

EDITORIAL OPINION

Hypertension Institute  
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ALLHAT Not All That It's Cracked Up to Be:  
Review of the Facts and the Science

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## Review of the Facts and the Science

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On December 17, 2002, the National Heart, Lung and Blood Institute (NHLBI) released the Antihypertensive Lipid Lowering Heart Attack Trial (ALLHAT) study. This is the largest prospective clinical hypertension study to date with 42,418 patients randomized and followed for 4 to 8 years (mean follow-up 4.9 years) in 623 clinical sites. This was a double-blind, randomized, multi-center clinical trial with a primary endpoint of fatal coronary heart disease (CHD) or nonfatal myocardial infarction (MI), and secondary endpoints of all cause mortality, stroke, combined CHD (nonfatal MI, CHD, death, coronary artery bypass graft [CABG], and hospitalization for angina), combined cardiovascular disease (CVD) (combined CHD, stroke, lower extremity revascularization, treated angina, fatal, hospitalized or treated congestive heart failure [CHF], hospitalized or outpatient peripheral arterial disease [PAD]), and finally other events such as renal outcomes (reciprocal serum creatinine, end-stage renal disease [ESRD], estimated glomerular filtration rate [GFR]) and cancer. Metabolic parameters such as cholesterol, potassium, glucose and new onset diabetes mellitus were also measured.

It is our belief that the results of this study have been largely misinterpreted and misquoted by the media. In fact, in the news release to the media, even the NHLBI had a misleading title with commissions and omissions that read as follows.... "NHLBI FINDS TRADITIONAL DIURETICS BETTER THAN NEWER MEDICATIONS FOR TREATING HYPERTENSION." Patients and physicians are once again confused about the data and what to do in the treatment of hypertension. The Hypertension Institute was one of the study sites for ALLHAT, and this is our interpretation of this hypertensive trial.

It is important to note that this study was performed in high risk patients with vascular disease or CHD risk factors consisting of an older age group over 55 years of age (average age was 67 years) with a large percentage of women (47%), African Americans (35%) and type 2 diabetic patients (36%). The drugs compared were Chlorthalidone, Amlodipine, Lisinopril and Doxazosin (dropped early in the trial). The drugs were given ONCE A DAY in the AM as follows: Chlorthalidone 12.5 to 25 mg, Amlodipine 2.5 to 10 mg, and Lisinopril 10 to 40 mg. Add-on therapy (tier 2 drugs) could be Reserpine, Clonidine, Atenolol and finally Hydralazine as tier 3 drug. The BP criteria for entry was UNTREATED SYSTOLIC OR DIASTOLIC HYPERTENSION defined as greater than or equal to 140/90 mm Hg but less than or equal to 180/110 mm Hg at two visits OR TREATED HYPERTENSION defined as less than or equal to 160/100 mm Hg on 1 to 2 antihypertensive drugs at visit one, or less than or equal to 180/110 mm Hg at visit 2 when med-

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ication may have been partially withdrawn. The mean BP at entry was 146/84 mm Hg. There were crossovers among the treatment groups of 7 to 9% at year five, and about 40% of the patients in each group were on tier 2 medications with an average of at least 2 antihypertensive medications per patient.

## WHAT ARE THE PRIMARY RESULTS?

### 1. BLOOD PRESSURE

- SBP:
- Amlodipine group was 1 mm Hg higher than the Chlorthalidone group ( $p < 0.05$ )
  - Lisinopril group was 2 mm Hg higher than the Chlorthalidone group ( $p < 0.05$ )
  - However the SBP was 4 mm Hg higher in the black population treated with Lisinopril than with Chlorthalidone ( $p < 0.01$ )
- DBP:
- Amlodipine group was 1 mm Hg lower than the Chlorthalidone group ( $p < 0.05$ )
  - Lisinopril group was the same as Chlorthalidone group

Therefore, Amlodipine was equally effective to Chlorthalidone in reducing mean arterial blood pressure. As is evident, although these small differences reached statistical significance because of the larger group sizes, the absolute differences are quite small. Actually, when one compares Chlorthalidone directly with Amlodipine, since each had  $< 1$  mm Hg difference compared to the other with systolic and diastolic respectively, there was no real difference. It should also be pointed out that significantly more patients enrolled in the Chlorthalidone arm than the other two (15,255 Chlorthalidone versus 9,048 for Amlodipine and 9,054 for Lisinopril).

### 2. PRIMARY ENDPOINT OF NONFATAL MI AND CHD DEATH

Amlodipine = Chlorthalidone = Lisinopril. THERE WAS NO SIGNIFICANT DIFFERENCE AMONG THE THREE DRUGS ( $p = .65$  for A/C and  $p = .81$  for L/C.) C = 11.5%; A = 11.3%; L = 11.4% (all 6-year rates)

The lack of any difference in the *primary end point* in this study is a key and significant finding that was not clearly emphasized in the press (remember this is a high risk, elderly, hypertensive population). It also points out that the small BP differences had no clinical significance.

