ALLHAT Trial & ALLHAT Meta-Analysis Critique

Table of Contents

ALLHAT Trial Critique- Overview

The ALLHAT hypertension study came to conclusions not supported by the results of the trial. The ALLHAT trial is a trial with a reasonable data set, but a "political" set of conclusions. The controversy that immediately followed the publication of the ALLHAT trial was a marker for conclusions that extended beyond a reasonable and conservative interpretation of the data.

The ALLHAT trial compared three blood pressure treatment regimens, one starting with a diuretic (cholthalidone), another with an ACE inhibitor (lisinopril), and a third with a calcium channel blocker (amlodipine-Norvasc).

The ALLHAT trial authors inappropriately concluded that their study proved that a diuretic is the best initial treatment for high blood pressure.

Why are the ALLHAT authors' conclusions that their trial proves that a diuretic is the best initial treatment for high blood pressure invalid?

1. *Blood pressure treatment trials compare specific multiple drug treatment trials rather than isolated drugs.* The ALLHAT trial protocol called for suboptimal subsequent drug combinations to be used with the ACE inhibitor (lisinopril) and calcium channel blocker (amlodipine) groups. This put the ACE inhibitor and calcium channel treatment regimens at a disadvantage in a way that does not reflect the routine clinical practice of physicians using these drugs.

2. Despite the suboptimal combinations of medication mandated by trial protocol, the primary trial endpoint of fatal coronary heart disease and nonfatal myocardial infarction, as well as all cause mortality were identical for all three treatment groups.

3. Many modern day blood pressure trials create treatment protocols allowing for equivalent blood pressure endpoints to be achieved. The ALLHAT trial protocol, however, resulted in a 3mm lower systolic blood pressure with the diuretic treatment arm compared to the ACE inhibitor initiated group. *The ALLHAT authors then tried to statistically correct for the effects of this 3mm difference, but substantially underestimated the effect on outcome of the 3mm difference in blood pressure that occurred between diuretic arm compared to ACE inhibitor arm of the trial.*

4. *The ALLHAT trial actually withdrew diuretic therapy from a large number of patients when they first were enrolled into the trial.* (Over 90% of the patients at the time they entered the trial had blood pressure medications withdrawn.) Many

of these patients had a prior heart attack or had thickening of the heart muscle (LVH). Withdrawing diuretic therapy placed these patients at special risk for developing CHF (congestive heart failure) when they previously had otherwise been without problem. This helps explain the higher incidence of CHF in the nondiuretic treatment arms of the trial. *The protocol contrived situation may also explain why the increased CHF incidence in the ALLHAT trial was not associated with the usual increase risk in mortality which usually otherwise routinely accompanies CHF.*

5. *The ALLHAT authors discount the significance of the 43% higher rate of diabetes developing with the diuretic protocol compared to the ACE inhibitor protocol and the 17% increase in incidence of diabetes of the diuretic protocol above the amlodipine protocol.* This was not associated with an increase in mortality during the trial, but neither was the increased incidence of CHF, which in contrast, the ALLHAT authors treat as tremendously important in their analysis. This difference in emphasis is a bias that adversely affected the conclusions of the ALLHAT authors.

ALLHAT influenced JNC 7 guidelines for hypertension compared to European Society for Hypertension Guidelines

The United States guidelines for the treatment of hypertension were formulated shortly after the publication of the ALLHAT trial. A number of the ALLHAT authors were on that commission. (Joint National Committee on Hypertension.) There was considerable debate within that committee, but the ALLHAT authors prevailed and the JNC-7 guidelines for the United States published recommended diuretic therapy as initial therapy for uncomplicated hypertension.

The European Society for Hypertension guidelines for hypertension are quite different from the ALLHAT influenced JNC 7 guidelines for hypertension. In contrast to the JNC 7, the European Society for Hypertension guidelines created in response to the same studies state that the major classes of antihypertensive agents, (including diuretics, beta-blockers, ACE inhibitors, calcium channel blockers, and angiotensin receptor blockers) are ***all*** *suitable for initial and maintenance therapy.*

The ALLHAT trial conclusions are only broadly applicable to the treatment of hypertension if the following fallacies are true:

1. The initial treatment with an ACE inhibitor or a calcium channel blocker precluded the use of a diuretic.

2. Starting an ACE inhibitor or calcium channel blocker required stopping diuretic therapy, including in patients with prior myocardial infarction or

patients with LVH.

3. An ACE inhibitor and calcium channel blocker could not be used in combination.

4. Equivalent blood pressure endpoints could not be achieved if an ACE inhibitor was used as the initial drug.

1. 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: 2981-2997.

Critique of the Flawed Meta-Analysis Subsequently Written By ALLHAT Authors

The construction and interpretation of a meta-analysis involves a series of choices and decisions that are subject to potential bias. A meta-analysis[1] was subsequently published shortly after the ALLHAT trial publication[2] by the some of the same authors who were involved in formulating ALLHAT's inappropriate conclusions. The authors of this meta-analysis try to bolster the contention that the ALLHAT trial demonstrated that a diuretic drug should be the initial drug used for the treatment of hypertension. Their meta-analysis has major limitations and biases.

