Heterogeneity in Early Responses in ALLHAT
(Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)

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Abstract—Randomized trials of hypertension have seldom examined heterogeneity in response to treatments over time and the implications for cardiovascular outcomes. Understanding this heterogeneity, however, is a necessary step toward personalizing antihypertensive therapy. We applied trajectory-based modeling to data on 39,763 study participants of the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) to identify distinct patterns of systolic blood pressure (SBP) response to randomized medications during the first 6 months of the trial. Two trajectory patterns were identified: immediate responders (85.5%), on average, had a decreasing SBP, whereas nonimmediate responders (14.5%), on average, had an initially increasing SBP followed by a decrease. Compared with those randomized to chlorthalidone, participants randomized to amlodipine (odds ratio, 1.20; 95% confidence interval [CI], 1.10–1.31), lisinopril (odds ratio, 1.88; 95% CI, 1.73–2.03), and doxazosin (odds ratio, 1.65; 95% CI, 1.52–1.78) had higher adjusted odds ratios associated with being a nonimmediate responder (versus immediate responder). After multivariable adjustment, nonimmediate responders had a higher hazard ratio of stroke (hazard ratio, 1.49; 95% CI, 1.21–1.84), combined cardiovascular disease (hazard ratio, 1.21; 95% CI, 1.11–1.31), and heart failure (hazard ratio, 1.48; 95% CI, 1.24–1.78) during follow-up between 6 months and 2 years. The SBP response trajectories provided superior discrimination for predicting downstream adverse cardiovascular events than classification based on difference in SBP between the first 2 measurements, SBP at 6 months, and average SBP during the first 6 months. Our findings demonstrate heterogeneity in response to antihypertensive therapies and show that chlorthalidone is associated with more favorable initial response than the other medications. (Hypertension. 2017;70:94-102. DOI: 10.1161/HYPERTENSIONAHA.117.09221.)

Key Words: antihypertensive agents ■ blood pressure ■ cardiovascular diseases ■ hypertension ■ precision medicine

Identification of heterogeneity in risk and response to different antihypertensive therapies, a goal of precision medicine, and the factors associated with different responses could help to improve the outcomes for >1 billion people with hypertension.1–4 Understanding variation in response to treatment with antihypertensive medications is an important first step. However, previous studies of antihypertensive therapy have primarily relied on stratification by predetermined patient characteristics (eg, age, race, and diabetes mellitus status) to detect heterogeneity.7 This approach may constrain us to existing understanding and limit our ability to identify unforeseen factors that influence treatment response.

An additional strategy is to use data-driven approaches to uncover important patterns in patients’ response to antihypertensive therapy. Blood pressure (BP) response to medication is critical to determining treatment effectiveness. Although variation in BP response to treatment has been observed in clinical practice,2 heterogeneity in such response patterns has not been systematically studied. Moreover, few studies have examined how BP response to treatment is associated with outcomes. Previous attempts to
understand the impact of different BP responses on clinical trial outcomes have relied on dichotomized response status based on predetermined criteria. Such approaches do not use repeated measurements of BP values over time. Alternatively, heterogeneity in BP response over time making use of repeated measures can be captured by methods that take into account the entire course of change to define response types. Characterizing BP response as trajectories provides more dynamic information on treatment effectiveness, and understanding heterogeneity in BP response to antihypertensive therapy may ultimately inform more effective treatment strategies.

Accordingly, we analyzed data from the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) using a data-driven trajectory modeling method to determine whether there were distinct systolic blood pressure (SBP) response patterns to the 4 randomized antihypertensive medications. We further assessed whether the identified SBP trajectories were predictive of adverse cardiovascular outcomes. The identification of these distinct response trajectories to medications could provide better understanding of specific treatment effects and lay the foundation for development of personalized treatment strategies for people with hypertension.

Methods
The current study was a secondary analysis of data from ALLHAT. The Human Investigation Committee at the Yale School of Medicine reviewed and approved this study protocol. We analyzed SBP response during the first 6 months after randomization to characterize early response to randomized medications and identify distinct response trajectory patterns. We examined the association of the different SBP response trajectories with cardiovascular outcomes occurring within the first 6 months and between 6 months and 2 years post-randomization. We also evaluated discriminant power of the SBP trajectories in predicting cardiovascular outcomes in comparison to other classification strategies.

Data Source and Study Sample
The design, rationale, baseline characteristics, and main results of ALLHAT have been described in detail previously. ALLHAT was a randomized, double-blinded multicenter 4-arm trial to determine whether a calcium channel blocker (amlodipine), angiotensin-converting enzyme inhibitor (lisinopril), or an α-blocker (doxazosin) was superior to a diuretic (chlorothalidone) in lowering incidence of fatal coronary heart disease (CHD) or nonfatal myocardial infarction (MI). A total of 42,418 participants aged ≥55 years with hypertension and at least 1 additional cardiovascular risk factor were enrolled at 623 North American clinical sites between February 1994 and January 1998. Study participants were treated with a starting dose of 1 of 4 medications and then titrated, with the goal BP ≤140/90 mm Hg using the lowest possible dose. If needed, a choice of open-label second-line drugs (reserpine, oral clonidine, or atenolol) and a third-line drug (hydralazine) was provided.

All participants in ALLHAT were included in our sample, except for those who had no SBP measurements available during the first 6 months (n=2655) after randomization (Figure 1A). The remaining 39,763 participants (sample 1; Figure 1A) form the base population for our analyses. When analyzing cardiovascular outcomes between 6 months and 2 years, we further excluded participants who had cardiovascular outcomes during the first 6 months (n=2304; Figure 1A and 1B) and focused on the remaining 37,729 participants (sample 2; Figure 1A).

SBP Measurements for Trajectory Modeling
We used the average of the 2 SBP measurements at baseline and 1, 3, and 6 months post-randomization.

