Commentary

The ALLHAT study: results and clinical implications

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Introduction

The Antihypertensive Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) just published, is the largest clinical trial so far conducted. Under the auspices of the National Heart Lung and Blood Institute (NHLBI), it included over 40 000 high-risk hypertensive patients (aged 55 years or older) who were followed over 5 years (with the exception of the doxazosin treatment arm, which was discontinued prematurely due to a higher incidence of heart failure). It included 33 357 patients who were randomized to treatments, including chlorthalidone 12.5–25.0 mg/day (n = 15 255), amlodipine 2.5–10 mg/day (n = 9048) and lisinopril 10–40 mg/day (n = 9054). The doses of these drugs were increased until a blood pressure goal of < 140/90 mmHg was achieved. In addition, other drugs could be added to the baseline treatments such as atenolol (25–100 mg/day), reserpine (0.1–0.2 mg/day) or clonidine (0.1–0.3 mg bid) at the discretion of the investigator. Also, hydralazine 25–100 mg bid could be added as a step 3 drug. The pre-specified primary outcome of this trial was fatal coronary heart disease or non-fatal myocardial infarction combined. Secondary outcomes included all-cause mortality, fatal and non-fatal stroke, coronary artery disease, peripheral vascular disease, heart failure, end-stage renal disease and cancer. The mean age of the study population was 67 years, 47% were women, 35% were Black, 19% were Hispanic and 36% were diabetic.

The results

The major clinical findings of this large study were as follows.

Some 60% of treated hypertensive patients reached a blood pressure goal of < 140/90 mmHg, compared to current estimates of 34%. This despite the protocol limitations on proper drug combination, on which I will comment later.

There was no difference in the primary outcome of combined fatal CHD or non-fatal or fatal MI, and the secondary outcomes of all cause mortality, end stage renal disease, peripheral vascular disease or cancer, between the three treatment groups. Amlodipine had a 38% higher incidence of heart failure compared to chlorthalidone. Lisinopril had a 10% higher incidence of combined CVD, a 15% higher incidence of stroke and a 19% higher incidence of HF than chlorthalidone. A careful examination of the protocol treatment guidelines may explain these at first surprising findings. Patients on chlorthalidone treatment were allowed the addition of atenolol, which is a good combination with additive effects. The same applies to those randomized to amlodipine. However, in those randomized to lisinopril, the addition of atenolol does not make it an appropriate combination, since both drugs act on the renin-angiotensin system. This may be the reason that the systolic blood pressure in the lisinopril group was higher by 2 mmHg compared to chlorthalidone for the 5-year observation period.
which could account for the higher incidence of complications.

The better blood pressure control with chlorthalidone could be attributed to the make-up of the study population, which consisted of older patients and a large proportion of Black patients (35%) and diabetics (36%), all low renin and volume-dependent hypertensives, who respond better to monotherapy with a diuretic or calcium channel blocker than to ACE inhibitors. A recent Australian study in a more uniformly White population, demonstrated that the ACE inhibitor enalapril had similar antihypertensive effects to hydrochlorothiazide, but was slightly superior to the diuretic in reducing cardiovascular morbidity and mortality. A low-dose ACE inhibitor-diuretic combination is an excellent combination and reduces the blood pressure in over 80% of the patients and also eliminates the ethnic disparity.

The calcium channel blocker amlodipine appeared to be a very good antihypertensive as monotherapy, and was not associated with increased cardiovascular morbidity or mortality or end-stage renal disease, as has been previously reported, with the exception of a higher incidence of heart failure. Although this complication could be real, the criteria for diagnosing heart failure in this study were very loose, and ankle oedema caused by amlodipine could have been interpreted as heart failure by some investigators. This study was conducted in busy private practice sites, and the closeness of supervision is uncertain. Amlodipine, on the other hand, had a beneficial effect in the incidence of strokes, although this was not statistically significant. Similar findings have been previously reported for other calcium channel blockers.

Implications for the practicing physician

Based on the results of the ALLHAT trial, diuretics are being revisited as effective and safe drugs given in low doses of 12.5–25.0 mg/day. These drugs have always been effective for the treatment of hypertension and have been advocated as such by the JNC reports, especially the recent JNC-7, which advocates the use of diuretics as preferred drugs for the initial treatment of hypertension, without compelling indications for other drugs. However, diuretics were ostracized from antihypertensive treatment regimens due to some poorly controlled studies blaming hypokalemia as cause of cardiac arrhythmias and sudden death. These reports were discredited by other investigators, but physicians have tended to ignore these subsequent reports and continue to withhold their use for the treatment of hypertension. The end result has been polypharmacy and poor blood pressure control, despite the fact that it is an axiom that for any triple drug regimen, one should be a diuretic. Part of the reason for their banishment may be the sexual impotence in men and the metabolic side-effects seen at higher doses, or their low cost, which makes them less attractive commercially. The metabolic side-effects of hypokalemia, hyperuricemia, hyperglycemia and hyperlipidemia are less frequent and occur at much lower scale when diuretics are given in low doses or combined with other drugs. Diuretics should always be combined with potassium-sparing drugs such as amiloride, spironolactone or triamterene. Other excellent combinations are with an ACE inhibitor, angiotensin receptor blocker or beta-blocker.

ACE inhibitors and angiotensin receptor blockers are excellent first or second choice drugs, especially when combined with a low-dose diuretic or calcium channel blocker. Calcium channel blockers are safe and effective drugs, and should be used for good blood pressure control. Although their use should be reserved as a second- or third-line drug, they also are effective as monotherapy in older patients, Black hypertensive patients, and in patients who are unable to restrict their sodium intake. Beta blockers are excellent drugs for hypertensive patients with a hyperdynamic circulation and those who have active coronary artery disease or are post-myocardial infarction patients. They are also good drugs in controlling arrhythmias. These drugs work well with a combination of a diuretic or a calcium channel blocker, preferably a dihydropyridine. Essential hypertension is an interplay of plasma volume and peripheral vascular resistance. In some patients, typically Black, volume is the predominant underlying mechanism, while in most White hypertensives, resistance predominates. Based on these assumptions, Laragh has proposed that a V drug (diuretic) should be the initial treatment in volume-dependent hypertension, and an R drug (ACE inhibitors, ARBs) should be the initial treatment when peripheral vascular resistance is the predominant mechanism. Eventually, due to counter-regulatory mechanisms, a V drug will require the addition of an R drug, and conversely, an R drug will require the addition of a V drug for better blood pressure control. Blood pressure control to goal should be the guiding force behind the treatment of hypertension and should be achieved with any drug combination or combinations. In reality, patients with more severe forms of...
hypertension will require 2- to 3-drug combinations for good blood pressure control. In that sense, JNC-7\(^3\) recommends the use of drug combinations as initial therapy for stage-2 hypertension (SBP \(\geq 160\) mmHg or DBP \(\geq 100\) mmHg) to avoid drug titration and multiple patient visits.

Thus, the pendulum has swung back to its original place with respect to the use of diuretics. In these days of budgetary cuts, and rising health care costs, diuretic use should provide some relief, because they are inexpensive, effective and safe.

References

1. The ALLHAT Officers and coordinators for the ALLHAT Collaborative Research Group: Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs. Diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288**:2981–97.


