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ALLHAT FINDINGS REVISITED IN THE CONTEXT OF SUBSEQUENT ANALYSES, OTHER TRIALS AND META-ANALYSES

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Abstract

Background: This paper re-evaluates the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) considering information from new clinical trials, meta-analyses, and recent ALLHAT analyses, especially those regarding heart failure and the association of drug treatment with new-onset diabetes (NOD) and its cardiovascular disease (CVD) consequences.

Methods: Subgroup and explanatory analyses from a long-term 4-arm double-blind randomized antihypertensive treatment trial in diverse North American settings.

Results: Chlorthalidone was superior to 1) doxazosin in preventing combined CVD (CCVD) (RR=1.20, 95% CI 1.13-1.27), especially HF (RR=1.80, CI 1.40-2.22) and stroke (RR=1.26, CI 1.10-1.46); 2) lisinopril, in preventing CCVD (RR=1.10, CI 1.05-1.16), including stroke (in Black persons only) and HF (RR=1.20, CI 1.09-1.34); and 3) amlodipine, in preventing HF, overall (by 28%) and in hospitalized/fatal cases (by 26%). Central independent blinded re-review of HF hospitalizations confirmed each comparison. Results were consistent by age, sex, race (except for stroke and CCVD), diabetic status, metabolic syndrome status, and renal function level. Neither amlodipine nor lisinopril was superior to chlorthalidone in preventing end-stage renal disease overall, by diabetes status or by renal function level. In the chorthalidone arm, NOD was not significantly associated with CCVD (RR=0.96, CI 0.88-2.42).

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Conclusions: Evidence from subsequent analyses of ALLHAT and other clinical outcome trials confirm that neither α-blockers, ACE-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 heart failure, and new-onset diabetes associated with thiazides does not increase CVD outcomes.

INTRODUCTION

The Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT), a clinical outcome trial in 42,418 high-risk hypertensive patients, compared four classes of antihypertensive agents as initial therapy of hypertension for their effect on cardiovascular (CVD) outcomes and published its main results in 2002. Some trial findings were unexpected and generated much discussion and several questions.(1-3). Despite the favorable metabolic effects of α-blocker and the angiotensin converting enzyme inhibitor (ACEI), and the demonstrated benefits of inhibitors of the renin-angiotensin-aldosterone system versus 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 prompt a re-assessment of ALLHAT in light of the new information derived from these data,(17;18) with special emphasis on the heart failure findings and the association of drug use with new-onset diabetes and its CVD consequences.

ALLHAT Design and Main Results

ALLHAT was a randomized, double-blind, multicenter clinical trial, designed to determine whether incidence of major coronary heart disease (CHD) events (nonfatal MI and CHD death; primary endpoint) is reduced in high-risk (defined by age ≥ 55 years with at least one additional CVD risk factor [e.g. left ventricular hypertrophy, history of diabetes, current cigarette smoking, high density lipoprotein cholesterol < 35 mg/dl or < 0.91 mmoles/l, or documented history of atherosclerotic CVD]) hypertensive patients by a calcium-channel blocker (CCB; represented by amlodipine), an ACEI (represented by lisinopril), or an α-blocker (represented by doxazosin), each compared with diuretic (represented by chlorthalidone) as first-step therapy.(19). Overall findings of the trial, summarized in Figure 1, 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) However, diuretic-based therapy was superior to α-blocker, ACEI, and CCB-based therapies in preventing one or more major forms of CVD, including stroke and heart failure (HF).

Chlorthalidone was superior to doxazosin in prevention of combined CVD, especially HF and stroke. Chlorthalidone was superior to lisinopril in preventing combined CVD, including stroke (in black persons only), HF, angina, and coronary revascularizations. Chlorthalidone was superior to amlodipine in preventing HF, overall (by 28%) and in hospitalized or fatal cases (26%). These results were consistent by age, sex, diabetic status and level of renal function for all outcomes, and by race, except for stroke and combined CVD (see below). Amlodipine and lisinopril were not superior to chlorthalidone in preventing end-stage renal disease (ESRD) overall, or when stratified by diabetes or baseline estimated glomerular filtration rate (GFR). (7;8)

Results in Subgroups (Figure 1)

ALLHAT, by design, recruited a very diverse patient population allowing important pre-specified subgroup analyses by gender, age, race and diabetic status. This was the most diverse experience to date for comparison of antihypertensive drug therapy in adults with diabetes

mellitus (n=13,101) and impaired fasting glucose (n=1399).(2;9) There was no evidence of superiority for treatment with α-blocker, CCB or ACEI compared to diuretic in any glycemic stratum. In diabetic and non-diabetic ALLHAT participants, HF was significantly less frequent among participants assigned to diuretic than among those assigned other treatments.(2;9;10) Thus, compared to diuretic-based treatment, CCB and ACEI-based therapies failed to demonstrate superiority in the prevention of CVD or ESRD in diabetic participants.