The typical meta-analysis tries to combine studies that are similar enough to be grouped and then analyze the pooled trials with the benefit of the increased statistical power available from larger numbers. The "son of ALLHAT" meta-analysis tries to examine prior blood pressure studies on the basis of which antihypertensive is used as the initial agent and then make conclusions about which is the comparatively preferred initial blood pressure agent.

A meta-analysis is more reliable if the trials are which are combined are highly similar. In this analysis, only the first blood pressure agent used was the same in what might be multiple drug regimens used for blood pressure control. In addition, this was a network meta-analysis which adds an additional variable to a meta-analysis. Rather than simply summing up trials that have evaluated the same treatment compared to placebo (or compared to an identical medication), different treatments are compared by statistical inference. (If A is better than B, and B equals C, then A is better than C.

The overly broad conclusions of this meta-analysis do not reflect the differences in blood pressure between the diuretic led therapy vs. the other therapies studied. In this network meta-analysis by Psaty et al, the diuretic led protocols had 3.0 mm lower systolic BP than ACE inhibitors, 4.9 mm lower than angiotensin receptor blockers, 2.4 mm lower than calcium channel blockers, and 1.8 mm lower than beta blockers[1].

Outcomes differences would be expected to follow differences in blood pressure. The authors state that "none of the differences was significant." and refer to a table in the report that shows p values including .08, .09, 0.11. However, the inability to find p differences of less than .05 for these differences in blood pressure does not negate the potential effect of these blood pressure differences on the outcomes reported.

The most powerful effect on cardiovascular disease of an antihypertensive medication is though the direct effects of lowering blood pressure which usually overpowers any other differences that may exist between antihypertensive classes of medications.

If this difference in achieved BP was a necessary result of the initial blood pressure agent, then it would be of primary importance since achieving a blood pressure endpoint has the most potent effect on reducing the complications of hypertension. However, modern day blood pressure protocols for comparing blood pressure treatment medication protocols can achieve equal blood pressure endpoints. (INVEST trial, ANBP2, Life trial).

The authors of this meta-analysis make a decision to exclude all past trials using higher dose of diuretic because the lower diuretic dosage reflects current care guidelines. However, just as trials using high dose diuretics are outmoded, so are trials that construct inadequate antihypertensive treatment protocols that routinely fail to achieve equivalent blood pressure results between groups of medication. If equivalent blood pressure endpoints are not achieved (with perhaps a different number of antihypertensive agents) then the trial results are going to be driven by the difference in blood pressure. The ALLHAT generated meta-analysis has clinical relevance if equal blood pressure endpoints can not be achieved with drug protocols using a calcium channel blocker, ACE inhibitors, or angiotensin receptor blocker as the initial blood pressure agent.

In the end, the whole concept of a single preferred initial blood pressure agent for all antihypertensive patients has considerable less meaning given that multiple drugs are routinely needed for to achieve current guidelines for blood pressure.

The potential for bias in a meta-analysis exist in multiple areas (details). The "son of ALLHAT" meta-analysis shows bias in the following areas of its construction and conclusions.

1. Inclusion/exclusion criteria used.
2. Statements of reliability concerning the methods used to perform this meta-analysis.
3. The conclusions which are reached.
4. Emphasis or lack of emphasis on factors potentially affecting this meta-analysis such as differences in levels of blood pressure achieved.
5. Declarations of broad applicability for the conclusions from this meta-analysis.

1. Psaty B, Lumley T, Furberg C, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents, a network meta-analysis. JAMA 2003; 289: 2534-2544

2. 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: 2981-2997.

Unreliable Correction Estimations in ALLHAT for Differences in Blood Pressures in Treatment Groups

Blood pressure studies comparing a combination of medications should ideally adjust medications in each treatment protocol until the same blood pressure is achieved in each treatment arm of the trial if possible. The ALLHAT trial protocol resulted in the diuretic arm achieving a resting blood pressure 3mm lower than the ACE inhibitor led strategy. This inappropriately favored the diuretic initiated treatment strategy.

The statistical manipulations and estimations available to correct for the differences in trial outcome resulting from this difference in blood pressure in the ALLHAT study are inaccurate.

*The ALLHAT authors attempt to statistically correct for the difference in blood pressure between the groups and appear to have substantially underestimated the effects of creating blood treatment protocols that did not obtain the same levels of blood pressure in their stud*y.

The ALLHAT investigators while discussing differences in stroke rate in black patients between diuretic and ACE inhibitor protocols in their initial 2002 report state that the 4 mm difference in systolic blood pressure is not consistent "with the difference seen in black patients (13%-16% expected, 40% increase in stroke rate observed)."

Hence the ALLHAT investigators are implying that the 4 mm difference in systolic blood pressure for black patients for the diuretic led therapy vs. ACE inhibitor led therapy explains only a 13-16% difference in stroke rate, not the 40% difference in stroke rate observed.

