ALLHAT in Perspective: Implications to Clinical Practice and Clinical Trials

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Summary

The ALLHAT study is the biggest randomized clinical trial in hypertension ever conducted. Its objective was to compare the efficacy of newer (calcium channel blocker amlodipine and angiotensin-converting enzyme inhibitor lisinopril) to the older (diuretic chlorthalidone) antihypertensive agents in the treatment of patients with hypertension. After enrolling 42 000 patients who were followed for an average of 4.9 years, ALLHAT did not find significant differences in the primary end-points between these antihypertenive agents. ALLHAT however found significant differences in the secondary end-points such as heart failure and strokes between chlorthalidone and amlodipine or lisinopril. Based on these and on economic reasons, the investigators unequivocally recommended diuretics as the first line therapy for hypertension. Since its publication, ALLHAT has been much discussed, debated and opined. The choice of drugs for study, the study design, the conduct of the study and the conclusions drawn by the investigators had all been criticised or controversial. Yet ALLHAT has been widely quoted, commented upon or referred to and it has been instrumental in initiating the JNC VII Guidelines. Thus a thorough understanding of ALLHAT is necessary for clinical practice and in designing and evaluating clinical trials in the future. *Moving Points in Medicine* will capture the essence of ALLHAT, discusses its implications to clinical trials and explores its possible impact on the practice of medicine in this country.

Key Words: Hypertension, Clinical trials, Clinical practice, ALLHAT

Introduction

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[1] aims to determine whether treatment with calcium channel blocker or an angiotensin-converting enzyme inhibitor would lower the incidence of coronary heart disease (CHD) other cardiovascular disease (CVD) events when compared to a diuretic. Since its publication on December 18, 2002 there had been numerous reference to this important study; by now there have been over 200 publications addressing, quoting or referring to ALLHAT. Even by January 2005, there had been reference to it[2]. It was an important driving force and a major source of reference for JNC VII[3]. It is thus a very important publication with potential wide-ranging implications to the care of patients with hypertension worldwide.

The burden of hypertension and its implications

Hypertension is common and increasing in developed countries. Between 1990 to 2000, the US population grew by 13.2%, yet in the same period the estimated number of individuals with hypertension increased by 30%[4]. The prevalence of hypertension in the US rose from 28.9% in 1990 to 31.3% in 2000, from 50 million to 65 million adults[5]. But hypertension is also a common public health issue across all regions in the world. Kearney et al[6] estimated that 26.4% of the world's adult population in 2000 had hypertension

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involving some 972 million individuals (developing countries contributed two-thirds to the total). They predicted that there would be a 60% increase in the number of individuals with hypertension to a total of 1.56 billion individuals in 2025 (the developing countries will contribute three-quarters of the total). In Malaysia, whilst high prevalence of hypertension is to be expected in urban areas, it should not be underestimated among the rural population. The Raub Heart Study shows that the prevalence of hypertension among adults in the Raub district (a rural area) was high and increasing in both male and female adults[7, 8]. Hypertension is of course causally related to a number of cardiovascular and renal diseases[9, 10]. It is a leading cause of mortality and is the third leading cause of disability-adjusted life-years[11]. Control of hypertension leads to significant mortality and morbidity benefits[12-14] but achieving blood pressure control (BP < 140/90 mmHg) is variable between populations and remains an elusive goal in many populations[15]. Thus any initiative which leads to better control of hypertension is welcome and watched intently.

