

## ALLHAT, or the Soft Science of the Secondary End Point

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The recent Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed that the primary end point, coronary heart disease, was identical in the chlorthalidone, lisinopril, and amlodipine groups. Yet the major conclusion of this trial was that thiazide diuretics are superior in preventing 1 or more major forms of cardiovascular disease and should be preferred for first-line antihypertensive therapy. This conclusion was based solely on an analysis of secondary end points and cost. As evidenced by the dictum to “use thiazides for most patients with uncomplicated hypertension” in the Seventh Report of the Joint

National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, this interpretation of ALLHAT broadly adumbrated these guidelines. Although diuretics will rightfully remain a cornerstone in antihypertensive therapy, we should remember (as we were told by the ALLHAT investigators) that secondary end points are “soft data” that should not form a basis for main conclusions or lead to a labeling of a drug class as preferred.

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The recently reported Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) concluded with the statement that “thiazide-type diuretics are superior in preventing one or more major forms of cardiovascular disease” and that these drugs “should be preferred for first-step antihypertensive therapy” (1). The investigators also stated that when choosing first-line therapy with other antihypertensive drugs, such as calcium-channel blockers or angiotensin-converting enzyme (ACE) inhibitors, in patients who cannot take a diuretic, clinicians should consider these drugs’ higher risk for major manifestations of cardiovascular disease (1). These conclusions of this National Heart, Lung, and Blood Institute–sponsored study are provocative and deserve to be scrutinized.

First and foremost, ALLHAT had an unequivocal null result: The primary end point of the study, the combination of fatal coronary heart disease and nonfatal myocardial infarction, was identical in the chlorthalidone, amlodipine, and lisinopril groups. Similarly, total mortality (a secondary end point) did not differ among the 3 groups. When ALLHAT began in 1996, the investigators assured that “Although other secondary end points will be examined, these will be regarded as ‘soft data’ that will at best confirm or supplement the primary end point” (2). Now, 7 years later, these good intentions seem to have withered—the main conclusion of the study, that thiazide diuretics should be preferred, are based *solely* on secondary end points. Indeed, ALLHAT analyzed more than 50 primary, secondary, and composite end points. Because of the sheer size of ALLHAT, its statistical power is enormous and extensive analyses of secondary end points are tempting. However, with such analyses, we should keep in mind the null result of the primary end point. After all, the primary end point is called “primary” for the simple reason that it reflects the main question of the study. We also should remember that 1) statistical significance does not necessarily mean clinical significance and 2) what looks black and white in clinical trials may rapidly become gray in clinical practice (3).

The interpretation of secondary end points in

ALLHAT was hampered by the fact that outcomes were based on reports from physicians, copies of death certificates, and hospital discharge summaries; the investigators did not systematically verify all end points. No other end point is more difficult to diagnose than congestive heart failure (CHF) in the absence of objective criteria, such as echocardiographic or radionuclear studies. In ALLHAT, this difficulty was compounded by the fact that the calcium antagonist (amlodipine) facilitates the diagnosis of congestive heart failure and that chlorthalidone masks the diagnosis. Not uncommonly, amlodipine causes pedal edema in a dose-dependent manner; this may increase the suspicion of CHF. In contrast, diuretics deplete fluid volume and thus are likely to mask symptoms and signs of CHF, such as pedal edema, dyspnea, or bibasilar rales. In addition, the sudden switch from prerandomization therapy to amlodipine may have caused fluid retention and pedal edema and contributed to the diagnosis of CHF. Scrutiny of the Kaplan–Meier curves in ALLHAT shows that the major difference in CHF occurred almost immediately after randomization. Thereafter, the curves ran parallel, at least for up to 4 years of follow-up. After this time, the small numbers of patients make interpretation of the curves difficult. Despite the reported higher incidence of CHF, mortality did not differ between the amlodipine and chlorthalidone groups. Not only was CHF significantly more common in the amlodipine group, but lisinopril was significantly less efficacious than chlorthalidone. This is puzzling since ACE inhibitors have been a cornerstone in the treatment of CHF (4), whereas the efficacy of diuretics in this disorder has never been clearly established. Given these challenges, I wonder how much of the difference in CHF among the 3 groups was confounded by the switch from prerandomization therapy or by diagnostic artifacts.