Covariates
Covariates were selected for risk adjustment based on clinical possibility of their potential associations with SBP and outcomes. Clinical variables assessed at ALLHAT enrollment were prespecified: baseline age, sex, ethnicity, body mass index, education, region, smoking status, glomerular filtration rate, type II diabetes mellitus, fasting glucose, total cholesterol, high-density lipoprotein cholesterol, high-density lipoprotein cholesterol ≤35 mg/dL twice in the past 5 years, fasting triglycerides, history of MI or stroke, coronary revascularization, other atherosclerotic cardiovascular disease (CVD), major ST depression or T-wave abnormality, left ventricular hypertrophy (LVH) by ECG in the past 2 years, LVH by echocardiogram in the past 2 years, aspirin use, use of antihypertensive medication before randomization, and randomization assignment. During the trial, the clinical variables assessed included prescribed dosage of blinded study drug, prescription of step 2 and 3 medications, open-label antihypertensive medication use, and self-reported adherence. At each follow-up visit, study participants reported whether they had taken ≥80% of their randomly assigned medication and, if so, were classified as low adherence during that time period.

Clinical Outcomes
After modeling SBP trajectories, we examined their relationship with ALLHAT’s primary and clinically important secondary outcomes. The primary outcome was fatal CHD or nonfatal MI. Five secondary outcomes were also assessed: all-cause mortality, stroke, combined CHD (fatal CHD, nonfatal MI, coronary revascularization, or hospitalization for angina), combined CVD (combined CHD, stroke, treated angina without hospitalization, heart failure, and...
Peripheral arterial disease, and heart failure. Study outcomes were assessed at follow-up visits. The average follow-up was 4.9 years. For the current study, we included outcomes occurring within 2 years post-randomization.

**Statistical Analyses**

We used growth mixture modeling to identify distinct classes of SBP trajectories.\(^{12}\) Growth mixture modeling captures heterogeneity in trajectories of 2 different natures: heterogeneity by class (ie, distinct subpopulations of individual trajectories around different mean trajectories) and heterogeneity by degree within class (ie, variation across individual trajectories around the same mean trajectory).\(^{3,14}\) As allowed by the modeling procedure, we used all available SBP measurements during the first 6 months, including individuals with some missing SBP measurements. For the shape of the SBP trajectory, we considered linear, quadratic, and piecewise linear trends over time, each with varying number of trajectory classes. The optimal model was selected based on the Bayesian Information Criterion, the average posterior probability of belonging to the trajectory class among those classified in each class, and the restriction that the percentage of participants classified into an individual class was not <5%. (Details of model fitting and selection are available in the online-only Data Supplement.)

After the optimal model was identified, participants were assigned to the trajectory class corresponding to their highest posterior probability. Differences in participant characteristics at baseline and during the first 6 months of the trial across trajectory classes were assessed using \(t\) tests or Wilcoxon–Mann–Whitney tests for continuous variables and \(χ^2\) tests for categorical variables. Missing baseline characteristics were imputed with 10 data sets using chained equations via multiple imputation.\(^{11}\)

We measured the independent effect of treatment on SBP trajectory class membership by calculating the odds ratio of being in a particular trajectory class, comparing amldipine, lisinopril, and doxazosin with chlorthalidone because ALLHAT compared the 3 drugs with chlorthalidone because ALLHAT compared the 3 drugs with chlorthalidone, adjusting for all patient baseline characteristics.

Outcomes occurring within the first 6 months and during 6 months to 2 years post-randomization were compared between participants in different SBP trajectory classes. The Kaplan–Meier method was used to determine the cumulative incidence of each outcome associated with a particular SBP trajectory class. Hazard ratios (HRs) were calculated using Cox proportional hazards regression models. We used nested models to examine the association between BP response trajectory and cardiovascular outcomes by sequentially adding the following adjustment: model 1 included baseline SBP; model 2 included factors in model 1, baseline demographics, and treatment assignment; model 3 included factors in model 2 and baseline medical history; model 4 included factors in model 3 and self-reported adherence within the first 6 months. The covariates included in these models can be found in Tables S3 and S5 in the online-only Data Supplement. For outcomes occurring between 6 months to 2 years, the fully adjusted HRs were also calculated for subgroups defined by age (<65 and ≥65 years), sex, race (black and nonblack), diabetes mellitus, history of atherosclerotic CVD, history of LVH, and treatment assignment. Interaction of these subgroups with trajectory classes was considered significant if \(P\) < 0.10. Furthermore, to investigate the effect of SBP throughout the study duration on cardiovascular outcomes, we also compared the mean SBP of participants during the first 2 years post-randomization in the different SBP trajectory classes.

The discriminant power of SBP trajectory classes for predicting cumulative incidence of cardiovascular outcome risk between 6 months and 2 years post-randomization was compared with 3 other classification strategies: difference between randomization and 1-month follow-up SBP, 6-month SBP, and average SBP during the first 6 months compared with 140 mmHg. Comparison was performed on participants without any missing follow-up SBP measurements within the first 6 months. Fully adjusted HRs between the 2 classes derived from each classification strategy were calculated. Finally, we calculated the fully adjusted HRs of outcomes associated with the posterior probability of trajectory classes, modeled as a continuous variable using B-splines.

Trajectory modeling was performed using R package OpenMx (version 2.5.2),\(^{16}\) and multiple imputation was performed using R package mice (version 2.25),\(^{17}\) and continuous HR was calculated using R package smooth HR (version 1.0.2).\(^{18}\) All \(P\) values reported are nominal. For sensitivity analyses, we repeated the growth mixture modeling and the analyses of baseline characteristic association and Cox proportional HRs for participants without any missing follow-up SBP measurements within the first 6 months (complete case).

**Results**

**Patterns of 6-Month SBP Response Trajectories**

Of the 42418 study participants, 39763 participants (93.7%) had at least 1 SBP measurement in the first 6 months of ALLHAT and were included in our analyses. Among these, 29735 participants (74.8%) had 3 follow-up visits; 7287 participants (18.3%) had 2 visits; and 2741 participants (6.9%) had 1 visit. When modeling SBP trajectories for these participants, based on model convergence, Bayesian Information Criterion, proportions of participants in each class, and average posterior probability of each class, the piecewise linear model with 2 classes best fit the data (Table S1).

Figure 2 shows the estimated mean trajectory classes and individual trajectories associated with each class. Two response patterns were identified. The immediate responder class, comprising 33978 participants (85.5%), on average, had a decreasing SBP during the first 6 months with an initially steep decline during the first month, followed by a more gradual decline. The nonimmediate responder class, comprising 5785 participants (14.5%), on average, had an initially increasing SBP until about 1 month, after which the SBP began to gradually decrease.