### 3. SECONDARY ENDPOINTS

#### A. STROKE:

- There was a trend towards Amlodipine being better than Chlorthalidone (7% reduction in Amlodipine group but this was non significant) ( $p = .28$ )
- Chlorthalidone better than Lisinopril by 15% overall (6.3% vs. 5.6%; RR 1.15; 95% CI 1.02 – 1.30) ( $p < 0.02$ ). This was 40% less in the black population only, but there was

- NO DIFFERENCE IN NON-BLACK POPULATION: *i.e.* Lisinopril was as effective as Chlorthalidone (NS) in the non-black population.

#### B. CHF:

- Chlorthalidone better than Amlodipine by 38% (10.2% vs. 7.7%; RR 1.38; 95% CI 1.25 – 1.52 [6 years]) ( $p < 0.001$ ) in preventing new onset non-fatal CHF.
- Chlorthalidone better than Lisinopril by 20% (8.7% vs. 7.7%; RR 1.19; 95% CI 1.07 – 1.31) ( $p < 0.001$ ) in preventing new onset non-fatal CHF.

#### C. ALL CAUSE MORTALITY:

- The three treatment groups were identical for mortality. For A/C  $p = .20$  and for L/C  $p = .90$ .

D. COMBINED CVD (combined CHD, stroke, lower extremity revascularization, treated angina, fatal, hospitalized or treated CHF, hospitalized or outpatient PAD):

- Amlodipine equals Chlorthalidone
- Lisinopril had 10% higher rate compared to Chlorthalidone (33.3% vs 30.9%; RR 1.10; 95% CI 1.05 – 1.16) ( $p < 0.001$ )

#### E. BIOCHEMICAL RESULTS:

Chlorthalidone caused significantly more hypokalemia (.3 to .4 mm ol/L), which has been linked to sudden death, hyperglycemia, (3-5 mg%) hypercholesterolemia (1-2 mg%), and new onset diabetes mellitus (1.8 to 3.5%) than Amlodipine or Lisinopril ( $p < 0.05$ ).

Chlorthalidone also induced significantly more reduction in GFR (7-8 ml/min decrease) over 4.9 years and increased serum creatinine more than either Amlodipine or Lisinopril ( $p < 0.05$ ). This demonstrates a potentially greater risk for CRI and ESRD and future need for renal replacement therapy such as dialysis or transplant in the Chlorthalidone treated patients. The expected decrease in GFR over 4.9 years is about 3 to 5 ml/min. Thus, Chlorthalidone approximately doubled the expected decline in GFR.

There was no increased risk of cancer or GI bleeding in the Amlodipine or Lisinopril group.

## CONCLUSIONS

1. There is no difference in the PRIMARY END POINT of the study – FATAL CHD OR NONFATAL MI – among the three treatment drug groups.
2. ALL CAUSE MORTALITY was identical among the three treatment groups.
3. Chlorthalidone was superior to Amlodipine and Lisinopril in the prevention of new onset, non-fatal CHF. With Lisinopril, this was much more apparent in the black population.

4. Chlorthalidone was superior to Lisinopril in stroke prevention in blacks but NOT in non-blacks. Chlorthalidone was NOT better than Amlodipine in any subgroup of patients in stroke prevention.
5. Chlorthalidone induced more biochemical abnormalities such as hypokalemia, hyperglycemia and hypercholesterolemia than Amlodipine and Lisinopril.
6. Chlorthalidone produced significantly more new onset diabetes mellitus than Lisinopril and Amlodipine.
7. Chlorthalidone produced a significantly greater decline in GFR than Amlodipine and Lisinopril (7-8 ml/min). Expected rate is 3 to 5 ml/min. Thus, Chlorthalidone approximately doubled the decline in GFR during the study period.
8. Amlodipine trended toward superiority compared to Chlorthalidone in stroke prevention, but it did not reach statistical significance.
9. Blood pressure control was better with Chlorthalidone than Lisinopril, but this varied among the drugs, racial groups and between SBP and DBP. Chlorthalidone reduced SBP more than Amlodipine and Lisinopril, but Amlodipine reduced DBP more than Chlorthalidone. Thus, Amlodipine was equally effective to Chlorthalidone in lowering mean arterial pressure.
10. To get blood pressure from 146/86 to 134/75 required an average of 2 drugs.

#### **INTERPRETATION AND IMPLICATIONS FOR TREATMENT OF HYPERTENSION**

Most of the SECONDARY OUTCOME RESULTS in ALLHAT are driven by the reductions in CHF and the reductions in stroke in the black population. Some, but not all of the differences can be explained by the differences in blood pressure control as opposed to the specific drug class. For example there was a 4 mm Hg difference in SBP in black patients in the Lisinopril vs. the Chlorthalidone groups. Based on meta-analysis studies, this could account for up to a 16% difference in stroke. In the CHF patients, a 4 mm Hg difference in SBP could account for up to a 21% difference in CHF and 6% reduction in CHD and MI. Therefore, if one corrects for the SBP difference of 4 mmHg in the Lisinopril group then the stroke and CHF reduction with Chlorthalidone are not as impressive (*i.e.*, 24% and 0%, respectively). In fact, Lisinopril may have been better than Chlorthalidone related to CHD and MI risk by 6% if SBP had been equivalent. In addition, both Chlorthalidone and Amlodipine are long acting antihypertensive agents that control BP beyond 24 hours, whereas Lisinopril loses its antihypertensive effect at about 16 hours. Would longer acting ACEI or those with tissue selectivity have done better as was seen in HOPE and PROGRESS? In both of those trials, a long acting tissue selective ACEI was administered result-

