 51 mL/min), total cholesterol of 180 mg/dL, HDL-cholesterol of 45 mg/dL, and triglycerides of 110 mg/dL. A first-morning voided urine specimen contained 15 mg of protein per gram of creatinine (normal <20 mg of protein per gram of creatinine). An ECG showed sinus bradycardia at rest but no other abnormalities, even at stage 4 of the Bruce protocol.

He expressed special concern about avoiding stroke (and the nursing home placement that he had seen too often in his patients) and heart failure (the most common reason Americans >65 years of age are admitted to hospital). He felt that these sequelae of hypertension would be so limiting to his quality of life that he wished to focus discussion on them. His major questions are given as headers for the remainder of our discussion.

For Me, Elevated Systolic BP Is Not Important, Right?
The relative importance of systolic versus diastolic readings in hypertension has changed as our knowledge of their prognostic implications has grown. Fifty years ago, insurance companies held most of the data relating BP to adverse outcomes on the basis of examination of young people after they obtain their first job or have their first child. Early studies of BP measurements showed a much higher coefficient of variation in systolic BP than diastolic, suggesting that the latter was more “accurate” and “reproducible.” Those who thought physiologically made the point that BP is never lower than the diastolic reading, whereas systolic BP is present only for a few milliseconds during each cardiac cycle. These factors all led to the teaching that diastolic was more important than systolic BPs.

During the last 15 years, clinical trials and many epidemiological studies have provided much information about the relative importance of systolic and diastolic BPs. In a compilation of 61 such studies involving nearly 1 million individuals, systolic BP predicted 89% of the strokes and 93% of the cardiac events, whereas the predictive value of diastolic BP was only 83% and 73%, respectively. Particularly important in this context are the results from >20 000 deaths during 194 000 person years of observation in individuals >80 years of age, for whom an increase in systolic BP of 60 mm Hg is associated with a graded and nearly 4-fold increase in the risk of ischemic heart disease or stroke.

A meta-regression analysis of all clinical trials performed through March 2003 concluded that nearly all the prevention of cardiovascular events could be explained by the differences in systolic BPs between the randomized groups. Together, these data suggest that for older individuals (probably >53 years of age), systolic BP is more predictive of adverse outcomes than diastolic readings.

Will Lowering This Level of BP Prevent Me From Having a Cardiovascular Event?
Elevated systolic BP is common in the United States. “Isolated systolic hypertension” was the most common form of hypertension in older people in Framingham, Mass: 57% of men and 65% of women with hypertension between 65 and 89 years of age were affected. Approximately 12 million Americans >60 years of age currently have treated but uncontrolled hypertension. This number of people in this category is larger than any of the other 11 age group or control categories (unaware, untreated, or controlled). In the National Health and Nutrition Examination Survey III, systolic BP was >140 mm Hg in 66% of those with uncontrolled hypertension.

The public health problem of isolated systolic hypertension has been addressed by 3 clinical trials that expressly enrolled individuals with only elevated systolic BP. The first of these was the Systolic Hypertension in the Elderly Program (SHEP), which randomized 4736 people >65 years of age to initial treatment with low-dose chlorthalidone or placebo. The primary end point was fatal or nonfatal stroke, which was 36% lower in those given chlorthalidone, despite a 44% prevalence of antihypertensive drug therapy by the end of the study among those assigned to placebo. Essentially all subtypes of stroke were equally prevented, and there was evidence that achieving a lower systolic BP (<150 mm Hg) was more effective than leaving it higher (<160 mm Hg). Cardiovascular events were also significantly reduced (by
Because no large-scale clinical trial has yet been done in hypertensive people >80 years of age, the best available data come from a patient-level metaanalysis of all 1670 hypertensive patients in 7 clinical trials that compared active drug therapy versus placebo or no treatment. Octogenarians comprised only 13% of the overall population in these trials, averaged 83 ± 3 years of age, and had an average BP of 180/84 mm Hg at enrollment; 70% were women. In this metaanalysis, active drug therapy significantly reduced strokes by 34%, heart failure by 39%, and major cardiovascular events by 22%. Nonsignificant differences were found for coronary heart disease (CHD) events (reduced by 22%), but mortality and cardiovascular death were higher, by 6% and 1%, respectively (Figure).

