Older Generics Better Than Newer Antihypertensives

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Treatment and complications among the 50 to 60 million people in the US with hypertension are estimated to cost $37 billion annually, with antihypertensive drug costs alone accounting for an estimated $155 billion per year. Antihypertensive drug therapy substantially reduces the risk of hypertension-related morbidity and mortality. However, the optimal choice for initial pharmacotherapy of hypertension was still uncertain until now.

The take-home message from the just released results of the **A**ntihypertensive and **L**ipid **L**owering Treatment to Prevent **H**eart **A**ttack **T**rial (**ALLHAT**), the largest antihypertensive therapy trial ever conducted, is that ***cheap, generic diuretics are as good or better than newer more expensive antihypertensive drugs***. Results from ALLHAT showed that the incidence of fatal and non-fatal myocardial infarction (MI)—the primary endpoint—was the same for the diuretic chlorthalidone, the ACE inhibitor lisinopril and the calcium antagonist amlodipine. The researchers concluded, however, that thiazide-type diuretics should be considered for first-line pharmacologic therapy because of better results in secondary outcomes—six-year rates of combined cardiovascular disease (CVD), stroke, heart failure (HF) and coronary revascularization—and lower cost.[1] This *Heartbeat* will discuss the results, touch on some of the controversies and finally make some practical conclusions.

ALLHAT

ALLHAT enrolled 33,357 patients older than 55, who had hypertension and one other risk factor for coronary heart disease (CHD). Fifty percent were women and 35% were black. This randomized, double-blinded trial compared the occurrence of fatal CHD or non-fatal MI in high-risk hypertensive patients treated with amlodipine 2.5 to 10mg/day (n = 9,048), lisinopril 10 to 40mg/day (n = 9,054), or **low-dose** chlorthalidone 12.5 to 25mg/day (n = 15,255).

Primary Outcomes Results:

During follow-up of 4-8 years (mean 4.9 years), the primary outcome (fatal and non-fatal MI) and all-cause mortality did not differ among the groups, ranging in the area of over 11% (Table 1).

Table 1. ALLHAT: Primary end point

Drug	6-year rate of events (%)	Relative risk (95% CI)	p vs chlorthalidone
Chlorthalidone	11.5	—	—
Lisinopril	11.4	0.99 (0.91-1.08)	0.81
Amlodipine	11.3	0.98 (0.90-1.07)	0.65

Secondary Outcome Results:

Although chlorthalidone did not differ from amlodipine in overall CHD prevention and blood pressure (BP) control, the six-year rate of HF was higher with amlodipine (10.2% vs. 7.7%)—Table 2. Chlorthalidone was superior to lisinopril in lowering blood pressure and in six-year rates of combined CVD (30.9% vs. 33.3%), stroke (5.6% vs. 6.3%), and

HF (7.7% vs. 8.7%), angina and coronary revascularization—Table 3.

End Point	Amiodipine	Chlorthalidone	Relative Risk (95% CI)	p
6-year rate of HF	10.2	7.7	1.38 (1.25-1.52)	0.001

Table 2. Secondary outcomes: Amiodopine vs chlorthalidone

End point	Lisinopril	Chlorthalidone	Relative risk (95% CI)	p
6-year rate of combined CHD	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 HF	8.7	7.7	1.19 (1.07-1.31)	<0.001

Table 3. Secondary outcomes: Lisinopril vs chlorthalidone

Since a large proportion of participants required more than one drug to control their blood pressure, the authors felt that it is reasonable to infer that ***a low-dose diuretic should be included in all multi-drug regimens*.** Low dose is important because moderate or high doses are associated with worse outcomes.

End of a Passionate Debate

In an editorial, Dr Lawrence J Appel (Johns Hopkins University, Baltimore) writes, "ALLHAT is one of the most important trials in antihypertensive therapy.[2] For decades experts have passionately debated which agent is best for the initiation of therapy? Resolution of this issue which has enormous clinical, public health, and economic implications comes at a time of intense pressure to reduce health care costs while improving clinical outcomes." The major finding of ALLHAT, "a striking and unequivocal null result", is particularly noteworthy, he writes, "there is no cost-quality trade-off, the most effective therapy is also the least expensive."

He also points out, since most patients will require two or more drugs to control blood pressure, we need more data to go beyond first line treatment. So which drug should be used next? "While physicians may be tempted to use an on-patent calcium channel blocker (CCB) or ACE-inhibitor, there is an impressive armamentarium of low-cost, off-patent drugs that can be used as add-on therapy after diuretics", he writes, "including a CCB, 3 ACE inhibitors and several beta-blockers." He concludes, "A logical strategy that incorporates these low-cost agents may differ from those that are more popular, but contemporary strategies may be somewhat artificial because of the heavy influence of marketing that preferentially leads to the use of expensive medications."

