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Scientific Update™

The Clinical Implications and Applications of Recent Trial Evidence from the ALLHAT Trial

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When the ALLHAT trial was designed in the early 1990s, previous clinical trials had clearly shown that blood pressure reduction by 5-6 mm Hg in patients with moderately severe hypertension reduced the risk of stroke by 35%-40%.[1] However, coronary heart disease-related outcomes, such as sudden cardiac death and myocardial infarction (MI), were reduced to a lesser extent. New antihypertensive agents such as angiotensin-converting enzyme inhibitors (ACEi) and calcium channel blockers (CCBs) were subsequently introduced, with potential antiatherosclerotic properties. In contrast, diuretics were considered to have potential pro-atherosclerotic effects due to their adverse effects on glucose and lipid metabolism. Consequently, between 1980 and 1994, thiazide diuretics were replaced (without clinical trial justification) by ACEi, CCBs, and beta adrenergic blockers as first line treatment for hypertension. After the ALLHAT trial was initiated in the mid-1990s, there was concern that CCBs (particularly dihydropyridine agents) may be associated with more MI, as well as cancer and gastrointestinal bleeding.[2]

ALLHAT

Trial design

The Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT) was designed to test the hypothesis that newer antihypertensive agents, such as ACEis, CCBs and alpha adrenergic blocking agents were superior to thiazide diuretics in the prevention of fatal and non-fatal MI.[3] As secondary outcomes, the trial was designed to show the superiority of the newer antihypertensive agents for all-cause mortality, stroke, combined coronary heart disease ([CHD], primary outcome plus coronary revascularization, and hospitalized angina), and combined cardiovascular disease ([CVD],combined CHD plus stroke, other treated angina, heart failure and peripheral vascular disease). The heart failure endpoint included fatal, hospitalized, or treated nonhospitalized events. Entry criteria for the trial are shown in Table 1.

The ALLHAT trial[4] included 42,418 participants, of which 33,357 were randomized to receive chlorthalidone, amlodipine, or lisinopril at 623 centres in the USA, Canada, Puerto Rico, and the US Virgin Islands. A large majority of the centres were community clinics with very few academic health centres. Follow-up was for a mean of 4.9 years with a range of 3 years 8 months to 8 years and one month.

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Table 1: Inclusion and exclusion criteria for the ALLHAT Trial

Inclusion criteria

- Patients >55 years old with stage 1 and 2 hypertension
- On no treatment (BP ≥140/90 mm Hg and <180/110 mm Hg)
- On treatment with 1 or 2 agents (BP ≤160/100 mm Hg at visit 1 and ≤180/110 mm Hg after visit 2 following partial withdrawal of treatment)

plus

- 1 additional risk factor for CHD events (eg, prior MI or stroke [>6 months; left ventricular hypertrophy [ECG or echo]; type 2 diabetes; current smoker; HDL cholesterol <35 mg/dL [<0.91 mmol/l]; documentation of atherosclerotic disease [coronaries, cerebrovascular, peripheral])

Exclusion criteria

- MI or stroke in past 6 months
- Left ventricular ejection fraction <35% (if known)
- History of heart failure in past 6 months
- Creatinine >180 µMol/L (if known)

Treatment regimens

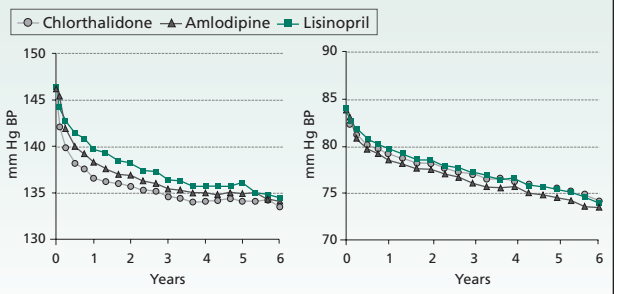
Participants were randomized to receive double-blind allocation to chlorthalidone (12.5-25 mg/day), amlodipine (2.5-10 mg/day), lisinopril (10-40 mg/day) or doxazosin. Treatment was started without a washout period for the 90% of patients who were receiving antihypertensive treatment prior to starting the study medication. Since subjects randomized to receive doxazosin had an early increase in combined CVD events, this arm of the trial was discontinued prematurely[5] and is not discussed further.