ALLHAT was also 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 and older (n= 24,330).(1;8;11;20) In both subgroups, there was no evidence of significant superiority for primary or major secondary outcomes in those assigned to the α-blocker, CCB or ACEI versus the diuretic. Other apparent benefits of diuretic therapy included better reduction in BP (4 mmHg difference at four years), stroke incidence and CCVD compared to ACEI in Blacks. Also CCB was more effective than ACEI in this population for BP reduction and prevention of stroke.(21)

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 Blood Pressure Differences on Interpretation of ALLHAT Findings

Goal BP in ALLHAT was <140/90 mmHg in all four 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 (Fig 1). SBP was higher in participants randomized to doxazosin (by 2-3 mmHg), lisinopril (by 2 mmHg [4 mmHg in Blacks]), and amlodipine (by <1 mmHg) than in those on chlorthalidone. BP differences in Blacks accounted for the major BP difference between treatment arms, particularly between the ACEI and diuretic arms. However, non-Black participants made up 2/3rd of the study population. Despite negligible BP differences between treatment arms in the non-Black group, newer agents did not offer an advantage over diuretic.(8;11)

ALLHAT was not the only clinical trial to report differences in achieved BP levels across randomized treatment groups. Perfect comparability in achieved BP is unlikely in a double-blind randomized practice-based trial due to differences in intrinsic BP-lowering efficacy of agents and/or synergistic efficacy with available add-on therapies.(5;12;22) Serial median matching has been used in some studies to account for the observed differences in achieved BP levels.(22;23) This approach leaves out substantial amounts of participant information, is susceptible to bias, disturbs randomized comparison (may interject bias), and favors the drug less effective in lowering BP. 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, with only slight reduction in the RR.(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.(6) Therefore, BP differences may account for some but not all of the advantages seen with chlorthalidone.

Do Chlorthalidone Findings Generalize to Other Thiazide-type Diuretics?

Since chlorthalidone is not widely used in practice, clinicians have questioned why it was chosen as the comparator agent. Previous NHLBI-sponsored trials (HDFP(25), SHEP(26), and MRFIT in post-hoc subgroup analyses(27) showed beneficial effects on clinical outcomes with this agent. Comparison of doses of chlorthalidone used with standard thiazides is a subject of

considerable discussion. Recent data suggest a 1 ½-2 fold greater antihypertensive potency for chlorthalidone in comparison to HCTZ.(28) A meta-analysis of trials using other thiazide-type agents reported similar clinical cardiovascular outcomes across the class.(29) However, these studies used higher doses of these agents than the 12.5-25 mg/day dose of HCTZ currently used in clinical practice and one recent outcome trial (see below). Thus, at doses equivalent to that used in ALLHAT (chlorthalidone, average of 20 mg/day),(30) it is likely that attributes of chlorthalidone extend to others in the class.

Validity of the Heart Failure Results in ALLHAT

In ALLHAT, HF was a pre-specified outcome encompassing fatal and non-fatal treated HF whether participants required hospitalization or not. It was defined in the Manual of Operations as a combination of symptoms and signs/test findings, similar to methods used in other studies.(14;31) Individuals with a history of symptomatic HF and/or known ejection fraction<35% were not eligible for randomization. When the initial publications from ALLHAT reported that chlorthalidone-based treatment was superior to each of the three other agents in preventing new-onset HF,(1;2) some found these results unexpected and raised questions about their validity.(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 blinded-to-treatment-assignment reviewers.(14) Source documentation for HF hospitalizations (n=2778 in 1935 patients) was centrally reviewed using pre-specified algorithms (based on SHEP/ALLHAT and Framingham criteria) and reviewers' global clinical judgment. This review confirmed site-physicians' diagnoses in the majority of patients (71%, 80%, and 84% respectively using ALLHAT, Framingham and reviewer diagnoses). More importantly, the originally reported higher risk of HF associated with first-step therapy using amlodipine, lisinopril or doxazosin compared with chlorthalidone was confirmed by RRs calculated when applying various validation criteria. RRs across criteria sets ranged as follows: 1.41-1.46 for amlodipine, 1.12-1.21 for lisinopril, and 1.71- 1.80 for doxazosin, each compared with chlorthalidone. Results of other active drug comparison trials are mixed, but overall consistent with the ALLHAT findings.(6;12;32) Mortality risk subsequent to hospitalized HF (over 50% at 5 years) underscores the importance of preventing new-onset HF in high-risk patients, and provides an indirect validation of the diagnosis. Thus, thiazide-type diuretics would appear to provide better protection against new-onset HF (particularly HF with preserved ejection fraction) in high-risk patients with hypertension,(14;33) though treatment of patients with established HF should follow appropriate guidelines.(34;35)

Implications of Diuretic-Associated Diabetes 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 4-6 mg/dl higher fasting plasma glucose levels compared with other agents. Among non-diabetic participants (baseline fasting glucose level<126 mg/dl), mean baseline fasting glucose level was approximately 94 mg/dl in all groups.(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).

