COMMENTARY

ALLHAT: A Critical Assessment

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The ALLHAT study has attracted considerable attention in the media and in the research community, partly due to the study’s unexpected and controversial conclusions. However, the study has several serious shortcomings. The primary end-points in ALLHAT were negative and the conclusions are based entirely on secondary end-points and subgroup analyses. Moreover, there is good reason for skepticism concerning the findings on heart failure in ALLHAT, because of ambiguity in the diagnosis, lack of information on blood pressure and absence of a “washout” period. The study design was severely flawed and does not reflect clinical reality. Also, blood pressure differences between groups severely complicate interpretation. From a patient perspective in ALLHAT, there are drug safety concerns with the thiazides, as there was evidence of excess diabetes development. The ALLHAT results are difficult to generalize and have limited relevance in European settings. Thus, the ALLHAT study suffers from several major shortcomings and there is a huge body of evidence that contradicts the ALLHAT interpretations. Key words: ALLHAT study, diabetes, ethics, myocardial infarction, side-effects, thiazide.

INTRODUCTION

The ALLHAT study (Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) has attracted considerable attention in the media and in the research community, mainly due to the study’s unexpected and controversial conclusions. ALLHAT has previously been comprehensively analyzed in a previous editorial in this journal [1]. ALLHAT was at the time the largest study performed on treatment of hypertension [2]. Over 42,000 patients 55 years of age or older (average age 67) were initially randomized; an impressive study, with an impressive budget. However, the strength of a study is not determined only by its size, but also by the precision of its results. So what novel information did ALLHAT provide and how relevant is it for European patients?

DISCUSSION

Negative effects on primary end-points ignored

The original publication [3] states that the aim of ALLHAT was to answer the question of whether “newer types of antihypertensive agents are as good as or better than diuretics in reducing myocardial infarction and mortality due to coronary heart disease”. This is clearly a highly pertinent and interesting question. ALLHAT thus had two primary end-points: fatal and non-fatal myocardial infarction and fatal coronary heart disease. Total mortality and coronary heart disease were secondary end-points. The results show that in terms of the primary end-points, there was no significant difference between the three test substances: the diuretic chlorthalidone, the calcium antagonist amlodipine and the ACE inhibitor lisinopril. This should have led to the conclusion that the new drugs tested were just as good as chlorthalidone when the primary end-points were concerned. Primary end-points are called “primary” simply because they are meant to shed light on the study’s primary research question. A believer in evidence-based medicine (EBM) could in fact argue that the newer drugs are somewhat better than diuretics because they achieved the same lifesaving effect despite higher blood pressure, but none of these points was discussed in the ALLHAT paper or the press releases that followed.

New research question formulated retrospectively

Faced with these negative results, the ALLHAT study formulated a completely new research question [2], one that had definitely not been mentioned in the original publication that carefully described the study design [3]: What drugs are to be preferred for first-line antihypertensive therapy? Why and how this research objective was chosen retrospectively is not discussed, and is a deviation from good scientific principles [4]. The research objective should preferentially also have included analysis of
combination strategies, as most patients with hypertension are not controlled by monotherapy.

If we accept the retrospectively formulated research objective, then does it have any relevance and validity in the ALLHAT study? Certainly none, as 90% of the participants in ALLHAT had already been taking antihypertensive drugs for an unknown number of years before they were randomized to ALLHAT, and, moreover, there was no washout period in the study. This fact could be important for the final results of the study. The ALLHAT study was not a study of uncomplicated, newly diagnosed hypertension that would have been suitable for studies of “first-line therapy”. Further to that, blood pressures were poorly registered in 90% of the patients before entry into the study. Thus, the study design, as defined in 1994, precludes the possibility of answering the newly formulated research question. It is not possible to extrapolate findings from the high-risk individuals in the upper middle age range included in ALLHAT (47% of whom had atherosclerotic coronary heart disease) to the groups of people with mild, uncomplicated hypertension who predominate in Europe’s clinics. The ALLHAT authors conclude that, diuretics are both economically and medically “superior” as first-line therapy for the great majority of patients with mild hypertension. This claim however finds no support in ALLHAT, as a health economical analysis was not done. Some of the physicians involved in ALLHAT have even publicly deplored that the results of the study had been knowingly misinterpreted [5].