For patients who did not achieve target blood pressure (<140/90 mm Hg) on the double-blind allocation, an open-label step 2 medication was added. The choices for step 2 medications were: atenolol (25-100 mg/day), reserpine (0.05-0.2 mg /day), or clonidine (0.1-0.3 mg/day). The step 3 medication was hydralazine (25-100 mg/day).

Results

The mean age of the subjects was 66.9 years with 57.6% over 65 years old. Almost half were women and 32% were black. At the time of randomization, 90% of patients were taking unspecified antihypertensive medication. There was a history of atherosclerotic CVD in 52%, CHD in 25%, and type 2 diabetes in 36%. The majority was obese with a mean BMI of 29.8. The mean blood pressure in the patients not receiving treatment was 157/90 mm Hg and for those on treatment at baseline, it was 145/83 mm Hg.

Figure 1: Systolic and diastolic blood pressure during the ALLHAT trial



Compared to chlorthalidone: SBP significantly higher in the amlodipine group (~1 mm Hg) and the lisinopril group (~2 mm Hg).

Compared to chlorthalidone: DBP significantly lower in the amlodipine group (~1 mm Hg).

Target blood pressure of <140/90 mm Hg was achieved by the end of the trial in 66% of subjects. Improved control was achieved in association with an increase in the number of medications. At one year, subjects were taking on average 1.4-1.5 medications. However, at the time of the 5-year follow-up, an average of 1.8-2.0 medications were being taken.

Blood pressure control was optimally achieved in the chlorthalidone-allocated patients, and the lisinopril-treated group had systolic blood pressure (BP) that was 2 mm Hg higher after 5 years treatment (Figure 1). The difference in systolic BP between the chlorthalidone and lisinopril groups was 4 mm Hg in black and 1 mm Hg in the non-black patients. Older patients (>65 years old) had systolic BP that was 3 mm Hg higher in the lisinopril group compared to the chlorthalidone group, and in patients <65 years old, there was a 0.5 mm Hg difference. After one year, amlodipine-treated subjects had systolic BP that was 1.6 mm Hg higher than the chlorthalidone group, and after 5 years, there was a 0.8 mm Hg difference.

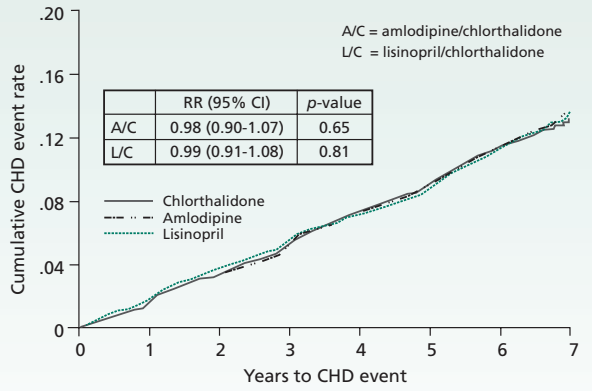
Primary end-point

There was no difference in the primary outcome (the incidence of fatal and non-fatal MI) between either the chlorthalidone and amlodipine or chlorthalidone and lisinopril groups, despite the better BP control achieved with chlorthalidone (Figure 2).

Secondary end-points

Total mortality was 18% over the 6-year follow-up period, with approximately 50% resulting from cardio-

Figure 2: Cumulative primary event rates (Fatal and non-fatal myocardial infarction)



Number at Risk:

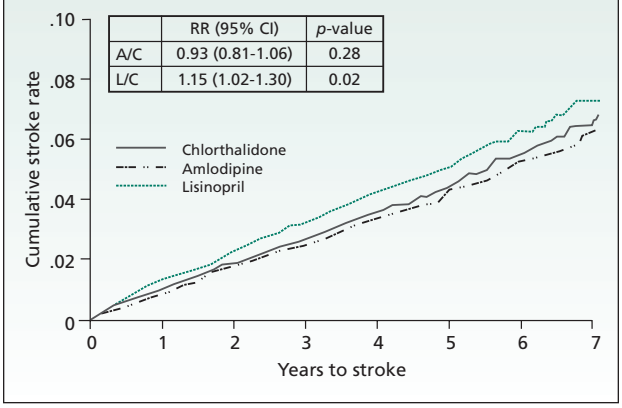
Chlorthalidone	15,255	14,477	13,820	13,102	11,362	6,340	2,956	209
Amlodipine	9,048	8,576	8,218	7,843	6,824	3,870	1,878	215
Lisinopril	9,054	8,535	8,123	7,711	6,662	3,832	1,770	195

vascular deaths. Both amlodipine and lisinopril – when compared with chlorthalidone – resulted in no significant difference in the secondary outcomes of all-cause mortality, combined CHD, peripheral arterial disease, cancer, or end-stage renal disease. Other differences between the secondary outcomes are described in relation to the individual agents.