The proportion of participants who developed levels of fasting glucose consistent with diabetes (>125 mg/dl) after 4 years was 11.6% in the chlorthalidone group, compared to 9.8% in the amlodipine (p=0.01) and 7.8% in the lisinopril (p<0.001) groups. In the doxazosin arm, the comparison with chlorthalidone was 8.8% vs. 10.6%, although (due 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 diabetes in the amlodipine versus chlorthalidone arms (9.8% versus 11.6%), suggests that only 17% of new-onset diabetes associated with thiazide use in studies like ALLHAT is likely due to the diuretic (diuretic-induced as opposed to diuretic-associated changes).(36)

Despite showing that diuretics were at least as effective as newer agents in preventing major clinical outcomes, ALLHAT results seemed to heighten rather than lessen the interest in diuretic-induced dysglycemia. However, focus changed from speculations regarding significance of the absolute increase in glucose levels to a focus on increases in incident diabetes. This focus suggested that the risk of CVD events in diuretic-treated patients is more dependent on crossing the threshold for diabetes than on the magnitude of glucose elevation (i.e. that risk of diabetic complications in a patient with a fasting glucose of 121 mg/dl following a 5 mg/dl increase in glucose is determined more by crossing the 126 mg/dl threshold than by the 5 mg/dl increase). However, regression analysis of ALLHAT data (15) showed that while incident diabetes during the first two years was associated with a subsequent 64% higher risk of CHD, as much as a 10 mg/dl increase in glucose during that two year period resulted in no subsequent significant increase in CVD (Table 1). Importantly, the increase in aggregate clinical CVD associated with both incident diabetes and a 10 mg/dl increase in glucose 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 and adverse clinical outcomes. Lack of congruence between these effects was demonstrated in many comparative trials and confirmed by recent prospective meta-analyses involving >26,000 patients, with almost 4,000 CVD events, nearly 1900 coronary events, and in both diabetic and non-diabetic hypertensive individuals.(6;37) In addition, recent reports provide data on diuretic-induced glucose elevations and long term CVD risk.(15;38;39) While one study 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 hypertensives (54% treated with diuretics) who developed new-onset diabetes, no relationship was seen between diuretic usage and CVD events. Analysis of the 14.3 year follow-up from the SHEP revealed that incident diabetes during the trial among subjects on placebo was associated with a more than 50% increase in CV mortality (adjusted 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).(38) Thus, diuretic-induced glucose changes may underlie the lesser prognostic significance.

Implications of ALLHAT in Patients with the Metabolic Syndrome

Hypertensive patients meeting criteria for metabolic syndrome (MetS) represent a population with or at high risk for diabetes mellitus and for CVD and renal events.(40-42) Use of antihypertensive drugs with favorable metabolic profiles has been advocated over those with less favorable profiles (e.g., beta-blockers and thiazide-type diuretics).(43-46) In ALLHAT, almost 55% of participants met criteria for MetS. This permitted the first test of this issue based on clinical outcomes.(8;47) Participants with MetS randomized to α-blocker experienced lower plasma glucose and total cholesterol (by 10 mg/dl and 9 mg/dl respectively) compared to diuretic, and those randomized to ACEI experienced reductions of 6 mg/dl and 2 mg/dl respectively. HDL-cholesterol was 0.9 mg/dl higher on α-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 α-blocker or ACEI compared to the diuretic in ALLHAT participants with MetS, including in those without diabetes.(47) In Black ALLHAT participants with MetS, α-blocker and ACEI treatment provided considerably less protection compared to the diuretic for stroke (RR=1.49 (1.09-2.03)

and 1.37 (1.07-1.76) respectively), HF (RR=1.88 (1.42-2.47) and 1.49 (1.17-1.90) respectively), combined CVD (RR=1.37 (1.19-1.58) and 1.24 (1.09-1.40) respectively) and ESRD (RR=1.17 (0.62-2.22) and 1.70 (1.13-2.55) respectively).(8)

ALLHAT Findings versus Those from Other Studies

Differences in Trial Design—ALLHAT was an active-controlled trial comparing effects of antihypertensive treatments on clinical outcomes. There are several design possibilities for active-controlled outcome trials. The randomized, double-blind design used in ALLHAT is the most rigorous. While prospective, randomized, open-label, blinded end point (PROBE) design, used in trials such as ANBP-2 and ASCOT, should lead to comparable groups at baseline, the presence of bias in applying the randomized treatment assignments cannot be determined (e.g. 15-16% of ANBP2 participants did not start their assigned treatment).(48) Additionally, although outcomes are evaluated in a blinded fashion, they are not ascertained that way. Thus, there could be bias in event reporting, especially for events or side effects that might have been "expected" to be lower in one arm versus another.

Recent Trials – What do they imply for ALLHAT?—Recent antihypertensive trials have compared initial therapy between different drugs representing various antihypertensive classes. Several trials utilized a "standard therapy" regimen or investigator's choice of either a thiazide-type diuretic or a □-blocker, although these classes have different mechanisms of action and differences in CVD outcomes.(49-52) Thus, the relative contributions of the diuretic and □-blocker cannot be interpreted, since allocation to therapies is not randomized.

Aside from ALLHAT, only one outcome trial in hypertension (ANBP-2) directly compared a diuretic with an ACEI as initial therapy.(1;48) The combined incidence of first and recurrent CVD events was significantly reduced by an ACEI-based regimen compared with one based on thiazide-type diuretic (only in men). However, there was no significant difference for time to first CVD event, the primary outcome used in most trials (though usually requiring a significantly larger sample size).