ALLHAT study design

ALLHAT was a large randomized, double-masked, multicentre clinical trial involving over 42 000 adults with hypertension followed up for a mean of 4.9 years sponsored by the National Heart, Lung and Blood Institute. At the time that ALLHAT was designed, diuretics and beta-blockers had been shown to be of benefit to patients with hypertension and so did newer antihypertensive agents such as angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers (CCB). However, the comparative value of these agents and their relative benefit in high risk patients such as those with diabetes, blacks or elderly was not yet certain. ALLHAT was to determine whether fatal coronary heart disease and nonfatal myocardial infarction in high risk patients with hypertension was lower when treated with a CCB (amlodipine), an ACE inhibitor (lisinopril) or an alpha-blocker (doxazosin) as compared individually with a diuretic (chlorthalidone). Secondary end-points included all-cause mortality, stroke, and other CVD events. Included in ALLHAT were men and women aged 55 years or older with stage 1 or stage 2 hypertension with at least 1 additional cardiovascular risk factor. Excluded were those hospitalized or treated for symptomatic heart failure and/or those with left ventricular ejection fraction < 35%. Subjects could continue with any prior antihypertensive drugs till randomization, and the study drug initiated the following day. The subjects were randomized into four arms, each consisting 9000 – 15 000 subjects. The target BPs during the trial was less than 140/90 mmHg. If this was not achieved, the study drug was up-titrated (Step 1), failing which open-label agents (Step 2 or 3) were added. Step 2 drugs consisted of atenolol, clonidine, or reserpine and Step 3 drug was hydralazine.

Study outcomes were ascertained during follow-up clinic visits (at 1, 3, 6, 9 and 12 months and thereafter every 4 months). Events were not however adjudicated except for the doxazosin arm where agreement rates between Endpoints Subcommittee and clinic investigators were 90% for the primary outcome, 85% for heart failure hospitalization and 84% for stroke. ALLHAT subjects had a mean age of 67 years; 47% were women, 35% were black, and 36% had diabetes. The mean length of follow-up was 4.9 $\pm$ 1.4 years; visit adherence was 92% at 1 year and 84% - 87% at 5 years while study drug adherence was 87.1%, 87.6% and 82.4% at 1 year and 80.5%, 80.5% and 72.6% at 5 years for chlorthalidone, amlodipine and lisinopril respectively.

ALLHAT findings

Chlorthalidone was shown to be superior to doxazosin which was terminated early[16]. The mean baseline BP was 146/ 84 mmHg. Over the study period, the BPs were well controlled in all the groups but equivalent BPs were not achieved. The mean systolic BP was 2 mmHg higher in the lisinopril group than the clorthalidone group, 4 mmHg higher in blacks, and 3 mmHg higher in patients aged 65 and older. The mean diastolic BP was 1 mmHg higher in the chlorthalidone group than the amlodipine group. Achievement of BP goal was 68.2%, 66.3% and 61.2% chlorthalidone, amlodipine and lisinopril groups respectively.

There was no significant difference observed in the primary outcome of fatal CHD and nonfatal myocardial infarction or secondary outcomes between chlorthalidone and amlodipine, and chlorthalidone and lisinopril except for the lisinopril group had a 15% higher risk for the secondary end-points stroke (P = 0.02) and a 10% higher risk for combined CVD (P < 0.001) compared to chorthalidone. Amlodipine when compared to chlorthalidone was associated with a 38% higher risk of heart failure (P<0.001) and a 35% higher risk of hospitalized/fatal heart failure (P <0.001). Lisinopril when compared to chlorthalidone was associated with a 19% higher risk for heart failure (P = 0.001), an 11% increase in the risk for hospitalized /

treated angina (P = 0.01), a 10% higher risk for coronary revascularisation (P = 0.05).

Conclusions by ALLHAT investigators

The ALLHAT investigators concluded that 'thiazide-type diuretics should be considered first for pharmacologic therapy in patients with hypertension'.

The strengths of ALLHAT

ALLHAT has a number of strengths. It is a randomized, double-blind clinical trial and to date the largest clinical trial on hypertensive patient population with good statistical power. It involves important population groups which are often understudied eg. women, blacks and the diabetics

Criticisms of ALLHAT

Despite the considerable and multiple strengths of ALLHAT as stated above, concerns and criticisms of the study had been expressed, viz:

1. Study design. There was no washout period. At randomization, 90% of the subjects were on active antihypertensive treatment. This study design might unmask asymptomatic heart failure in the group randomized to either amlodipine or lisinopril, especially if their diuretics were quickly withdrawn. Over the study period, there was a substantial cross over; 13-17% of the study subjects took comparator drugs.
2. Choice of drugs. While the choice of drugs may portray the practice in the United States, chlorthalidone is not as widely used as chlorothiazide elsewhere. Step 2 (clonidine and reserpine) and step 3 drug (hydrallazine) are drugs which are seldom, if ever, used in other places currently. The drugs used do not seem to portray modern antihypertensive therapeutic regime. Angiotensine receptor blockers were of course not tested.