Amlodipine versus chlorthalidone: In addition, no differences were identified for the pre-specified secondary outcomes of combined CVD, stroke (Figure 3), or coronary revascularization. The amlodipine patients had a 38% greater risk of heart failure, with a 2.5% absolute increase after 6 years. (Figure 4)

Lisinopril versus chlorthalidone: Lisinopril-treated patients had a relative 15% higher risk of stroke (Figure 3) and a 10% higher risk of combined CVD (absolute difference of 2.4% after 6 years). The individual components of the combined CVD endpoint included a 19% higher risk of heart failure (Figure 4), a 10% higher risk of hospitalized or fatal heart failure, and a 10% higher risk for coronary revascularization. For the stroke and combined CVD endpoints, there were significant differences between black and non-black race. There was a 40% increase in stroke in black patients receiving lisinopril versus chlorthalidone, which was in contrast to no increase in non-black patients. CVD endpoints were increased by 19% in black subjects receiving lisinopril versus 6% in non-blacks.

Figure 3: The cumulative event rates for stroke



Claims, surprises, and comments

The ALLHAT trial failed to achieve the primary goal of the trial, as neither lisinopril nor amlodipine were shown to be superior to chlorthalidone in reducing fatal or non-fatal MI. Can it be inferred that chlorthalidone was superior or equivalent to the ACE inhibitor or calcium channel blocker based upon the secondary endpoints of the trial when the primary endpoint of the study was unproven? At the most, the secondary endpoints are hypothesis-generating and not of sufficient power to change clinical practice. Differences in blood pressure control and the incidence of the secondary endpoints, stroke and heart failure, will be discussed individually.

Blood pressure control

Chlorthalidone (when used as a first line agent), compared to either lisinopril or amlodipine, resulted in superior blood pressure control (Figure 1). Although the mean follow-up systolic BP was 2 mm Hg higher with lisinopril compared to chlorthalidone, larger differences are apparent during the first years of the study. Furthermore, the BP difference was greater in blacks (average 4 mm Hg), the group with the greatest incidence of stroke and heart failure.

The failure of the study to achieve equivalent blood pressure control is perhaps inherent in the study design. In 1996, when the study design was first published, an editorial commented that the nonidentical escalation of doses across antihypertensive agents may bias the study in favour of chlorthalidone.[6] Furthermore, the permissible combination of agents was not conducive to the best BP control. Although adding atenolol to chlorthalidone or amlodipine has an

Figure 4: The cumulative event rates for heart failure

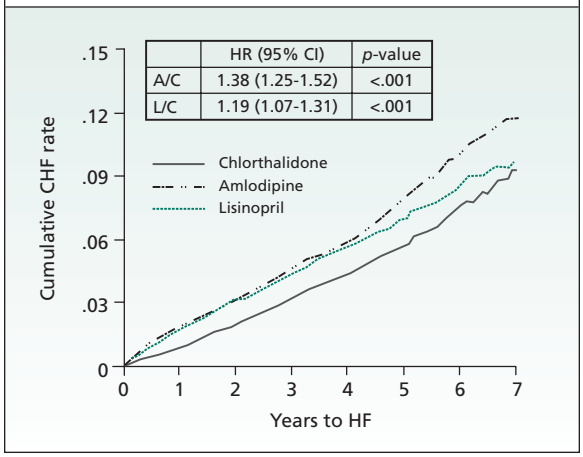
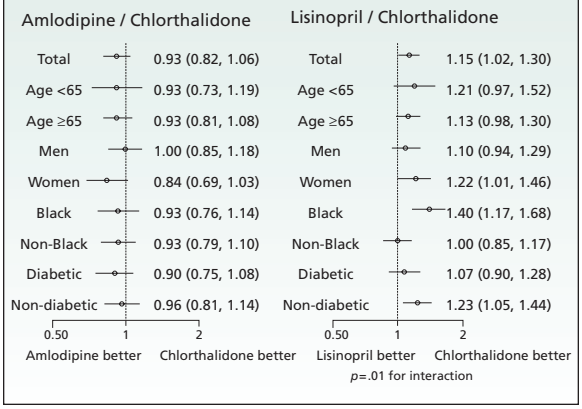


Figure 5: Relative risks and 95% confidence intervals for stroke subgroup comparison



additive benefit on BP control, the combination of atenolol with lisinopril was unlikely to enhance BP control, especially in a black population where neither agent is a very effective antihypertensive agent.

