ALLHAT Findings Revisited in the Context of Subsequent Analyses, Other Trials, and Meta-analyses

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The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is reevaluated considering information from new clinical trials, meta-analyses, and recent subgroup and explanatory analyses from ALLHAT, especially those regarding heart failure (HF) and the association of drug treatment with new-onset diabetes mellitus (DM) and its cardiovascular disease (CVD) consequences. Chlorthalidone was superior to (1) doxazosin mesylate in preventing combined CVD (CCVD) (risk ratio [RR], 1.20; 95% confidence interval [CI], 1.13-1.27), especially HF (RR, 1.80; 95% CI, 1.40-2.22) and stroke (RR, 1.26; 95% CI, 1.10-1.46); (2) lisinopril in preventing CCVD (RR, 1.10; 95% CI, 1.05-1.16), including stroke (in black persons only) and HF (RR, 1.20; 95% CI, 1.09-1.34); and (3) amlodipine besylate in preventing HF, overall (by 28%) and in hospitalized or fatal cases (by 26%). Central independent blinded reassessment of HF hospitalizations confirmed each comparison. Results were consistent by age, sex, race (except for stroke and CCVD), DM status, metabolic syndrome status, and renal function level. Neither amlodipine nor lisinopril was superior to chlorthalidone in preventing end-stage renal disease overall, by DM status, or by renal function level. In the chlorthalidone arm, new-onset DM was not significantly associated with CCVD (RR, 0.96; 95% CI, 0.88-2.42). Evidence from subsequent analyses of ALLHAT and other clinical outcome trials confirm that neither α-blockers, angiotensin-converting enzyme inhibitors, nor calcium channel blockers surpass thiazide-type diuretics (at appropriate dosage) as initial therapy for reduction of cardiovascular or renal risk. Thiazides are superior in preventing HF, and new-onset DM associated with thiazides does not increase CVD outcomes.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a clinical outcome trial in 42,418 high-risk patients with hypertension, compared 4 classes of antihypertensive agents as initial therapy of hypertension for their effect on cardiovascular disease (CVD) outcomes and published its main results in 2002.1 Some trial findings were unexpected and generated much discussion and several questions.1-3 Despite the favorable metabolic effects of α-blockers and the angiotensin-converting enzyme (ACE) inhibitors, and the demonstrated benefits of inhibitors of the renin-angiotensin-aldosterone system vs placebo in well-conducted outcome trials, these advantages did not translate into improvement for CVD or renal outcomes.4,6 Since publication of the ALLHAT results, new clinical trials and meta-analyses have been reported, and ALLHAT data have been further analyzed.6,16 Continuing attention to the issue of preferred antihypertensive drugs prompts a reassessment of ALLHAT in light of the new information derived from these data,17,18 with special emphasis on the heart failure (HF) findings and the association of drug use with new-onset diabetes mellitus (DM) and its CVD consequences.

ALLHAT DESIGN AND MAIN RESULTS

The ALLHAT was a randomized, double-blind, multicenter clinical trial, designed to

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Group Information: A complete list of the participants in the ALLHAT Collaborative Research Group is available in JAMA (2002;288[23]:2981-2997).
determine whether incidence of major coronary heart disease (CHD) events (nonfatal myocardial infarction [MI] and CHD death; primary end point) is reduced in high-risk (defined by age ≥55 years with at least 1 additional CVD risk factor [e.g., left ventricular hypertrophy, history of DM, current cigarette smoking, high-density lipoprotein [HDL] cholesterol level <35 mg/dL (or <0.91 mmol/L), or documented history of atherosclerotic CVD]) patients with hypertension treated with a calcium-channel blocker (CCB) (represented by amlodipine besylate), an ACE inhibitor (represented by lisinopril), or an α-blocker (represented by doxazosin mesylate), each compared with diuretic (represented by chlorthalidone) as first-step therapy.10 (To convert HDL cholesterol to millimoles per liter, multiply by 0.0259.) Overall findings of the trial, summarized in Figures 1, 2, and 3, showed that CHD (fatal CHD plus nonfatal MI) risk was not improved for any of the 3 newer agents compared with chlorthalidone as first-step therapy.1,2

