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Hypertension from Framingham to ALLHAT: Translating clinical trials into practice

■ ABSTRACT

Despite decades of observational and clinical data about the effectiveness of treating hypertension, most Americans are still not being adequately treated. It makes little sense that much of our efforts are directed toward performing large trials to find out whether newer, more expensive agents are superior to conventional therapy, especially when little evidence shows any benefit to the newer drugs. Rather, our priority should be to treat more patients and to treat them more aggressively.

MOST PEOPLE with hypertension are either not treated or are treated inadequately. We make considerable efforts to evaluate new drugs to treat the condition, but thus far standard therapy with a diuretic has not been surpassed in safety and efficacy in clinical trials. We should instead direct our effort and resources to treating more patients and treating more aggressively to control hypertension to less than 140/90 mm Hg (or less than 130/80 in patients with diabetes, heart failure, or chronic kidney disease).

Although we know that diet and lifestyle intervention lower blood pressure, we have not created the right environment in medicine to encourage patients to implement these changes. Dietary counseling should consist of more than handing patients a sheet of dietary guidelines at the end of an appointment.

This article reviews how blood pressure tends to change with age and discusses the

risks of hypertension—particularly of systolic blood pressure elevation in older people. It also highlights clinical trials that show that lowering high blood pressure dramatically reduces the rates of stroke, myocardial infarction, heart failure, and death, and compares current antihypertensive therapies. The article also discusses obstacles to effective blood pressure control in the United States.

■ HYPERTENSION IS A RISK FACTOR, EVEN IN THE ELDERLY

Hypertension is common in every industrialized country, affecting about one fourth of adults. About 65 million people in the United States have hypertension; older people and African Americans are disproportionately affected.

An American's lifetime risk of developing hypertension is about 90%.¹ We could approach this sobering news in one of two ways: "We're destined to develop hypertension, so let's wait until we have it to do something about it," or "We're destined to develop hypertension, so let's consider early approaches to try to reduce its occurrence or minimize the associated target-organ damage."

Kannel et al² summarized data from the first 30 years of the Framingham Heart Study and found that the risk of developing coronary artery disease increases continuously with higher blood pressure, with no threshold for defining people at high risk. This makes any definition of hypertension entirely arbitrary, and today's definition is likely to change in the future.

Hypertension is not benign in the elderly. Although many physicians believe that older patients are "entitled" to a higher blood pres-

**Complication
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A woman with isolated systolic hypertension

A 67-year-old woman comes in for a routine physical examination. Her blood pressure is 164/76 mm Hg. She has no other medical problems and takes no medications. A physical examination reveals no evidence of target organ damage. Her electrocardiogram shows borderline left ventricular hypertrophy by voltage but no repolarization abnormalities. Her blood glucose level is 94 mg/dL, blood urea nitrogen 23 mg/dL, and creatinine 1.1 mg/dL. All other laboratory values are normal.

You recommend a low-salt diet and recheck her blood pressure several times over the next few months. Despite dietary efforts, her blood pressure remains 162/78 mm Hg, based on the average of multiple readings. You decide to initiate drug treatment for her hypertension. She has no contraindication to any antihypertensive drugs and has no special indication for any particular class of drug.

Q: Which class of antihypertensive drug would you begin with?

- ☐ An angiotensin-converting enzyme (ACE) inhibitor
- ☐ An alpha-blocker
- ☐ An angiotensin II receptor blocker
- ☐ A beta-blocker
- ☐ A calcium channel blocker
- ☐ A diuretic
- ☐ Combination therapy

A: The correct answer is combination therapy.

The Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure¹⁷ recommends that a thiazide diuretic (either alone or combined with other drug classes) be used for initial drug therapy for most patients, unless a contraindication to the diuretic or a compelling indication for another drug class exists. This patient has neither, so a diuretic would be a reasonable choice. However, the goal is to bring her blood pressure below 140/90 mm Hg, and her current systolic blood pressure is more than 20 mm Hg above that goal. The JNC 7 report recommends that if blood pressure is more than 20 mm Hg systolic or 10 mm Hg diastolic above the goal blood pressure, consideration should be given to starting therapy with two agents, one of which usually should be a thiazide-type diuretic.

