Medscape Medical News from the:

American Heart Association (AHA) 2009 Scientific Sessions

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From Medscape Medical News

ALLHAT Investigators Report 10-Year Follow-up and Stand by Diuretics as First-Step Antihypertensive Treatment

Susan Jeffrey

November 19, 2009 (Orlando, Florida) — A new analysis looking at 10-year mortality and morbidity data from the landmark **Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial** (ALLHAT) would appear to confirm the previous trial conclusions, the investigators say.

Combining data from the trial plus information on death and events that occurred after the trial taken from administrative databases, the researchers found that differences seen in cardiovascular outcomes, such as stroke, during the trial did not persist at 10 years, except for a 34% increase in heart failure with amlodipine vs chlorthalidone that had become evident during the trial but did not increase in the interim.

They concluded that their findings confirm conclusions put forward after the original trial was reported that, used as a first step in treating hypertension, amlodipine-, lisinopril-, and doxazosin-based treatments were not superior to chlorthalidone-based treatment in preventing major cardiovascular disease (CVD) events, but during the original randomized trial at least, chlorthalidone was superior to each of these other agents on at least 1 major cardiovascular outcome.

"Therefore, thiazide-type diuretics should still be preferred as first-step treatment in most older patients with hypertension, and it suggests that if you want to see the differences that were seen, you should keep the participants on the drugs," William C. Cushman, MD, from the Veterans Affairs Medical Center in Memphis, Tennessee, concluded.

Dr. William Cushman

Dr. Cushman presented the results here on behalf of the ALLHAT Collaborative Research Group at the American Heart Association 2009 Scientific Sessions.

Same Evidence, Different Conclusions

Daniel W. Jones, MD, from the University of Mississippi in Oxford, was the invited discussant for the ALLHAT presentation here. He said the results of ALLHAT generally confirm those of a number of superiority trials that have taught a number of lessons. Among

these, he said, is that lowering blood pressure is more important than the drug chosen for initial therapy and that several drugs have been shown to have a mortality benefit.

"Combination therapy is often necessary for control, and superiority trials have mixed results, with some drugs appearing better than others in some circumstances, but no drug or drug class appears consistently superior to all others," Dr. Jones said.

Mixed results in superiority trials such as ALLHAT have led to different recommendations from "reasonable groups looking at the same information." He pointed to 3 major guidelines: the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) in the United States that followed the conclusions of ALLHAT and recommend diuretics as a first step, the European Society of Hypertension/European Society of Cardiology document that recommends any of the 5 drug classes, and the British guidelines that discourage use of diuretics and beta-blockers.

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Although the ALLHAT investigators concluded from their new analysis that chlorthalidone is superior to the other drugs tested, he said, "likely others looking at the same evidence might offer an alternative conclusion: several classes appear to provide cardiovascular protection."

In his view, blood pressure should be lowered using drugs demonstrated to reduce cardiovascular mortality using the "least intrusive" approach for an individual patient, taking into account adverse effects, cost and potential inconvenience.

"For many clinicians, either approach would lead to the use of thiazide-diuretics as an initial choice for many patients," Dr. Jones concluded. "It's likely the debate over superiority of blood pressure drugs will continue, and we should all be reassured that with available drugs, blood pressure can be lowered to goal in most patients, and we can be confident of cardiovascular protection with a number of drugs.

ALLHAT Revisited

ALLHAT made headlines when it was first reported in 2002 because of the novel finding that an old, cheap drug might compete and actually appear to be better than what were then newer and more expensive drugs.

Initially launched in 1994, the sometimes controversial ALLHAT trial randomized more than 40,000 hypertensive patients to initial therapy based on a drug from 1 of 4 classes then in use: the alpha-blocker doxazosin, the angiotensin-converting enzyme inhibitor lisinopril, the calcium channel blocker amlodipine, and the thiazide diuretic chlorthalidone. After the doxazosin arm was terminated because of poor results compared with the diuretic at 3 years after the study was begun, the 3 other agents emerged as essentially equivalent on the composite primary outcome of fatal coronary heart disease (CHD) or nonfatal myocardial infarction (MI).

However, chlorthalidone seemed to work the best on some secondary endpoints: heart failure was almost 40% higher with amlodipine than chlorthalidone, and heart failure was 19% higher and strokes 15% higher with lisinopril vs the diuretic. For black patients, stroke was 40% higher with lisinopril than chlorthalidone (ALLHAT Investigators. *JAMA*. 2002;288:2981–2997).

In this analysis, the researchers used in-trial data up to 5 years and then posttrial events gleaned from administrative databases, including the National Death Index, the Social Security Administration, the Center for Medicare and Medicaid Services, and the US Renal Data System.

"Since the clinics were not continued to be funded at the end of the 5 years, we have no information on posttrial blood pressure or medications that were used," Dr. Cushman noted. "We assumed that after the trial there were similarities in what the groups were treated with after that."