Figure 1. Four-year systolic/diastolic blood pressure difference and RRs (95% CIs) for clinical outcomes for newer agents compared with chlorthalidone, 12.5 to 25 mg/d, in prespecified subgroups. Data are given for coronary heart disease (CHD), combined cardiovascular disease (CCVD), heart failure (HF), stroke, and end-stage renal disease (ESRD). CI indicates confidence interval; DM, diabetes mellitus; and RR, relative risk. The figure is adapted from articles by the ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group1 and Whelton et al.9 Amlodipine besylate and chlorthalidone are compared.

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stroke and combined CVD (Figures 1, 2, and 3). Amlodipine and lisinopril were not superior to chlorthalidone in preventing end-stage renal disease (ESRD) overall or when stratified by DM or baseline estimated glomerular filtration rate.7,8

RESULTS IN SUBGROUPS

By design, ALLHAT recruited a very diverse patient population, which allows important prespecified subgroup analyses by sex, age, race, and DM status (Figures 1, 2, and 3). This was the most diverse experience to date for comparison of antihypertensive drug therapy in adults with DM (n = 13,101) and impaired fasting glucose (n = 13,990).7,9 There was no evidence of superiority for treatment with an \(
\alpha\)-blocker, CCB, or ACE inhibitor compared with the diuretic in any glycemic stratum. In ALLHAT participants with and without DM, HF was significantly less frequent among participants assigned to diuretic than among those assigned other treatments (range of \(P\) values: <.001 to .01).7,9,10 Thus, compared with the diuretic-based treatment, CCB- and ACE-inhibitor based therapies failed to demonstrate superiority in the prevention of CVD or ESRD in participants with DM.

In addition, ALLHAT was the first large randomized controlled trial to provide a head-to-head comparison of major drug classes in a substantial number of black participants (n = 15,094) and persons 65 years or older (n = 24,330).1,8,11,20 In both subgroups, there was no evidence of superiority for primary or major secondary outcomes in those assigned to the \(\alpha\)-blocker, CCB, or ACE inhibitor vs the diuretic. Other
apparent benefits of diuretic therapy included better reduction in blood pressure (BP) (4 mm Hg difference at 4 years), stroke incidence, and CCVD compared with ACE inhibitors in blacks. Also, CCB was more effective than ACE inhibitors in this population for BP reduction and prevention of stroke.21

The ALLHAT findings generated considerable discussion, and several questions about the results were raised. The remainder of this article addresses those issues in the context of newly available information.

**IMPLICATIONS OF THE BP DIFFERENCES ON INTERPRETATION OF ALLHAT FINDINGS**

The goal BP in ALLHAT was less than 140/90 mm Hg in all 4 treatment groups. Intensification of therapy was required by protocol if BP was not controlled. During the trial, small but significant differences in achieved BP levels occurred among randomized treatment groups (Figures 1, 2, and 3). Systolic BP was higher in participants randomized to doxazosin (by 2-3 mm Hg; P < .001 at all annual visits), lisinopril (by 2 mm Hg; P < .001 [4 mm Hg in blacks; P < .001]), and amlodipine (by <1 mm Hg; P < .001 to .03) than in those randomized to chlorthalidone. The BP differences in blacks accounted for the major BP difference between treatment arms, particularly between the ACE inhibitor and diuretic arms. However, non-black participants made up two-thirds of the study population. Despite negligible BP differences between treatment arms in the non-

Figure 3. Four-year systolic/diastolic blood pressure difference and RRs (95% CIs) for clinical outcomes for newer agents compared with chlorthalidone, 12.5 to 25 mg/d, in prespecified subgroups. Data are given for coronary heart disease (CHD), combined cardiovascular disease (CCVD), heart failure (HF), stroke, and end-stage renal disease (ESRD). CI indicates confidence interval; DM, diabetes mellitus; and RR, relative risk. The figure is adapted from articles by the ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group and Whelton et al.9 Doxazosin mesylate and chlorthalidone are compared.
black group, newer agents did not offer an advantage over the diuretic.\textsuperscript{8,11}