ing in significant reductions in cardiovascular and cerebrovascular morbidity and mortality. In the HOPE trial, the small reduction in BP did not account for the dramatic reductions in CV events, suggesting that the ACEI had non-antihypertensive effects that were beneficial to the vascular system. Depending on the timing of the BP measurements this also could have made a difference in the final BP results. Also, the inaccuracy, observer bias or "rounding off effect" as well as the infrequency of cuff BP measurements must be considered in ALLHAT.

The CHF differences may be explained by several theories:

1. Chlorthalidone is superior to other drugs?
2. Withdrawal of diuretics or other drugs at initiation of the study during randomization may have unmasked asymptomatic CHF and resulted in a greater frequency in the non-Chlorthalidone treated patients. This is very plausible.
3. The improvement in other CVD endpoints may have shifted the CVD to CHF due to longer survival.
4. The definitions or clinical evaluation and diagnosis for CHF may not be accurate or consistent among the various clinical sites.
5. An elderly, high risk population with possible unrecognized CHF presents a different population subset than younger, lower risk hypertensives, or it may simply reflect the better follow-up and evaluation in study patients.
6. The Chlorthalidone treated patients may have masked mild or silent pre-existing CHF symptoms prospectively that would have biased clinical evaluation.
7. It should be remembered that in controlled clinical trials of patients with CHF, over 10,000 patients have been treated with ACEI vs. placebo and the ACEI (or ARB's) is better. ALLHAT results are difficult to explain in the face of the amassed world literature favoring ACEI's.

#### **WHAT SHOULD PHYSICIANS DO NOW TO TREAT HYPERTENSION ?**

This study addresses only Chlorthalidone, not other diuretics and suggests that new onset non-fatal CHF is reduced more than with the other two drugs studied. It also suggests that strokes in blacks (but not non-blacks) are reduced more than with Lisinopril, but not when compared to Amlodipine. However, with the caveats and BP differences above, is Chlorthalidone really better for CHF and strokes? How can this be explained in view of the LIFE trial where an ARB was superior to a beta blocker and in the HOPE and PROGRESS trials that used ACEI's?

What are the long-term implications for the kidney and decline in GFR with Chlorthalidone? How can ALLHAT be explained in view of the data with RENAAL, IDNT,

IRMA, AASK, INSIGHT, HOPE, and other studies? ESRD and dialysis are very expensive. Are there differences in specific drugs related to target organ protection?

What are the implications, long term, *i.e.* more than the 4-8 years of this study and the new onset diabetes and probable insulin resistance in the Chlorthalidone group related to CVD and ESRD? Type II diabetes mellitus is the most common cause of kidney failure in the U.S., but diabetic kidney disease is not usually seen until more than a decade after onset of diabetes. This has enormous economic, morbidity and mortality issues that are not addressed in ALLHAT since ALLHAT was limited to six years of follow-up.

What are the long-term implications for the biochemical abnormalities resulting from Chlorthalidone use?

Practically, most hypertensive patients will be on 3 to 4 hypertensive agents to reach new goal BP levels. These will need to be Chlorthalidone (or other low dose diuretic), Amlodipine, or other CCB, ACEI or ARB, or possibly other agents. Control of BP and combination drugs must be paramount in the therapeutic regimen. Studies have suggested that in certain populations, the CCB, ACEI and ARB may actually be the preferred agents.

One must weigh the results of ALLHAT with other studies (HOT, LIFE, HOPE, PROGRESS, SYST-EUR, INSIGHT, MRFIT, NORDIL, MRC, OSLO, RENAAL, IDNT, IRMA, AASK and others). ALLHAT results are not

supported by the results in all of these other clinical trials.

One must also evaluate the patient demographics, underlying CVD and renal diseases and risk factors to select the most appropriate initial drug or drug combinations. Side effects and contraindications to Chlorthalidone are important as well (sulfa allergy, pregnancy, metabolic and renal problems, etc.).

ALLHAT will create guidance and some clarifications, but also confusion and criticism as the data is analyzed more carefully and the later subset studies are published. In the meantime, it is not clear just how much new data has really been generated from ALLHAT that we did not already know and just how much it will change the practice of treating hypertension in practical terms. This story is unfolding and is far from being fully revealed. All data is good if only to increase our questions and awareness of the complexity of treating hypertension. More studies are on the way with better and different designs and different population demographics that may challenge ALLHAT's ambiguous conclusions. It is known that elderly patients and those with concomitant CV risk factors, CV, or renal disease respond sooner and with more benefit at equal BP reductions compared to younger patients and those without concomitant CV or renal disease. After all, ALLHAT was really a study of high risk, elderly hypertensives (average age = 67 years) and correlations to a younger population with different CV risks may not be accurate or appropriate.

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