

ALLHAT: Is It All That?

The results of the hypertension arm of ALLHAT introduced the notion that an old, less expensive drug could come out looking better than its newer, more expensive counterparts. But what are the limitations of ALLHAT?



By Henry Chung, MD; and
Brett Heilbron, MB ChB, FRCPC, FACC

Mr. Saloman's case

- Mr. Saloman, 55, has had hypertension for eight months.
- Blood pressure is 162/82 mmHg despite, intensive non-drug therapy (exercise, diet, salt restriction, alcohol moderation).
- Other risk factors include:
 - family history (father died of myocardial infarction at 62); and
 - dyslipidemia.
- Otherwise well, Mr. Saloman is fit and active, and his physical exam is unremarkable.
- Routine laboratory tests display normal results.

1. Which drug should he take first?
2. How many drugs are likely to be necessary to achieve the target blood pressure of 140/90 mmHg?

For the answers, see page 52.

In this article:

1. What were the results?
2. What are its limitations?
3. What is the final analysis?

Immediately upon their release in December 2002, results from the hypertension arm of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) were widely publicized. The notion that an old, less expensive drug could come out looking better overall than its newer, more expensive counterparts was appealing to many, and good news for those paying for anti-hypertensive medications.

The trial was sponsored by the National Heart, Lung, and Blood Institute and was a randomized, double-blind, actively-controlled clinical trial which ran from February 1994 to March 2002. The study

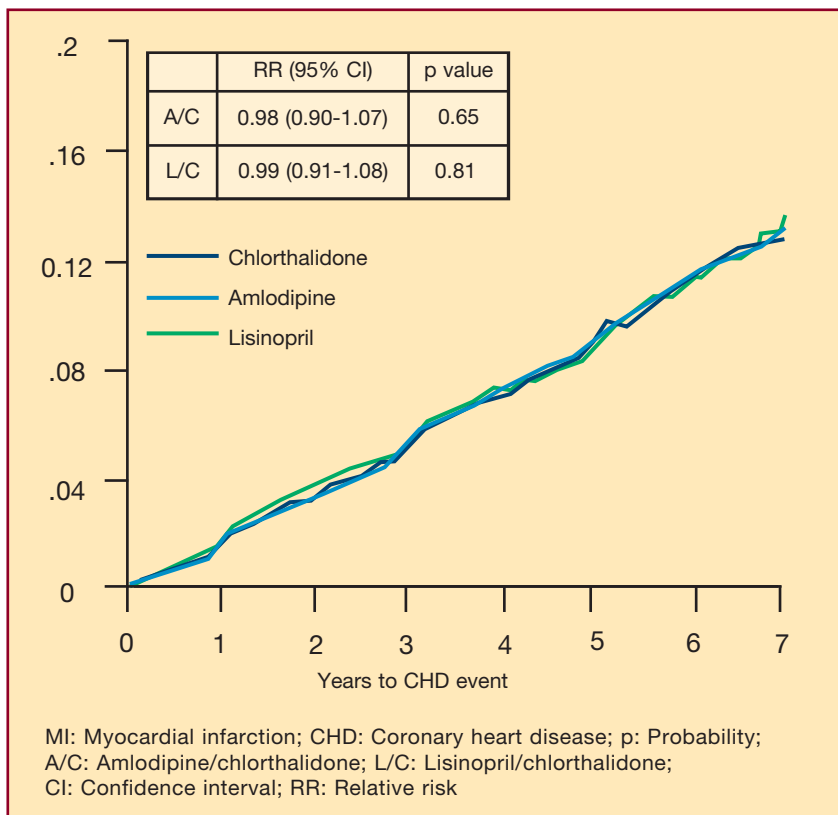


Figure 1. Cumulative Event Rates for the Primary Outcome (Fatal CHD or Nonfatal MI) by ALLHAT Treatment Group.

was designed to compare a low-cost diuretic (chlorthalidone) to an angiotensin-converting enzyme (ACE) inhibitor (lisinopril), a calcium channel blocker (CCB) (amlodipine), and an alpha blocker (doxazosin). These agents were selected to represent their class. The doxazosin arm, however, was stopped in January 2000, owing to a large excess of major adverse cardiac events in that group.