There were substantial differences between ANBP2 and ALLHAT. ANBP2 had approximately ¼ the participants (6,083 versus 24,309 in ALLHAT for thiazide and ACEI arms) and 1/5 to 1/10 the CVD endpoints as ALLHAT. ANBP2 also had an open-label design. Only 83% of subjects in ANBP2 ever received assigned treatment, and only 58% of subjects randomly assigned to ACEI and 62% of those assigned to diuretic were still receiving assigned treatment at the end of the study (83% and 89% in ALLHAT). Drug dosing in ANBP2 was left to the investigator, and doses administered during the trial have not been reported.(32)

Only two large CVD outcome hypertension trials other than ALLHAT have compared initial treatment with CCB versus one with thiazide-type diuretic, INSIGHT (n=6,321) and the diuretic arm of CONVINCE (n=16,602). Both used a double-blind design.(1;53) Neither trial reported a significant difference in composite CVD primary outcomes. However, as in ALLHAT, fatal and non fatal HF events were significantly higher in the CCB arm in INSIGHT (RR=2.20 [95% CI 1.07–4.49], p=0.028) and CONVINCE (RR=1.30 [95% CI 1.00–1.69], p=0.05), compared with a RR=1.38 (CI 1.25-1.52, p=0.001 in ALLHAT.

The ASCOT trial randomized participants to initial treatment with either amlodipine or atenolol but is frequently portrayed as providing contradictory results to ALLHAT.(12) Although there were amlodipine-based arms in both trials, ALLHAT used atenolol as add-on therapy for all treatment groups. In ASCOT an ACEI was added, if needed, to amlodipine and a thiazide diuretic was added, if needed, to atenolol. Since these second drugs were not allocated randomly or consistently, a definitive comparison cannot be made between second drugs, while ALLHAT was designed to directly compare thiazide diuretic with ACEI, CCB and α-blocker

arms. In addition, the dose of thiazide diuretic, bendroflumethiazide 1.25-2.5 mg/d, was 1/4 to 1/2 of the dose of bendroflumethiazide or other thiazide-type diuretics used in previous relevant antihypertensive trials.(29)

The recently completed Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension (ACCOMPLISH) trial appears to be inconsistent with ALLHAT findings.(16) The study was stopped early when the difference in primary endpoint between the two arms crossed a pre-specified endpoint favoring CCB/ACEI combination (RR 0.81, CI 0.72-0.90; p=0.0002). A randomized double-blind study (n=11,462), it compared effects of two single-pill combination antihypertensive regimens, an ACEI–diuretic combination (benzapril/hydrochlorothiazide force titrated to 40/12.5 mg), and ACEI-CCB combination (benazapril/amlodipine besylate force titrated to 40/5 mg), on a composite outcome of CVD mortality and morbidity (CHD and stroke but not HF). The doses could be further titrated to 40/25 mg and 40/10 mg respectively, and other classes of drugs added for BP control. While the dose of amlodipine (5-10 mg/day) in ACCOMPLISH was similar to that demonstrating favorable outcomes in other outcome trials,(1;12;22) dose range for HCTZ (12.5-25 mg) was lower than dose ranges (25-50 mg/day, or equivalent dose of other thiazide-type diuretic) used in trials demonstrating benefits on CVD of thiazide-type diuretics.(6; 54-56) A significant though small BP difference was reported between arms favoring the ACEI/CCB arm. 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) Results of ACCOMPLISH trial may suggest that doses of thiazide-type diuretics equivalent to ≤ 25 mg/day of HCTZ may be less effective in preventing CVD outcomes than full doses of amlodipine or doses of diuretics used in previous trials.

Meta-Analyses

The largest meta-analyses of randomized outcome trials of antihypertensive treatment conducted since 2002(6;37;57-61) were conducted by the BPLTTC. (6;37;57;58) These meta-analyses were designed to include trials selected prospectively (62) based on study design before their results were available. The most comprehensive of these analyses included 29 trials (including 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 less effective in preventing HF than ACEIs or diuretics and/or beta-blockers (D/BB): pooled relative risk for CCB versus D/BB was 1.33 (95% CI, 1.21-1.47). In contrast, results for stroke were suggestive but not significantly in favor of CCB: the relative risk of 0.93 (0.86-1.00), based on 9 trials, also virtually identical to that from ALLHAT alone.

BPLTTC results comparing D/BB with ACEI regimens were less clear with a trend toward differences favoring D/BB.(6) These may have been influenced by a 2 mmHg advantage for D/BB arms, especially with regard to stroke, where the RR (ACEI vs. D/BB), based on 5 trials, was 1.09 (1.00-1.18). For HF, findings were also similar to ALLHAT, RR=1.07 (0.96-1.19). BPLTTC analyses merged treatment arms with regimens based on thiazide diuretics, BBs, or either (according to local investigator choice). One report from BPLTTC suggested a modest BP-independent benefit of ACEI (not ARB) compared to D/BB for CHD but not stroke or HF. (58) This finding was not supported in a network meta-analysis that was able to assess the effect of diuretics on CV outcomes separate from that of the beta blockers.(59) Aggregate trial evidence for patients with and without diabetes have also been reported from BPLTTC.(37) Based on a total of 6 trials (including ALLHAT) with 47,430 participants randomized to either ACEI or diuretic/BB, no difference was seen in rates of major CV events including CHD, nor any specific CV outcome between arms for either non-diabetic or diabetic patients.

