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Treatment Resistant Hypertension and Outcomes based on Randomized Treatment Group in ALLHAT

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All authors had access to the data and a role in writing the manuscript

Disclosures

S Bangalore has received honoraria from Daiichi Sankyo, Boerhinger Ingelheim, Merck, Abbott, and Pfizer. H.R. Black has received honoraria from Bayer, Novartis, Pfizer, Phase Bio, Servier, and Takeda. J.B. Kostis has received honoraria from Bristol-Myers Squibb. J.L. Probstfield has received honoraria from Sanofi.

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for the ALLHAT Collaborative Research Group

Abstract

Background—Although hypertension guidelines define treatment resistant hypertension as blood pressure uncontrolled by ≥3 antihypertensive medications, *including* a diuretic, it is unknown whether patient prognosis differs when a diuretic is included.

Methods—Participants in the Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial were randomly assigned to first-step therapy with chlorthalidone, amlodipine, or lisinopril. At a Year 2 follow-up visit, those with average BP≥140 mmHg systolic or ≥90 mmHg diastolic on ≥3 antihypertensive medications, or BP<140/90 mmHg on ≥4 antihypertensive medications, were identified as having apparent treatment resistant hypertension. The prevalence of treatment resistant hypertension and its association with ALLHAT primary (combined fatal coronary heart disease or nonfatal myocardial infarction) and secondary (all-cause mortality, stroke, heart failure, combined coronary heart disease, and combined cardiovascular disease) outcomes were identified for each treatment group.

Results—Of participants assigned to chlorthalidone, amlodipine and lisinopril, 9.6%, 11.4% and 19.7%, respectively, had treatment resistant hypertension. During mean follow-up of 2.9 years, primary outcome incidence was similar for those assigned to chlorthalidone compared to amlodipine or lisinopril (amlodipine vs. chlorthalidone adjusted HR=0.86; 95% CI 0.53–1.39; P=0.53; lisinopril vs. chlorthalidone adjusted HR=1.06; 95% CI 0.70–1.60; P=0.78). Secondary outcome risks were similar for most comparisons except coronary revascularization, which was higher with amlodipine than with chlorthalidone (HR=1.86; 95% CI 1.11–3.11; P=0.02). An as-treated analysis based on diuretic use produced similar results.

Conclusions—In this study, which titrated medications to a goal, participants assigned to chlorthalidone were less likely to develop treatment resistant hypertension. However, prognoses in those with treatment resistant hypertension were similar across treatment groups.

Clinical Trial Registration—www.clinicaltrials.gov, NCT00000542

Keywords

hypertension; resistance; diuretics; calcium channel blocker; angiotensin-converting enzyme inhibitor

Introduction

The 2008 American Heart Association (AHA) scientific statement defines treatment resistant hypertension as: “blood pressure that remains above goal in spite of concurrent use of 3 antihypertensive agents of different classes. Patients whose blood pressure is controlled with 4 or more medications should be considered to have resistant hypertension.” (1) The scientific statement indicates that the antihypertensive medications prescribed should include, if possible, a diuretic. (1) Likewise, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), (2) European Society of Cardiology (ESC)/European Society of Hypertension (ESH) (3) and the British National Institute for Health and Care Excellence (NICE) (4)

guidelines on hypertension all require that the BP remain uncontrolled on at least 3 antihypertensive agents *including* a diuretic to qualify as TRH. Despite this, the reason for requiring that the definition of TRH mandate one of the 3 medications is a diuretic has not been clearly demonstrated. In a recent analysis from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), we have shown a significant increase in the risk for coronary heart disease, stroke, all-cause mortality, heart failure, peripheral artery disease and end-stage renal disease comparing participants with versus without TRH.(5) However, it is not clear if this risk of adverse outcomes would be different whether TRH is defined with or without a diuretic.

Our objectives were therefore two-fold: (1) to evaluate the prevalence of apparent treatment resistant hypertension in participants randomized to first-step therapy with the thiazide-type diuretic chlorthalidone, the calcium channel blocker (CCB) amlodipine, or the angiotensin converting enzyme inhibitor (ACEi) lisinopril in ALLHAT; (2) to assess whether the outcomes of patients with treatment resistant hypertension differed based on whether their first-step therapy was with chlorthalidone, amlodipine, or lisinopril.

Methods

Study Design

Our study was based on a non-prespecified post hoc analysis of the ALLHAT dataset. The rationale, design, and main results of ALLHAT have been published previously.(6–8) In brief, ALLHAT was a randomized, double-blind, multicenter clinical trial designed to determine whether first-step treatment with amlodipine, lisinopril, or the α-blocker doxazosin would significantly reduce the incidence of fatal coronary heart disease or nonfatal myocardial infarction (primary outcome) compared to treatment with chlorthalidone in 42,418 high-risk hypertensive individuals. The doxazosin treatment arm was discontinued in 2000.(7) In the remaining 33,357 participants, incidence of the primary outcome was not significantly different during an average follow-up of 4.9 years between those assigned to chlorthalidone and those assigned to amlodipine or lisinopril. However, chlorthalidone was superior to amlodipine and lisinopril in preventing one or more additional forms of cardiovascular disease.(8) The outcomes comparing ALLHAT participants with and without treatment resistant hypertension have been described previously.(5)

Blood Pressure Measurements

All the BP measurements were obtained by trained observers using a standardized technique. Measurements were taken in the seated position, with back supported and with the arm at the level of the heart after participants had rested quietly for at least 5 minutes. Two BP readings, separated by at least 30 seconds, were obtained and the measurements were recorded to the nearest even number. Visit BP was the average of the two readings.