An advantage of combination therapy is that because side effects of drugs are more likely to occur at high doses, combination therapy allows using lower dosages of each drug, minimizing the risk of side effects.

The ALLHAT study¹² (see text) did not include a beta-blocker as one of the step 1 therapies it evaluated, so a beta-blocker was not compared directly with the other drugs. Instead, a beta-blocker was used as step 2 therapy. Other trials that have evaluated beta-blockers as initial therapy for hypertension have found that beta-blockers were not superior and, in the elderly, were clearly inferior to treatment with diuretics. Atenolol has especially been found to be ineffective in clinical trials in treating hypertension.

sure and need not be treated aggressively, at any level of either systolic or diastolic blood pressure older people are at greater risk than their younger counterparts. Complication rates rise sharply with increasing blood pressure in even the oldest age groups.

Systolic blood pressure matters

For many years, experts believed that diastolic blood pressure was the only important consideration in diagnosing risk from hypertension and in determining the need for treatment. From the 1940s through the 1970s, hyperten-

sion treatment was almost exclusively given to patients with elevated diastolic blood pressure because increasing systolic pressure was thought to be part of normal aging. But isolated systolic hypertension is associated with a dramatically increased risk of cardiovascular disease.

Willing et al³ found that Framingham participants with isolated systolic hypertension had about a 2.5 times higher risk of cardiovascular disease than did age-matched controls with normal blood pressure.

Early clinical trials focused on diastolic hypertension and ignored systolic blood pres-

Which drugs prevent heart failure?

Q: Which drug class is best at preventing heart failure in patients with hypertension?

- ☐ An ACE inhibitor
- ☐ An alpha-blocker
- ☐ A calcium channel blocker
- ☐ A diuretic

A: The correct answer is a diuretic. Studies showed that alpha-blockers actually double the risk of heart failure compared with a diuretic, and calcium channel blockers and ACE inhibitors are also inferior to a diuretic for preventing congestive heart failure. The drug that is best at preventing heart failure in patients with hypertension is a thiazide-type diuretic.

sure. Only recently have large clinical trials been conducted to determine if treating systolic hypertension is beneficial, even though observational data from Framingham and elsewhere have shown for decades that the systolic pressure is at least as predictive of risk—and in older people is even more predictive—than the diastolic pressure.

The Multiple Risk Factor Intervention Trial⁴ screened more than 350,000 men, a population large enough to allow investigators to evaluate risk over the continuum of blood pressure levels. For both systolic and diastolic pressures, the higher the level, the greater the risk of coronary death, but the relationship was stronger for systolic pressure than for diastolic pressure. Men in the highest decile of systolic pressure (> 151 mm Hg) had nearly four times the risk of coronary death as those in the lowest decile (< 112 mm Hg). For diastolic blood pressure, a nearly threefold risk separated the highest decile (≥ 98 mm Hg) and the lowest decile (< 71 mm Hg).

Interestingly, the diastolic blood pressure associated with a threefold risk of coronary death—98 mm Hg or above—is universally treated in the United States. But the systolic level associated with a fourfold risk—151 mm Hg or higher—is still often untreated in clinical practice today.

The Prospective Studies Collaboration⁵ performed a meta-analysis of 61 studies, including more than 1 million adults, 12.7 million person-years at risk, and 56,000 deaths due to vascular events. For every decade of age from 40 to 90 years, the risk of coronary death was exponentially related to systolic and diastolic blood pressures: the risk of dying of coronary disease approximately doubled with

every 20-mm Hg increase in systolic pressure or 10-mm Hg increase in diastolic pressure. The risk was continuous, with no apparent threshold to define hypertension.