SUMMARY AND IMPLICATIONS FOR THERAPY

In summary, more complete ALLHAT analyses, subsequent trial and meta-analytic data are consistent in confirming initial ALLHAT findings that (despite more favorable effects on glucose, lipid, and other surrogate variables) neither the α-blocker, ACEI 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 ten years of experience should provide additional insights.

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Dr. Davis had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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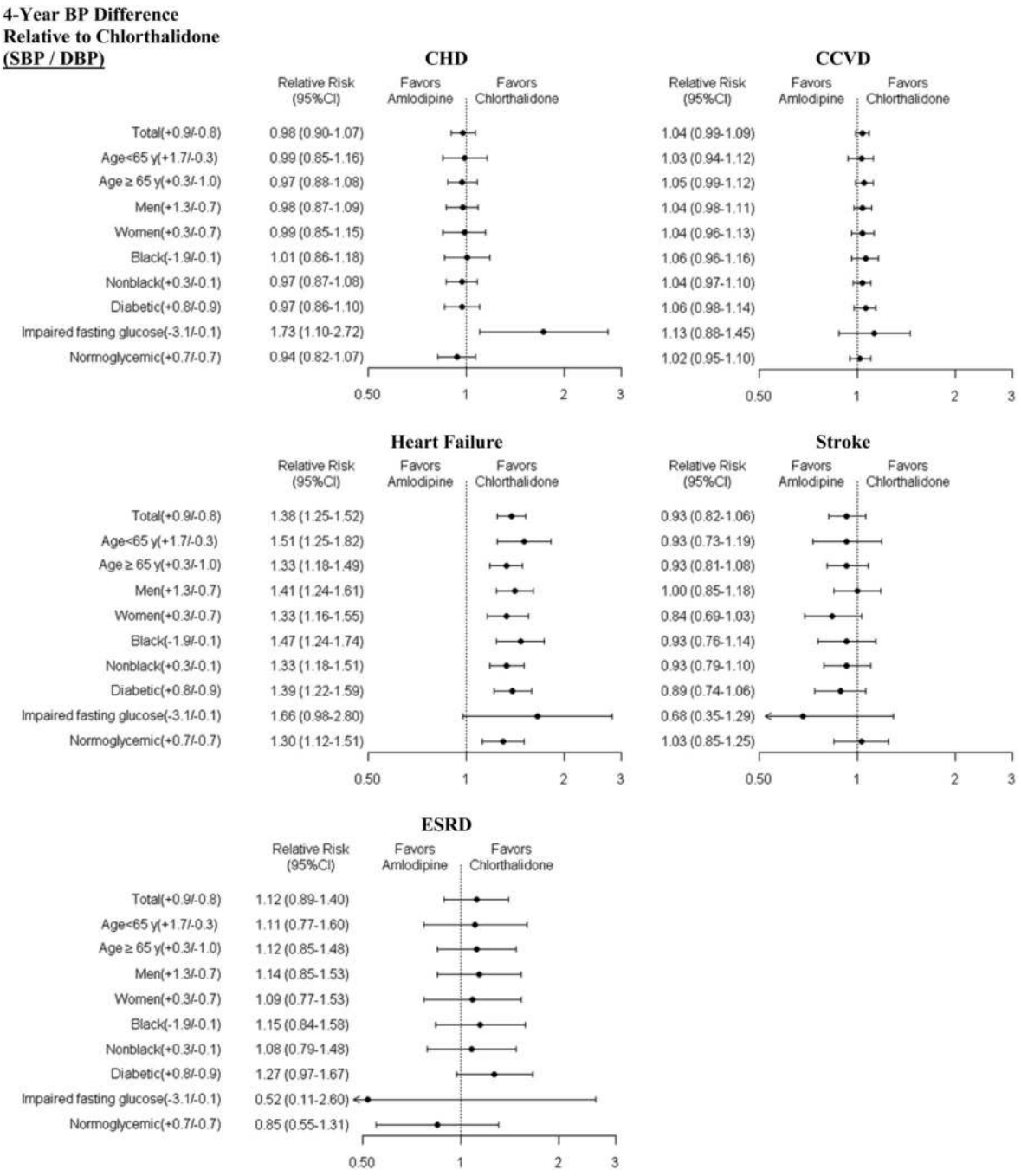