Trials other than ALLHAT have also reported differences in achieved BP levels across randomized treatment groups. Perfect comparability in achieved BP is unlikely in a double-blind, randomized, practice-based trial owing to differences in intrinsic BP-lowering efficacy of agents and/or synergistic efficacy with available add-on therapies.\textsuperscript{9,12,22} Serial median matching has been used in some studies to account for the observed differences in achieved BP levels.\textsuperscript{22,23} This approach leaves out substantial amounts of participant information, is susceptible to bias, distorts randomized comparison (may interject bias), and favors the drug less effective in lowering BP. The ALLHAT has reported analyses using achieved BP levels as time-dependent covariates in a Cox proportional hazard regression model, showing that after adjustment for BP, the differences in risk of stroke and HF between treatment arms remain statistically significant (P < .05), with only slight reduction in the RR.\textsuperscript{1,2,13,24} However, the Blood Pressure Lowering Treatment Trialists’ Collaboration (BPLTTC) meta-analysis reported that differences in achieved BP reduction between randomized groups accounted for the observed difference in risk for every outcome except HF.\textsuperscript{9} Therefore, BP differences may account for some, but not all, of the advantages seen with chlorthalidone.

**VALIDITY OF THE HF RESULTS IN ALLHAT**

In ALLHAT, HF was a prespecified outcome encompassing fatal and nonfatal treated HF whether or not participants required hospitalization. It was defined in the trial manual of operations as a combination of symptoms and signs and/or test findings, similar to methods used in other studies.\textsuperscript{14,31} Individuals with a history of symptomatic HF and/or known ejection fraction of less than 35% were not eligible for randomization. When the initial publications from ALLHAT reported that chlorthalidone-based treatment was superior to each of the 3 other agents in preventing new-onset HF,\textsuperscript{1,2} some found these results unexpected and raised questions about their validity.\textsuperscript{3} Given the public health importance of HF among older individuals, extensive steps to validate these findings were undertaken. The ALLHAT Heart Failure Validation Study rigorously evaluated all hospitalized HF events, using independent reviewers who were blinded to treatment assignment.\textsuperscript{14} Source documentation for HF hospitalizations (n = 2778 in 1935 patients) was centrally reviewed using site and adjudicated by independent reviewers who were blinded to treatment assignment.\textsuperscript{14} Source documentation for HF hospitalizations (n = 2778 in 1935 patients) was centrally reviewed using site and adjudicated by independent reviewers who were blinded to treatment assignment.\textsuperscript{14} Source documentation for HF hospitalizations (n = 2778 in 1935 patients) was centrally reviewed using site and adjudicated by independent reviewers who were blinded to treatment assignment.\textsuperscript{14} Source documentation for HF hospitalizations (n = 2778 in 1935 patients) was centrally reviewed using site and adjudicated by independent reviewers who were blinded to treatment assignment.\textsuperscript{14} Source documentation for HF hospitalizations (n = 2778 in 1935 patients) was centrally reviewed using site and adjudicated by independent reviewers who were blinded to treatment assignment.\textsuperscript{14} Source documentation for HF hospitalizations (n = 2778 in 1935 patients) was centrally reviewed using site and adjudicated by independent reviewers who were blinded to treatment assignment.