**Participant Characteristics Associated With the Distinct Trajectory Classes**

Compared with immediate responders, nonimmediate responders were \(\geq 1\) year older and less often men (Table). Nonimmediate responders compared with immediate responders were also more often black (42.4% versus 34.1%) and less often Hispanic (11.4% versus 17.7%). Equivalently, 17.5% of black, 13.0% of white, and 9.9% of Hispanic study participants were nonimmediate responders. Nonimmediate responders were also more likely to have previously used antihypertensive medications and had higher mean randomization SBP, diastolic blood pressure, and pulse pressure. During the first 6 months of the trial, nonimmediate responders were more likely to have low adherence. They were also more than twice as likely to receive a medication change at any visit during the first 6 months including having study drug dose intensified (84.0% versus 44.9%), study drug stopped (15.3% versus 11.7%), step 2 or 3 medication prescribed (34.0% versus 13.4%), and having received an open-label antihypertensive medication (15.5% versus 11.7%).

**Effect of Medication on SBP Trajectory Class**

Of all participants included in this analysis, 11.4% of those randomized to chlorthalidone were nonimmediate responders (Figure 3; Table S2). The corresponding values were 13.2% for amldipine, 18.8% for lisinopril, and 17.0% for doxazosin. Compared with participants randomized to chlorthalidone,
adjusted odds ratios associated with being a nonimmediate responder were higher for study participants randomized to amlodipine (odds ratio, 1.20; 95% confidence interval [CI], 1.10–1.31), lisinopril (odds ratio, 1.88; 95% CI, 1.73–2.03), and doxazosin (odds ratio, 1.65; 95% CI, 1.52–1.78). Excluding participants who had missing SBP measurements or cardiovascular events did not significantly change the odds ratios.

**Association of SBP Response Trajectories With Outcomes During the First 6 Months**

In the first 6 months, ALLHAT nonimmediate and immediate responders had a similar incidence of nonfatal MI and fatal CHD, all-cause mortality, and combined CHD (Figure 4). Nonimmediate responders had a higher incidence of combined CVD, stroke, and heart failure. After adjustment for baseline SBP and demographics, nonimmediate responders had an increased hazard of combined CVD and heart failure (Table S3). After additional adjustment for medical history, the HR for heart failure was no longer significant. After adjustment for 6-month adherence, the HR of combined CVD remained statistically significant (HR, 1.21; 95% CI, 1.07–1.37).

**Association of 6-Month SBP Response Trajectories With Subsequent Outcomes**

We used study sample 2 (Figure 1A), comprising the 37,729 participants who did not have a primary or major secondary cardiovascular event during the initial 6 months of ALLHAT, to study the predictive power of the first 6-month trajectories. Growth mixture modeling of study sample 2 resulted in identical classification of participants to the classification derived from modeling study sample 1 (n=39,763; Figure 1A). Associations between participant characteristics and trajectory classes were also similar (Table S4).

Between 6 months to 2 years post-randomization, nonimmediate responders and immediate responders had a similar risk for the primary outcome of nonfatal MI or fatal CHD (Figure 5). The unadjusted incidence of each secondary outcome (all-cause mortality, combined CHD, combined CVD, stroke, and heart failure) was higher among nonimmediate responders compared with immediate responders (Table S5). In models with multivariable adjustment, nonimmediate responders compared with immediate responders had a higher HR of stroke (HR, 1.48; 95% CI, 1.20–1.83), combined CVD (HR, 1.21; 95% CI, 1.11–1.33), and heart failure (HR, 1.50; 95% CI, 1.25–1.80). The adjusted HR of all-cause mortality was 1.03 (95% CI, 0.87–1.21) and of combined CHD was 1.12 (95% CI, 0.99–1.27). With a few exceptions, the association of 6-month SBP trajectory classes with 6-month to 2-year incidence of stroke, combined CVD, and heart failure was consistent across subgroups of age, sex, race, diabetes status, and history of atherosclerotic CVD, LVH, and treatment assignment (Figure S1). Of note, the mean SBP for nonimmediate responders between enrollment and 2 years was 156.3 mm Hg and for immediate responders was 138.3 mm Hg. The higher SBP of nonimmediate responders throughout the study may contribute to their increased risk of multiple cardiovascular outcomes.

The posterior probability of a study participant being a nonimmediate responder had a near linear relationship with risk of combined CVD and heart failure (Figure S2). For stroke, risk increased progressively but became more gradual for posterior probability >0.5.

**Discriminative Ability of SBP Trajectories**

In their association with combined CVD, stroke, and heart failure risk between 6 and 24 months, SBP trajectory classes were superior in discrimination compared with 3 other possible stratification strategies: positive or negative difference between randomization SBP and SBP at first available follow-up, SBP at 6 months, and average SBP during the first 6 months above or below the 140 mm Hg target (Figure S3). The fully adjusted HRs between the 2 classes derived from SBP trajectory modeling were consistently higher than those derived from other stratification strategies for stroke, combined CVD, and heart failure.