Treatment

The BP goal for participants in ALLHAT was <140/90 mm Hg. Up-titration of double-blind assigned study medications to achieve the BP goal occurred at monthly titration visits (step

one-chlorthalidone 12.5 to 25 mg; lisinopril 10 to 40 mg; amlodipine 2.5 to 10 mg), followed by addition of open-label agents (step two medications-atenolol, reserpine, clonidine; step 3 medication-hydralazine) as needed.(6, 7)

Apparent Treatment Resistant Hypertension

We used the following definition of apparent treatment resistant hypertension: participants with an average BP≥140 mm Hg systolic or ≥90 mm Hg diastolic on ≥3 antihypertensive medications or BP<140/90 mm Hg on ≥4 antihypertensive medications at their Year-2 follow-up visit.(1) The rationale for use of this visit was to provide an adequate balance between allowing sufficient time for titration of the antihypertensive agents while maximizing the period of follow-up for recognition of study outcomes once the diagnosis of treatment resistant hypertension was established. Participants randomized to doxazosin had limited follow-up beyond their Year-2 study visit and they were therefore omitted from the current analyses. A total of 14,864 participants were available for inclusion in the current analyses (Figure 1).

Follow-up and Outcomes

After their initial monthly titration visits, participants were examined every 3 months during the first year and every 4 months thereafter. The mean period of follow-up during the treatment phase of the trial was 4.9 years. For this analysis, participants with treatment resistant hypertension were followed from the date of their Year-2 visit (i.e., when treatment resistant hypertension status was determined) to the date of each study outcome, with censoring on their date of death or the end of active follow-up.

The primary outcome was combined fatal coronary heart disease or nonfatal myocardial infarction. Secondary outcomes included all-cause mortality, stroke, combined coronary heart disease (primary outcome, coronary revascularization, or angina with hospitalization), combined cardiovascular disease (combined coronary heart disease, stroke, treated angina without hospitalization, heart failure, and peripheral arterial disease) and hospitalization for gastrointestinal bleeding.

Statistical Analysis

Data were analyzed according to each participant's treatment assignment (chlorthalidone, amlodipine, or lisinopril) regardless of their subsequent therapy (intention-to-treat analysis). The prevalence of treatment resistant hypertension in each of the three treatment groups was calculated at the Year-2 visit. The risk of treatment resistant hypertension was calculated using a logistic regression model with treatment resistant hypertension as the dependent variable and adjusted for baseline characteristics as discussed in models 2–5 below. In addition, the risk of treatment resistant hypertension was compared across the three groups after adjusting for low treatment adherence (defined as<80% adherence by pill count). Additional models were created to evaluate whether the risk of treatment resistant hypertension across the three groups differed in blacks vs. non-blacks. Cox proportional hazards regression models were used to evaluate the risk of outcomes for the amlodipine and lisinopril groups in comparison with the chlorthalidone group. Five models were used for adjustment: 1) Model 1: unadjusted; 2) Model 2: adjusted for age, sex, race/ethnicity, and

region of residence; 3) Model 3: adjusted for variables in model 2 plus practice setting, education level, smoking status, and body mass index (BMI); 4) Model 4: adjusted for variables in models 2 and 3 along with estimated glomerular filtration rate (eGFR), diabetes, low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, history of coronary heart disease, left ventricular hypertrophy, and taking blood pressure medications prior to randomization; and 5) Model 5: adjusted for variables in models 2, 3 and 4 along with baseline and Year-2 blood pressure.

Sensitivity analyses were performed based on components of the definition for treatment resistant hypertension. Specifically, the hazard ratios for outcomes associated with being in the amlodipine and lisinopril groups, each versus the chlorthalidone group, were calculated separately for the cohort with uncontrolled BP on ≥3 medications and for the cohort with controlled BP on ≥4 medications. In addition, sensitivity analyses were performed based on the actual status of thiazide or thiazide like diuretic use (on-treatment analysis) at or before the Year-2 visit rather than the intention-to-treat analysis. Moreover, sensitivity analyses were performed defining treatment resistant hypertension at 1 year. In addition, further sensitivity analyses were performed on an alternate/expanded cohort where patients with an event other than death were not excluded and in patients with a missing BP value at Year-2 visit, BP values were replaced by 20 month or 28 month values when available, with preference given to 20 month values. All statistical analyses were performed using STATA version 12.0 (STATA Corp. College Station, TX), with a *P*-value <0.05 considered to reflect statistical significance.

Results

Baseline Characteristics

Among the 14,684 ALLHAT participants who met our inclusion criteria, (672) 9.6%, (441) 11.4% and (757) 19.7% of those who had been assigned to chlorthalidone, amlodipine, and lisinopril, respectively, had treatment resistant hypertension (Figure 1). The increased odds of treatment resistant hypertension with lisinopril and amlodipine when compared with chlorthalidone was seen in blacks (lisinopril vs. chlorthalidone: OR=3.42; 95% CI 2.86–4.09; P<0.0001; amlodipine vs. chlorthalidone: OR=1.30; 95% CI 1.06–1.60; P=0.01) as well as non-blacks (lisinopril vs. chlorthalidone: OR=1.80; 95% CI 1.55–2.09; P<0.0001; amlodipine vs. chlorthalidone: OR=1.30; 95% CI 0.98–1.35; P=0.09). When compared with the chlorthalidone group (reference OR=1.0), the odds of treatment resistant hypertension were significantly increased in the lisinopril group (adjusted OR=2.32; 95% CI 1.86–2.90; P<0.0001) and numerically increased in the amlodipine group (adjusted OR=1.24; 95% CI 0.98–1.56; P=0.07) after adjusting for baseline characteristics. The odds of treatment resistant hypertension were significantly increased in the lisinopril group (adjusted OR=2.39; 95% CI 1.88–3.04; P<0.0001) when compared with chlorthalidone group even after adjustment for low treatment adherence. Baseline characteristics of the group with treatment resistant hypertension by treatment assignment are listed in Table 1. When compared with those assigned to chlorthalidone, a lower proportion of participants assigned to amlodipine were Hispanic whereas the lisinopril group was younger, with higher percent of Blacks, those with left ventricular hypertrophy on ECG but a smaller percentage had an