**IMPLICATIONS OF DIURETIC-ASSOCIATED DM ON LONG-TERM CVD RISK**

An important ALLHAT rationale was to determine whether newer drugs with more favorable effects on glucose and other metabolic parameters would result in a lower incidence of major clinical outcomes, especially coronary events, compared with diuretics. As anticipated from previous studies, diuretic treatment resulted in 4- to 6-mg/dL higher fasting plasma glucose levels compared with other agents. Among participants without DM (baseline fasting glucose level, <126 mg/dL), mean baseline fasting glucose level was approximately 94 mg/dL in all groups.\textsuperscript{15} Fasting glucose levels increased in all treatment groups, with the largest increase in the chlorthalidone group to 104 mg/dL at 4 years. The increase was intermediate in the amlodipine arm (to 102 mg/dL at 4 years) and smallest in the lisinopril (to 100 mg/dL at 4 years) and doxazosin arms (to 99 mg/dL at 4 years). (To convert glucose to millimoles per liter, multiply by 0.0555.)

The proportion of participants who developed levels of fasting glucose consistent with DM (>125 mg/dL) after 4 years was 11.6% in the chlorthalidone group, compared with 9.8% in the amlodipine (P = .01) and 7.8% in the lisinopril (P < .001).
groups. In the doxazosin arm, the comparison with chlorthalidone was 8.8% vs 10.6%, although (owing to early termination of the doxazosin arm) values are available for less than 10% of participants at 4 years. Assuming that CCBs are metabolically neutral, comparison of 4-year rates of incident DM in the amlo-
dipine vs chlorthalidone arms (9.8% vs 11.6%) suggests that only 17% of new-onset DM associated with thia-
zide use in studies like ALLHAT is likely the result of the diuretic (di-
uretic-induced as opposed to di-
uretic-associated changes). 36

Despite showing that diuretics were at least as effective as newer agents in preventing major clinical outcomes, the ALLHAT results seemed to heighten rather than lessen the interest in diuretic-induced dysglycemia. However, focus changed from specula-
tions regarding the clinical significance of the absolute increase in glu-
cose levels to a focus on increases in incident DM. This focus suggested that the risk of CVD events in diuretic-treated patients is more dependent on crossing the threshold for DM than on the magnitude of glucose elevation (ie, that risk of diabetic complications in a patient with a fasting glucose level of 121 mg/dL following a 5 mg/dL in-
crease in glucose level is determined more by crossing the 126 mg/dL threshold than by the 5 mg/dL in-
crease). However, regression analysis of ALLHAT data 15 showed that while incident DM during the first 2 years was associated with a subsequent 64% higher risk of CHD, as much as a 10 mg/dL increase in glucose level during that 2-year period resulted in no subsequent significant increase in CVD (see Table 1 for 95% confidence in-
tervals [CIs]). Importantly, the increase in aggregate clinical CVD asso-
ciated with both incident DM and a 10-mg/dL increase in glucose level was lowest in the chlorthalidone arm and highest in the lisinopril arm, with the CCB arm intermediate or similar (Table 1).

These recent analyses from ALLHAT are consistent with other data evaluating the link between diuretic-
induced increases in glucose level and adverse clinical outcomes. Lack of con-
gruence between these effects was demonstrated in many comparative trials and confirmed by recent prospective meta-analyses involving more than 26,000 patients, with almost 4000 CVD events, nearly 1900 coronary events, and in patients with hypertension and with or without DM. 5,37 In ad-
dition, recent reports provide data on diuretic-induced glucose elevations and long-term CVD risk. 13,38,39 Al-
though one study 38 reported a nearly 3-fold higher (2.92; 95% CI, 1.33-6.41) CVD risk after up to 16 years of follow-up in treated patients with hypertension (54% treated with diuretics) who developed new-onset DM, no relationship was seen between diuretic usage and CVD events. Analysis of the 14.3-
year follow-up from the SHEP revealed that incident DM during the trial among participants randomized to pla-

![Table 1. Hazard Ratios (HRs) for Clinical Outcomes Associated With Glucose Abnormalities in ALLHAT](image)
cebo was associated with a more than 50% increase in CVD mortality (adjusted hazard ratio [HR], 1.56; 95% CI, 1.12-2.18) but not in those randomized to the diuretic (adjusted HR, 1.04; 95% CI, 0.75-1.46). Thus, diuretic-induced glucose changes may underlie lesser prognostic significance.