Stroke

Stroke rates were 15% higher in the lisinopril group (p=0.02). However, there was a significant interaction between black race and stroke (Figure 5). The black subjects receiving lisinopril had a 40% increase in the risk of stroke compared to the chlorthalidone group, yet there was no increased hazard for stroke for non-black subjects. As the higher risk for stroke paralleled the higher blood pressure in the black subjects receiving lisinopril, it seems likely that the greater incidence of stroke was related to inferior blood pressure control. As was well known before ALLHAT, a 5-6 mm Hg reduction of BP results in a 35%-40% reduction of stroke.[1]

Heart failure

Subjects randomized to either amlodipine or lisinopril were at higher risk of developing heart failure than the group treated with chlorthalidone. This observation came as a surprise, as amlodipine is usually well-tolerated and has been considered an appropriate antihypertensive agent in patients with left ventricular dysfunction.[7] Furthermore, ACE inhibitors have been shown in multiple studies to reduce mortality for patients with heart failure and to prevent the development of heart failure in patients with impaired systolic function.[8] Explanations for these surprising observations in ALLHAT include the following:

The difference in blood pressure control between chlorthalidone and both lisinopril and amlodipine was responsible for the increase in heart failure. Hypertension is a known risk factor for heart failure and improved blood pressure control is associated with a reduction in the development of heart failure.[7,9]

Did the patients have heart failure? The criteria for determining heart failure were symptoms (dyspnea at rest, nocturnal dyspnea, NYHA class III exertional dyspnea, or orthopnea) and signs (edema, rales, tachycardia, cardiomegaly, jugular venous pressure elevation, S3 gallop, chest x-ray compatible). Yet, heart failure can be a difficult diagnosis, especially for community family physicians without specialized diagnostic equipment. However, a post-hoc validation of the endpoint of heart failure hospitalization in the patients randomized to either doxazosin or chlorthalidone, showed there was an 85% agreement between the endpoint sub-committee and the clinic investigator in the 39 cases examined. Furthermore, the patients hospitalized with heart failure had a 25% two-year mortality, compatible with the diagnosis. Despite the greater incidence of heart failure associated with both amlodipine and lisinopril compared to chlorthalidone, there was no excess in heart failure mortality attributed to the nondiuretic agents.

Did the patients have diastolic heart failure? ACE inhibitors prevent heart failure in patients with systolic dysfunction, yet there is little evidence for benefit in the patient with diastolic dysfunction. Furthermore, symptomatic diastolic heart failure is more likely to be responsive to diuretics than ACE inhibition.

Did withdrawal of diuretics at the time of randomization induce heart failure in susceptible individuals? Ninety per cent of the ALLHAT participants were on antihypertensive medication at the time of randomization. Unfortunately, no record was kept of the pre-randomization medication, but it is likely that a significant proportion of patients were taking a diuretic. As there was no washout period, the study drug was started immediately on discontinuing the pre-study medication. It is noticeable from the "survival" curve (Figure 4) that most of the episodes of heart failure occurred very early after randomization for both lisinopril and amlodipine allocated patients. It is possible that a number of patients had pre-existing heart failure that was suppressed or masked by the diuretic.

Is the failure of lisinopril to prevent heart failure related to the choice or dosage of ACE inhibitor? Although there are differences between ACE inhibitors,[7,10] lisinopril has been shown to be effective at the doses used in ALLHAT. In the GISSI 3 study, lisinopril 10 mg daily reduced mortality by 12% following MI.[11] The ATLAS study[12] demonstrated that lisinopril, at a daily dose of 32.5-35 mg compared to low dose (2.5-5 mg), reduced the combined endpoint of death and hospitalization for heart failure by 15%. Yet, for effective blood pressure control, lisinopril may need to be given twice daily. Furthermore as lisinopril is one of the least lipid soluble and least tissue specific ACE inhibitors, it may differ from agents (eg, ramipril) with proven vasculoprotective properties.