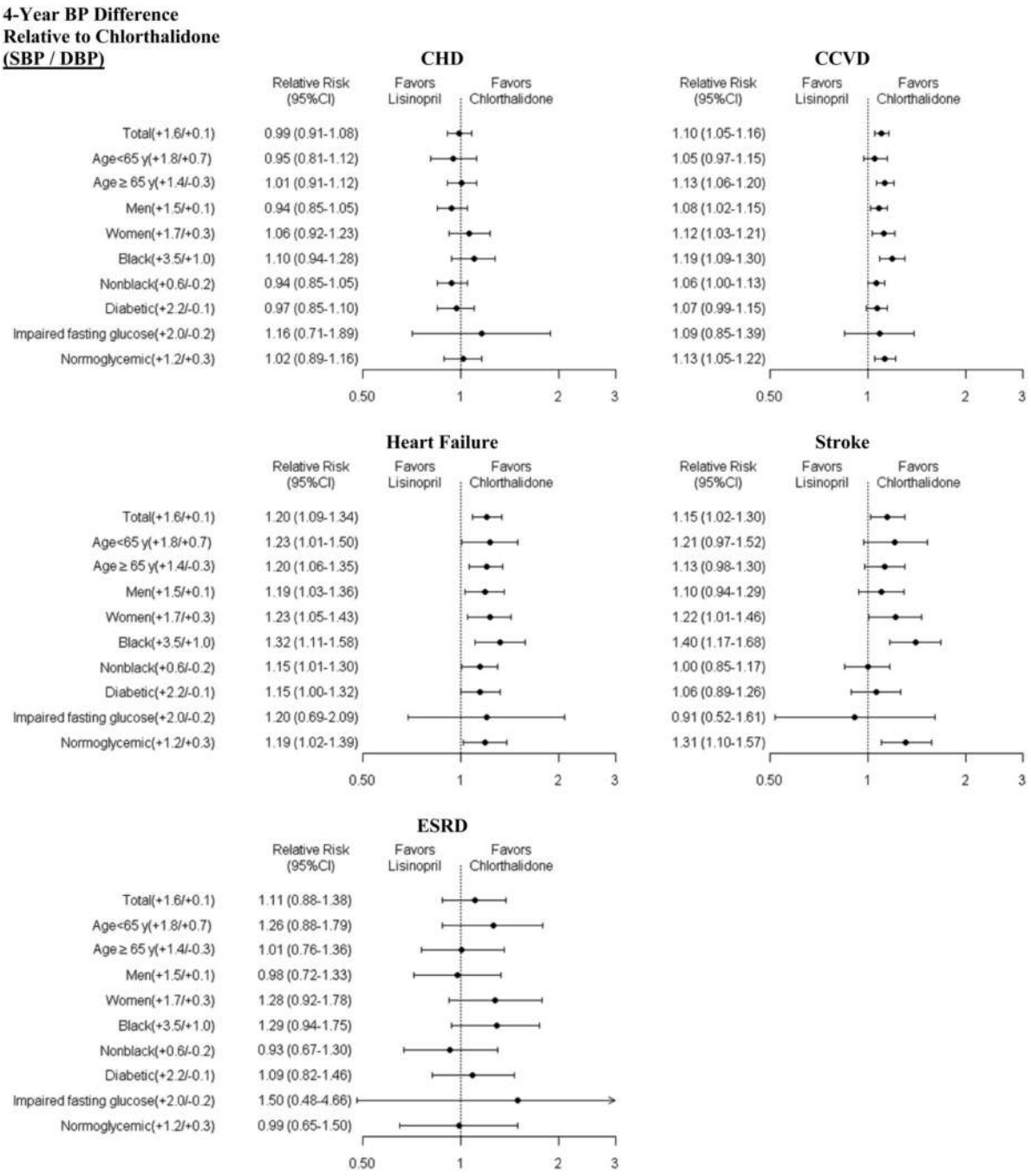

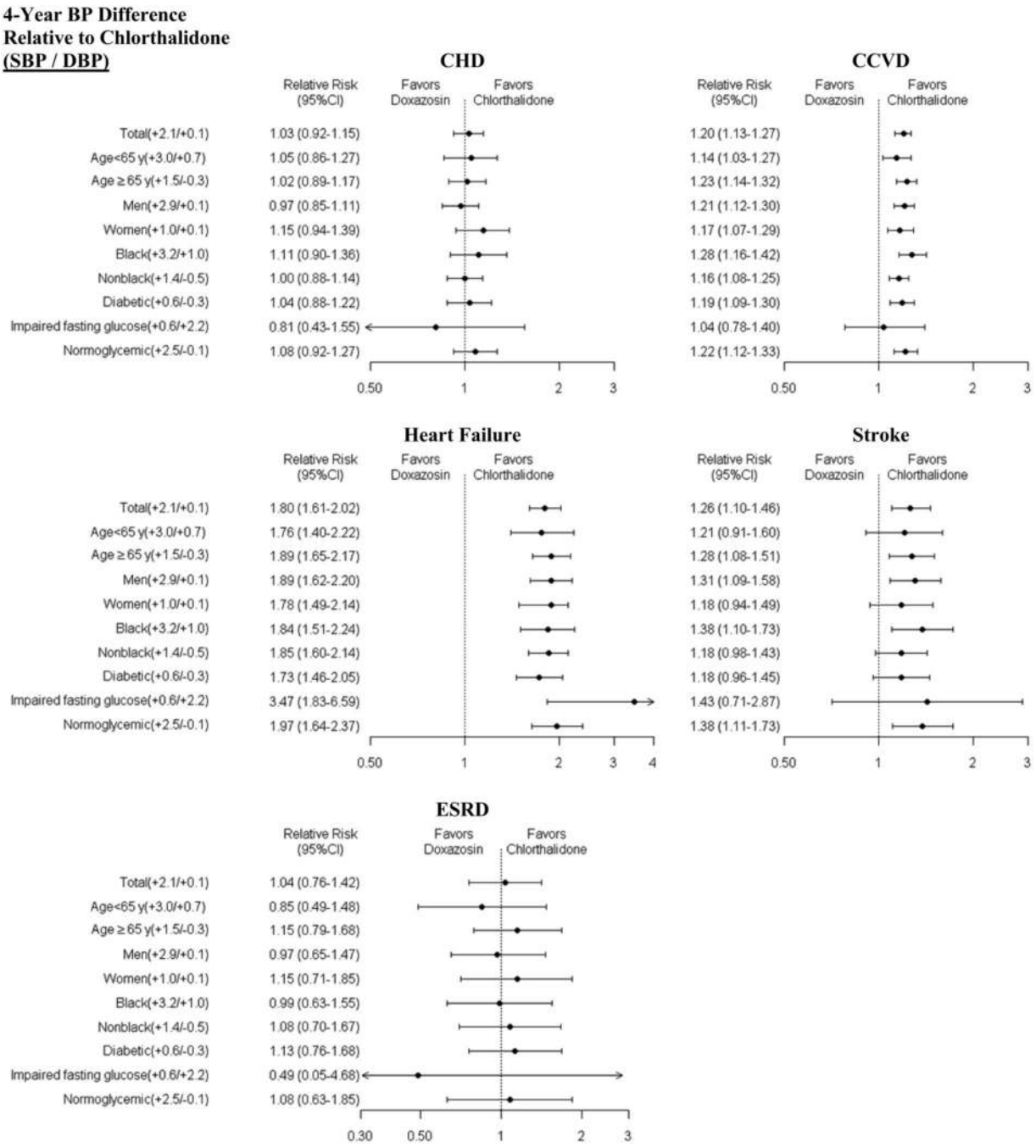

Figure 1.

Figure 1a. Blood pressure (BP) difference and relative risks (95% confidence intervals) for clinical outcomes for newer agents compared to chlorthalidone 12.5-25 mg/day in pre-specified subgroups – amlodipine vs. chlorthalidone. Coronary heart disease (CHD), combined cardiovascular disease (CCVD), heart failure (HF), stroke, and end-stage kidney disease (ESRD)

Figure 1b. Blood pressure (BP) difference and relative risks (95% confidence intervals) for clinical outcomes for newer agents compared to chlorthalidone 12.5-25 mg/day in pre-specified subgroups – lisinopril vs. chlorthalidone. Coronary heart disease (CHD), combined

cardiovascular disease (CCVD), heart failure (HF), stroke, and end-stage kidney disease (ESRD)

Figure 1c. Blood pressure (BP) difference and relative risks (95% confidence intervals) for clinical outcomes for newer agents compared to chlorthalidone 12.5-25 mg/day in pre-specified subgroups – doxazosin vs. chlorthalidone. Coronary heart disease (CHD), combined cardiovascular disease (CCVD), heart failure (HF), stroke, and end-stage kidney disease (ESRD)

Table 1

Hazard Ratios for Clinical Outcomes Associated with Glucose Abnormalities in ALLHAT

	Nonfatal MI / Fatal CHD	All-Cause Mortality	Stroke	HF	CCVD	ESRD
Incident Diabetes vs. No Diabetes - RR (95% CI)*						
Chlorthalidone, amlodipine, lisinopril						
Overall	1.64 (1.15-2.33)	1.31 (0.95-1.81)	1.61 (0.92-2.84)	1.37 (0.84-2.24)	1.04 (0.80-1.35)	2.86 (0.97-8.39)