For people younger than 50 years, coronary risk is better predicted using diastolic blood pressure, but for people older than 50 years it is better predicted from systolic blood pressure.⁶ The oldest group (80–89 years) continued to be at high risk with increasing blood pressure levels: as systolic blood pressure varied from 120 mm Hg to 180 mm Hg, event rates increased from about 64 to 200 per thousand per year.

Both short-term and long-term risk should be treated

In older people, the risk of a vascular event from hypertension is high, so treatment is important to prevent events occurring in the short term. On the other hand, treating high blood pressure in people in their 40s and 50s is not aimed at preventing events in the short term, because risk at that age is very low. Although people in their 40s had a greater increase in rates of coronary mortality from increasing blood pressure, the absolute number of events was much lower (from about 1 to 10 deaths/1,000 people/year as systolic blood pressures varied from 120 mm Hg to 180 mm Hg).⁵ But treating young people is important to prevent organ damage and the accumulation of complications from hypertension that may cause stroke, heart failure, and other problems over a lifetime.

Systolic hypertension tends to develop with age

Franklin et al⁷ evaluated data from 2,036 Framingham participants from a 30-year peri-

Systolic hypertension predicts risk better than diastolic in people over age 50, but it is not often treated

od. The population was divided into four groups according to systolic blood pressure levels at an index examination done between the age of 50 and 79 years (< 120 mm Hg, 120–139 mm Hg, 140–159 mm Hg, and \geq 160 mm Hg). Patient ages throughout the study ranged from 30 to 84 years. In each group, systolic blood pressure rose linearly with advancing age.

The study similarly tracked diastolic blood pressure over time. They found that regardless of the starting level, diastolic blood pressure tends to increase continuously from age 30 to 50, stay about the same between 50 and 60 years, and decrease after about age 60.

As a result of systolic blood pressure increasing while diastolic blood pressure levels off and then decreases, a person's pulse pressure tends to widen during and after middle age. This pattern leads to different types of hypertension that tend to occur in various age groups.

Sagie et al⁸ categorized Framingham participants with different types of hypertension by sex and age. Sex differences were not detected, but age differences were prominent: most people with hypertension between ages 30 and 50 had diastolic hypertension, either alone or combined with systolic hypertension. On the other hand, a large proportion of people with hypertension in their 80s had isolated systolic hypertension of either stage 1 (systolic blood pressure 140–159 mm Hg) or stage 2 (\geq 160 mm Hg) severity.

The reversal in the relative prevalence of diastolic vs systolic hypertension in young vs old ages probably reflects underlying physiology: in young people, hypertension is largely a problem of altered peripheral resistance, whereas in old people, it is mostly due to altered conduit vessel compliance. Old people tend to have “stiff pipes,” which cause the systolic blood pressure to increase and the diastolic blood pressure to decrease because of loss of aortic recoil. A normal aorta maintains blood pressure during diastole, but as the aorta stiffens with age, that function is lost.

■ TREATING SYSTOLIC HYPERTENSION REDUCES RISK

Observational data clearly show that high systolic blood pressure is associated with an increased risk of cardiovascular disease.

Clinical trials are needed to determine whether treating hypertension can reduce the risk and by how much.

The first randomized, placebo-controlled hypertension trial was published in 1967 by the Veterans Administration Cooperative Study Group.⁹ Thereafter, for nearly 25 years, we were in the dark about treating systolic hypertension in older people.

The Systolic Hypertension in the Elderly Program (SHEP),¹⁰ published in 1991, was one of the most important clinical trials in hypertension ever conducted. In this placebo-controlled, double-blind trial, 4,736 men and women age 60 years or older with isolated systolic hypertension of stage 2 severity (systolic blood pressure \geq 160 mm Hg and diastolic pressure < 90 mm Hg) were given either a chlorthalidone (a thiazide-type diuretic) or placebo. If this first-step agent did not control the blood pressure, atenolol or placebo was added as step 2, also given in a double-blind manner. After an average of 5 years, the systolic blood pressure of patients in the treated group was an average of 12 mm Hg lower than in patients taking placebo. The treatment group had a 36% lower incidence of stroke, the primary end point. In addition, overall coronary risk was 25% lower, heart failure incidence lower by more than 50%, and overall cardiovascular disease risk was lower by about one third. The large reduction in heart failure was especially noteworthy: few medical interventions are so effective.