As yet, neither ALLHAT nor any other study has provided an answer to the important question of which antihypertensive therapy is to be preferred in the large group of patients with mild hypertension. No such study has yet been carried out. Perhaps a more clinically relevant question would be which initial or which combination of antihypertensive drugs is best. Currently, this remains unanswered, even though the LIFE-study [6] essentially compared combinations of old and new drugs, as thiazides were used for supplementary therapy to a major extent (90%) in both treatment arms. Indisputably, diuretics constitute valuable agents in the therapeutic arsenal, especially for treatment of elderly patients.

“Soft” secondary end-points given undue emphasis

What arguments do the authors of the ALLHAT study use to justify their conclusions? Because the primary end-points showed no difference, the authors were forced to emphasize “soft” secondary end-points and engage in subgroup analyses, which are a common strategy when dealing with such results, but questionable science [4]. One of the secondary end-points studied was “heart failure”, a condition even experienced cardiologists have difficulty diagnosing clinically. Remarkably, there was no washout period in ALLHAT, i.e. no medication-free period before introduction of the therapeutic agents. How was heart failure diagnosed, in the ALLHAT study? First of all, “heart failure” was not an independent variable, but constituted part of the secondary end-point “combined cardiovascular disease”. In other words, a subgroup analysis was done retrospectively, a procedure that substantially reduces the scientific value of the study [4]. Moreover, heart failure as defined in ALLHAT was not a “hard” end-point, and the study protocol included no standardized criteria for the diagnosis or monitoring of “heart failure”. The research protocol was part of a comprehensive 77-page manual that defined meticulously how stroke, myocardial infarction and mortality due to coronary heart disease should be diagnosed. On the other hand, all that was required for a clinical diagnosis of heart failure was that the physician in attendance put a checkmark in a box. ALLHAT reported increased risk of heart failure in patients who had been given lisinopril or amlodipine as compared to chlorthalidone [2]. This is quite a surprising finding, at least when lisinopril is concerned, as ACE inhibitors are among the most effective drugs available in the management of heart failure. Along with the spurious increased risk of stroke, heart failure accounted for all the supposedly increased risk of cardiovascular disease in patients treated with lisinopril. Heart failure is a condition with a high mortality rate, so one would expect the purportedly superior effect of chlorthalidone to have resulted in an unequivocal reduction of mortality in this group. However, this was obviously not the case, which casts even more doubt on the results of the analysis of heart failure.

Because 90% of the patients were known to have been hypertensive even before the study began, and a majority of them was already on diuretic therapy, it is likely that many of them had latent heart failure (though the symptoms were masked by the diuretics). If one studies the graphs showing heart failure in the patients treated with chlorthalidone and lisinopril, it is clear that the curves diverge very early, i.e. the patients are diagnosed as having heart failure very early. This is precisely the kind of curve one would expect to see if the effects of previous diuretic therapy lingered on, a problem that could have been circumvented by the usual practice of allowing a few weeks’ washout. This remarkable – and serious – weakness might also explain the apparent increase in the risk of heart failure in the group treated with doxazosin (which led to this treatment being discontinued ahead of schedule). In conclusion, there is good reason for skepticism concerning the findings on heart failure in ALLHAT, because of ambiguity in the diagnosis, lack of information on blood pressure and absence of a “washout” period.
Unrealistic study design and differences in blood pressure

A basic prerequisite for drawing sound conclusions about the effects of the various antihypertensive drugs on the end-points is – obviously – that the same blood pressure is achieved in the different study groups. This was not the case in ALLHAT. Systolic blood pressure after 5 years was significantly higher (2 mmHg; \( P < 0.001 \)) in the lisinopril group than in the chlorthalidone group, a difference that was even more pronounced at the beginning of the study. This precludes interpretation of the outcome of the effect measures done in the ALLHAT paper.

The differences in blood pressure are a likely result of the fact that one-third of the study population was Afro-American, in whom ACE inhibitors are known to be relatively ineffective [1, 7–9]. This unfortunate anomaly is compounded by the pre-defined – but highly unrealistic – study design, which banned the use of ACE inhibitors in combination with diuretics, which would have been an obvious, effective choice in the clinic. Instead, one was forced to combine the ACE inhibitor with the beta-blocker atenolol, a poor combination that is uncommon in clinical practice, as it is well known that atenolol inhibits the renin–angiotensin system [7–9]. The authors of the ALLHAT study admit in the article that this “…led to a somewhat artificial regimen…in the ACE inhibitor group” [2].