A short-term feasibility study for the recently launched HYVET enrolled 1283 patients with systolic and diastolic BPs exceeding 160/95 mm Hg >80 years of age, and randomized them to either a diuretic (usually bendroflumethiazide; n = 426), an angiotensin-converting enzyme (ACE) inhibitor (usually lisinopril; n = 431), or placebo (n = 426). The mean age was 84 years; 63% were women. The initial BP was 181/100, but the average follow-up was only 1.1 years. Preliminary results have been presented but not yet published. The mean age was 84 years; 63% were women. The results of the metaanalysis of Staessen et al indicate that the number of deaths and cardiovascular deaths were slightly lower with the ACE inhibitor (27 and 22, respectively) than the diuretic (30 and 23), but no further results are available.

The initial experience in the HYVET pilot has resulted in several changes to the protocol for the main trial, which soon expects to complete enrollment of 2100 patients >80 years of age with either systolic or diastolic elevations in BP. The primary end point is still fatal or nonfatal stroke, which is expected (with 90% power at a 1% level of significance) to be reduced by 35% with indapamide, followed by perindopril (if needed), compared with placebo. Other cardiovascular end points, including mortality, will also be examined during a 5-year average follow-up period. Much effort is being devoted to measurements of quality of life, cognitive function, and dementia, which was significantly prevented in Syst-Eur (but not the Study on Cognition and Prognosis in the Elderly [SCOPE] with active treatment. Although we wait for the results of the main HYVET trial, current metaanalyses suggest that antihypertensive drug therapy results in a significant prevention of stroke and heart failure, 2 events of most concern to many older individuals.

**Should I Start Taking a Drug, and if So, Which One?**

The benefits of lifestyle modification in reducing BP are well established; the most effective modalities are weight loss and sodium restriction. However, the numbers of patients >80 years of age in these studies are exceedingly small. Furthermore, there has never been a study proving that lifestyle modifications prevent cardiovascular events, perhaps because many people cannot maintain them over time. Nonetheless, our subject should limit his salt intake, especially because he is not involved in its preparation and does not know its salt content. The question of whether a drug is necessary can be most easily answered by remembering that in the metaanalyses cited above, hypertensive individuals assigned to placebo were also given information about lifestyle modifications, indicating that lifestyle modifications and no drug is generally associated with a higher risk for cardiovascular events than lifestyle modifications plus a drug.

Despite 2 metaanalyses that suggest there are few significant differences in cardiovascular events if BP was controlled to an equivalent extent, the metaanalysis of Psaty et al indicates that no class of antihypertensive drug has so far proven superior to an initial diuretic in either BP lowering or prevention of heart failure. A recent and more inclusive metaanalysis indicates that stroke may be slightly better prevented by an initial calcium antagonist than an initial diuretic or β-blocker (by 8%) but at a much higher risk of heart failure (by 29%).

These metaanalyses are heavily weighted by the results of ALLHAT. Octogenarians made up only 6.5% of its participants, but because of its huge size, ALLHAT nearly doubled the number of studied hypertensive patients in this age group. Separate analyses of this age group in ALLHAT...
have not yet been published, but analyses limited to the older age group (>65 years) were wholly consistent with the overall trial results. ALLHAT was a National Institutes of Health–sponsored multicenter clinical trial designed by an expert committee that chose chlorthalidone as the thiazide-like diuretic, despite its low prescription volume. Two recent publications have suggested that little difference might be expected in outcomes among patients treated with chlorthalidone or the much more popular hydrochlorothiazide. The results of a head-to-head comparison of these 2 diuretics in the Multiple Risk Factor Intervention Trial (MRFIT) have been largely forgotten. More than 8000 hypertensive men were randomized to “usual care” in the community or “stepped care,” for which the choice of the initial diuretic was left to the principal investigator of the site. After an interim analysis at 5 years of follow-up, the steering committee recommended that only chlorthalidone be used thereafter. This was because unfavorable higher CHD (by 44%) and all-cause mortality (16%) were observed in the 9 clinics where the staff initially prescribed hydrochlorothiazide predominantly, compared with men referred back to the community. Conversely, in the 6 clinics where the staff predominantly used chlorthalidone, the trends for CHD mortality and mortality were favorable (lower than in the comparator group, by 58 and 41%, respectively). After changing to chlorthalidone, the excess CHD and all-cause mortality in clinics where the staff initially used hydrochlorothiazide decreased, becoming 28% and 26% lower than that seen in the comparator group (P=0.04 and 0.06 for difference between time periods, respectively). The longer-term success of MRFIT can also be attributed, in part, to chlorthalidone because men randomized to care in the community predominantly received hydrochlorothiazide. A second line of reasoning that favors chlorthalidone is less direct but more contemporary. In ALLHAT, chlorthalidone was superior to lisinopril in reducing BP and preventing stroke, combined cardiovascular events, and heart failure. In the Second Australian National Blood Pressure Trial, enalapril was said to be superior to hydrochlorothiazide in preventing major cardiovascular events or death, especially in men, despite roughly equal BP lowering. Although the patient populations and protocols of these 2 trials were quite different, the rank ordering of drugs in preventing major cardiovascular events was: chlorthalidone, ACE inhibitor, then hydrochlorothiazide.