eGFR <60 ml/min/1.73 m^2, atherosclerotic vascular disease or diabetes with lower mean systolic BP (Table 1).

Blood Pressure and Antihypertensive Agents

In the participants with treatment resistant hypertension, systolic BP at the Year-2 visit in the chlorthalidone group (153.9 mm Hg) was similar to the amlodipine group (154.1 mm Hg) but higher than in the lisinopril group (151.0 mm Hg) (Table 1). At the Year-2 study visit, 25–30% of the participants with treatment resistant hypertension were taking 4 or more antihypertensive agents, with a smaller percent taking 5 or more antihypertensive agents (Table 1).

Outcomes

Incidence of the primary outcome was similar among the 3 groups (Figure 2). When compared with the chlorthalidone group, there were no significant differences in the adjusted risk of the primary outcome with amlodipine (fully adjusted model HR=0.86; 95% CI 0.53–1.39; P=0.53) or lisinopril (fully adjusted model HR=1.06; 95% CI 0.70–1.60; P=0.78) across all the models tested (Table 2).

Similarly, there were no significant differences for the secondary outcomes of all-cause mortality (HR=1.06; 95% CI 0.73–1.54; *P*=0.77 and HR=1.12; 95% CI 0.81–1.55; *P*=0.50), combined coronary heart disease (HR=1.08; 95% CI 0.76–1.54; *P*=0.67 and HR=0.96; 95% CI 0.70–1.32; *P*=0.80), stroke (HR=1.63; 95% CI 0.86–3.12; *P*=0.14 and HR=1.33; 95% CI 0.72–2.45; *P*=0.37), combined cardiovascular disease (HR=1.21; 95% CI 0.92–1.58; *P*=0.17 and HR=0.95; 95% CI 0.74–1.22; *P*=0.69), end-stage renal disease (HR=1.58; 95% CI 0.52–4.84; *P*=0.42 and HR=1.08; 95% CI 0.37–3.13; *P*=0.89), heart failure (HR=1.38; 95% CI 0.88–2.17; *P*=0.16 and HR=0.81; 95% CI 0.51–1.27; *P*=0.35) and other secondary outcomes (Table 2) in the fully adjusted models comparing amlodipine vs. chlorthalidone and lisinopril vs. chlorthalidone respectively. However, the risk of coronary revascularization was higher with amlodipine when compared with chlorthalidone (HR=1.86; 95% CI 1.11–3.11; *P*=0.02) in the fully adjusted model and the risk of peripheral artery disease was lower with lisinopril compared with chlorthalidone, although this did not reach statistical significance in the fully adjusted model (*P*=0.09) (Table 2).

Sensitivity Analysis

The results were largely similar in a number of sensitivity analyses performed: 1) cohort with uncontrolled BP while taking ≥3 antihypertensive agents (eTable 1); 2) cohort with controlled BP on ≥4 antihypertensive agents (eTable 2); 3) on-treatment analysis after dividing the cohort into those with treatment resistant hypertension on a thiazide-type diuretic vs. those not on a thiazide-type diuretic (eTable 3); 4) cohort where treatment resistant hypertension was defined at Year-1 visit rather than Year-2 visit (eTable 4) and 5)Alternate/expanded cohort of patients (n=2359 patients) (eTable 5).

Discussion

The study evaluated the prevalence of treatment resistant hypertension and outcomes in patients with treatment resistant hypertension based on treatment assignment in the ALLHAT trial. The study showed that the prevalence of treatment resistant hypertension was significantly lower in the group allocated to thiazide-type diuretic-based treatment when compared with the non-diuretic groups with consistent results in blacks and non-blacks. Despite this, the incidences of primary and secondary outcomes were largely similar across all 3 groups, indicating worse outcomes with treatment resistant hypertension regardless of the randomized treatment group in ALLHAT.

Definition of TRH

There has been an exponential increase in the number of publications on TRH, especially in the last decade.(9) Yet, there is no consensus on the definition of TRH. The JNC-7, ESC/ESH and NICE guidelines require uncontrolled BP on at least 3 agents *including a diuretic* to qualify as TRH. This, along with differences in implementation of the definition and the population studied has led to wide variability in the reported prevalence of TRH with reported rates of 1.9% to 30%.^{RW.ERROR - Unable to find reference:1444} (10–12) In the REduction of Atherothrombosis for Continued Health (REACH) Registry, the prevalence of TRH was 12.7% using the JNC-7/ESC/ESH definition, 21.6% using the AHA definition,(13) and 6.0% using the definition that is commonly employed for identification of patients for renal artery denervation (14) (systolic BP of at least 160 mm Hg despite being on 3 antihypertensive agents including a diuretic).(13) The AHA scientific statement on TRH therefore notes that the exact prevalence of treatment resistant hypertension is unknown.(1) The definition is important as it aids in the identification of patients for advanced therapeutics, including aldosterone antagonists, or assessment for secondary causes of hypertension.