Chlorthalidone	1.46 (0.88-2.42)	1.05 (0.66-1.67)	1.83 (0.85-3.95)	0.96 (0.46-2.00)	0.96 (0.66-1.37)	3.05 (0.82-11.33)
Amlodipine	1.71 (0.87-3.34)	1.92 (1.07-3.44)	2.63 (0.97-7.09)	1.29 (0.53-3.10)	1.14 (0.69-1.90)	NA
Lisinopril	2.23 (1.07-4.62)	1.31 (0.64-2.70)	0.48 (0.06-3.60)	3.66 (1.30-10.32)	1.31 (0.76-2.26)	3.80 (0.39-36.83)
Chlorthalidone and doxazosin						
Overall	1.22 (0.62-2.40)	1.25 (0.71-2.20)	2.46 (1.10-5.47)	1.31 (0.56-3.03)	1.03 (0.65-1.62)	2.66 (0.58-12.15)
Chlorthalidone	1.18 (0.55-2.56)	1.28 (0.66-2.50)	4.14 (1.34-12.79)	0.80 (0.23-2.78)	0.78 (0.44-1.37)	1.77 (0.29-10.87)
Doxazosin	1.18 (0.27-5.19)**	1.21 (0.40-3.60)	1.70 (0.53-5.47)	2.25 (0.70-7.25)	1.81 (0.85-3.86)	NA
Per 10 mg/dl Increase in Fasting Glucose - RR (95% CI)*						
Chlorthalidone, amlodipine, lisinopril						
Overall	1.02 (0.97-1.07)	1.01 (0.97-1.05)	1.00 (0.92-1.08)	1.02 (0.96-1.08)	1.00 (0.97-1.04)	1.07 (0.96-1.19)
Chlorthalidone	1.01 (0.94-1.07)	0.99 (0.93-1.05)	1.01 (0.91-1.11)	0.99 (0.90-1.09)	0.99 (0.94-1.03)	1.03 (0.88-1.21)
Amlodipine	0.99 (0.89-1.10)	1.01 (0.93-1.10)	1.02 (0.88-1.18)	1.02 (0.93-1.12)	1.00 (0.94-1.07)	1.08 (0.71-1.65)
Lisinopril	1.09 (1.01-1.17)	1.07 (0.98-1.17)	0.95 (0.77-1.17)	1.08 (0.93-1.26)	1.06 (1.00-1.13)	1.18 (0.87-1.58)
Chlorthalidone and doxazosin						
Overall	0.97 (0.86-1.08)	1.01 (0.94-1.09)	1.02 (0.90-1.15)	0.97 (0.84-1.12)	0.99 (0.93-1.05)	1.01 (0.77-1.34)
Chlorthalidone	0.95 (0.83-1.09)	1.02 (0.94-1.11)	1.07 (0.96-1.20)	0.94 (0.77-1.14)	0.95 (0.87-1.03)	0.96 (0.68-1.37)
Doxazosin	1.00 (0.80-1.24)	0.99 (0.84-1.16)	0.95 (0.77-1.18)	1.01 (0.81-1.27)	1.06 (0.95-1.18)	NA