**Discussion**

In the first 6 months of ALLHAT, we identified heterogeneity in SBP response that varied by antihypertensive medication.
Table. Characteristics of Study Participants (S1 Study Sample) by SBP Trajectory Classes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonimmediate Responders</th>
<th>Immediate Responders</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of study participants</td>
<td>5785</td>
<td>33978</td>
<td></td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>67.9 (7.8)</td>
<td>66.7 (7.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>51.2</td>
<td>54.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White, %</td>
<td>53.3</td>
<td>61.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black, %</td>
<td>42.4</td>
<td>34.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hispanic, %</td>
<td>11.4</td>
<td>17.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Geographic region, %</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>East</td>
<td>12.3</td>
<td>15.9</td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>21.1</td>
<td>18.3</td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>49.7</td>
<td>41.2</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>8.5</td>
<td>10.2</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>1.5</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Puerto Rico and US Virgin Islands</td>
<td>6.9</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>10.8 (4.0)</td>
<td>11.1 (4.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>29.4 (5.9)</td>
<td>29.6 (5.9)</td>
<td>0.018</td>
</tr>
<tr>
<td>Cholesterol, mean (SD), mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>219.0 (45.9)</td>
<td>215.4 (44.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL</td>
<td>47.8 (15.5)</td>
<td>46.7 (15.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL</td>
<td>138.6 (40.6)</td>
<td>135.9 (38.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estimated GFR, mean (SD), mL/min</td>
<td>74.7 (21.2)</td>
<td>78.3 (20.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin use, %</td>
<td>36.3</td>
<td>37.0</td>
<td>0.301</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>22.1</td>
<td>21.8</td>
<td>0.138</td>
</tr>
<tr>
<td>History of MI or stroke, %</td>
<td>22.6</td>
<td>23.3</td>
<td>0.245</td>
</tr>
<tr>
<td>History of coronary revascularization, %</td>
<td>12.7</td>
<td>13.3</td>
<td>0.234</td>
</tr>
<tr>
<td>History of major ST depression or T-wave inversion, %</td>
<td>10.9</td>
<td>10.4</td>
<td>0.252</td>
</tr>
<tr>
<td>History of other atherosclerotic CVD, %</td>
<td>22.9</td>
<td>24.2</td>
<td>0.027</td>
</tr>
<tr>
<td>Type II diabetes mellitus, %</td>
<td>37.8</td>
<td>35.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL &lt;35 mg/dL twice in past 5 y, %</td>
<td>9.5</td>
<td>12.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVH by ECG in past 2 y, %</td>
<td>21.9</td>
<td>15.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVH by echocardiogram in past 2 y, %</td>
<td>4.5</td>
<td>4.7</td>
<td>0.531</td>
</tr>
<tr>
<td>Previous antihypertensive treatment, %</td>
<td>93.8</td>
<td>89.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP at randomization, mean (SD), mm Hg</td>
<td>153.7 (15.2)</td>
<td>144.8 (15.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP at randomization, mean (SD), mm Hg</td>
<td>84.7 (10.7)</td>
<td>83.7 (9.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse pressure, mean (SD), mm Hg</td>
<td>69.0 (14.8)</td>
<td>61.1 (13.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Characteristics 0–6 mo post-randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low adherence 0–6 mo, %</td>
<td>13.8</td>
<td>12.8</td>
<td>0.032</td>
</tr>
<tr>
<td>Change in medication at any visit (any of below), %</td>
<td>92.6</td>
<td>59.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Study drug dose intensified</td>
<td>84.0</td>
<td>44.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Study drug discontinued</td>
<td>15.3</td>
<td>11.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Step 2 drug prescribed</td>
<td>31.8</td>
<td>12.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Step 3 drug prescribed</td>
<td>4.7</td>
<td>0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Open-label antihypertensive drug use</td>
<td>15.5</td>
<td>11.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; MI, myocardial infarction; and SBP, systolic blood pressure.
Specifically, our data-driven approach classified patients into 2 subpopulations: a larger group of immediate responders who, on average, experienced an initial decrease in SBP followed by a more gradual decrease and a smaller group of nonimmediate responders who, on average, had an initial increase in SBP followed by a decrease thereafter. Participants randomized to chlorthalidone were more likely to be immediate responders than those randomized to amiodpine, lisinopril, and doxazosin.

Our finding that medications are associated with different SBP response classes may explain differences in SBP control and outcomes in ALLHAT. People randomized to chlorthalidone had lower SBP evident within 1 year than those in other arms, which persisted to the end of the trial. More importantly, ALLHAT found that chlorthalidone reduced heart failure, stroke, and combined CVD risk more than other treatments, which was maintained in long-term follow-up, thus, the investigators concluded that it should be the initial antihypertensive medication of choice. Our analysis provides a possible explanation: people randomized to chlorthalidone were more likely to have an immediate SBP response within the trial’s first 6 months, which was associated with lower downstream cardiovascular risk.

Of note, not all cardiovascular outcomes were associated with immediate response; the primary end point of fatal CHD or nonfatal MI was not significantly reduced and neither were combined CHD or mortality. Although the risk of all cardiovascular outcomes is increased with hypertension, previous studies have shown that stroke and heart failure incidence are reduced the most by lowering BP: ≈35% to 40%

![Figure 3](image-url) Adjusted odds ratios of treatment assignment with being a nonimmediate responder. Odds ratios are adjusted for all covariates in model 4 (please see Table S3).

![Figure 4](image-url) Zero to 6 mo cumulative incidence of outcomes by systolic blood pressure (SBP) trajectory classes. Hazard ratios (HRs) are the fully adjusted HR shown in model 4 (Table S3). CHD indicates coronary heart disease; CVD, cardiovascular disease; and MI, myocardial infarction.
MI risk is only reduced by ≈20% to 25%. Therefore, the overall outcomes benefit that we found is consistent with known greater risk reduction of stroke and heart failure than CHD from antihypertensive therapy. Poor SBP control in the nonimmediate responders may have also unmasked heart failure, because elevated BP can increase the risk of pulmonary edema and, therefore, lead to heart failure symptoms and hospitalization. Additionally, because mortality also depends on multiple noncardiovascular causes that may be unrelated to SBP, it is unsurprising that there was no significant mortality difference.

Although diuretics are the most commonly prescribed antihypertensive therapy, hydrochlorothiazide is overwhelmingly used, with 50 million prescriptions in 2013 (excluding fixed-dose combinations). Chlorthalidone only accounted for 3% of prescriptions in patients with resistant hypertension, who may need a more potent diuretic. It is an open question, however, if hydrochlorothiazide has the same cardiovascular benefit as chlorthalidone.

There are several possible reasons for the distinct responses to initiation of antihypertensive medications. One explanation is that nonimmediate responders were more often on multiple antihypertensive medications before randomization, when all patients received a starting antihypertensive dose. This initial dose may have been inadequate compared with previous therapy. Some nonimmediate responders may also have been inadequately tapered from previous antihypertensive therapy and had a rebound SBP increase, such as is seen with clonidine. As information about baseline antihypertensive medications is unavailable, this hypothesis cannot be tested. However, evidence from the Systolic Hypertension in the Elderly trial shows that previous treatment with antihypertensive therapy did not impact risk for stroke, which could be true also for the ALLHAT population. Furthermore, patients were randomized across all 4 study arms, and, thus, this possibility does not reduce confidence in our finding that chlorthalidone is more often associated with a beneficial SBP response.