The ALLHAT trial provides an opportunity to answer the question as to whether the prevalence of treatment resistant hypertension would be different for a diuretic-based strategy versus a non-diuretic-based strategy, as this is a prospective trial where medications were titrated to a goal. The results show that the prevalence of treatment resistant hypertension varied from 9.6% to 19.7% based on the randomized groups in ALLHAT, with the lowest prevalence in the diuretic arm of the trial. Moreover, previous analysis from ALLHAT has shown that blacks treated with lisinopril demonstrated poorer blood pressure (BP) control (5/2mm Hg higher BP), and worse outcomes than those randomized to diuretics.(15) In order to account for this, we performed separate analysis for blacks vs. non-blacks to evaluate the odds of treatment resistant hypertension with lisinopril when compared with chlorthalidone. Our analysis showed increased odds of treatment resistant hypertension with lisinopril in both blacks and non-blacks when compared with chlorthalidone.

Outcomes in Patients with TRH

Several studies have reported that outcomes of patients with TRH are worse than those without TRH.(10, 13) In an analysis from the REACH registry, an increased risk of cardiac

death/myocardial infarction/stroke, non-fatal stroke, and heart failure hospitalization was observed in patients with TRH, using a TRH definition that was similar to that of JNC-7 and ESC/ESH (diuretic based).(13) Moreover, when the AHA definition was used, there was increase in all cardiovascular outcomes, including all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, and hospitalization for heart failure. Similarly, in an analysis from the Treating to New Targets trial, treatment resistant hypertension (using the AHA definition without the need for diuretic) was associated with significant increase in cardiovascular events when compared with patients without treatment resistant hypertension.(16) In a recent analysis from ALLHAT we have shown a significant increase in the risk of cardiovascular and renal events in patients with treatment resistant hypertension (using the AHA definition without the need for diuretic) when compared with patients without treatment resistant hypertension.(5)

The results of the present study show that the incidence of cardiovascular outcomes was similar whether a diuretic-based or a non-diuretic–based definition was used. It is therefore interesting to note that although the prevalence of treatment resistant hypertension was lowest on a diuretic (chlorthalidone), the prognosis was similar across all randomized groups. These relationships are important to consider when the diuretic-based definitions cannot be used, such as in patients intolerant to a diuretic. However, it is possible that, as the diuretic controlled blood pressure in a higher proportion of participants than the other agents, those meeting criteria for treatment resistant hypertension on a diuretic may have been a higher risk group on average than those on the other drugs. In addition, there were a greater proportion of black patients in those with treatment resistant hypertension assigned to lisinopril when compared to those assigned to the chlorthalidone group. Prior studies and analyses have shown that angiotensin converting enzyme inhibitors are less effective in blacks when compared with non-blacks.(15, 17)

Study Limitations

Although the analyses were performed based on the randomized treatment groups in ALLHAT, this post hoc analysis loses the benefit and balance of randomization given the definition of treatment resistant hypertension at Year-2 follow-up and inclusion of a subset of the overall patients randomized. Our various exclusion criteria led to exclusion of a consideration number of patients who were originally randomized in the ALLHAT trial with only 14864 patients out of the 33357 randomized included. In order to minimize this large number of excluded patients, we performed sensitivity analyses in an alternate/expanded cohort and the results were largely similar. In our definition of TRH we did not have data to rule out secondary causes of TRH (including medication noncompliance, white coat hypertension, etc.) and hence the definition conforms to the definition of treatment resistant hypertension used by Egan et al.(11) However, we do not believe the lack of out-of-office BP measurements to rule out secondary causes would differentially affect the three treatment groups. In addition, the small number of outcomes for certain endpoints (such as stroke) may have limited statistical power to detect differences among the groups. Moreover, we did not account for multiple testing.

Conclusions

In patients randomized in the ALLHAT trial, a prospective trial where medications were being titrated to a goal, the prevalence of treatment resistant hypertension using the AHA definition was lowest in the group of patients randomized to chlorthalidone when compared with the groups randomized to amlodipine or lisinopril. Yet, the risk of cardiovascular outcomes was largely similar for patients with treatment resistant hypertension across all 3 groups. These associations should be tested in future trials and be taken into consideration for the design of future trials with treatment resistant hypertension.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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- Patients who were in the diuretic treatment group of the ALLHAT trial were less likely to develop treatment resistant hypertension than were patients in the calcium channel blocker or angiotensin converting enzyme inhibitor groups.
- For patients who had treatment-resistant hypertension, cardiovascular outcomes were similar across all treatment groups.