More than one third of all patients in ALLHAT had diabetes at study entry, and during the study an additional 10% of patients developed de novo diabetes, defined as a fasting blood glucose level greater than 7.00 mmol/L (126 mg/dL). The risk for diabetes sharply differed among the 3 treatment groups: Patients receiving chlorthalidone had a

risk 43% to 65% higher than the risk in those receiving lisinopril and 18% to 30% higher than the risk in those receiving amlodipine (5). The ALLHAT investigators attempted to reassure us by stating that despite the higher incidence of diabetes with chlorthalidone, “these metabolic differences did not translate into more cardiovascular events.” Of course not—it is highly unlikely that a patient who develops de novo diabetes today will have diabetic complications within 2 to 6 years of diagnosis (the time frame of ALLHAT).

Although randomized clinical trials such as ALLHAT provide powerful evidence, we should not forget that they have some limitations, the most important of which is their necessarily short duration (most often 4 to 5 years). Long-term therapeutic effects can be assessed by using intermediate (surrogate) end points, such as subclinical organ damage or metabolic changes. Admittedly, evidence that an improvement in such surrogate end points is associated with a reduction in cardiovascular events is largely indirect, although solid evidence suggests that these alterations consistently herald major fatal and nonfatal events. In the case of diabetes, devastating complications may take more than a decade to manifest clinically. Younis and colleagues (6) showed this time dependence of diabetic complications: In patients who had diabetes for longer than 20 years, the 3-year cumulative incidence of sight-threatening diabetic retinopathy was almost 20-fold higher than in patients who had diabetes for less than 10 years. Similar to ALLHAT, the recent Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE) study (7) showed that the risk for the metabolic syndrome was more than 13 times higher in patients who were treated with hydrochlorothiazide (and atenolol) than with an ACE inhibitor (and a calcium antagonist) after a follow-up of merely 12 months.

ALLHAT did shatter the halo of ACE inhibitors as a class. The Heart Outcomes Prevention Evaluation (HOPE) (8) study had suggested that these drugs have a blood pressure-independent cerebroprotective (and vasculoprotective) effect. Lisinopril reduced the risk for stroke significantly less well than did amlodipine or chlorthalidone; this effect may have been partially due to the smaller decrease in blood pressure. The blood pressure pattern of ALLHAT mirrors the one in HOPE; the difference between the ACE inhibitor and the control groups and between the ACE inhibitor and chlorthalidone groups was 2 to 3 mm Hg. Although clinicians may quibble with the significance of such small differences in systolic blood pressure, a recent report (9) based on 1 million people showed that a 2-mm Hg difference in systolic blood pressure translated into a 10% difference in stroke mortality and a 7% difference in coronary mortality. Little surprise, then, that in both HOPE and ALLHAT the event rate with ACE inhibitor therapy varied in parallel with these small blood pressure changes. However, both of these studies underscore

the importance of lowering blood pressure, even by a few millimeters of mercury.

In the text of the ALLHAT report, no fewer than 3 times do the authors emphasize the superior antihypertensive efficacy of chlorthalidone. This is inappropriate since blood pressure was not an end point and the study was designed to achieve similar blood pressures in the 3 groups. What ALLHAT documents, however, is that blood pressure goals can be reached more easily by a diuretic- $\beta$ -blocker combination than by an ACE inhibitor- $\beta$ -blocker combination. Most cognizant physicians would have predicted that a combination of a  $\beta$ -blocker and an ACE inhibitor is not an efficacious antihypertensive therapy in patients with more severe hypertension, particularly in African-American patients. Thus, the fact that diuretics were “unsurpassed” (1) in their antihypertensive efficacy merely reflects the odd study design.

Three years ago, *The New York Times* reported (10) that “The use of such drugs known as calcium channel blockers is leading to nearly 85,000 unnecessary heart attacks each year worldwide”—findings that were based on a meta-analysis (11). No excess coronary heart disease mortality was observed with amlodipine in ALLHAT. If anything, all-cause mortality was slightly lower ( $P < 0.2$ ), and mortality from extracardiovascular causes even lower, with amlodipine than with chlorthalidone. If nothing else, this should send out a powerful, conspicuous message to investigators who generate dubious conclusions from meta-analyses, case-control studies, and observational studies (12). When these unsound data were sensationalized and widely broadcast, many patients were unnecessarily harmed and practicing physicians were frustrated.