Metabolic consequences

Cholesterol levels, the prevalence of hypokalemia, and new-onset diabetes were greater in the chlorthalidone than in the other treatment groups. Over the relatively short period of the trial, follow-up of these metabolic abnormalities did not appear to result in more cardiovascular events. However, diabetes and increased cholesterol may take many years to cause MI or stroke.

Hydrochlorothiazide is not chlorthalidone

The ALLHAT group generalized their observations to all thiazide diuretics; however, chlorthalidone is a more powerful and long-acting diuretic than hydrochlorothiazide, which is the most commonly used diuretic for blood pressure control in Canada today.

Impact of ALLHAT on the use of CCBs and ACEis in managing hypertension

Dihydropyridine CCBs (DHP-CCBs): ALLHAT showed that amlodipine resulted in similar outcomes as chlorthalidone except for an apparent increase in heart failure. Claims that the DHP-CCBs increase mortality and MI appear to be unfounded by this large study.

ACE inhibitors: The higher incidence of heart failure in the ACE inhibitor-treated patients goes against previous clinical trial findings. ACE inhibitors have been shown to improve survival in patients with heart failure and prevent its onset in patients with left ventricular dysfunction, with or without a recent MI.[13] However, for patients with heart failure, ACE inhibitors alone do not suppress either dyspnea or edema, and diuretics are usually required for symptomatic control.

Other studies

The STOP 2 study[14] compared blood pressure control with an ACE inhibitor versus diuretic or beta-blocker based therapy. Although there was no significant reduction in cardiovascular mortality, heart failure was 16% less in the ACE inhibitor group. In contrast, the CAPP trial[15] showed a strong trend for a reduction in cardiovascular mortality by 20%, yet a neutral effect on the incidence of heart failure.

The recently reported Second Australian National Blood Pressure Study ($ANBP_2$) trial[16] showed that an antihypertensive strategy using ACE inhibition resulted in an 11% reduction of cardiovascular events or death compared to a diuretic-based strategy. In this study, where identical blood pressures were achieved in both treatment arms of the study, there was no difference in heart failure or stroke.

The HOPE study[17] in patients with vascular disease or diabetes (with at least one risk factor) demonstrated that treatment with ramipril, when added to conventional treatment, resulted in a 22% reduction in death, stroke, or nonfatal MI. Although the HOPE study was not a hypertension trial, almost half the patients had a history of hypertension. Yet, the observed reduction of events was similar in both the hypertensive and the non-hypertensive patients. Thus, a reduction in major cardiovascular outcomes with ramipril was observed in the hypertensive cohort when the ACE inhibitor was given in addition to the pre-randomization antihypertensive medication.

The 3 mm Hg difference in systolic blood pressure observed in ramipril-treated patients is unlikely to have been a sufficient reduction in blood pressure to result in the observed large reduction of cardiovascular events.[18]

ACE inhibitors will remain an important agent for both blood pressure control and vascular protection, with a large body of evidence supporting their use in high-risk patients. Diuretics will continue to be essential medications for blood pressure control, especially in the elderly and in a black population. The combination of an ACE inhibitor and a diuretic is often required to achieve blood pressure targets, and the combination is probably as important as the agents used.

Conclusions

The ALLHAT study shows that effective blood pressure control to target levels can be achieved in a high proportion of older patients from a wide range of ethnic groups using 1 of 3 treatment regimens. Using chlorthalidone, amlodipine, or lisinopril, there was no difference in the incidence of death or MI rates over the 6-year period of the trial. The higher stroke rates observed in the lisinopril-treated patients are likely a consequence of poorer BP control in the black patient group. Increased heart failure was observed early after randomization, especially in those randomized to lisinopril and may reflect prior suppression of congestive symptoms because of pre-trial treatment with a diuretic. A more complete understanding of mechanisms and subgroup findings may be forthcoming after further analyses of the ALLHAT database.

In the absence of a positive primary end-point, ALLHAT is most unlikely to negate the benefits of large trials with clearly positive outcomes. The trial confirms the safety and efficacy of diuretics as first line treatment for mild-to-moderate hypertension over the 6-year period of the study. Furthermore, diuretics will continue to play a major role in combination therapy, along with multiple antihypertensive drugs, as these are usually required to achieve blood pressure targets.

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