**IMPLICATIONS OF ALLHAT IN PATIENTS WITH THE METABOLIC SYNDROME**

Patients with hypertension meeting criteria for metabolic syndrome (MetS) represent a population with or at high risk for DM and for CVD and renal events. Use of antihypertensive drugs with favorable metabolic profiles has been advocated over those with less favorable profiles (eg, β-blockers [BBs] and thiazide-type diuretics). In ALLHAT, almost 55% of patients were classified as MetS. This permitted the first test of this issue based on clinical outcomes. Participants with MetS randomized to a-blocker experienced lower plasma glucose and total cholesterol levels (by 10 mg/dL and 9 mg/dL, respectively) compared with a diuretic, and those randomized to ACE inhibitor experienced reductions of 6 mg/L and 2 mg/L, respectively. (To convert total cholesterol to milli-moles per liter, multiply by 0.0259.) The HDL lipoprotein cholesterol level was 0.9 mg/dL higher when a patient was prescribed an a-blocker vs diuretic. Despite these differences, there was no evidence of benefit from newer agents on CVD outcomes. As seen in **Table 2**, no CVD or renal outcome was significantly reduced by the a-blocker or ACE inhibitor compared with the diuretic prescribed in ALLHAT participants with MetS, including in those without DM. In black ALLHAT participants with MetS, a-blocker and ACE inhibitor treatment provided considerably less protection compared with the diuretic for stroke (RRs, 1.49 [95% CI, 1.09-2.03] and 1.37 [95% CI, 1.07-1.76], respectively), CHD (RRs, 1.19 [95% CI, 1.01-1.40], respectively), and ESRD (RRs, 1.26 [95% CI, 1.09-1.40] and 1.17 [95% CI, 1.00-1.34], respectively).

**Table 2. ALLHAT Findings in Participants With and Without the Metabolic Syndrome (MetS)**

<table>
<thead>
<tr>
<th>MetS Status and Treatment Group</th>
<th>Nonfatal MI/Fatal CHD HR (95% CI) vs Diuretic</th>
<th>All-Cause Mortality CCHD HR (95% CI) vs Diuretic</th>
<th>Stroke HR (95% CI) vs Diuretic</th>
<th>HF HR (95% CI) vs Diuretic</th>
<th>CCVD HR (95% CI) vs Diuretic</th>
<th>ESRD HR (95% CI) vs Diuretic</th>
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<td>Participants without MetS</td>
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<tr>
<td>Doxazosin mesylate</td>
<td>1.11 (0.96-1.26)</td>
<td>1.05 (0.83-1.04)</td>
<td>1.04 (0.83-1.29)</td>
<td>1.12 (0.76-1.65)</td>
<td>1.05 (0.96-1.15)</td>
<td>0.85 (0.51-1.42)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>1.04 (1.10-0.96)</td>
<td>0.96 (0.79-1.07)</td>
<td>0.94 (0.75-1.18)</td>
<td>0.93 (0.65-1.31)</td>
<td>0.96 (0.78-1.15)</td>
<td>0.92 (0.63-1.36)</td>
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<tr>
<td>Amlodipine</td>
<td>0.96 (0.76-1.21)</td>
<td>1.00 (0.92-1.04)</td>
<td>0.87 (0.74-1.04)</td>
<td>1.00 (0.76-1.30)</td>
<td>1.00 (0.88-1.13)</td>
<td>1.27 (0.96-1.70)</td>
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<tr>
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<td>1.27 (0.96-1.70)</td>
</tr>
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</table>

**Abbreviations:** ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CCHD, combined coronary heart disease; CCVD, combined cardiovascular disease; CHD, coronary heart disease; CI, confidence interval; DM, diabetes mellitus; ESRD, end-stage renal disease; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.
ences in CVD outcomes.49,52 Thus, the relative contributions of the diuretic and BBs cannot be interpreted because allocation to therapies is not randomized.