Blood pressure differences of the magnitude observed in ALLHAT can have major effects on morbidity and mortality, especially in high-risk populations like the one studied in ALLHAT [7, 9, 10]. For instance, the difference could very well explain the unexpected increase in the risk of stroke among patients randomized to the ACE inhibitor. Notably, in the HOPE study, ACE inhibitors were shown to have a favorable effect [11]. In addition, the entire increase in the incidence of stroke in ALLHAT is explained by lisinopril having increased the risk of stroke by 40% among Afro-Americans alone [2] for the reasons given above. Moreover, the difference in systolic blood pressure in the lisinopril group compared to chlorthalidone was 4 mmHg, corresponding to a 33% difference.

It is also noticeable that about 40% of the patients randomized to diuretics in ALLHAT were also given atenolol. As no subgroup analysis was done, we do not even know whether it was chlorthalidone alone or the combination of chlorthalidone and atenolol that influenced the primary end-points. Furthermore and of great importance, there was no end-point committee in ALLHAT, indicating that the principal investigator was not blinded throughout the study, and that there was no statement on sources of industrial funding.

Little relevance in a European setting

Can the findings from ALLHAT be extrapolated to European patients with high blood pressure? Not easily, as the diuretic tested in ALLHAT was chlorthalidone, a preparation that was removed from the Swedish market already in 1993 due to side-effects, particularly hypokalemia, gout and impotence. This thiazide preparation differs in several important ways from the thiazides that remain on most markets (i.e. hydrochlorothiazide and bendroflumethiazide). Chlorthalidone has an extremely long half-life (47 h) compared to the other thiazides (3 h). In addition, there are no head-to-head studies that directly compare chlorthalidone and the other thiazides currently in use. Given this background, is it not compatible with EBM to extrapolate the ALLHAT findings to the other thiazides.

Another weakness of the ALLHAT study that hampers extrapolation of its results to European conditions is the lack of a treatment arm involving beta-blockers. Even more serious is that the population studied in ALLHAT consisted to more than 55% of patients of Afro-American or Latin American background. In this respect, the study population differs markedly from the average population in Europe. As mentioned above, it is known that Afro-Americans respond less readily to ACE inhibitors and beta-blockers than do Caucasians. On the other hand, diuretics work very well in Afro-Americans. Ethnic background also has a major impact on how well various antihypertensive drugs are tolerated, and hence influences compliance. Moreover, the panorama of additional risk factors in hypertensives differs considerably between Americans and Europeans with high blood pressure.

In contrast to ALLHAT, the recent Australian study ANBP-2 (Second Australian National Blood Pressure Study) is of far greater relevance for European settings [12, 13]. The study population comprised 6083 individuals aged 65–84, with uncomplicated hypertension, and only 5% were non-Caucasian, making it similar to the European population. Unlike ALLHAT, ANBP-2 shows that therapy based on ACE inhibitors (enalapril) was significantly more effective than treatment with thiazides (hydrochlorothiazide) in reducing total mortality and preventing cardiovascular events in elderly patients with high blood pressure. The results of ANBP-2 show that treatment with ACE inhibitors leads to an 11% reduction of the relative risk of the primary end-point, and this effect was even more pronounced among men (17% reduction of the relative risk). It is worth noting that the groups in ANBP-2 showed no differences in blood pressure, another important advantage over ALLHAT. ANBP-2 also employed a broad, clinically relevant primary end-point, namely total mortality and cardiovascular events.

Lack of patient perspective in ALLHAT

Whatever effects various therapeutic drugs may have on
“hard” end-points, the drugs will be useless if untoward side-effects impel patients to stop taking them (i.e. poor compliance), frequently without telling their physician. In many countries, the patient’s right to participate in and be informed about his or her own treatment is regulated by law. This has generally been interpreted to mean, among other things, that doctors must notify their patients about the possible side-effects of drugs. In this respect, a diuretic such as chlorthalidone will increase the risk of impotence, hypokalemia, hypomagnesemia, hyperuricemia and gout, hyperlipidemia, hyperglycemia, insulin resistance and diabetes.