The study initially included 44,000 randomized patients, but this number dropped to 33,357

About the authors...

Dr. Chung is an internal medicine resident, University of British Columbia, Vancouver, BC.

Dr. Heilbron is a clinical assistant professor, University of British Columbia, and clinical and invasive diagnostic cardiologist at St. Paul's Hospital, Vancouver, BC.

after the halt of the doxazosin arm. Patients were drawn from 623 centres in the U.S., Canada, Puerto Rico, and the U.S. Virgin Islands.

Eligible patients were 55 or older, with hypertension and at least one other coronary heart disease (CHD) risk factor. The risk factors included previous (more than six months ago) myocardial infarction (MI), left ventricular hypertrophy, stroke, history of Type 2 diabetes, current cigarette smoking, high-density lipoprotein of < 0.91 mmol/L, or record of other atherosclerotic cardiovascular disease (CVD). Individuals with an ejection fraction < 35%, history of heart failure, or renal insufficiency were excluded.

Patients were randomized to receive:

- chlorthalidone (12.5 mg/day to 25mg/day) (15,244 patients from the study population)
- amlodipine (2.5 mg/day to 10 mg/day) (9,048 patients from the study population)
- lisinopril (10 mg/day to 40 mg/day) (9,054 patients from the study population)

Almost 50% of the participants were women, and 35% of the total participants were black.

About 90% of patients were already on antihypertensive treatment and they were instructed to continue their previous medications until the morning after randomization, when they would begin their study drug, unless a tapering period was required for safety reasons.

If on the study drug, their blood pressure (BP) was not below 140/90 mmHg, an open-labelled

Table 1

Secondary outcomes: Lisinopril vs. chlorthalidone

End Point	Lisinopril (%)	Chlorthalidone (%)	Relative risk (95%CI)	Probability
6-year rate of combined CVD	33.3	30.9	1.10 (1.05-1.16)	< 0.001
6-year rate of stroke	6.3	5.6	1.15 (1.02-1.30)	0.02
6-year rate of heart failure	8.7	7.7	1.19 (1.07-1.31)	< 0.001

CVD: Cardiovascular disease; CI: Confidence interval

Table 2

Secondary outcomes: Amlodipine vs. chlorthalidone

End Point	Amlodipine (%)	Chlorthalidone (%)	Relative risk (95% CI)	Probability
6-year rate of combined CVD	32.0	30.9	1.04 (0.99-1.09)	0.12
6-year rate of stroke	5.4	5.6	0.93 (0.82-1.06)	0.28
6-year rate of heart failure	10.2	7.7	1.38 (1.25-1.52)	< 0.001

CVD: Cardiovascular disease; CI: Confidence interval

treatment with atenolol, clonidine, or reserpine was added at the physician's discretion. Atenolol was by far the most commonly used second-line agent. If BP was still not controlled, hydralazine was added. Additional open-labelled study drugs were permitted if clinically indicated.

The primary outcome was combined fatal CHD or non-fatal MI, analyzed by intent-to-treat. Secondary outcomes were all-cause mortality, stroke, combined CHD (primary outcome, coronary revascularization, or angina with hospitalization), and combined CVD (combined CHD, stroke, treated angina without hospitalization, heart failure, and peripheral arterial disease).¹

What are the results?

The primary end point, as well as the all-cause mortality, was similar for each of the three drugs

(Figure 1). The results of the secondary cardiovascular end points generally revealed superiority of chlorthalidone. The rates of combined CVD, stroke, and heart failure were significantly higher in the lisinopril arm compared to the chlorthalidone arm (Table 1). In the amlodipine arm, there was a higher rate of heart failure, but the other secondary outcomes were similar (Table 2).

There were small, but statistically significant, BP differences between the groups (Figure 2).

The biochemical results indicated slightly, but statistically significant, higher serum cholesterol, serum potassium, and diabetes incidence, and lower glomerular filtration rates in the chlorthalidone group compared to the amlodipine and lisinopril arms (Tables 3 and 4).