Aside from ALLHAT, only 1 outcome trial in hypertension (ANBP2) directly compared a diuretic with an ACE inhibitor as initial therapy.1,48 In ANBP2, the combined incidence of first and recurrent CVD events was significantly reduced by an ACE inhibitor–based regimen compared with one based on a thiazide-type diuretic (only in men; \( P = .02 \)). However, there was no significant difference for time to first CVD event \( (P = .06) \), the primary outcome used in most trials (although usually requiring a significantly larger sample size).

There were substantial differences between ANBP2 and ALLHAT. The ANBP2 trial had approximately one-fourth the participants \((6083 vs 24,309 in ALLHAT for the thiazide and ACE inhibitor arms) and one-fifth to one-tenth the CVD end points as ALLHAT. The ANBP2 trial also had an open-label design. Only 83% of participants in ANBP2 ever received assigned treatment, and only 58% of participants randomly assigned to ACE inhibitor and 62% of those assigned to diuretic were still receiving assigned treatment at the end of the study \((83% and 89\%\), respectively, in ALLHAT). Drug dosing in ANBP2 was left to the investigator, and doses administered during the trial have not been reported.32

Only 2 large CVD outcome hypertension trials other than ALLHAT have compared initial treatment with CCB vs one with a thiazide-type diuretic, International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) \((n = 6321)\), and the diuretic arm of Controlled Onset Verapamil Investigators of Cardiovascular Endpoints \((CONVINCE) (n = 16,602)\). Both used a double-blind design.31,53 Neither trial reported a significant difference in composite CVD primary outcomes. However, as in ALLHAT, fatal and nonfatal HF events were significantly higher in the CCB arm in INSIGHT \((RR, 2.20 [95\% CI, 1.07-4.49]; P = .03)\) and CONVINCE \((RR, 1.30 [95\% CI, 1.00-1.69]; P = .05)\), compared with an RR of 1.38 \((95\% CI 1.25-1.52; P = .001)\) in ALLHAT.

The ASCOT \((n = 10,285)\) randomized participants to initial treatment with either amloidipine or atenolol but is frequently portrayed as providing results contradictory to those of ALLHAT. Although there were amloidipine-based arms in both trials, ALLHAT used atenolol as add-on therapy for all treatment groups. In ASCOT an ACE inhibitor was added, if needed, to amloidipine, and a thiazide-type diuretic was added, if needed, to atenolol. Because these second drugs were not allocated randomly or consistently, a definitive comparison cannot be made between second drugs, whereas ALLHAT was designed to directly compare a thiazide-type diuretic with an ACE inhibitor, a CCB, and an \( \alpha \)-blocker. In addition, the dose of the thiazide-type diuretic, bendroflumethiazide, 1.25 to 2.5 mg/d, was one-fourth to one-half of the dose of the bendroflumethiazide or the other thiazide-type diuretics used in previous relevant antihypertensive trials.20

Findings from the recently completed Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension \((ACCOMPLISH)\) trial seem to be inconsistent with those of ALLHAT.16 The study was stopped early when the difference in the primary end point between the 2 arms crossed a prespecified end point favoring the CCB/ACE inhibitor combination \((RR, 0.81; 94\% CI, 0.72-0.90; P < .001)\). A randomized double-blind study \((n = 11,462)\), ACCOMPLISH compared the effects of 2 single-pill combination antihypertensive regimens, an ACE inhibitor–diuretic combination \((benazepril and hydrochlorothiazide, 40 mg [force-titrated] and 12.5 mg, respectively)\) and an ACE inhibitor–CCB combination \((benazepril and amlodipine besylate, 40 mg [force-titrated] and 5 mg, respectively)\), on a composite outcome of CVD mortality and morbidity \((CHD and stroke but not HF)\). The hydrochlorothiazide and amloidipine components of the single-pill combination could be further titrated to 25 mg and 10 mg, respectively, and other classes of drugs could be added for BP control. Although the dose of amloidipine \((5-10 mg/d)\) in the ACCOMPLISH trial was similar to that demonstrating favorable outcomes in other outcome trials,1,12,22 the dose range for hydrochlorothiazide \((12.5-25 mg/d)\) was lower than dose ranges \((25-50 mg/d, or an equivalent dose of other thiazide-type diuretic)\) used in trials demonstrating benefits on CVD of thiazide-type diuretics.6,59-60 A statistically significant though small BP difference \((0.9 \text{ mm Hg systolic, } 1.1 \text{ mm Hg diastolic}; P < .001 \text{ for both comparisons})\) was reported between arms favoring the ACE inhibitor–CCB combination. Dosage details of supplementary drugs are not available; however, recommended supplementary drugs were BBs and \( \alpha \)-blockers, whose effects on clinical outcomes are inferior.2,17

