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Scientific Update™

Practice Implications of Recent Hypertension Trials: Weighing the evidence

A Report on a Presentation at a Satellite Symposium at the American College of Cardiology 52nd Annual Scientific Session

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Hypertension is a highly prevalent disease in both industrialized and non-industrialized countries. The relationship between systolic blood pressure (BP) and mortality from coronary heart disease (CHD) is continuous, with no evidence of a threshold, and is steeper than the relationship with diastolic BP. The benefits of treating systolic hypertension have been established conclusively in several landmark trials. Observations of the beneficial effects with angiotensin-converting enzyme (ACE) inhibition in selected groups of patients, and meta-analyses that raised concerns about the safety of calcium channel blockers (CCBs), have challenged the established paradigm that lowering BP was sufficient to reduce cardiovascular (CV) events. These factors also raised a new possibility: that the *type* of anti-hypertensive agent used may be important, independent of its BP-lowering effects. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is the largest hypertension study ever conducted and was designed to address this question. The main results of ALLHAT have been published and reviewed critically in a recent issue of *Cardiology Scientific Update*. This *Update* will review and discuss epidemiological data regarding the relationship between BP and CV risk, the background and rationale of ALLHAT, the results of ALLHAT in context of other recent hypertension trials, as well as their implications for clinical practice and future guidelines.

The importance of reducing systolic BP: Lessons from observational studies and clinical trials

Hypertension is the key factor contributing to mortality from CHD in both industrialized and nonindustrialized countries.[1] Recent data from the Framingham Heart Study indicate that residual lifetime risks – the cumulative incidence not adjusted for competing causes of mortality – for developing hypertension and stage 1 or higher hypertension (ie, ≥140/90 mm Hg, regardless of treatment) were 90% in both 55- and 65-year-old participants.[2] Systolic BP increases with age, whereas diastolic BP increases with age up to middle-age and then starts to decline.[3] The relationships between both systolic and diastolic BP and mortality from CHD are continuous, graded, and without evidence of reaching a threshold, with the relationship between systolic BP and mortality being steeper than diastolic BP.[4] The age-specific relevance of BP to cause-specific mortality was recently assessed by a collaborative meta-analysis of individual participant data from 61 prospective studies of BP and mortality.[5] At age 40-69 years, each 20 mm Hg difference in SBP is associated with more than a twofold difference in the rate of death from stroke and a twofold difference in the rate of death from CHD. At age 80-89 years, all of these relative differences in vascular mortality are about half as extreme as at age 40-49 years, but the annual absolute differences in risk are greater in old age. Throughout middle and old age, usual blood pressure is strongly and directly related to vascular and total mortality, without any evidence of a threshold down to at least BP of 115/75 mm Hg.

The observational data of the strong relationship between BP – especially systolic BP – and adverse clinical outcomes are corroborated by observations of large randomized trials demonstrating the benefits of treating systolic hypertension.[6,7] The Systolic Hypertension in the Elderly Program (SHEP) study demonstrated that lowering SBP by 12 mm Hg over 4.5 years (chlorthalidone and atenolol) in 4736 subjects, aged ≥60 years, resulted in a 37% risk reduction in stroke, a 25% reduction in CHD (nonfatal myocardial infarction [MI] and coronary death), a 32% reduction in major CV events, a 54% reduction in heart failure, and an insignificant 13% in total mortality (Figure 1).[6] Likewise, the Systolic Hypertension-Europe (Syst-Eur) study demonstrated that lowering systolic BP by 10 mm Hg over 2 years (nitrendipine and hydrochlorothiazide) in 4696 subjects, aged ≥60, resulted in a 42% reduction in stroke, a 26% reduction in fatal and nonfatal cardiac endpoints, and an insignificant 14% reduction in total mortality.[7]

Despite these convincing observational and clinical trials data, fewer than 30% of hypertensive patients in industrialized countries have their BP lowered to the treatment goal of <140/90 mm Hg.[8] The problem of inadequate BP control is especially great in older patients in whom the prevalence of high BP is greatest and isolated systolic hypertension (ISH) predominates.[9,10]

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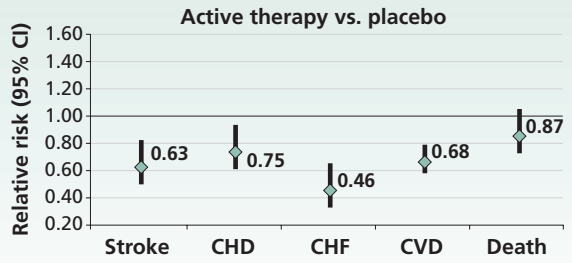
Figure 1: SHEP: Cardiovascular disease endpoints



CHD = coronary heart disease; CHF = congestive heart failure;
CVD = cardiovascular disease;
SHEP = Systolic Hypertension in the Elderly Program

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

The ALLHAT study is the largest hypertension study ever conducted. The main results of the ALLHAT study have been published[11] and reviewed critically in a recent issue of *Cardiology Scientific Update*. In the following sections, the background and rationale of ALLHAT, the results of ALLHAT in context of other recent hypertension trials, as well as their implications for clinical practice and future guidelines are reviewed.

