Editorial

A new era in hypertension research: discussing the findings of ALLHAT

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Abstract

The key question in hypertension research today is, "Does it matter how elevated blood pressure is lowered?" The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) initiated in 1994 serves as a model for comparative trials. Its strengths include its independent sponsorship, scope and design. The alpha-blocker arm was stopped early; doxazosin was shown to be clearly inferior to low-dose chlorthalidone not only in preventing heart failure, but also stroke, in spite of similar blood pressure reduction. The findings have major public health implications as pointed out by Krakoff in this journal. Other commentaries by Gavras and Gavras and Hooper discuss possible mechanisms behind the excess of cardiovascular events in doxazosin-treated patients.

Keywords alpha-blockers, clinical trial, diuretics, hypertension

It was established by the 1980's that drug treatment of elevated blood pressure (BP) reduces the risks of cardiovascular complications of hypertension. The prevailing assumption among clinicians and regulators was, and probably continues to be, that the benefits of antihypertensive treatment were a direct consequence of the reduction in systolic and/or diastolic BP. Based on this premise, we have seen a flood of new antihypertensive agents from multiple classes of drugs introduced into the marketplace. The scientific documentation has often consisted of small, short-term trials. As long as the new agents are superior to placebo in reducing BP, and as long as they are reasonably free of side effects, the drugs receive regulatory approval. Clinicians now have more than 100 antihypertensive drugs from which to choose. Because the blood-pressure-lowering potential of these drugs is fairly similar, use of individual pharmaceutical agents is determined more by marketing forces than by science. A health services concern is that there is a greater than 20-fold difference in drug cost [1].

The key question today is, "Does it matter how elevated BP is lowered?" This question is best answered by randomized clinical trials that compare antihypertensive agents. However, a number of issues and concerns have been raised about the design of these trials. Regulatory agencies prefer placebo-controlled trials, since they want to know whether a drug is effective for its intended use and whether it is reasonably safe. Comparative or active-controlled trials have other objectives and provide answers along the superiority–inferiority axis. Although extremely relevant clinically, the regulatory agencies have limited interest and use for information regarding which drug is superior. It is currently not a regulatory issue.

Comparative trials are a cause for concern to the pharmaceutical industry, since such trials may produce losers (inferior drugs), whereas the outcome of placebo-controlled trials of new antihypertensive agents is, for the industry, less risky. To lessen the risks that a drug may be inferior to that of a competitor, there is an unfortunate tendency to compare the new agent to the least effective standard therapy, sometimes in an inadequate dose. Another approach is to proceed with only a small sample size, which is inadequate to detect reliably meaningful differences among drugs. Thus, a drawback of comparative trials is the large-scale required.

ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.
BP = blood pressure.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), initiated in 1994, was one of the first major comparative trials with clinical outcomes [2]. Its strengths include: independent sponsorship (the National Heart, Lung, and Blood Institute); its scope (comparison of 4 drugs from different drug classes); optimal selection of standard/control treatment (low-dose diuretics); a double blind design; its sample size (40,000 high-risk hypertensives to be treated for 4–8 years); and the selection of trial outcomes (all major vascular complications of hypertension).

ALLHAT addresses the question of whether representatives of the newer and more expensive antihypertensive agents: lisinopril (angiotensin-converting enzyme inhibitor), doxazosin (alpha-blocker), and amlodipine (calcium-channel blocker), are more effective as first-line drugs than a generic agent, chlorthalidone (low-dose diuretic), in reducing the risk of cardiovascular disease. A total of 42,448 patients were randomized to ALLHAT by January, 1998.

The doxazosin arm was terminated two years early for two reasons [3]. First, there was a highly significant (25%) excess risk of major cardiovascular events (a prespecified secondary endpoint) in the doxazosin group in comparison to the chlorthalidone group. Second, the likelihood of doxazosin emerging as superior to low-dose chlorthalidone was very remote. This excess of cardiovascular events with doxazosin was driven by a doubling in the risk of congestive heart failure, both primarily hospitalized and fatal cases. The annual heart failure rate was 2% in the doxazosin group but 1% in the chlorthalidone group. In addition, there was a 20% excess in the relative risk of stroke, and 15% excesses in coronary revascularizations and angina, in the doxazosin group. However, the risks of major coronary events (the prespecified primary endpoint) and all-cause mortality were not different between the two treatment groups. The fact that the achieved blood pressures were similar throughout the duration of the trial indicates that non-blood-pressure-related mechanisms are involved, which could explain these differences.

Many commentaries have been written about the doxazosin findings. The more persuasive ones conclude that alpha-blockers should no longer be considered first-line agents for hypertension in high-risk, elderly adults [4–6]. Others raise questions of a technical nature, but fail to realize the public health implication of the ALLHAT findings [7–9]. Among the approximately one million users of doxazosin in the United States and Europe, one could expect as many as 10,000 *unnecessary* cases of advanced heart failure every year [6].

This issue of *Current Controlled Trials in Cardiovascular Medicine* features three commentaries on ALLHAT. Krakoff [10] raises a critical question, “Should the results of ALLHAT be considered as revealing drug toxicity or of the lesser charge of ineffectiveness?” He suggests that doxazosin, “may be ineffective and perhaps little better than placebo, for the many patients at higher risk for heart failure”. Regardless of the answer, actions should be taken to inform treating clinicians. To date, the manufacturer of doxazosin, Pfizer, has refused to issue even a “Dear Doctor” letter with a proper warning.

The other two commentaries by Gavras and Gavras [11] and Hooper [12] discuss potential mechanisms behind the observed excess of cardiovascular events. Gavras and Gavras speculate that alpha-adrenergic blockage would lead to small elevations of arginine vasopressin. This systemic pressor hormone could become important through its pressor action in elderly patients and in those with diabetes, triggering congestive heart failure and myocardial ischemia. Hooper discusses the potential role of heat shock proteins in explaining the ALLHAT findings. These proteins have vital functions in the body, protecting cells from injury through multiple mechanisms. Alpha-adrenergic stimulation with norepinephrine increases the levels of heat shock proteins, while alpha-adrenergic blockade decreases it. A drug-induced decrease could lead to increased vulnerability of the cardiovascular system to injury.

Mechanisms of action are always difficult to prove. We may never know with certainty why doxazosin had unfavorable cardiovascular effects in ALLHAT. However, we stand on a solid scientific foundation when we conclude that doxazosin is an inferior antihypertensive agent and it should only be used if first-line agents – low-dose diuretics, beta-blockers, and angiotensin-converting enzyme inhibitors – fail to achieve blood pressure control or cannot be tolerated.

Competing interests

Curt Furberg serves as Chairman of the ALLHAT Steering Committee.

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