An alternative interpretation of the ACCOMPLISH trial is that doses of thiazide-type diuretics equivalent to 25 mg/d or less of hydrochlorothiazide may be less effective in preventing CVD outcomes than full doses of amloidipine or doses of diuretics used in previous trials.

**META-ANALYSES**

The largest meta-analyses of randomized outcome trials of antihypertensive treatment performed since 200237,57,61 were conducted by the BPLTTC.6,37,57,58 These meta-analyses were designed to include trials selected prospectively62 based on study design before their results were available. The most comprehensive of these analyses comprised 29 trials \((including \text{ ALLHAT})\) that collectively enrolled 162,341 patients and concluded that treatment based on main drug classes reduced major CVD events, with most of the benefits being attributable to BP lowering.6 However, CCBs were reported to be less effective in preventing HF than ACE inhibitors or diuretics and/or BBs (diuretics/BBs): the pooled RR for CCB vs diuretics/BBs was 1.33 \((95\% CI, 1.21-1.47)\). In contrast, results for stroke were suggestive but not significantly in favor of CCB: the RR of 0.93 \((95\% CI, 0.86-1.00)\), based on 9 trials, also was virtually identical to that from ALLHAT alone.

The BPLTTC results comparing diuretics/BBs with ACE inhibitor regimens were less clear with a trend toward differences favoring diuretics/BBs.6 These may have been influ-
enced by a 2–mm Hg advantage for diuretics/BB arms, especially with regard to stroke, where the RR (ACE inhibitor vs diuretics/BBs), based on 5 trials, was 1.09 (95% CI, 1.00–1.18). For HF, findings were also similar to those of ALLHAT: RR, 1.07 (95% CI, 0.96–1.19). The BPLTTC analyses merged treatment arms with regimens based on thiazide-type diuretics, BBs, or either (according to local investigator choice). One report from BPLTTC suggested a modest BP-independent benefit of ACE inhibitor (not angiotensin receptor blocker) compared with diuretics/BBs for CHD but not stroke or HF. This finding was not supported in a network meta-analysis that was able to assess the effect of diuretics on CV outcomes separately from that of the BBs. Aggregate trial evidence for patients with and without DM have also been reported from BPLTTC. Based on a total of 6 trials (including ALLHAT) with 47 430 participants randomized to either ACE inhibitor or diuretics/BBs, no difference was seen in rates of major CVD events, including CHD, nor any specific CVD outcome between arms for patients either with or without DM.

CONCLUSIONS

In summary, more complete ALLHAT analyses and subsequent trial and meta-analytic data are consistent in confirming initial ALLHAT findings that (despite having more favorable effects on glucose and lipid levels and other surrogate variables) neither the α-blocker, ACE inhibitor, nor the CCB surpasses the thiazide-type diuretic as initial therapy for control of BP or reduction of cardiovascular or renal clinical outcomes (when compared at appropriate dosage). Although initial unveiling of ALLHAT findings met with a number of questions and some controversy, further analyses of ALLHAT data and findings from subsequent trials continue to support the original findings. In conclusion, extensive further analyses from ALLHAT and data from other sources underscore the original conclusions from ALLHAT that thiazide-type diuretics remain the preferred first-step therapy in most patients with hypertension. Passive follow-up of ALLHAT participants for morbidity and mortality using administrative databases continues, and this nearly 10 years of experience should provide additional insights.

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