Clinicians in the United States are appropriately asking why ALLHAT used chlorthalidone instead of the more familiar hydrochlorothiazide. In the Multiple Risk Factor Intervention Trial (MRFIT) (13), the robust difference in mortality trends with hydrochlorothiazide and chlorthalidone led to a protocol change—all patients were switched from hydrochlorothiazide to chlorthalidone. The investigators of that National Heart, Lung, and Blood Institute-sponsored study argued that this switch in diuretic treatment appeared to have contributed to the more favorable mortality outcome. Although no studies have directly compared these 2 diuretics, the MRFIT data are suggestive enough to prohibit extrapolation of benefits documented with chlorthalidone to other thiazide diuretics. Unlike ALLHAT, the recent Australian National Blood Pressure-2 study (14) showed that patients receiving enalapril did slightly better than those receiving hydrochlorothiazide.

While diuretics are inexpensive, their long-term use in comprehensive care requires the not-so-inexpensive monitoring of electrolyte, renal, and metabolic measures. The Systolic Hypertension in the Elderly Program (SHEP) study emphasized the importance of such monitoring by showing that patients whose potassium levels decreased below 3.5 mmol/L while receiving chlorthalidone did not do

better than those receiving placebo, despite a reduction in blood pressure (15).

ALLHAT has cast a long shadow on the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) (16); more than half of the authors of this document were ALLHAT investigators, which in itself may represent a conflict of interest. Not surprisingly, therefore, JNC-7 states that “Thiazide type diuretics should be used in drug treatment for most patients with uncomplicated hypertension.” Other drug classes, such as ACE inhibitors, calcium antagonists,  $\beta$ -blockers, and angiotensin-receptor inhibitors, are relegated to use for compelling indications only. Even in diabetic patients, thiazide diuretics lead the list, and the guidelines provide no special considerations for drug selection in patients with the metabolic syndrome. Had the JNC-7 guidelines been based on an objective assessment of the ALLHAT study, all 3 drugs or drug classes (diuretics, ACE inhibitors, and calcium antagonists) would have been accepted on equal footing as first-line therapy, whereas  $\beta$ -blockers would have been recommended only for compelling indications since outcome data supporting their use in uncomplicated hypertension are lacking (17, 18).

ALLHAT was designed to answer a simple question: Are newer antihypertensive agents as good as or better than diuretics in reducing coronary heart disease? More than 100 000 patient-years and a \$100 million later, ALLHAT fell short in conclusively answering this question. Fortunately, the question is no longer very relevant since we have learned that even in patients with mild hypertension, a combination of 2 or more drugs is usually needed to lower blood pressure to target levels (16).

However, ALLHAT is a milestone in hypertension research because it showed that amlodipine, lisinopril, and chlorthalidone have equal efficacy for coronary heart disease and all-cause mortality. Thiazide diuretics have been, are, and will be a cornerstone in the antihypertensive arsenal. However, their long-term safety, particularly with regard to carcinogenicity, remains unsettled (19, 20). Some secondary end points (and cost) may have favored 1 drug over another in ALLHAT; according to the ALLHAT investigators (2), however, we should consider these findings “soft data” and not use them to form a basis for main conclusions or to label a drug as preferred. All classes of antihypertensive drugs have effects and adverse effects that define risk–benefit ratios. Only a thorough and comprehensive assessment of a drug’s risks and benefits in a given patient will allow us to optimize the treatment of hypertensive cardiovascular disease.

From Ochsner Clinic Foundation, New Orleans, Louisiana.