Other possibilities could help explain the distinct classes of trajectories. Nonimmediate responders had a higher pulse pressure than immediate responders, suggesting that large artery stiffness in nonimmediate responders may have contributed to poor initial response to antihypertensive therapy. Biologically, patients with high plasma renin activity have vasoconstriction-dependent hypertension that may respond better to renin–angiotensin–aldosterone system inhibitors, whereas people with low plasma renin activity may have volume-dependent hypertension that is more responsive to diuretics. Pressor responses have been described in people with low plasma renin activity.

Figure 5. Six to 24 mo cumulative incidence of outcomes by systolic blood pressure (SBP) trajectory classes. Hazard ratios (HRs) are the fully adjusted HR shown in model 4 (Table S5). CHD indicates coronary heart disease; CVD, cardiovascular disease; and MI, myocardial infarction.
renin activity given angiotensin-converting enzyme inhibitors. Therefore, nonimmediate responders may have been randomized to receive an antihypertensive medication that was treating a subtype of hypertension to which it was not best suited; indeed, a recent study demonstrated superior BP control by selecting antihypertensive therapy based on plasma renin activity levels instead of an age- and race-based strategy or giving all patients thiazides. We found that black participants were significantly more likely to be nonimmediate responders. Blacks, on average, are more likely to have low renin levels because of genetic factors that predispose to salt and water sensitivity; therefore, they are less likely to respond to renin–angiotensin–aldosterone system inhibitors such as lisinopril. Race can be an important factor in antihypertensive effectiveness; although our overall outcome associations were adjusted for race, a thorough investigation would require future study.

Ultimately, a trajectory-based analysis using 6 months of data had greater predictive power than multiple other strategies, even after adjustment for baseline data and, early within the trial, indicated chlorthalidone was the superior medication. Previous observational studies have shown that trajectories of rising BP are associated with adverse clinical cardiovascular outcomes; our findings extend these by including the role of antihypertensive medications.

Our findings have implications for clinicians who are switching patients’ antihypertensive therapy. Initiating the lowest starting medication dose, as in ALLHAT, could result in an initially increased SBP and increased downstream cardiovascular risk. Early BP lowering reduces cardiovascular risk. Some patients may need vigilant monitoring to ensure appropriate decreases in SBP, with therapy adjustments as necessary. Chlorthalidone is most likely to reduce SBP and cardiovascular risk compared with amlodipine, lisinopril, and doxazosin.

Our study has several limitations. First, this is a post hoc analysis of ALLHAT data, and, therefore, associations should be considered with caution, and we did not adjust for multiple comparisons. There is, however, biological and clinical plausibility that nonimmediate responders have increased risk for cardiovascular outcomes. Second, ALLHAT did not abstract data for trial participants on antihypertensive medications before study initiation, which could have influenced patient’s trajectories. However, our conclusion of treatment difference on SBP response remains valid because participants on previous antihypertensive therapies were randomly assigned to the 4 arms. Third, we focused on SBP instead of diastolic blood pressure, but ALLHAT only included people aged ≥55 years, and after 60 years of age, SBP is more predictive of CHD risk than diastolic blood pressure. Fourth, there were missing follow-up data, but our sensitivity analysis for people with complete data showed no differences in placement on a trajectory or cardiovascular risk. Fifth, ALLHAT was conducted in patients with established CVD or at least 1 additional risk factor for CHD events in addition to age. Thus, our conclusions may not apply to people at low risk. Sixth, ALLHAT assessed adherence through self-report and took 2 BP measurements at each session; these may not reflect what occurs in clinical practice and may not fully capture the true range of BP in a given time period. Ideally, our findings would be validated in analyses of similar randomized controlled trials comparing different antihypertensive therapies.

**Perspectives**

Our trajectory-based analysis of ALLHAT identified 2 distinct subpopulations: one of immediate responders and another of nonimmediate responders. Nonimmediate responders were more likely to have an increased long-term risk of stroke, combined CVD, and heart failure. Study participants randomized to chlorthalidone were more likely to be immediate responders and, therefore, had a lower risk of multiple adverse cardiovascular outcomes. These findings demonstrate heterogeneity in response to medical therapy in people at high risk for cardiovascular events and suggest that chlorthalidone is the more favorable antihypertensive medication, on average, for this population. Future studies of antihypertensive treatments can use similar trajectory-based approaches to help inform efforts to understand differences in response to different therapies and their associated cardiovascular outcomes. This work offers the potential to tailor antihypertensive medical therapy using a data-driven approach, with the goal of providing people with the treatment most likely to produce a beneficial BP response and reduction in cardiovascular risk.

**Acknowledgments**

We would like to thank the ALLHAT study participants and trial investigators. This article was prepared using ALLHAT Research Materials obtained from the National Heart, Lung, and Blood Institute (NHLBI) Biological Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the ALLHAT investigators or the NHLBI. We would like to thank Tara Liptak and Kristina Werther for project management. We would also like to thank Jerome Kassirer for his insightful comments on an earlier version of this article.

**Disclosures**

H.M. Krumholz is a recipient of research agreements from Medtronic and from Johnson & Johnson (Janssen), through Yale, to develop methods of clinical trial data sharing; is the recipient of a grant from the Food and Drug Administration and Medtronic, through Yale, to develop methods for post-market surveillance of medical devices; chairs a cardiac scientific advisory board for UnitedHealth; is a participant/participant representative of the IBM Watson Health Life Sciences Board; is a member of the Advisory Board for Element Science and the Physician Advisory Board for Actea; and is the founder of Hugo, a personal health information platform.

**References**


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**Novelty and Significance**

**What Is New?**

- Within the first 6 months of the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack) trial, there were 2 distinct trajectory classes of systolic blood pressure: immediate responders and nonimmediate responders.
- People randomized to chlorothalidone had higher odds ratios associated with being immediate responders compared with those randomized to amldipine, lisinopril, and doxazosin.
- Nonimmediate responders had an increased risk of stroke, combined cardiovascular disease, and heart failure between 6 months and 2 years.

