
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.