A single drug may not be sufficiently effective to maintain target BP; additional agents may be required. In ALLHAT, the average number of agents used per patient at 5 years was 2.0, despite the exclusion of patients with baseline systolic BP >180 mm Hg. JNC 7 recommends consideration of initial 2-drug therapy if pretreatment BP is >20/10 mm Hg above goal.

What Are the Risks of Such Treatment?
The most common adverse effects of thiazide-like diuretics include hypotension, hemococoncentration (leading, in part, to higher serum levels of creatinine, urate, glucose, cholesterol, and calcium), nocturia, erectile dysfunction, and hypokalemia. The latter is particularly uncommon when an ACE inhibitor or an angiotensin II receptor blocker is used currently. In HYVET pilot, an orthostatic systolic BP fall >19 mm Hg was seen in 7.7% of subjects. ALLHAT showed a significantly increased risk of incident hyperglycemia compared with initial amlodipine or lisinopril, but this apparently did not increase cardiovascular risk during the 4.9 years of follow-up. However, even among those with diabetes at baseline in ALLHAT, chlorthalidone was still the best agent for preventing combined cardiovascular events and heart failure.

Will We Know the Answer During My Lifetime?

Sufficient data have been gathered from 5710 patients >80 years of age in the INDANA metaanalysis, ALLHAT, and HYVET pilot to provide an initial estimate, but the results have not yet been commingled. The results in octogenarians in the last 2 studies have not yet been published, and the number and outcomes in Syst-China are still not public. ALLHAT did not include a placebo arm, so it cannot be used in a metaanalysis comparing active treatment with placebo, which leaves only 2953 patients until the main HYVET trial is completed, when the number will be 5053.

It is unlikely that antihypertensive drug treatment will be associated with a significant difference in all-cause mortality among individuals >80 years of age given current data. A metaanalysis of the INDANA data and the publicly available data from HYVET pilot indicate that the number of deaths in the actively treated groups was only 302 (of 1731). Among those randomized to placebo, there would have had to have been a highly significant nearly 3-fold increase in the risk of mortality (or 69 deaths among 426 participants) compared with those given active treatment in HYVET pilot for the overall point estimate to be significant at P<0.05. Conversely, only if the number of deaths in HYVET pilot was <14 (among the 426 participants randomized to placebo) would the point estimate show a significant increase in mortality. If either of these had been observed, the investigators would surely have made the world more aware of it than currently is the case.

Therefore, the existing data indicate an overall benefit of drug treatment of hypertension to prevent stroke and heart failure, the 2 most feared sequelae of hypertension for most very elderly patients. Whether such treatment is associated with a significant change in risk of death is unclear but should be more firmly established when the main HYVET trial is completed. Until then, most elderly people would probably accept the notion that antihypertensive drug treatment prevents a debilitating stroke or heart failure, even if it does not prolong life.

References


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Hypertension. 2004;44:800-804; originally published online October 25, 2004;
doi: 10.1161/01.HYP.0000146909.69161.8c

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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