   The order in which the drugs were introduced may lead to unhelpful combinations such as beta-blockers with ACE inhibitor rather than diuretic with ACE inhibitor. Further, the three antihypertensive drugs compared in ALLHAT unfortunately did not have similar pharmacodynamic characteristics. For instance, whilst amlodipine and chlorthalidone are long-acting, lisinopril (taken once daily) has a duration of action of only about 16 hours[17]. In addition, lisinopril is not tissue selective as ramipril or perindopril which achieved remarkable successes in the HOPE[18] and PROGRESS[19] studies respectively.
3. Study populations. The large number of women recruited into the study is certainly commendable. However the inclusion of a large number of blacks in a study where ACE inhibitor was widely used might complicate results as blacks are widely known as less responsive to ACE inhibntors[20, 21]. In ALLHAT, there was a 15% overall advantage of chlorthalidone attributed to a 40% benefit with the blacks and no detectable difference in nonblacks.
4. Lack of adjudication of events may lead to errors in conclusions of observations. The high incidence of heart failure among amlodipine group may be due to misclassifying ankle oedema as CCF, thus overdiagnosing the condition[22]. However post-hoc validation study in a subset of patients confirmed the validity of the diagnosis of CCF requiring hospitalization or resulting in death[23, 24].
5. As BP is an important determinant of future cardiovascular risks, in blood pressure study comparing the effects of two drugs, it is imperative that equivalent BP lowering be achieved during the course of the study. BP equivalence was however not achieved in ALLHAT. This was especially so among the blacks; the systolic BP was 4mmHg higher in those randomized to lisinopril as compared to chlorthalidone. This was translated into a 16% difference in CVA, 21% difference in heart failure and 6% difference in CHD or MI. Further only 61.2% - 68.2% of the overall subjects studied achieved the BP target of 140 / 90 mmHg; more than a third of the subjects did not get optimal therapy. Therapy and concepts of disease evolved over the years. It is now accepted that 140 / 90 mmHg is probably too high and suboptimal for patients with diabetes[25] who constituted more than a third of the ALLHAT subjects.
6. The occurrence of newly diagnosed diabetes significantly differed between the three groups by two years into the study, ie. 9.6% in chlorthalidone group vs 7.4% in the amlodipine group (P = 0.006) and 5.8% in the lisinopril group (P < 0.001). This was further exaggerated at 4 years to 11.6% in the chlorthalidone group vs 9.8% in the amlodipine group (P = 0.04) and 8.1% in the lisinopril group (P < 0.001). These marked differences did not seem to have affected clinical outcomes. These observations of course stimulated considerable interest, comments and opinions. Does new onset diabetes have a different prognostic implication to the patients? Was the observation in ALLHAT limited by the duration of the study? It has been known that hypertension is often associated with

insulin resistance and that these patients tend to develop diabetes[26-28]. Use of diuretics as compared with calcium channel blockers or angiotensin converting enzyme inhibitors has been shown to be associated with an increased risk of developing diabetes[29,30]. Verdecchia et al.[31] recently showed that after a 1 to 16 year follow-up of 795 initially untreated hypertensive subjects, 5.8% developed new onset diabetes (53.5% of these were on diuretics, compared to 30.4% of those who did not develop diabetes, P=0.002) and were associated with a 2.92 relative risk of developing cardiovascular events compared to those who did not develop diabetes (3.57 for those with previous diabetes).

