

# Amlodipine or lisinopril was not better than chlorthalidone in lowering CHD risk in hypertension

Although not mentioned by Dr. Psaty in his commentary (1), concerns have been raised over the heart failure results in ALLHAT (2). Asymptomatic left ventricular (LV) systolic dysfunction is common in older patients, particularly men and patients with cardiovascular risk factors (3, 4). ALLHAT participants were high-risk patients, and many may have had asymptomatic LV dysfunction that could have been unmasked at the start of the study by withdrawal of diuretic therapy. The early difference in heart failure (HF) incidence observed between the lisinopril and chlorthalidone groups, as well as the merging of the HF curves toward the end of the trial, is consistent with this possibility. Furthermore, a true difference in HF incidence over 5 years should have resulted in greater mortality in the lisinopril group; this did not occur.

A second concern is the validation of the HF endpoint, the diagnosis of which was up to the local ALLHAT investigator. An ALLHAT subcommittee, which reviewed a small fraction of HF hospitalizations, only agreed with 85% of diagnoses (5). In contrast, blinded endpoint committees in STOP-Hypertension 2 (6) and in ANBP2 (7), both of which included an angiotensin-converting enzyme (ACE) inhibitor group, found no difference in HF incidence. In the latter study, men appeared to benefit more from ACE inhibitors than diuretics, consistent with the epidemiology of asymptomatic LV dysfunction (3, 4).

Third, there seem to be race-based differences between the lisinopril and chlorthalidone groups with respect to the risks for stroke, and possibly combined coronary heart disease, combined cardiovascular disease, as well as HF. Though the statistical significance of these apparent interactions is not provided in the original report, they are not unexpected (2, 8).

The ALLHAT results emphasize the importance of diuretics in hypertension treatment. However, data do not support Dr. Psaty's assertion that "If BP is controlled with a nondiuretic, the patient should be switched to a low-dose diuretic." By ignoring the arguments for and against the ALLHAT results, we may neglect to pursue potentially important racial and gender differences in hypertension treatment.

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**In response:** Dr. Heckman reiterates a number of published criticisms of ALLHAT. In the Cardiovascular Health Study (1), only 46 (1.3%) of 3579 older adults without clinical cardiovascular disease had an abnormal ejection fraction on echocardiography. New HF events in older adults usually occur with preserved systolic function (2). ACE inhibitors have not been evaluated in the setting of HF with preserved systolic function, so generalizations from the existing HF trials may well be uninformative. Except in the setting of myocardial infarction, the case-fatality for new HF is low, and the follow-up time after HF events in ALLHAT would have provided little or no power to assess associations with mortality.

Trials should be judged and interpreted by the quality of their methods. In double-blind trials such as ALLHAT, misclassification of an endpoint introduces a nonsystematic error that generally moves point estimates toward the null. Heckman cites the STOP-Hypertension 2 trial. In this trial, only the endpoint classification is blinded. Thus, physicians and subjects, aware of the treatment allocation, have considerable influence in "ascertaining" which events go to this blinded endpoint committee. The absence of double blinding yields effect estimates that are exaggerated by 17% on average (3).

Many patients who entered ALLHAT had been receiving treatment at recruitment. At randomization, some of them were switched to low-dose diuretic therapy. Patients randomized to low-dose diuretics had reduced risks of  $\geq 1$  major cardiovascular outcome. The public health rationale for using a diuretic as first-line therapy is well supported. Switching patients from ACE inhibitors to low-dose diuretics would save billions of dollars and prevent tens of thousands of cardiovascular events.

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