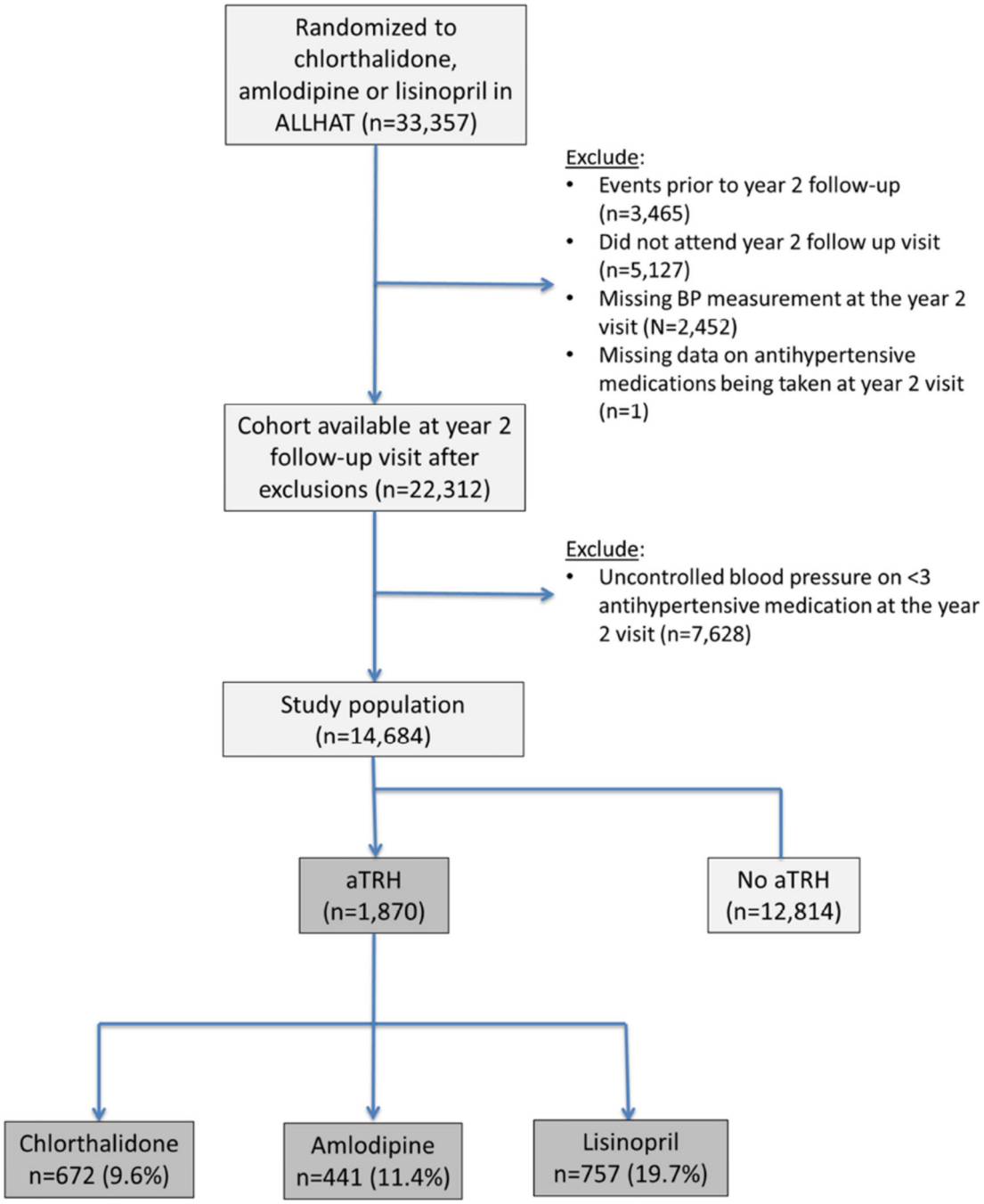

Figure 1.
Patient flow.