*All hazard ratios controlled for treatment group (overall cohort), 2-year blood pressure, age, race, sex, smoking status, baseline fasting glucose level, baseline body mass index, 2-year serum potassium level, and atenolol and statin administration at 2 years.

**Due to limited follow-up (average 3.2 years) for the doxazosin/chlorthalidone comparisons, the numbers of CHD events are very small for this comparison.

Table 2

ALLHAT Findings in Participants with the Metabolic Syndrome

	RR (95% CI) vs. Diuretic						
	Non Fatal MI / Fatal CHD	**All-Cause Mortality**	**CCHD**	**Stroke**	**HF**	**CCVD**	**ESRD**
Participants without MetS							
α-Blocker	1.00 (0.82-1.22)	0.99 (0.86-1.15)	1.14 (0.99-1.31)	1.19 (0.92-1.55)	1.91 (1.53-2.38)	1.17 (1.05-1.29)	0.81 (0.44-1.49)
ACEI	1.02 (0.88-1.20)	1.02 (0.91-1.14)	1.07 (0.96-1.21)	1.20 (0.97-1.48)	1.02 (0.83-1.25)	1.07 (0.98-1.17)	0.76 (0.48-1.21)
CCB	1.05 (0.90-1.22)	0.93 (0.83-1.04)	1.03 (0.92-1.16)	1.04 (0.83-1.29)	1.45 (1.20-1.75)	1.05 (0.96-1.15)	0.81 (0.51-1.26)
Participants with MetS							
α-Blocker	1.11 (0.96-1.28)	1.08 (0.95-1.22)	1.06 (0.96-1.17)	1.31 (1.08-1.58)	1.83 (1.57-2.14)	1.23 (1.14-1.33)	1.18 (0.79-1.77)
ACEI	1.01 (0.90-1.13)	1.01 (0.93-1.12)	1.04(0.96-1.14)	1.09 (0.93-1.28)	1.28 (1.12-1.47)	1.14 (1.06-1.21)	1.22 (0.92-1.63)
CCB	0.95 (0.84-1.07)	0.97 (0.88-1.06)	1.00(0.92-1.04)	0.87 (0.74-1.04)	1.32 (1.15-1.51)	1.05 (0.98-1.12)	1.27 (0.96-1.68)
Non-diabetic Participants with MetS							
α-Blocker	1.15 (0.91-1.44)	1.10 (0.89-1.36)	1.07 (0.92-1.25)	1.34 (0.97-1.84)	1.86 (1.44-2.41)	1.24 (1.10-1.39)	0.86 (0.40-1.83)
ACEI	1.05 (0.88-1.27)	1.04 (0.89-1.22)	1.04(0.89-1.22)	1.22 (0.94-1.58)	1.31 (1.04-1.64)	1.19 (1.07-1.32)	1.08 (0.61-1.91)
CCB	0.96 (0.79-1.16)	0.98 (0.83-1.15)	1.01(0.88-1.15)	0.84 (0.62-1.13)	1.09 (0.85-1.38)	1.03 (0.92-1.14)	0.69 (0.36-1.36)
Black Participants with MetS							
α-Blocker	1.18 (0.87-1.58)	1.09 (0.87-1.35)	1.15 (0.93-1.41)	1.49 (1.09-2.03)	1.88 (1.42-2.47)	1.37 (1.19-1.58)	1.17 (0.62-2.22)
ACEI	1.17 (0.95-1.47)	1.14 (0.97-1.34)	1.19 (1.01-1.40)	1.37 (1.07-1.76)	1.49 (1.17-1.90)	1.24 (1.09-1.40)	1.70 (1.13-2.55)
CCB	0.96 (0.76-1.21)	1.02 (0.86-1.20)	1.09 (0.92-1.29)	1.01 (0.77-1.33)	1.50 (1.18-1.90)	1.14 (1.00-1.29)	1.50 (0.99-2.28)