**What Is Relevant?**

- Systolic blood pressure trajectories are a data-driven approach to identi- fying heterogeneity using repeated measurements.

**Summary**

Systolic blood pressure trajectories can uncover latent heterogene- ity and, when applied to ALLHAT, demonstrated that people ran- domized to chlorothalidone were most likely to be immediate sys- tolic blood pressure responders; this response was associated with reduced cardiovascular risk.
Heterogeneity in Early Responses in ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)

Sanket S. Dhruva, Chenxi Huang, Erica S. Spatz, Andreas C. Coppi, Frederick Warner, Shu-Xia Li, Haiqun Lin, Xiao Xu, Curt D. Furberg, Barry R. Davis, Sara L. Pressel, Ronald R. Coifman and Harlan M. Krumholz

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Heterogeneity in Early Responses in ALLHAT

Running Head: Heterogeneity in Early Responses in ALLHAT

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Ronald R. Coifman, PhD; Harlan M. Krumholz, MD, SM

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Methods Appendix: Model Fitting and Selection

We used growth mixture models to capture heterogeneity in the repeated systolic blood pressure (SBP) measurements over time (i.e., SBP trajectories). The SBP trajectories were modeled as being generated from a mixture of a finite number of Gaussian distributions with different mean trajectories but the same residual variances. The mean trajectories were modeled as a function of time, and we considered 3 different parametric functional forms of time: linear, quadratic, and piecewise linear with a single non-predetermined change point. The parameters of these functional forms were modeled as random to characterize heterogeneity within the mixture class. For each of the 3 parametric functional forms above, we derived models with varying numbers of trajectory classes. We started with 1 class and increased the number of classes until either 1 of 3 circumstances occurred: The Bayesian Information Criteria (BIC) did not improve, there were convergence issues, or reliable estimation results could not be obtained. After each model was derived, the posterior probability of participants belonging to each trajectory class was calculated. Participants were then classified to the trajectory class according to their highest posterior probability. The average posterior probability in each class was then calculated from those who were classified to the same trajectory class.

The optimal model was primarily selected based on the BIC value, where lower BIC indicates better fit. We applied 2 additional restrictions: The average posterior probability in each class needed to be >0.7, and the percentage of participants classified to a class needed to be >5% of the total study sample.
REFERENCE

Table S1. Results for model selection.

<table>
<thead>
<tr>
<th>Model</th>
<th>(-2\text{Log-likelihood})</th>
<th>BIC</th>
<th>Proportion in class (%)</th>
<th>Average posterior probability in class</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Linear model</td>
<td></td>
<td></td>
<td>93.3</td>
<td>6.7</td>
</tr>
<tr>
<td>1 class</td>
<td>1214979</td>
<td>1215043</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 classes</td>
<td>1213034</td>
<td>1213139</td>
<td>89.5</td>
<td>6.3</td>
</tr>
<tr>
<td>3 classes</td>
<td>1213021</td>
<td>1213149</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quadratic model</td>
<td></td>
<td></td>
<td>87.6</td>
<td>12.4</td>
</tr>
<tr>
<td>1 class</td>
<td>1213004</td>
<td>1213110</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 classes</td>
<td>1209933</td>
<td>1210092</td>
<td>13.6</td>
<td>76.2</td>
</tr>
<tr>
<td>3 classes</td>
<td>1209582</td>
<td>1209794</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piecewise linear mixed model</td>
<td></td>
<td></td>
<td>85.5</td>
<td>14.5</td>
</tr>
<tr>
<td>1 class</td>
<td>1211816</td>
<td>1211932</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 classes</td>
<td>1208150</td>
<td>1208352</td>
<td>78.9</td>
<td>17.0</td>
</tr>
<tr>
<td>3 classes*</td>
<td>1207565</td>
<td>1207819</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BIC= Bayesian Information Criterion

*Solution did not satisfy convergence criteria
Table S2. Systolic blood pressure trajectory class membership and odds of being in non-immediate responder class by randomization treatment assignment.

<table>
<thead>
<tr>
<th>Select Samples</th>
<th>Chlorthalidone</th>
<th>Amlodipine</th>
<th>Lisinopril</th>
<th>Doxazosin</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 follow-up SBP measurement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-immediate responders (N, %)</td>
<td>1636, 11.4%</td>
<td>1127, 13.2%</td>
<td>1583, 18.8%</td>
<td>1432, 17.0%</td>
</tr>
<tr>
<td>Unadjusted odds ratio</td>
<td>1.00 (ref)</td>
<td>1.18 (1.09, 1.28)</td>
<td>1.79 (1.66, 1.93)</td>
<td>1.58 (1.47, 1.71)</td>
</tr>
<tr>
<td>Adjusted odds ratio*</td>
<td>1.00 (ref)</td>
<td>1.20 (1.10, 1.31)</td>
<td>1.88 (1.73, 2.03)</td>
<td>1.65 (1.52, 1.78)</td>
</tr>
<tr>
<td>Excluding participants with missing follow-up SBP measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-immediate responders (N, %)</td>
<td>1285, 12.0%</td>
<td>866, 13.5%</td>
<td>1234, 19.6%</td>
<td>1135, 18.1%</td>
</tr>
<tr>
<td>Unadjusted odds ratio*</td>
<td>1.00 (ref)</td>
<td>1.15 (1.05, 1.26)</td>
<td>1.80 (1.65, 1.96)</td>
<td>1.63 (1.49, 1.78)</td>
</tr>
<tr>
<td>Adjusted odds ratio*</td>
<td>1.00 (ref)</td>
<td>1.15 (1.05, 1.27)</td>
<td>1.91 (1.74, 2.08)</td>
<td>1.71 (1.57, 1.88)</td>
</tr>
<tr>
<td>Excluding participants with events prior to 6-month follow-up visit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-immediate responders (N, %)</td>
<td>1528, 11.2%</td>
<td>1071, 13.2%</td>
<td>1478, 18.5%</td>
<td>1343, 16.9%</td>
</tr>
<tr>
<td>Unadjusted odds ratio*</td>
<td>1.00 (ref)</td>
<td>1.21 (1.11, 1.31)</td>
<td>1.80 (1.67, 1.95)</td>
<td>1.62 (1.50, 1.75)</td>
</tr>
<tr>
<td>Adjusted odds ratio*</td>
<td>1.00 (ref)</td>
<td>1.23 (1.13, 1.34)</td>
<td>1.90 (1.75, 2.06)</td>
<td>1.70 (1.56, 1.84)</td>
</tr>
<tr>
<td>Excluding participants with missing SBP measurements and events in the first 6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-immediate responders (N, %)</td>
<td>1215, 11.7%</td>
<td>830, 13.4%</td>
<td>1152, 19.3%</td>
<td>1056, 17.9%</td>
</tr>
<tr>
<td>Unadjusted odds ratio*</td>
<td>1.00 (ref)</td>
<td>1.17 (1.06, 1.28)</td>
<td>1.80 (1.65, 1.96)</td>
<td>1.64 (1.50, 1.79)</td>
</tr>
<tr>
<td>Adjusted odds ratio*</td>
<td>1.00 (ref)</td>
<td>1.17 (1.06, 1.30)</td>
<td>1.92 (1.75, 2.10)</td>
<td>1.73 (1.58, 1.90)</td>
</tr>
</tbody>
</table>