As yet, recurrence of adverse effects in the two groups are scarcely mentioned in ALLHAT. For instance, the renal effects are described in terms of “a slower decline in kidney function in the amlodipine group” [2]. This effect was highly significant ($P < 0.001$) and is to the disadvantage to chlorthalidone. In fact, chlorthalidone was inferior to amlodipine on all counts where metabolic effects were concerned. Thus, in ALLHAT, chlorthalidone led to a highly significant increase in the risk of high cholesterol levels, hypokalemia, reduced renal function, hyperglycemia and diabetes [2,7–9]. These effects are likely to be of long-term disadvantage to patients on the diuretic therapy.

**Thiazides increase the risk of diabetes and heart attack**

Early as well as recent meta-analyses of hypertension studies have shown that reduction of blood pressure achieved by drug therapy did not reduce mortality due to coronary heart disease to the extent expected based on epidemiological data [14]. This was particularly true in studies of young people with hypertension who were treated with diuretics [14]. One possible explanation pointed out to this discrepancy could be that the deleterious side-effects of diuretics cancel out the positive effects of blood pressure reduction. It has therefore been argued that other classes of antihypertensive drugs, which do not have these untoward metabolic side-effects could benefit the patient in more ways than merely by lowering blood pressure.

In ALLHAT, treatment with chlorthalidone conferred a relative risk increase of 43% over lisinopril in terms of 4-year incidence of new diabetes. However, it could not be clearly demonstrated that the pro-diabetic effect of chlorthalidone resulted in any complications. This led the authors to the remarkable conclusion that the diabetogenic effect would probably be of no importance in patients treated with thiazides. This casual dismissal of the risk of diabetes is naïve for several reasons. It is well realized that hypertension and diabetes are chronic conditions that require treatment for many years (perhaps 30–50), far longer than the 4.9 years studied in ALLHAT.

It takes years before angiopathic complications become apparent in diabetics and result in clinical symptoms. A study time just short of 5 years is clearly inadequate to substantiate the safety of antihypertensive but potentially diabetogenic drugs. It is also difficult to understand why “endogenous” diabetes would cause cardiovascular damage that is in any way different from that caused by “iatrogenic” diabetes especially in patients with hypertension.

Indeed, in a recent study from Uppsala [15], 1860 Swedish males were examined at age 50, again at 60, and then followed up for 17.4 years. Those participants who at age 60 were being treated for hypertension with beta-blockers and/or thiazide diuretics showed a greater increase in blood glucose levels between the 50- and 60-year examinations than the participants who were not being treated for hypertension. The increase in blood glucose was an independent risk factor for incident myocardial infarction after age 60 in the group taking antihypertensives, even when one took into account the usual risk factors, such as fasting glucose, insulin, BMI, blood pressure and lipids [15]. This shows that the diabetogenic effect of some common antihypertensive agents in patients also confers on these patients an increased risk of myocardial infarction within a clinically relevant time frame. It should be pointed out that these calculations did not include or take into account the microvascular complications (e.g. in eye and kidney) that would also be expected to occur as a consequence of the drug-induced diabetes.

The positive metabolic effects of ACE inhibitors and angiotensin receptor antagonists in terms of increased insulin sensitivity, reported in several studies [11, 16–18], should be considered when a physician is selecting a strategy for treatment of hypertension, especially when the patient already has diabetes or runs a risk of developing abnormal glucose tolerance. Patients at risk include those with high BMI, high blood pressure, smokers, people of advanced age and people with heredity for type 2 diabetes [19]. Above all, this selection is of importance because several treatment options are available, including thiazide diuretics, which have a well-documented capacity significantly to reduce glucose tolerance. Add to this the cost of late complications of diabetes, in particular renal failure, which in the USA alone costs over 15 billion dollars annually.

Clearly, hypertension and diabetes is a particularly unfavorable combination, as has been shown by UKPDS [20]. Hypertension *per se* more than doubles the risk of diabetes [21]. The physician can further increase this risk and simultaneously increase the patient’s risk of myocardial infarction, or do the opposite, simply by choosing what to prescribe to his or her hypertensive patients.
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