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## References

1. 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;288:2981-97. [PMID: 12479763]
2. Davis BR, Cutler JA, Gordon DJ, Furberg CD, Wright JT Jr, Cushman WC, et al. Rationale and design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT Research Group. *Am J Hypertens*. 1996;9:342-60. [PMID: 8722437]
3. McAlister FA. Applying evidence to patient care: from black and white to shades of grey [Editorial]. *Ann Intern Med*. 2003;138:938-9. [PMID: 12779305]
4. Colucci WS, Wright RF, Braunwald E. New positive inotropic agents in the treatment of congestive heart failure. Mechanisms of action and recent clinical developments. 1. *N Engl J Med*. 1986;314:290-9. [PMID: 2867470]
5. Messerli FH, Weber MA. Long-term cardiovascular consequences of diuretics vs calcium channel blockers vs angiotensin-converting enzyme inhibitors [Letter]. *JAMA*. 2003;289:2067-8; author reply 2069-70. [PMID: 12709457]
6. Younis N, Broadbent DM, Vora JP, Harding SP. Incidence of sight-threatening retinopathy in patients with type 2 diabetes in the Liverpool Diabetic Eye Study: a cohort study. *Lancet*. 2003;361:195-200. [PMID: 12547541]
7. Lindholm LH, Persson M, Alaupovic P, Carlberg B, Svensson A, Samuelsson O. Metabolic outcome during 1 year in newly detected hypertensives: results of the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE study). *J Hypertens*. 2003;21:1563-74. [PMID: 12872052]
8. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*. 2000;342:145-53. [PMID: 10639539]
9. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Prospective Studies Collaboration*. *Lancet*. 2002;360:1903-13. [PMID: 12493255]
10. Altman LK. Use of some hypertension drugs questioned. *The New York Times*. 29 August 2000; A17.
11. Pahor M, Psaty BM, Alderman MH, Applegate WB, Williamson JD, Cavazzini C, et al. Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomized controlled trials. *Lancet*. 2000;356:1949-54. [PMID: 11130522]
12. Messerli FH. Case-control study, meta-analysis, and bouillabaisse: putting the calcium antagonist scare into context [Editorial]. *Ann Intern Med*. 1995;123:888-9. [PMID: 7486476]
13. Mortality after 10 1/2 years for hypertensive participants in the Multiple Risk Factor Intervention Trial. *Circulation*. 1990;82:1616-28. [PMID: 2225366]
14. Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL, et al. A comparison of outcomes with angiotensin-converting—enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med*. 2003;348:583-92. [PMID: 12584366]
15. Schrier RW. Diuretic treatment of systolic hypertension in the elderly [Editorial]. *Hypertension*. 2000;35:1031. [PMID: 10818058]
16. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560-72. [PMID: 12748199]
17. Messerli FH, Grossman E, Goldbourt U. Are beta-blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. *JAMA*.

1998;279:1903-7. [PMID: 9634263]

18. Messerli FH, Beevers DG, Franklin SS, Pickering TG. Beta-blockers in hypertension—the Emperor has no clothes. *Am J Hypertens*. [In press.]

19. Messerli FH. Diuretic therapy and renal cell carcinoma—another contro-

versy? [Editorial] *Eur Heart J*. 1999;20:1441-2. [PMID: 10493838]

20. Tenenbaum A, Motro M, Jonas M, Fisman EZ, Grossman E, Boyko V, et al. Is diuretic therapy associated with an increased risk of colon cancer? *Am J Med*. 2001;110:143-5. [PMID: 11165556]

. . . Mrs. Stiers spent all of her time at Mr. Zeno's bedside, where she was interrupted on the afternoon of the third day after the Bridger Mishap by three doctors, an intern, and two nurses who had stopped off at the ward for serious cases in order to examine Mr. Zeno. One of the doctors shined a flashlight in his eyes and the other one looked into his mouth while the intern adjusted all Mr. Zeno's tubes under the scrutiny of the two nurses, and then the five of them together cornered Mrs. Stiers on the far side of the ward and the first doctor, with his elbow in one hand and his chin in the other, told her Mr. Zeno's was indeed a serious case. "A very serious case," the second doctor added at the invitation of the first, and then the intern and the two nurses shook their heads most dolefully.

"Very serious?" Mrs. Stiers wanted to know.

And the two doctors present and the intern and the pair of nurses along with three additional doctors, another five interns, six more nurses and a radiologist had all concluded and agreed that Mr. Zeno would most probably not last out the night.

But he did anyway, notwithstanding the twenty professional opinions to the contrary, and when it became clear that Mr. Zeno was going to survive into the afternoon of the fourth day following the Bridger Mishap, an impressive assortment of medical personnel collected around his bed and ran several hours' worth of tests on him to find out how in the world he could do it. But the results were all inconclusive, the doctors called it, and so did not convince them to change their minds about Mr. Zeno, who they figured could not possibly hold on until the morning. But he did anyway and nobody could understand why, so Mr. Zeno's personal physician, Dr. Danbury of Ruffin, was called in along with a specialist from Winston-Salem who was at the time entertaining a doctor friend of his from Pennsylvania and brought him along as a bonus. And Dr. Danbury and the specialist from Winston-Salem and his doctor friend from Pennsylvania all examined Mr. Zeno together and then conferred for a full half hour before throwing in with the five doctors, six interns, eight nurses and solitary radiologist which made for a total of twenty-three professional opinions running contrary to Mr. Zeno. And though Mr. Zeno carried the load bravely for several hours, at 2:53 p.m. on the afternoon of the fifth day following the Bridger Mishap he finally yielded to the accumulated weight of informed medical opinion and expired. There was really nothing else he could do.

T.R. Pearson  
*A Short History of a Small Place*  
New York: Balatine Books: 1985:276.

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