Guest Editorial

ALLHAT: More Answers or Questions?

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Hypertension is one of the most important preventable causes of premature death worldwide. Although lowering of blood pressure by anti-hypertensive agents have been shown to reduce morbidity and mortality in major clinical trials, the optimal antihypertensive agent remains unclear. The recently completed and published Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[1] was the largest trial of antihypertensive therapy ever conducted. ALLHAT is also the first clinical trial that designed to compare different antihypertensive agents for prevention of coronary heart disease (CHD) with the combined incidence of fatal CHD and non-fatal myocardial infarction as the primary endpoint. Since the publication of the results of ALLHAT, there has been intense debate across the medical community about its implications. What is the clinical implication of the results of ALLHAT on our clinical practice in treating patients with hypertension, and are their findings applicable to the local Chinese population?

ALLHAT randomized 42,418 patients with mild to moderate hypertension aged >55 years old and at least one additional cardiovascular risk factors to one of four antihypertensive treatment: the diuretic chlorthalidone (12.5-25 mg daily), the angiotensin converting enzyme (ACE) inhibitor lisinopril (10-40 mg daily), the calcium channel blocker amlodipine (2.5-10 mg daily) or the α blocker doxazosin (1-8 mg daily).[1] This study included a higher percentage of women (47%), black Americans (35%) and patients with diabetes (36%). The doxazosin arm was terminated prematurely due to an excess of congestive heart failure. After a mean follow-up of 4.9 years, there was no difference in the primary outcome between treatment with chlorthalidone (11.5%), lisinopril (11.4%), amlodipine (11.3%). The ALLHAT investigators concluded that the thiazide-like diuretic is the preferred approach for the initial management of hypertension as it is no inferior to the other therapeutic classes in the primary outcome, but is less expensive. Furthermore, thiazide-like diuretic is more effective in blood pressure control and even superior than the other therapeutic classes on other outcome, such as congestive heart failure and stroke.[1]

However, there are some major flaws in the study design of ALLHAT. First, ALLHAT did not study the initiation of treatment which it was supposed to be. Rather, 90% of patients in ALLHAT were "roll-over" from previous treatment with no idea of their real starting blood pressure.[2,3] Ideally, there should have been a wash-out period to establish the baseline blood pressure. Second, there was partial and complete crossover of therapy in up to 20-25% of the study patients, which could potentially diminish the differences between the study drugs in an intention-to-treat analysis.[2,3] Third, up to 63% of patients in the study required two or more drugs to control blood pressure to the target level. The illogical combination of second step drugs (atenolol, clonidine and reserpine) made

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certain drug combination which both targeted the renin-angiotensin system (e.g. ACE inhibitor and beta-blocker) in an unfavourable position in blood pressure control. As a result, the groups treated with amlodipine and lisinopril did not achieve the same level of blood pressure control as chlorthalidone group. The final systolic blood pressure difference, albeit small, of 2 mmHg and of 0.8 mmHg in lisinopril and amlodipine group, respectively compared with chlorthalidone can account for the differences in the outcome in this large clinical trial. As a result, ALLHAT did not tell us the right combination of anti-hypertensive agents which could have a significant impact on the blood pressure lowering efficacy or cardiovascular outcome. In the LIFE study,[4] a losartan-based therapy together with a thiazide-type diuretics excelled in major cardiovascular outcome when compared with an atenolol-based therapy. Finally, in a subgroup of black people in which ACE inhibitor is well known to be less effective, a blood pressure disadvantage of 4 mmHg in the ACE inhibitor group was translated into a 40% increase in stroke risk when compared with diuretics.[1]

Furthermore, there is a major controversy about the interpretation of ALLHAT. The ALLHAT investigators concluded that a thiazide-type diuretics was more superior in reducing one or more major forms of cardiovascular disease over the ACE inhibitor and the calcium channel blocker.[1] However, this statement was primarily driven by a higher incidence of heart failure in the ACE inhibitor group and the calcium channel blocker group which was not a prespecified secondary end-point of the study. Indeed this finding goes in opposite direction to the meta-analysis of previous trials (Blood Pressure Lowering Treatment Trialists' Collaboration)[5] and a recent prospective clinical study (ANBP2)[6] that compared the incidence on heart failure of diuretics-based treatment with ACE inhibitor. In ALLHAT, congestive heart failure is diagnosed clinically by the primary-care physicians. It is possible that treatment with diuretics masked the signs of fluid-retention signs and might have led the investigators to the incorrect diagnosis. Moreover, the details on prior medication were not reported in ALLHAT.[1] It is probably a certain number of patients who were on diuretics were suddenly switched to the calcium channel blocker or ACE inhibitor which might contribute to fluid retention leading to an incorrect diagnosis of congestive heart failure. From the Kaplan-Meier curves of the study, it is evident that the difference in incidence of congestive heart failure occurred almost immediately after randomization and that the curves ran parallel at least up to the fourth year.

The ALLHAT investigators also ignore the potential long-term metabolic side-effects of diuretics.[1] They had implied that dyslipidemia, hypokalemia and new onset diabetes, which were more common among patients taking diuretics were not of clinical concern because they had no bearing on the final cardiovascular outcome. In particularly, considerably more patients developed new-onset diabetes in the chlorthalidone group (11.6%) than in the amlodipine (9.8%) and lisinopril (8.1%). However, the cardiovascular risk incurred over a 5-year period in the trial could not automatically assumed to be the same as the general population whom we are treating for a much longer period of time. In ALLHAT, there was no excess of sudden cardiac deaths (presumably due to arrhythmia) or all cause mortality in the diuretics arm, which apparently had negated the fear of electrolyte disturbance. It is well known that the Chinese diet is relatively deficient of potassium. Prior studies have demonstrated that the serum potassium concentrations in Chinese population is lower than those in Caucasian (3.82 mmol/L vs. 4.38 mmol/L),[7] In our local population, the use of diuretic for treatment of hypertension was associated a high prevalence of hypokalaemia.[8] Whether our local Chinese population being put on a diuretic-based therapy would fair equally well in cardiovascular mortality and morbidity outcome over the long term as the Caucasian remains unknown. Furthermore, it might not be correct to assume the efficacy and side-effect profile of the different thiazide-like diuretics (chlorthalidone, hydrochlorothiazides and indapamide) are equivalent,[6] which we based heavily on the latter two agents in our clinical practice at least in the government out-patient clinic.

Finally, the major consequence of hypertension in the Chinese population is stroke rather than CHD. In both ALLHAT[1] and large meta-analysis (Blood Pressure Lowering Treatment Trialists' Collaboration),[4] there was

a trend in favour of the calcium channel blocker for prevention of stroke. Therefore, calcium channel blocker may be more useful in Chinese patients with hypertension.

In summary, the results of ALLHAT do not provide us a clear answer to which agents should be used as first-line treatment for hypertension nor the ideal combination of drugs to achieve optimal blood pressure control. In this regard, the coming data from ASCOT (randomized treatment of a beta-blocker with or without diuretic vs. a calcium channel blocker with or without an ACE inhibitor) are awaited with interest.[9] However, this largest ever randomized hypertension trial have informed us that what matters most in managing hypertension is getting blood pressure controlled rather than which specific class of agents used. In the majority of patients, combination of several drugs will be required and the use of a low dose thiazide diuretic should be included.

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