Because they had the most data on cardiovascular mortality from these particular databases, that was selected as the primary outcome for this analysis. Secondary outcomes included all-cause and cause-specific mortality; stroke; CHD; heart failure; CVD; a composite of cardiovascular mortality, nonfatal MI, stroke, and heart failure; and end-stage renal disease.

Mortality data were available for all but the Canadian patients in the original trial (41,719) because of the databases used, as well as combined mortality and morbidity data on all but Canadians, Veterans Administration patients, and those without Medicare or a Social Security number (27,246).

For all-cause mortality and cardiovascular mortality, there was no difference among the 3 agents during the 10 years, Dr. Cushman reported. "This was also true for the doxazosin comparisons for mortality and cardiovascular mortality," he noted.

Table 1. Risk of Total and Cardiovascular Mortality With Amlodipine vs Chlorthalidone (A/C) and Lisinopril vs Chlorthalidone (L/C)

Comparison	Hazard Ratio (95% CI)	*P* Value
Mortality		
A/C	0.98 (0.94 – 1.03)	.43
L/C	0.97 (0.93 – 1.02)	.19
Cardiovascular mortality		
A/C	1.00 (0.93 – 1.06)	.89
L/C	0.97 (0.90 – 1.03)	.33

CI = confidence interval.

For the CHD outcome, again as in the main trial, there was no difference among the drugs, and this was true during the 10 years of follow-up with both amlodipine and lisinopril vs chlorthalidone and also for the doxazosin

comparison, Dr. Cushman noted.

Fatal heart failure in hospitalized patients was different with all the drugs vs chlorthalidone within the trial, favoring chlorthalidone. During the 10-year period, this difference persisted but did not increase for the amlodipine-chlorthalidone comparison. For lisinopril and doxazosin, the advantage of chlorthalidone was no longer significant at 10 years, as it had been during the 5 years of the trial.

For fatal stroke in hospitalized patients, he said, "again there was a higher rate during the trial with lisinopril but over the whole course of the 10 years of follow-up, these differences went away, and so it was not significantly different for either the amlodipine or lisinopril comparisons, and the same was true for the doxazosin-chlorthalidone comparison, which again was quite different during the trial but not over the whole 10 years of follow-up."

Table 2. Risk of Secondary Endpoints With Amlodipine vs Chlorthalidone (A/C), Lisinopril vs Chlorthalidone (L/C), and Doxazosin vs Chlorthalidone (D/C)

Comparison	Hazard Ratio (95% CI)	*P* Value
CHD		
A/C	1.00 (0.92 – 1.08)	.95
L/C	0.98 (0.90 – 1.06)	.64
Fatal heart failure in hospitalized patients		
A/C	1.12 (1.02 – 1.22)	.01
L/C	1.00 (0.91 – 1.09)	.94
D/C	1.07 (0.98 – 1.17)	.13
Fatal stroke in hospitalized patients		
A/C	0.99 (0.89 – 1.09)	.81
L/C	1.04 (0.94 – 1.15)	.41
D/C	1.02 (0.92 – 1.12)	.72

CHD = coronary heart disease; CI = confidence interval.

No new differences in major outcomes emerged after participants were removed from blinded therapies, he noted, except for a 10% lower CVD rate in the lisinopril vs chlorthalidone group. "However, since there was no difference [in CVD] over the entire 10-year period, we do not believe this suggests that lisinopril should be preferred over chlorthalidone for the initial treatment of hypertension," he added.

During the discussion, Dr. Jones asked Dr. Cushman if they had any data from the trial to quell concerns about the development of new-onset diabetes with the diuretic. He replied that data were presented at this meeting from ALLHAT looking at patients who had developed diabetes during the trial.

"They were at lower risk than those who had diabetes coming in for all 3 of the drugs that we looked at, but the diuretic subsequent events within the trial, we previously reported that the glucose changes [on the diuretic] were not associated with much increase and that's fairly well confirmed," Dr. Cushman said. "Certainly there is some increase in risk for those who develop diabetes, but actually it was less for some outcomes for those who developed it on the diuretic."

Reassuring Findings

Asked for comment on the ALLHAT findings, Mariell Jessup, MD, from the University of Pennsylvania School of Medicine, Philadelphia, and chair of the program committee for the meeting, said that it is always useful to have longer-term data on such a large group of patients.

There has also been a lingering concern about the effect of developing diabetes while taking a thiazide diuretic, she pointed out. "I thought it was particularly interesting to hear that in the patients who developed diabetes, still the thiazide diuretics reduced overall cardiovascular outcomes," Dr. Jessup told *Medscape Neurology*.

"Because there's been so much conversation about should thiazides still be used as a first line, this reinforces that concept, which is nice to know, and is good for our patients because the therapies are well tolerated and inexpensive, so I think this is very useful information," she added.

The ALLHAT trial was funded by the National Heart, Lung and Blood Institute. Dr. Jones has disclosed no relevant financial relationships.

American Heart Association (AHA) 2009 Scientific Sessions: Abstract 161. Presented November 18, 2009.

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