* Covariates for adjustment: baseline age, sex, race/ethnicity, body mass index, education, region of residence, smoking, glomerular filtration rate, diabetes, fasting glucose, total cholesterol, low high-density lipoprotein cholesterol (HDL), HDL, triglycerides, history of myocardial infarction/stroke, history of coronary revascularization, history of other atherosclerotic cardiovascular disease, major ST depression or T-wave, left ventricular hypertrophy, aspirin use, use of antihypertensive medications before randomization, adherence 0-6 month, and baseline systolic blood pressure. SBP=systolic blood pressure.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. events (%)</th>
<th>Non-immediate responders vs immediate responders, HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Model 1*</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Non-immediate responders</td>
<td>Immediate Responders</td>
</tr>
<tr>
<td>Nonfatal MI/Fatal CHD</td>
<td>44 (0.8)</td>
<td>214 (0.6)</td>
</tr>
<tr>
<td>Major secondary outcomes</td>
<td>All-cause mortality</td>
<td>36 (0.6)</td>
</tr>
<tr>
<td></td>
<td>Combined CHD</td>
<td>122 (2.1)</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>49 (0.9)</td>
</tr>
<tr>
<td></td>
<td>Combined CVD</td>
<td>338 (5.8)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>85 (1.5)</td>
<td>290 (0.9)</td>
</tr>
</tbody>
</table>

CHD=Coronary Heart Disease; CVD=Cardiovascular Disease

* Model 1: baseline SBP
† Model 2: model 1 + age, sex, race/ethnicity, region of residence, treatment assignment
‡ Model 3: model 2 + smoking, body mass index, education, estimated glomerular filtration rate, diabetes, fasting glucose, total cholesterol, low high-density lipoprotein cholesterol (HDL), HDL, triglycerides, history of myocardial infarction/stroke, history of coronary revascularization, history of other atherosclerotic CVD, major ST depression or T-wave, left ventricular hypertrophy, aspirin use, use of antihypertensive medications before randomization
§ Model 4: model 3 + adherence 0-6 months
Table S4. Characteristics of S2 study sample by systolic blood pressure trajectory classes.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-immediate Responders</th>
<th>Immediate Responders</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of study participants</td>
<td>5420</td>
<td>32309</td>
<td></td>
</tr>
</tbody>
</table>

**Baseline characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-immediate Responders</th>
<th>Immediate Responders</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>67.8 (7.8)</td>
<td>66.6 (7.6)</td>
<td>0.851</td>
</tr>
<tr>
<td>Male, %</td>
<td>52.9</td>
<td>53.4</td>
<td>0.533</td>
</tr>
<tr>
<td>White, %</td>
<td>52.6%</td>
<td>60.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black, %</td>
<td>43.0</td>
<td>34.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hispanic, %</td>
<td>11.7</td>
<td>18.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Geographic region, %</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>East</td>
<td>12.3</td>
<td>15.9</td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>21.0</td>
<td>18.1</td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>49.8</td>
<td>41.1</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>8.4</td>
<td>10.2</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>1.4</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Puerto Rico &amp; US Virgin Islands</td>
<td>7.1</td>
<td>12.9</td>
<td></td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>10.8 (4.0)</td>
<td>11.1 (4.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>29.4 (5.9)</td>
<td>29.7 (5.9)</td>
<td>0.006</td>
</tr>
<tr>
<td>Cholesterol, mean (SD), mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>218.9 (45.8)</td>
<td>215.4 (44.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL</td>
<td>47.9 (15.6)</td>
<td>46.8 (15.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL</td>
<td>138.6 (40.4)</td>
<td>135.8 (38.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estimated GFR, mean (SD)</td>
<td>75.0 (21.2)</td>
<td>78.5 (20.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin use, %</td>
<td>35.8</td>
<td>36.5</td>
<td>0.341</td>
</tr>
<tr>
<td>Current Smoking, %</td>
<td>22.2</td>
<td>21.7</td>
<td>0.450</td>
</tr>
<tr>
<td>History of MI or stroke, %</td>
<td>21.8</td>
<td>22.8</td>
<td>0.136</td>
</tr>
<tr>
<td>History of coronary revascularization, %</td>
<td>12.1</td>
<td>12.6</td>
<td>0.255</td>
</tr>
<tr>
<td>History of major ST depression or T-wave inversion, %</td>
<td>10.9</td>
<td>10.4</td>
<td>0.302</td>
</tr>
<tr>
<td>History of other atherosclerotic CVD, %</td>
<td>22.2</td>
<td>23.7</td>
<td>0.011</td>
</tr>
<tr>
<td>Type II diabetes, %</td>
<td>37.6</td>
<td>35.3</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL-C&lt;35mg/dl twice in past 5 years, %</td>
<td>9.3</td>
<td>12.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVH by electrocardiogram in past 2 years, %</td>
<td>22.1</td>
<td>15.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVH by echocardiogram in past 2 years, %</td>
<td>4.5</td>
<td>4.7</td>
<td>0.568</td>
</tr>
<tr>
<td>Prior antihypertensive treatment, %</td>
<td>93.6</td>
<td>89.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP at randomization, mean (SD), mm Hg</td>
<td>153.8 (15.2)</td>
<td>144.8 (15.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP at randomization, mean (SD), mm Hg</td>
<td>84.8 (10.6)</td>
<td>83.8 (9.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Characteristics 0-6 months after randomization</td>
<td>68.9 (14.7)</td>
<td>61.0 (13.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Pulse Pressure at randomization, mean (SD), mm Hg</td>
<td>68.9 (14.7)</td>
<td>61.0 (13.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