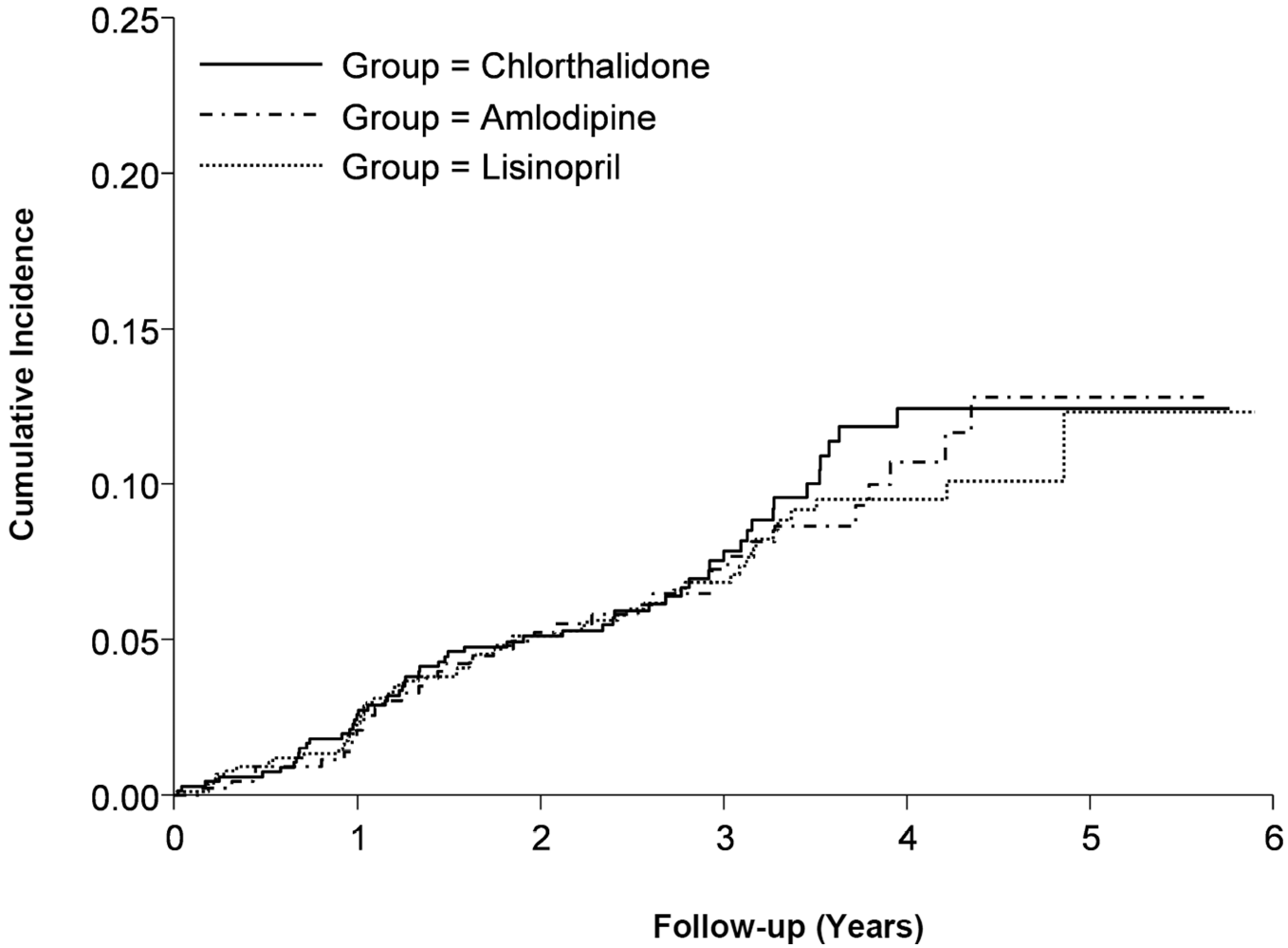

Figure 2.
Cumulative incidence of primary outcome (combined fatal coronary heart disease or nonfatal myocardial infarction) by treatment group in those with treatment resistant hypertension.

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Table 1

Baseline characteristics of study participants with treatment resistant hypertension* by randomized

	Chlorthalidone (N=672)	Amlodipine (N=441)	Lisinopril (N=757)	P value (Amlodipine vs. Chlorthalidone)	P value (Lisinopril vs. Chlorthalidone)
Age, years, mean (sd)	67.0 (7.7)	66.7 (7.4)	66.1 (7.5)	0.58	0.04
Men, %	55.5	58.7	58.0	0.29	0.34
Race-ethnicity, %					
Black	38.2	39.9	48.3	0.58	<0.001
Non-Black	61.8	60.1	51.7		
Hispanic	10.7	6.6	9.1	0.02	0.31
Non-Hispanic	89.3	93.4	90.9		
Region of residence, %				0.45	0.84
Northeast	14.0	12.7	13.7		
Midwest	19.8	17.9	18.2		
South	50.1	51.9	52.2		
West	10.4	12.9	10.2		
Canada	1.3	1.8	0.8		
Practice setting, %				0.07	0.74
Private	22.9	22.7	22.9		
Group	16.7	19.3	16.5		
Health Maintenance	2.4	2.3	2.4		
Organization					
Community Health Center	11.2	9.3	12.5		
University	8.0	10.2	9.5		
Other	9.2	9.3	8.6		
Veterans Affairs Medical	24.7	25.6	24.4		
Center					
Unknown	4.9	1.4	3.2		
Education less than high school, %	43.6	45.8	44.6	0.49	0.72
BMI, kg/m^2, mean(sd)	30.5 (6.2)	31.2 (9.1)	30.6 (6.4)	0.11	0.63
eGFR <60 , ml/min/1.73 m^2, %	29.6	26.6	22.6	0.28	0.003

	Chlorthalidone (N=672)	Amlodipine (N=441)	Lisinopril (N=757)	P value (Amlodipine vs. Chlorthalidone)	P value (Lisinopril vs. Chlorthalidone)
Diabetes, %	51.0	49.9	42.7	0.73	0.003
Cholesterol, mg/dL, mean(sd)					
Total	217.5 (42.0)	217.3 (44.9)	212.4 (42.3)	0.95	0.03
LDL	135.8 (36.6)	135.1 (35.9)	133.5 (35.9)	0.76	0.27
HDL	46.7 (15.3)	46.9 (15.4)	46.7 (14.9)	0.83	0.93
Left ventricular hypertrophy on ECG, %	18.6	20.4	24.6	0.45	0.006
ASCVD, %	51.5	50.6	43.2	0.76	0.002
On blood pressure medications prior to randomization, %	96.4	96.8	95.0	0.72	0.18
Systolic BP, mm Hg, mean (sd)	153.9 (14.6)	154.1 (15.5)	151.0 (15.2)	0.78	<0.001
Diastolic BP, mm Hg, mean (sd)	85.0 (11.0)	84.1 (10.7)	85.6 (10.3)	0.18	0.30
Antihypertensive agents at 2 years, n (%)					
On 3 or more agents at 2 years	672 (100.0)	441 (100.0)	757 (100.0)	-	-
On 4 or more agents at 2 years	180 (26.8)	111 (25.2)	237 (31.3)	0.55	0.06
On 5 or more agents at 2 years	27 (4.0)	8 (1.8)	40 (5.3)	0.04	0.26
On 6 or more agents at 2 years	5 (0.7)	1 (0.2)	4 (0.5)	0.25	0.61

Abbreviations: ASCVD, atherosclerotic vascular disease; ; BMI, body mass index; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate;.

*Treatment resistant hypertension was defined as having uncontrolled hypertension despite the use of antihypertensive medications from 3 or more classes or the use of 4 or more antihypertensive medication classes to achieve blood pressure control.