7. Generalisability of the results of ALLLHAT. The subjects studied in ALLHAT were high risk, elderly patients with fairly advanced hypertension state. Can the results of ALLHAT be extrapolated to the low risk hypertensive patients who form the vast majority of patients treated for hypertension? The goals of treating low risk patients are different from those for high risk patients. For stage 1 hypertensives, the goal is to prevent the development of high risk state whereas that of high-risk hypertensives is to prevent life-threatening complications of the already existing disease. Duration of therapy for chronic diseases such as hypertension may have implications to prognosis. Verdecchia[31] demonstrated the necessity for long-term follow-up to witness the prognostic impact of the newly developed diabetes which was not observed in ALLHAT. To what extent can a 4 - 5 years of trials be extrapolated to the much longer life expectation of middle aged patients with lower risk hypertension? Lifestyle of patients, hypertensive patients are not exempted, may have implications on therapy and outcomes. The often medium to high salt intakes among Americans might have blunted the beneficial effects of ACE inhibitors and hence would have perhaps contributed to the lower than expected performance of lisinopril in ALLHAT. Further, while ALLHAT enrolled a sizable number of blacks and whites, how much are its results applicable to the Hispanics and the Asians?
8. Some ALLHAT observations are divergent or in contradiction with other studies, some of which were milestone studies. ACE inhibitors have been found to be useful in heart failure in trials involving more that 10,000 patients with various background[32-35] and have been shown to offer renoprotection especially among patients with diabetes[36]. Statins have been found to be useful in various categories of patients with hyperlipidaemia or at high risk of cardiovascular events[37-40], yet the use of pravastatin in a moderately hypercholesterolaemic patients with high risk hypertension was not found useful in ALLHAT[41]. But this may be due to the fact that there was substantial use of statins among the usual-care group leading to only 9% and 17% differences in the levels of total cholesterol and LDL-cholesterol between the two groups by the end of the trial. Thus, the systematic divergence from other major studies calls to mind whether there was a systematic problem in the design and conduct of ALLHAT (or alternatively in those other studies), a chance finding (probably not, given the statistical power of ALLHAT) or a true reflection of the state of affairs.
9. ALLHAT was heralded as a clinical trial on the comparative efficacy of antihypertensive agents as the first-line treatment for hypertension. Given the sort of subjects recruited, that 90% of them had already been on antihypertensive agents and over the follow-up period, about 40% of them received step 2 or 3 therapies, ALLHAT was not really assessing the impact of first-line therapy on clinical events. Cardinal et al.[42] reported that persistence of the initiating therapy at one year of follow-up was between 5% - 75%. Perhaps it does not really matter with what antihypertensive agent the patients start up with, what matters is what they end up with.
10. Conclusions by the investigators. Perhaps this has been the most controversial of all. The investigators concluded in favour of diuretics based not on primary end-points (in which there was no difference between the antihypertensive agents used) but on secondary end-points and financial consideration. However this was taken up by JNC VII[3] which recommends initiating therapy with diuretics or beta-blockers.

Implications for clinical trials

Randomised controlled trials had been accepted as the gold standard by which the relative efficacy of drugs is being tested. This will then form an important evidence base for guidance in clinical practice. Of late, more and more mega-trials (recruiting more than 1000 patients) are being conducted, particularly when more often the control is not placebo but an alternative, active drug. ALLHAT shows that big is not always without problems. Attention to details (eg. study

design, event adjudication) and current clinical practice (eg. in the choice of study drugs) is important when designing a clinical trial so that it would truly reflect current clinical practice and current clinical dilemmas that require solution.

Implications for clinical practice

For those who have advocated diuretics or beta-blockers, ALLHAT comes in as a major justification for their views and practice. But the side effects of diuretics cannot be easily brushed aside. Newly diagnosed diabetes for example is not benign or innocuous[31]. Neither should diuretic-induced hypokalaemia be overlooked as it could abolish any benefit associated with BP lowering[43]. Further, adequate control of not just hypertension but also the prevention and/or control of hyperlipidaemia and diabetes and the promotion of healthy life-style (eg. avoiding smoking, overweight and sedentary) are tremendously important. Patient insight and society awareness of the burden of hypertension may be crucial in overcoming this malady.

Conclusions

Within the limitations of this study, ALLHAT shows that there is no difference in the cardiovascular outcome between CCB, ACE inhibitors or diuretics in the treatment of hypertension. The choice between these drugs may be influenced by other considerations such as availability and affordability. Adequate control of blood pressure remains a key driver of outcome among patients with hypertension. Patients and their carers must be prepared to use more than one antihypertensive agent in achieving this, and hence in improving the prognosis of these patients.

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