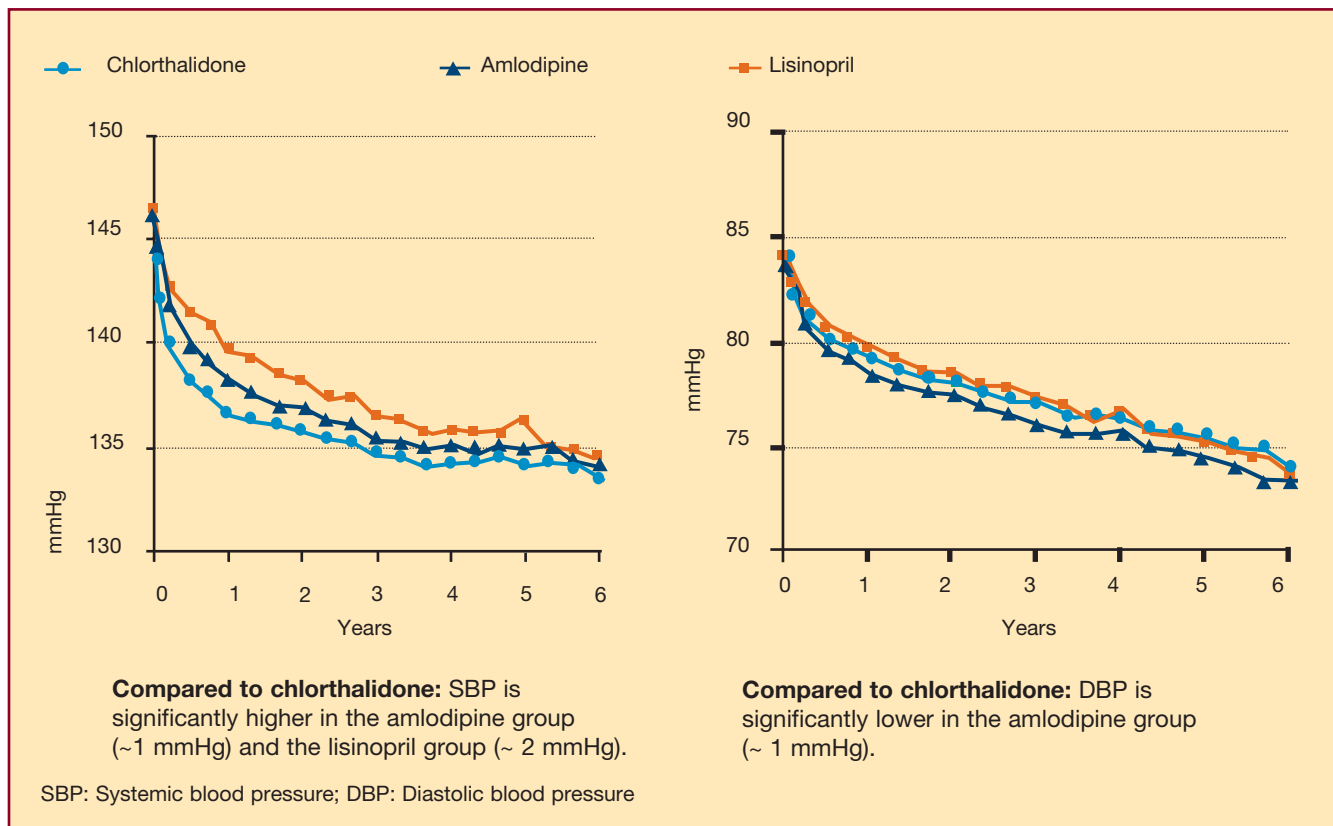


Figure 2. Blood pressure results by treatment group.

What are the limitations?