(The black patient population was the subgroup in the ALLHAT trial which had the largest difference in blood pressure (4mm) between the diuretic initiated treatment protocol vs. the lisinopril protocol and accounted for all the increased incidence in stroke in the *initial* ALLHAT report.)

There is no reason to accept this implication by the ALLHAT investigators that there is reason to assume there are special protective properties with diuretic therapy affecting the stroke rate beyond the well known established efficacy of a diuretic on BP control in the black population.

The ALLHAT's attempts to quantify the effects of the differences in blood pressure between the three blood pressure treatment protocols on the trial outcome are unreliable. To quote the ALLHAT investigators:

"However, such analyses are limited by the infrequency and imprecision of BP measurements for individual participants and regression dilution, which underestimates CVD risk associated with BP differences on single-visit (or even visit-averaged) measurements.[1]"

The estimation by the ALLHAT authors of the impact of the effect of the blood pressure differences on outcome for the blood pressure treatment regimens studied in the ALLHAT trial is inaccurate.

1. 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: 2981-2997.

ALLHAT TRIAL Treatment Protocol required Withdrawal of Diuretic Therapy from many Patients at Risk for CHF

The ALLHAT trial protocol[1] resulted in the withdrawal of preexisting diuretic therapy from many of the patients who were assigned to the lisinopril or amlodipine treatment protocols. (90% of the patients entered into the ALLHAT trial had prior blood pressure medications discontinued.)

In addition to the patients who had a diuretic withdrawn, there were patients at increased risk for CHF on the basis of prior MI and LVH, who were routinely not allowed to start a diuretic unless CHF developed or other difficulties arose.

It is not a surprise that CHF or volume overload developed in a significant number of patients over the course of the trial, since diuretic therapy could not be employed for early signs of volume excess. *And in contrast to CHF developing from a less contrived situation, the CHF occurring during the ALLHAT trial was subsequently treated without an increase in mortality when a diuretic could finally be instituted.*

ALLHAT Trial Provoked CHF: Impact of a High Threshold for Starting Diuretic

The frequency with which congestive heart failure develops in cardiovascular patients in a treatment arm without a diuretic in a blood pressure trial will tend to be inversely related to the threshold for starting or restarting a diuretic. The ALLHAT trial presumably had a high threshold for starting a diuretic in the protocol arms without diuretics.

Though this would enhance the purity of the treatment arms, this also would also lead to episodes of congestive heart failure that would not occur in routine clinical practice, even when other blood pressure medicines are initially used. In clinical practice, or in an open label trial, there will tend to be a lower threshold for the institution of a diuretic in the early stages of mild volume excess prior to the precipitation of full-fledged congestive heart failure**.** (A lower incidence of CHF would therefore tend to occur in those situations.) Similarly, every randomized hypertension trial involving treatment arms without diuretics will have a particular threshold for starting a diuretic as determined by trial protocol.

This increased incidence of protocol driven heart failure may be more readily treatable when the diuretics (which had been initially withheld by trial protocol) are ultimately initiated. This may help explain why the increased incidence of CHF in the ALLHAT trial occurred without the typical early increase in mortality associated with CHF.

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The ALLHAT Trial- Limitations of the Medication Protocols Used in this Trial

The ALLHAT hypertension trial[1] is a large study concerning the treatment of blood pressure which compares three drug treatment protocols. Blood pressure treatment trials are usually not the simple comparison of one single drug to another. *Since multiple drugs are often needed for blood pressure control, trials are actually comparing specific multiple drug treatment protocols against one another, rather individual antihypertensive drugs.* A set of drugs can have a good initial drug, but if the subsequent sequence of follow up drugs are not an optimal fit for the initial drug, it places the initial drug at a disadvantage.

One treatment strategy in the ALLHAT trial started with a diuretic. A second treatment strategy was initiated with lisinopril, an ACE inhibitor. A third treatment strategy started with amlodipine, a calcium channel blocker.

However, the ALLHAT trial protocol specified subsequent drugs to be given in combination with lisinopril and amlodipine that do not reflect optimal care or current medical practice.

An ACE inhibitor such as lisinopril is most commonly followed by a diuretic when a second drug for blood pressure is required. This combination was prohibited by the ALLHAT trial protocol until multiple other suboptimal choices for combination with lisinopril had been employed (atenolol, reserpine and clonidine). The potentially efficacious combination of a calcium channel blocker and ACE inhibitor was also not allowed by ALLHAT trial protocol. Neither an ACE inhibitor nor a calcium channel blocker could be used with a diuretic as a second medication.

The ALLHAT trial results reflect the outcome for the particular combination of drugs defined by trial protocol, not the outcome for the initial drugs in isolation.

Unfortunately, the ALLHAT authors came to conclusions unwarranted by the results and limitations of the trial. This same trial subsequently affected the current hypertension treatment guidelines (JNC7) in the United States.

The ALLHAT trial conclusions are only broadly applicable to the treatment of hypertension if the following fallacies are true:

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