The SHEP study design and the questions it addressed may seem obvious now, but the results form the basis of how we have treated systolic hypertension ever since. When the study was proposed, many people felt that the trial was a dangerous undertaking. The thinking of the day was that a patient with isolated systolic hypertension and without symptoms should not be treated.

Cardiologists in particular were worried: knowing that coronary perfusion occurs during diastole, they were afraid that treating systolic hypertension would cause diastolic pressure to be reduced to a dangerously low level, possibly causing cardiac ischemia, especially in older people. The fear was that although strokes might be prevented, heart attacks

Pulse pressure tends to widen during and after middle age

Which drugs prevent renal failure?

Q: Which drug class is best at preventing end-stage renal disease in patients with uncomplicated hypertension?

- ☐ ACE inhibitors
- ☐ Calcium channel blockers
- ☐ Diuretics

A: This is a controversial question with no definitive answer. The ALLHAT trial¹¹ evaluated the incidence of renal failure and found that patients in all treatment groups—chlorthalidone, amlodipine, and lisinopril—developed end-stage renal disease at a rate of about 2 per 100 over 6 years. So in a patient with uncomplicated hypertension, there is no reason to prefer any drug over a diuretic to prevent end-stage renal disease.

Which drug is the best for preventing end-stage renal disease in a patient with hypertension and diabetes? The ALLHAT trial¹² included about 12,000 patients with both diabetes and hypertension. The 6-year rates of end-stage renal disease were 2.7 with chlorthalidone, 3.3 with lisinopril (30% higher than with chlorthalidone; $P > .07$), and 3.6 with amlodipine (17% higher than with the diuretic; not statistically significant). Technically, no drug was found to be better for preventing end-stage renal disease, although a trend could be inferred that calcium channel blockers are

inferior to diuretics.

For patients with hypertension, diabetes, and mild chronic kidney disease (glomerular filtration rate 60–89 mL/minute, normal = 90 or greater), a 72% higher risk was found of developing end-stage renal disease for patients taking amlodipine vs chlorthalidone and 74% higher for those taking lisinopril ($P = .05$ for both). So for patients with diabetes and mild kidney impairment, chlorthalidone is slightly superior to the newer drugs.

For patients with severe kidney impairment (glomerular filtration rate < 60 mL/minute), no difference between the newer drugs and the diuretic with regard to end-stage renal disease was found.

In summary, when choosing between chlorthalidone, amlodipine, and lisinopril to treat hypertension and prevent end-stage renal disease:

- For patients with hypertension overall, all drugs were identical.
- For patients with hypertension and diabetes, all drugs were identical.
- For patients with hypertension, diabetes, and mild kidney disease, the diuretic was superior to the ACE inhibitor and to the calcium channel blocker.

Proteinuria as an indicator of renal impairment was not evaluated in the trial, which may have led to different results.

would increase. Because heart attacks are a more common problem than stroke, more harm than good could result. Clinical trials showed otherwise: coronary risk went down. The results were so definitive that it is surprising that so many patients since then with isolated systolic hypertension have remained untreated.