ALLHAT – background

In 1982, the final results of the Multiple Risk Factor Intervention Trial (MRFIT) were released and an unexpected outcome was that high-risk men in the special intervention group, who were hypertensive and had electrocardiographic abnormalities at baseline, had a significant higher rate of CHD and sudden death compared to similar usual-care subjects.[12,13] This result challenged the established paradigm that lowering BP was all that was needed to reduce the CV event rate and raised a new possibility that the type of drug used may be important, independent of its BP-lowering effect (Figure 2). Hypertension specialists have postulated that diuretic-induced metabolic effects might have mitigated the otherwise beneficial effects of BP lowering. This debate gained further momentum with the safety concerns about CCBs, driven mostly from meta-analyses.[14] More recent studies of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have suggested that these agents may be particularly useful for reducing CV events than for lowering BP, especially in patients with diabetes or renal insufficiency.[15-17]

The primary objective of ALLHAT was therefore to determine if treatment with newer agents (ie, a long-acting dihydropyridine CCB, amlodipine; an ACE inhibitor, lisinopril; or an α_1-receptor antagonist, doxazosin) lowered the incidence of fatal and non-fatal CHD. Each of these agents was compared with an older agent, the diuretic chlorthalidone. ALLHAT was conducted in 623 community-based clinical centres across the United States, Canada, Puerto Rico, and the Virgin Islands. A total of 42,418 participants were enrolled, all had hypertension and evidence of CV disease or at least one other risk factor.

ALLHAT– Main results

In brief, the doxazosin group was discontinued 2 years prior to the end of the study because of excess heart failure. In the 3 remaining groups, 2956 participants experienced a primary event (fatal and nonfatal CHD), with no difference between the 3 treatments (Figure 3).

Figure 2: Competing paradigm 1982-2002

In addition, all-cause mortality did not differ between groups. Five-year systolic BP was significantly lower in the chlorthalidone group, 0.8 mm Hg lower compared with amlodipine (p =0.03) and 2 mm Hg lower compared with lisinopril ($p \leq 0.001$). On the other hand, 5-year diastolic BP was significantly lower with amlodipine compared with the other 2 agents. There were no differences in outcomes between chlorthalidone and amlopdipine for all other secondary outcomes, although one component of CV outcome, heart failure, occurred at a higher rate with amlodipine compared with the diuretic. For the lisinopril-chlorthalidone comparison, subjects on lisinopril experienced a 10% higher rate of combined CV event (p <0.001), a 15% higher rate of stroke (p = 0.02), and a 19% higher rate of heart failure (p <0.001). There was significant heterogeneity observed by ethnicity, with blacks on lisinopril experiencing a 40% higher rate of stroke and a 19% higher rate of CV disease compared with chlorthalidone. There were no differences in non-CV events such as cancer.

ALLHAT in perspective with other recent trials of antiypertensive agents

Although the investigators of ALLHAT suggest that diuretics offer superior outcomes, one should keep in mind that the trial essentially showed no differences in outcome for the *primary* efficacy variable for the 3 arms. Differences were detected only with respect to selected secondary endpoints. To further understand the relationships between BP-lowering and risk reduction, it is useful to put ALLHAT in perspective with other hypertension trials. The effect of BP reduction on CV mortality is summarized in a recent meta-analysis of hypertension trials (Figure 4).[18] In general, the odds ratio (experimental/reference) decreases (risk-reduction increases) with increasing BP reduction by the experimental over the reference drugs (placebo or "old drugs").

The Heart Outcome Prevention Evaluation (HOPE) was designed to assess the effect of ACE inhibition in patients without a history of left ventricular dysfunction, but at high risk for CV events.[19] There is ongoing debate as to whether the profound benefit observed with ACE inhibition was attributable to BP lowering. Based on the BP-related