Table 2

Clinical outcomes in the antihypertensive treatment groups in patient with treatment resistant hypertension*

	Chlorthalidone (N=672)	Amlodipine (N=441)	Lisinopril (N=757)	Amlodipine vs. Chlorthalidone		Lisinopril vs. Chlorthalidone	
	No. of events (%)	No. of events (%)	No. of events (%)	HR (95% CI)	P–Value	HR (95% CI)	P–Value
Primary outcome coronary heart disease†	55 (8.2)	36 (8.3)	57 (7.6)				
Model 1				0.95 (0.63–1.45)	0.82	0.89 (0.62–1.29)	0.55
Model 2				0.96 (0.63–1.47)	0.86	0.94 (0.65–1.36)	0.74
Model 3				0.95 (0.61–1.48)	0.83	1.00 (0.68–1.47)	0.99
Model 4				0.86 (0.53–1.39)	0.53	1.06 (0.70–1.60)	0.78
Model 5				0.86 (0.53–1.40)	0.54	1.04 (0.69–1.58)	0.83
Secondary outcomes							
All-cause mortality	81 (12.1)	60 (13.6)	92 (12.2)				
Model 1				1.07 (0.76–1.49)	0.71	0.97 (0.72–1.31)	0.85
Model 2				1.12 (0.80–1.56)	0.52	1.05 (0.77–1.41)	0.77
Model 3				1.12 (0.79–1.58)	0.52	1.05 (0.77–1.43)	0.75
Model 4				1.06 (0.73–1.54)	0.77	1.12 (0.81–1.55)	0.50
Model 5				1.14 (0.78–1.66)	0.50	1.13 (0.82–1.58)	0.45
Combined coronary heart disease‡	102 (15.3)	71 (16.4)	93 (12.5)				
Model 1				1.04 (0.77–1.40)	0.81	0.78 (0.59–1.03)	0.08
Model 2				1.04 (0.77–1.41)	0.80	0.80 (0.61–1.07)	0.13
Model 3				1.10 (0.80–1.50)	0.56	0.85 (0.63–1.13)	0.26
Model 4				1.08 (0.76–1.54)	0.67	0.96 (0.70–1.32)	0.80
Model 5				1.08 (0.75–1.54)	0.68	0.95 (0.69–1.32)	0.77
Stroke	23 (3.5)	24 (5.5)	30 (4.0)				
Model 1				1.54 (0.87–2.73)	0.14	1.12 (0.65–1.93)	0.68
Model 2				1.60 (0.90–2.85)	0.11	1.18 (0.68–2.05)	0.54
Model 3				1.68 (0.93–3.04)	0.09	1.19 (0.68–2.10)	0.54
Model 4				1.63 (0.86–3.12)	0.14	1.33 (0.72–2.45)	0.37

	Chlorthalidone (N=672)	Amlodipine (N=441)	Lisinopril (N=757)	Amlodipine vs. Chlorthalidone		Lisinopril vs. Chlorthalidone	
	No. of events (%)	No. of events (%)	No. of events (%)	HR (95% CI)	P–Value	HR (95% CI)	P–Value
Model 5				1.71 (0.89–3.30)	0.11	1.34 (0.72–2.49)	0.35
Combined cardiovascular disease[§]	162 (24.3)	120 (27.6)	154 (20.6)				
Model 1				1.12 (0.88–1.41)	0.37	0.81 (0.65–1.01)	0.06
Model 2				1.11 (0.87–1.40)	0.40	0.83 (0.67–1.04)	0.10
Model 3				1.16 (0.91–1.48)	0.24	0.86 (0.68–1.08)	0.19
Model 4				1.21 (0.92–1.58)	0.17	0.95 (0.74–1.22)	0.69
Model 5				1.19 (0.91–1.56)	0.21	0.95 (0.74–1.22)	0.68
End-stage renal disease[‖]	13 (2.0)	7 (1.6)	9 (1.2)				
Model 1				0.84 (0.33–2.10)	0.70	0.69 (0.29–1.62)	0.39
Model 2				0.86 (0.34–2.21)	0.76	0.67 (0.28–1.61)	0.37
Model 3				1.01 (0.37–2.72)	0.99	0.88 (0.34–2.26)	0.80
Model 4				1.58 (0.52–4.84)	0.42	1.08 (0.37–3.13)	0.89
Model 5				1.87 (0.59–5.94)	0.29	1.26 (0.42–3.75)	0.68
Cancer	39 (5.9)	21 (5.0)	44 (6.0)				
Model 1				0.80 (0.47–1.37)	0.42	0.97 (0.63–1.49)	0.89
Model 2				0.82 (0.48–1.40)	0.47	1.00 (0.65–1.54)	0.99
Model 3				0.83 (0.49–1.43)	0.51	0.97 (0.63–1.50)	0.89
Model 4				0.95 (0.54–1.67)	0.85	1.03 (0.64–1.65)	0.91
Model 5				0.90 (0.50–1.59)	0.71	1.05 (0.65–1.69)	0.84
Hospitalized for gastrointestinal bleeding	32 (6.0)	19 (5.6)	35 (6.3)				
Model 1				0.91 (0.51–1.60)	0.73	1.00 (0.62–1.62)	0.99
Model 2				0.91 (0.51–1.60)	0.73	1.01 (0.62–1.63)	0.98
Model 3				0.98 (0.55–1.77)	0.95	1.09 (0.66–1.80)	0.75
Model 4				0.88 (0.46–1.70)	0.71	1.17 (0.68–2.01)	0.57
Model 5				0.83 (0.43–1.62)	0.59	1.22 (0.71–2.09)	0.48