The major limitation was that BP was significantly higher in the lisinopril and amlodipine arms in comparison to chlorthalidone (Table 4). BP equivalency was not achieved, probably owing to the design of the study, which specified certain drugs to be added if target BP was not met. Beta blockers were the main drugs added and this benefited the chlorthalidone group, but was unfavourable in the lisinopril group. ACE inhibitors and beta blockers both act on neurohormonal pathways and are less effective in combination than adding a diuretic to an ACE inhibitor. As well, in black patients neither ACE inhibitors nor beta blockers are drugs of choice for BP control, owing to a lower efficacy in these patients.²

The study also found that the incidence of stroke was higher in the lisinopril group com-

pared to chlorthalidone. However, stroke rates were virtually identical for the diuretic and the ACE inhibitor groups in non-black patients. Therefore, the entire overall difference could be accounted for by the 40% increase in events in black patients randomized to lisinopril.³ There was also a 4 mmHg discrepancy between black patients in the lisinopril group. Thus, the lack of equivalency in BP lowering could have also factored into this finding.

The finding that the chlorthalidone group had a lower incidence of heart failure compared to the other two drugs came as a surprise. From previous trials, ACE inhibitors are well regarded as the primary treatment for heart failure.⁴ In light of this finding, one needs to consider the BP discrepancy, which could play a part in this difference. Also, it has previously been shown that ACE

Table 3

Biochemical results

	Chlorthalidone	Amlodipine	Lisinopril
Serum cholesterol-mg/dL			
Baseline	216.1 (43.8)	216.5 (44.1)	215.6 (42.4)
4 Years	197.2 (42.1)	195.6 (41.0)*	195.0 (40.6)*
Serum potassium-mmol/L			
Baseline	4.3 (0.7)	4.3 (0.7)	4.4 (0.7)*
4 Years	4.1 (0.7)	4.4 (0.7)*	4.5 (0.7)*
Estimated GFR**- mL/min/1.73m			
Baseline	77.6 (19.7)	78.0 (19.7)	77.7 (19.9)
4 Years	70.0 (19.7)	75.1 (20.7)*	70.7 (20.1)*

* probability < .05 compared to chlorthalidone
 ** Levey, AS, Bosch, JP, Lewis, JB, et al: A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Ann Intern Med. 1999; 130: 461-470.

GFR: Glomerular filtration rate

Table 4

Biochemical results-fasting glucose-mg/dL

	Chlorthalidone	Amlodipine	Lisinopril
Total			
Baseline	123.5 (58.3)	123.1 (57.0)	122.9 (56.1)
4 Years	126.3 (55.6)	123.7 (52.0)	121.5 (51.3)*
Nondiabetics with baseline < 126 mg/dL			
Baseline	93.1 (11.7)	93.0 (11.4)	93.3 (11.8)
4 Years	104.4 (28.5)	103.1 (27.7)	100.5 (19.5)*
Diabetes Incidence (followup fasting glucose ≥ 126 mg/dL)			
4 Years	11.6%	9.8%*	8.1%*

* probability < 0.05 compared to chlorthalidone

inhibitors are not as effective in black patients with heart failure.⁵

One needs to consider how the diagnosis of heart failure was made. Ankle swelling was one of the criteria used, which could have resulted in overdiagnosis of heart failure in the amlodipine

arm. Rigorous diagnostic criteria for heart failure were not consistently applied. In ALLHAT, most of the patients prior to the study were already on a diuretic. Because they had to stop all prior drugs, the masking effect that diuretics had on patients who may have had signs of edema, may

have become prominent. Thus, those who were randomized to the diuretic could possibly still have

Take-home message

ALLHAT: The results

- The primary end point as well as all-cause mortality was similar for each of the three drugs. The results of the secondary cardiovascular end points generally revealed superiority of chlorthalidone. The rates of combined CVD, stroke, and heart failure were significantly higher in the lisinopril arm compared to the chlorthalidone arm. In the amlodipine arm, there was a higher rate of heart failure, but the other secondary outcomes were similar.
- There were small but statistically significant BP differences between the groups.
- The serum cholesterol and diabetes incidence were statistically significantly higher and the serum potassium lower in the chlorthalidone group compared to the amlodipine and lisinopril groups.