Figure 3: ALLHAT — Primary endpoint

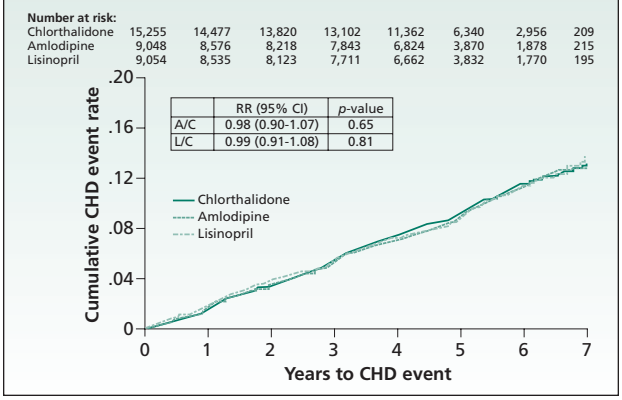
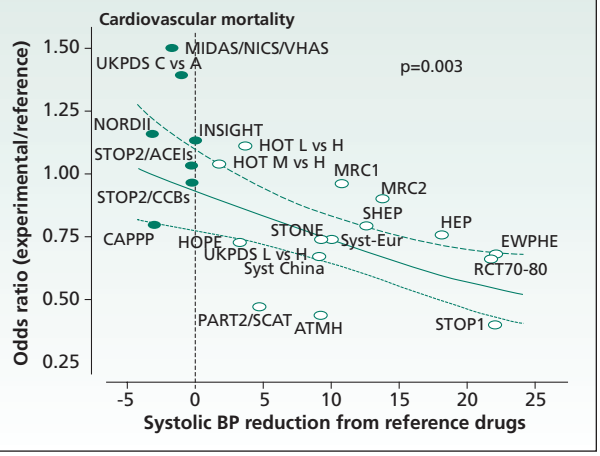


Figure 4: Blood pressure reduction and cardiovascular mortality: a meta-analysis of hypertension trials



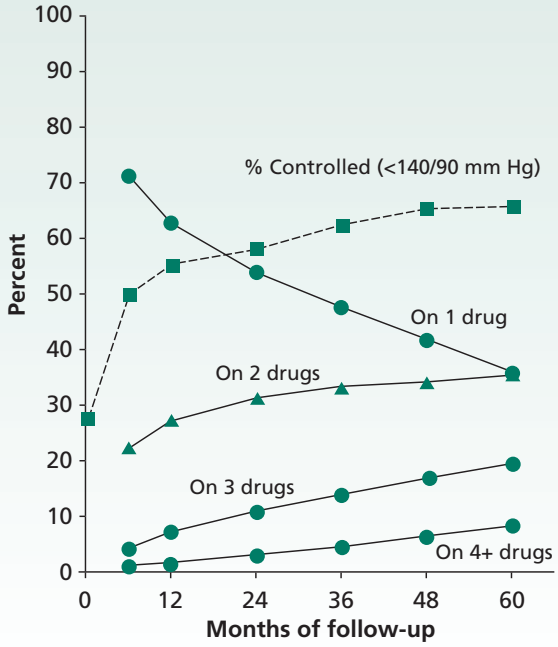
Adapted from Staessen et al. *Lancet* 2001;358:1305[18]

risk estimates of the placebo group, HOPE investigators argued that the risk reduction in CV events was 3 times greater than that expected from BP-lowering alone (3 mm Hg/1 mm Hg reported in the main trial).[20] On the other hand, according to the HOPE protocol, ramipril was administered once daily at bedtime and BP was measured during the day. The 24-hour impact of ramipril on BP may be underestimated, based on office BP determinations.

In this regard, 38 patients enrolled in the HOPE study underwent a substudy of 24-hour ambulatory blood pressure (ABP) measurement before randomization and after 1 year.[21] While ramipril did not significantly reduce office BP (8/2 mm Hg, p =NS) or day ABP (6/2 mm Hg, p=NS) after 1 year, 24-hour ABP was significantly reduced (10/4 mm Hg, p=0.03), mainly because of more pronounced BP lowering during nighttime (17/8 mm Hg, p<0.001). While the debate on the contribution of BP-lowering in HOPE continues, based on Figure 4, the 26% reduction in CV mortality in HOPE is consistent with 10 mm Hg systolic BP, similar to the magnitude observed in the ABP study.[21] Thus, the modest (2.0 mm Hg) difference in systolic BP between the lisinopril and the chlorthalidone group (lisinorpil higher) may have explained, at least in part, the modest differences in selected secondary outcomes, including stroke, risk ratio (lisinopril worse) 1.15 (95% confidence interval, 1.02-1.30), combined CV disease, 1.10 (1.05-1.16) and heart failure (1.20, 1.09-1.34).

The recently published Losartan Intervention for Endpoint Reduction in hypertension (LIFE) study demonstrated a benefit of the ARB losartan over the ß-blocker atenolol in the primary composite endpoint of combined death, MI, and stroke.[22] Blood pressure reductions at the end of follow-up were similar in the two groups. However, this beneficial effect was driven exclusively by the positive effect on stroke. Indeed, the test for heterogeneity for the 3 pre-specified secondary component endpoints – CV death, fatal and nonfatal stroke, and fatal and non-fatal MI – yielded a p-value of 0.023, with a point estimate favouring atenolol for MI. Furthermore, in the small black population, the event rate for stroke, as well as the composite secondary endpoints, was higher in the ARB group. Coupled with the unpublished data from the SCOPE study, it appears that ARBs may have a positive impact on stroke that is independent of their BP-lowering effect, whereas their benefits on other CV endpoints, independent of BP-lowering effect, still remain to be proven by placebo-controlled trials.