Quarrel with Conclusions

Even the best designed and executed trials raise critical interpretive issues. Some physicians feel that the results run counter to other scientific findings. Dr Franz Messerli (Ochsner Clinic Foundation, New Orleans) said, "The most disappointing aspect" of ALLHAT was the results seen with lisinopril. "It deflates **HOPE** (**H**eart **O**utcomes **P**revention **E**valuation)[3] completely, because it would indicate that there is no specific cardio-protective or vascular protective effect of ACE inhibitors." He also makes the point that the ACE inhibitor was probably disadvantaged by the fact that add-on therapy was often with a beta-blocker and this is not the most efficacious combination.

Dr Frans H. Leenen, one of the principal ALLHAT investigators feels that benefits seen in HOPE were from BP lowering, and not from an "extra vascular-protective effect". He comments further saying, "If a thiazide diuretic had been used in HOPE, a placebo controlled trial, the outcomes benefits would have been the same or better."

The findings with lisinopril may also reflect the fact that ACE inhibitors don't work as well in African Americans (a large cohort in the study) as evidenced by the overall poorer BP control in the lisinopril group. Simply, diuretics are better for BP control than ACE inhibitors. Compounding this was that, by design, the add-on therapy was a beta-blocker. The treatment of choice would be to add a diuretic or CCB, but they were prohibited by the study design. This is a major issue, and as a result, BP control was significantly poorer in the lisinopril group, and that can explain a lot of observations from this trial.

Because BP reduction was similar with the diuretic and the CCB, the superiority of the diuretic in that

comparison is clear. More information from studies other than ALLHAT will be needed to get a clearer answer on ACE inhibitors, especially in African American populations.

ACE inhibitors Still Great

ACE inhibitors have a lot of proven benefits (improved outcomes) in multiple patient groups particularly those with co-morbidity—i.e. post MI, vascular disease, heart failure, diabetes and renal disease. These benefits are probably more from vascular-protective effects rather than from BP lowering. That being said, the BP lowering effect cannot be discounted. Both are extremely important.

ALLHAT and HOPE could be considered complementary studies. When forced to choose between BP reduction and a vascular-protective drug, the focus should be on BP reduction, which offers the most vascular-protection—ALLHAT (diuretic). When co-morbidities are present, which includes a lot of patients, ACE inhibitors should be add-on therapy—HOPE. In patients with heart or vascular disease, kidney disease or diabetes, clinical evidence indicates that blocking the renin-angiotensin-aldosterone system (RAAS) is beneficial.

It is important to mention that the vascular-protective benefit of ACE inhibitors comes from blocking the RAAS, and an angiotensin receptor blocker (ARB), which also blocks the RAAS, offers the same benefits. ARB's are not included in this discussion because they were not included in ALLHAT or HOPE and are only more expensive than ACE inhibitors-and not proven better. If however ACE inhibitors are indicated and can't be tolerated, an ARB should be substituted.

Conclusions:

The reality is that the "playing field" in BP control now is systolic blood pressure (SBP). It is much more prevalent and difficult to control. Three drugs on average will be needed to achieve a 30-mm Hg BP reduction. Early and aggressive treatment by physicians will be necessary.[4] Results from ALLHAT indicate that ***low-dose thiazide-type diuretics should be considered first for pharmacolgic therapy in patients with hypertension. They are unsurpassed in lowering BP, reducing clinical events and tolerability and are less costly.***

The relationship between elevated BP and CV or stroke risk is striking. Even high-normal BP (130-140-mm Hg systolic) is associated with increased CV risk. Lower BP is better for all individuals, and efforts to lower BP to a level as close as possible to optimal (120/80) should be our goal. This is especially true in high-risk patients with co-morbidities. Clinical studies of patients with hypertension and renal dysfunction and/or diabetes have shown a clear correlation between BP reduction and improved outcomes.

The complexity of drug programs and the need for more intensive CV and renal risk reduction require strategies to simplify the approach to BP reduction. The paradigm shift will be to use combination therapy. The preferred combo will surely be a diuretic—" married" to an ACE inhibitor—to get the best results. This will be the preferred first-line means of decreasing risk and BP. Other add-on antihypertensive drugs will probably be necessary.

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[1] The ALLHAT Officers and Coordinators for the ALLHAT Cooperative 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* December 18 2002; 288: 2981-97.

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[3] Yusuf S et al. Effects of an angiotensin-converting-enxyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Investigators. *N Engl J Med* January 20 2000; 342: 145-53.

[4] Maiese M. Update on hypertension. *Heartbeat* 70 July/August 2002; www.sjhg.salu.net Patient Education- From Your Physician.