	Chlorthalidone (N=672)	Amlodipine (N=441)	Lisinopril (N=757)	Amlodipine vs. Chlorthalidone		Lisinopril vs. Chlorthalidone	
	No. of events (%)	No. of events (%)	No. of events (%)	HR (95% CI)	P–Value	HR (95% CI)	P–Value
Components of secondary outcomes							
Heart failure	47 (7.0)	43 (9.9)	39 (5.3)				
Model 1				1.37 (0.91–2.07)	0.14	0.71 (0.47–1.09)	0.12
Model 2				1.40 (0.92–2.12)	0.11	0.78 (0.51–1.20)	0.26
Model 3				1.29 (0.84–1.98)	0.24	0.76 (0.49–1.16)	0.20
Model 4				1.38 (0.88–2.17)	0.16	0.81 (0.51–1.27)	0.35
Model 5				1.35 (0.85–2.14)	0.20	0.79 (0.50–1.25)	0.32
Hospitalized/fatal heart failure	41 (6.1)	33 (7.6)	28 (3.8)				
Model 1				1.20 (0.76–1.90)	0.43	0.58 (0.36–0.94)	0.03
Model 2				1.24 (0.78–1.96)	0.37	0.64 (0.40–1.04)	0.07
Model 3				1.17 (0.73–1.88)	0.50	0.62 (0.38–1.01)	0.06
Model 4				1.27 (0.77–2.11)	0.35	0.70 (0.42–1.18)	0.18
Model 5				1.23 (0.73–2.05)	0.43	0.69 (0.41–1.16)	0.16
Angina (hospitalized or treated)	50 (7.5)	41 (9.4)	46 (6.2)				
Model 1				1.24 (0.82–1.87)	0.31	0.79 (0.53–1.18)	0.26
Model 2				1.21 (0.80–1.83)	0.36	0.78 (0.52–1.16)	0.22
Model 3				1.38 (0.90–2.11)	0.14	0.81 (0.53–1.24)	0.34
Model 4				1.43 (0.88–2.31)	0.15	0.92 (0.58–1.48)	0.74
Model 5				1.39 (0.85–2.27)	0.19	0.91 (0.56–1.46)	0.68
Angina (hospitalized)	40 (6.0)	31 (7.1)	32 (4.3)				
Model 1				1.16 (0.73–1.86)	0.53	0.69 (0.43–1.09)	0.11
Model 2				1.15 (0.72–1.85)	0.55	0.68 (0.43–1.08)	0.10
Model 3				1.26 (0.78–2.03)	0.35	0.68 (0.42–1.11)	0.13
Model 4				1.32 (0.76–2.30)	0.32	0.79 (0.46–1.37)	0.41
Model 5				1.33 (0.75–2.33)	0.33	0.78 (0.45–1.35)	0.37
Coronary revascularizations	44 (6.6)	41 (9.4)	32 (4.3)				

	Chlorthalidone (N=672)	Amlodipine (N=441)	Lisinopril (N=757)	Amlodipine vs. Chlorthalidone		Lisinopril vs. Chlorthalidone	
	No. of events (%)	No. of events (%)	No. of events (%)	HR (95% CI)	P–Value	HR (95% CI)	P–Value
Model 1				1.41 (0.92–2.16)	0.11	0.62 (0.39–0.98)	0.04
Model 2				1.43 (0.93–2.19)	0.10	0.66 (0.42–1.04)	0.08
Model 3				1.57 (1.01–2.43)	0.05	0.71 (0.44–1.13)	0.15
Model 4				1.86 (1.11–3.11)	0.02	0.94 (0.55–1.61)	0.82
Model 5				1.84 (1.09–3.13)	0.02	0.94 (0.55–1.60)	0.81
Peripheral arterial disease (hospitalized or treated)	27 (4.1)	9 (2.1)	14 (1.9)				
Model 1				0.49 (0.23–1.05)	0.07	0.45 (0.24–0.86)	0.02
Model 2				0.48 (0.23–1.02)	0.06	0.48 (0.25–0.91)	0.03
Model 3				0.49 (0.23–1.05)	0.07	0.49 (0.25–0.96)	0.04
Model 4				0.66 (0.28–1.56)	0.35	0.50 (0.22–1.11)	0.09
Model 5				0.60 (0.25–1.43)	0.25	0.51 (0.23–1.14)	0.10

Abbreviations: treatment resistant hypertension, apparent treatment resistant hypertension; HR indicates Hazard Ratio; CI, confidence interval;

*treatment resistant hypertension was defined as having uncontrolled hypertension despite the use of antihypertensive medications from 3 or more classes or the use of 4 or more antihypertensive medication classes to achieve blood pressure control.

†coronary heart disease includes nonfatal myocardial infarction and fatal coronary heart disease; end-stage renal disease: kidney disease death, kidney transplant, or start of chronic renal dialysis; and heart failure: fatal, nonfatal hospitalized, or treated.

‡Combined coronary heart disease indicates coronary heart disease death, nonfatal myocardial infarction, coronary revascularization procedures, and hospitalized angina.

§Combined cardiovascular disease indicates coronary heart disease death, nonfatal myocardial infarction, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, and peripheral arterial disease (hospitalized or outpatient revascularization).

//For end stage renal disease all models include baseline eGFR

Model 1: unadjusted;
Model 2: adjusted for age, sex, race/ethnicity and region of residence;
Model 3: adjusted for variables in model 2 plus practice setting, education level, smoking status and body mass index (BMI);
Model 4: adjusted for variables in model 2 and 3 along with estimated glomerular filtration rate (eGFR), diabetes, low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, history of coronary heart disease, left ventricular hypertrophy, and taking blood pressure medications prior to randomization
Model 5: adjusted for variables in model 2, 3 and 4 along with baseline and Year-2 blood pressure