Figure 5: Percent of ALLHAT participants who achieved their goal blood pressure (SBP/DBP <140/90 mm Hg) among those attending follow-up visits (dashed line) and proportions at those visits who were prescribed 1, 2, 3, or 4+ antihypertensive medications (solid lines)



What does ALLHAT mean for clinical practice and future guidelines?

Population studies from the US and Canada have consistently demonstrated relatively low BP control rate (defined as <140/90 mm Hg).[23-25] Mechanisms that have been proposed as barriers to BP control include access to care, practice patterns, and patient compliance. Recent reports have suggested that one of the important factors in inadequate BP control is the clinicians' failure to increase the dose or the number of anti-hypertensive agents.[8,9]

The ALLHAT trial,[26] by virtue of its design, provides a unique opportunity to examine the factors that predict BP control, including the number of agents used in diverse North American practice settings. In a recent analysis of the ALLHAT trial, the relationship between systolic and diastolic BP, the proportion of patients achieving BP control (<140/90 mm Hg), and the number of drugs required to achieve BP control in the 3 treatment arms combined, were examined.[27] Systolic and diastolic BP were reduced from baseline measurements of 144.8 and 83.3 mm Hg to 134.7 mm Hg and 75.3 mm Hg, respectively, at year 5; the number of drugs used was 2.0±1.0 (mean±SD). The percent of patients who achieved BP control and who were prescribed 1, 2, 3, or more than 4 agents over 5 years, is shown in Figure 5. At the first of two pre-randomization visits, BP was <140/90 mm Hg in only 27.4% of subjects. At 5 years post-randomization, the proportion of control (<140/90 mm Hg) improved to 66%. Systolic BP was <140 mm Hg in 67%, whereas diastolic BP was <90 mm Hg in 92%, indicating systolic BP is more difficult to control than diastolic BP in the ALLHAT patient population. The requirement for multiple drugs increased with time

and 63% of patients were on ≥ 2 drugs. However, among subjects who were prescribed ≥ 2 drugs during follow-up, a percent of patients not "stepped up" – defined as either an increase in the dose of the blinded drug, an increase in the number of drugs, or a change in prescription – remained high at 71.7%.

The ALLHAT composite data indicate that BP control rates can be increased significantly to include at least two-thirds of the treated hypertensive population. Most of the patients who did not achieve target BP control had persistent elevation of SBP. However, many of the patients were not titrated to the maximum doses or number of drugs permitted by the trial design. This suggests that more aggressive control of SBP, and with more agents, could have yielded even better BP controls in ALLHAT.

The reason that chlorthalidone was used (instead of hydrochlorothiazide (HCTZ), which was more widely used clinically) was that it was the diuretic used in most of the earlier National Institute of Health-sponsored antihypertensive trials. It should be noted, however, that the two diuretics may not be the same. Some studies have reported that HCTZ does not control BP for 24 hours,[28] while others report no differences in duration of action between chlorthalidone and HCTZ.[29] In the MRFIT 4-year interim analysis,[13,30] CHD mortality rate per 1000 person-years was higher in the HCTZ group. Change from HCTZ to chlorthalidone (50 mg/d) resulted in a 28% decrease in CHD mortality.

Another important observation of ALLHAT is that the study did not find meaningful differences in the 3 treatments arms in terms of cancer risk, gastrointestinal bleeding, and all-cause mortality, risks that have previously been associated with dihydropyridine CCBs.[14,31,32] Indeed, non-CV mortality was significantly lower in the amlodipine arm. This observation underscores the limitation of conclusions and recommendations based in meta-analyses.

Summary

In summary, optimal BP control is the primary goal in the treatment of patients with hypertension. For the majority of hypertensive subjects, the argument for the best initial agent, whether it is a diuretic like chorthalidone, an ACE inhibitor like lisinopril, or a CCB like amlodipine, may be a relatively moot point. The totality of data, including those from ALLHAT, suggests that, except for certain high-risk subgroups (eg, diabetics and patients with left ventricular dysfunction), ACE inhibitors may not be as useful as they have been suggested to be while, conversely, CCBs may not be as adverse as some meta-analyses have proposed them to be, as long as BP is adequately controlled. Diuretics should be the foundation of therapy in most patients and it is likely that the overwhelming majority of hypertensive patients could achieve BP goals with the use of a combination of agents currently available to clinicians.

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