The Syst-Eur trial¹¹ randomized 4,695 men and women older than 60 years with stage 2 isolated systolic hypertension to receive nitrendipine (a long-acting calcium antagonist that is unavailable in the United States) and the possible addition of enalapril (an angiotensin-converting enzyme [ACE] inhibitor) and hydrochlorothiazide, or matching placebo. After a median of 2 years, systolic blood pressure in treated patients

was an average of 10 mm Hg lower than in patients taking placebo, and diastolic blood pressure was an average of 5 mm Hg lower. The study ended early when the benefits of treatment became clear. Patients in the treatment group had a 42% lower incidence of stroke and about a 30% lower risk of myocardial infarction, heart failure, and cardiovascular disease.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)¹² was the largest trial of hypertension treatment ever conducted, with more than 40,000 men and women, age 55 years or older with hypertension and at least one other risk factor for cardiovascular disease. About one third were African Americans, and about one third had

diabetes. Patients were randomly assigned therapy with chlorthalidone, doxazosin (an alpha-blocker), lisinopril (an ACE inhibitor), or amlodipine (a calcium channel blocker).

The trial was designed to determine if new antihypertensive drugs were superior to or equivalent to standard therapy with a diuretic in preventing coronary events. Diuretics are much less expensive but have the disadvantage of tending to cause hypokalemia, hyperglycemia, and hyperuricemia. The primary outcome was combined fatal coronary heart disease or nonfatal myocardial infarction. Patients were followed for a mean of nearly 5 years.

The Data Safety and Monitoring Committee recommended terminating the doxazosin arm of the study early after noticing that patients taking this drug had about twice the risk of heart failure and an increased risk of stroke compared with those taking the diuretic.

Patients treated with lisinopril, amlodipine, or chlorthalidone had remarkably similar rates of the primary end point over the 7 years of the study.

However, the risk of stroke, a secondary end point, was 15% greater (a statistically significant difference) in patients taking lisinopril than with chlorthalidone.

The risk of heart failure was also significantly higher in patients taking either lisinopril or amlodipine (19% and 38% higher, respectively, than with chlorthalidone). Moreover, the risk was higher with lisinopril and amlodipine in every predefined subgroup: men and women, patients older and younger than age 65, blacks and nonblacks, and patients with and without diabetes. The increased risk attributed to lisinopril was particularly surprising, because ACE inhibitors had previously been shown to reduce symptoms and prolong life in patients with heart failure.

■ OBSTACLES TO BLOOD PRESSURE CONTROL

The National Health and Nutrition Examination Surveys (NHANES) show that rates of awareness, treatment, and control of hypertension increased steeply from the 1970s to

the 1990s but have leveled off since then.^{13–15} Currently, only about one third of patients with hypertension in the United States have blood pressure controlled to less than 140/90 mm Hg.

Diastolic hypertension can usually be controlled. Lloyd-Jones et al¹⁶ evaluated rates of control of hypertension from the Framingham Study. Among people who were treated for hypertension, rates of control of diastolic pressure to less than 90 mm Hg were 85% in those younger than age 60, 91% in those age 61 to 75, and 92% in those older than age 75. Similar rates have been found nationally based on the NHANES data.

In comparison, control rates of systolic blood pressure are much lower. Among treated patients age 60 or younger, 69% achieve a systolic level below 140 mm Hg, as do only 48% of patients 61 to 75 years, and only 34% of those older than 75 years.

■ FOCUS SHOULD BE ON EXPANDING STANDARD TREATMENT

Unfortunately, most people with hypertension are either not being treated or are being insufficiently treated.

Our first priority should be to treat more patients and to treat them more aggressively so that hypertension is controlled.

Nonpharmacologic lifestyle approaches can also help lower blood pressure, but we have not created the right environment in medicine for encouraging patients to successfully implement them. Abstinence from alcohol in people who are drinking heavily, weight reduction in people who are even mildly overweight, and sodium restriction are effective nonpharmacologic measures. The DASH (Dietary Approaches to Stop Hypertension) Diet, which is high in fruits, vegetables, fiber, nuts, and low-fat milk products, can be about as effective as low doses of a single agent in the treatment of hypertension. However, handing patients a sheet of paper and following up a couple months later is not an adequate approach to implementing lifestyle changes. We need support systems, such as reimbursement for seeing a nutritionist, to be serious about creating such changes. ■

Diuretics are at least as effective as new drugs in lowering blood pressure and reducing cardiovascular risk

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