ALLHAT: The limitations

- BP was significantly higher in the lisinopril and amlodipine arms in comparison to chlorthalidone probably owing to the design of the study.
- The incidence of stroke was higher in the lisinopril group compared to chlorthalidone, but stroke rates were virtually identical for the diuretic and the ACE inhibitor groups in non-black patients.
- Heart failure may have been overdiagnosed in the amlodipine arm based on ankle swelling, a common side-effect of CCBs.
- Increased incidence of new-onset diabetes in the chlorthalidone group did not translate to short-term cardiovascular events but possibly could in the long-term.

The final word

In view of their low cost and good tolerability, diuretics should be considered as part of most antihypertensive regimens, which typically require multiple agents to achieve target BP.

A followup on Mr. Saloman

1. Low-dose hydrochlorothiazide would be a reasonable first-line antihypertensive drug in this patient. Acceptable alternatives would include a beta blocker, ACE inhibitor, calcium channel blocker, or angiotensin receptor blocker.
2. This patient will likely require at least two antihypertensive drugs in order to achieve the target blood pressure of 140/90 mmHg.


had the findings masked.³ There was no difference in the cardiovascular end points of diabetic patients in the diuretic and ACE inhibitor arm. The discrepancy in BP, however, could have swayed the results in favour of chlorthalidone.

Interestingly, there was an increased incidence of new onset diabetes in the chlorthalidone group (11.6%) compared to the CCB group (9.8%), and the ACE inhibitor group (8.1%). This difference did not, however, translate into increased cardiovascular events over the duration of the study. Whether the increased rate of new-onset diabetes will translate into increased cardiovascular events over long-term followup is unknown.

Lastly, a large, randomized Australian study of over 6,000 hypertensive patients was recently published. The study showed that ACE inhibitors decreased all cardiovascular events or death from any cause unlike diuretic treatment. In this particular study, as opposed to ALLHAT, both groups in this study achieved equivalent BP control.⁶

Is ALLHAT all that?

ALLHAT confirmed the safety and efficacy of chlorthalidone, amlodipine, and lisinopril in the treatment of hypertension and dispelled many of the concerns previously raised about some of

these drugs. In view of their low cost and good tolerability, diuretics should be considered as part of most antihypertensive regimens, which typically will require multiple agents to achieve target BP. 

4. The Heart Outcomes Prevention Evaluation Study Investigators: Effects of an ACE inhibitor, ramipril, on cardiovascular events in high risk patients. *N Engl J Med* 2000; 342(3):145-53.
5. Exner DV, Dries DL, Domanski MJ, et al: Lesser response to angiotension-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. *N Engl J Med* 2001; 344(18):1351-57.
6. Wing LMH, Reid CM, Ryan P, et al: A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med* 2003; 348(7):583-92.

References

1. The 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(23):2981-97.
2. Neal B, MacMahon S, Chapman N: Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: Results of prospectively designed overviews of randomized trials. *Blood Pressure Lowering Treatment Trialists' collaborations. Lancet* 2000; 356(9246):1955-64.
3. Weber MA: The ALLHAT Report: A case of information and misinformation. *J Clin Hypertension* 2003; 5(1):9-13.

www.stacommunications.com

Back Forward Reload Home Search Images Print Security Shop Stop

Location: www.stacommunications.com

WE'RE ON-LINE

The Canadian Journal of
CME
Continuing Medical Education
Queen's University

48 The Constant Urge to Go
The Canadian Journal
52 Picking up the Pieces
54 How Can We Fight Insulin
Resistance in PCOS?
56 What's Old is New
58 This Deep
60 How do We Recognize Depressed
Mental Health
62

The Canadian Journal of
Diagnosis

81 The Leading Factor:
Hypertension & Diabetes
82 What's New in Domestic?
89 A Risk in the Public:
Risk to All
91

25 No More
Sleepless Nights
Leading to Obstructive
Sleep Apnea
95

le clinicien

25 La fibrillation
du sinus
est découverte
Articles
31 Quels sont les risques de
l'insuffisance cardiaque chronique?
32 Attention aux médicaments!
33 Comment préparer sa retraite?
34

29 The Grand Finale
2003 and Beyond
27 Frequently Asked Questions **Now!**

www.stacommunications.com