| Low adherence 0-6 months, % | 13.7 | 12.6 | 0.026 |
| Change in medication at any visit (any of below), % | 92.5 | 58.6 | <0.001 |
| Study drug dose intensification | 84.3 | 45.1 | <0.001 |
| Stop study drug | 14.2 | 10.9 | <0.001 |
| Step 2 drug prescribed | 31.9 | 12.6 | <0.001 |
| Step 3 drug prescribed | 4.8 | 0.9 | <0.001 |
| Open-label antihypertensive drug use | 14.4 | 10.8 | <0.001 |

DBP=diastolic blood pressure; CVD=cardiovascular disease; GFR=glomerular filtration rate; HDL=high-density lipoprotein; LVH=left ventricular hypertrophy; MI=myocardial infarction; SBP=systolic blood pressure
Table S5. 6-24 month outcomes by systolic blood pressure trajectory classes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. events (%)</th>
<th>Non-immediate responders vs immediate responders, HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Non-immediate responders</td>
</tr>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI/Fatal CHD</td>
<td>155 (2.9)</td>
<td>848 (2.6)</td>
</tr>
<tr>
<td>Major secondary outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>183 (3.4)</td>
<td>922 (2.9)</td>
</tr>
<tr>
<td>Combined CHD</td>
<td>327 (6.0)</td>
<td>1650 (5.1)</td>
</tr>
<tr>
<td>Stroke</td>
<td>128 (2.4)</td>
<td>401 (1.2)</td>
</tr>
<tr>
<td>Combined CVD</td>
<td>672 (12.4)</td>
<td>3025 (9.4)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>1.68 (3.1)</td>
<td>565 (1.7)</td>
</tr>
</tbody>
</table>

* Model 1: baseline SBP  
† Model 2: model 1 + age, sex, race/ethnicity, region of residence, treatment assignment  
‡ Model 3: model 2 + smoking, body mass index, education, estimated glomerular filtration rate, diabetes, fasting glucose, total cholesterol, low high-density lipoprotein cholesterol (HDL), HDL, triglycerides, history of myocardial infarction/stroke, history of coronary revascularization, history of other atherosclerotic CVD, major ST depression or T-wave, left ventricular hypertrophy, aspirin use, use of antihypertensive medications before randomization  
§ Model 4: model 3 + adherence 0-6 months
Table S6. 0-6 month outcomes by systolic blood pressure trajectory classes for participants without any missing SBP measurement during the first 6 months.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. events (%)</th>
<th>Non-immediate responders vs immediate responders, HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-</td>
<td>Immediate Responders</td>
</tr>
<tr>
<td></td>
<td>immediate</td>
<td>Responders</td>
</tr>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI/Fatal CHD</td>
<td>18 (0.4)</td>
<td>105 (0.4)</td>
</tr>
<tr>
<td></td>
<td>(0.58,1.58)</td>
<td>(0.55,1.52)</td>
</tr>
<tr>
<td>Major secondary outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>4 (0.08)</td>
<td>8 (0.03)</td>
</tr>
<tr>
<td></td>
<td>(0.84,9.27)</td>
<td>(0.70,8.42)</td>
</tr>
<tr>
<td>Combined CHD</td>
<td>74 (1.4)</td>
<td>356 (1.4)</td>
</tr>
<tr>
<td></td>
<td>(0.90,1.49)</td>
<td>(0.88,1.46)</td>
</tr>
<tr>
<td>Stroke</td>
<td>24 (0.5)</td>
<td>80 (0.3)</td>
</tr>
<tr>
<td></td>
<td>(1.06,2.65)</td>
<td>(0.97,2.48)</td>
</tr>
<tr>
<td>Combined CVD</td>
<td>230 (5.1)</td>
<td>902 (3.6)</td>
</tr>
<tr>
<td></td>
<td>(1.24,1.66)</td>
<td>(1.20,1.62)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>63 (1.4)</td>
<td>193 (0.8)</td>
</tr>
<tr>
<td></td>
<td>(1.38,2.43)</td>
<td>(1.29,2.31)</td>
</tr>
</tbody>
</table>

* Model 1: baseline SBP
† Model 2: model 1 + age, sex, race/ethnicity, region of residence, treatment assignment
‡ Model 3: model 2 + smoking, body mass index, education, estimated glomerular filtration rate, diabetes, fasting glucose, total cholesterol, low high-density lipoprotein cholesterol (HDL), HDL, triglycerides, history of myocardial infarction/stroke, history of coronary revascularization, history of other atherosclerotic CVD, major ST depression or T-wave, left ventricular hypertrophy, aspirin use, use of antihypertensive medications before randomization
§ Model 4: model 3 + adherence 0-6 months
Table S7. 6-24 month outcomes by SBP trajectory classes for participants without any missing SBP measurement and events prior to 6-month follow-up visit.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. events (%)</th>
<th>Non-immediate responders vs immediate responders, HR (95% CI)</th>
<th>Non-immediate responders</th>
<th>Immediate Responders</th>
<th>Unadjusted</th>
<th>Model 1*</th>
<th>Model 2†</th>
<th>Model 3‡</th>
<th>Model 4§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI/Fatal CHD</td>
<td>116 (2.7)</td>
<td>610 (2.5)</td>
<td>1.10 (0.90,1.34)</td>
<td>1.05 (0.86,1.29)</td>
<td>1.03 (0.84,1.27)</td>
<td>1.00 (0.81,1.22)</td>
<td>1.00 (0.81,1.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>129 (3.0)</td>
<td>597 (2.5)</td>
<td>1.23 (1.02,1.49)</td>
<td>1.17 (0.96,1.42)</td>
<td>1.10 (0.90,1.34)</td>
<td>1.04 (0.85,1.27)</td>
<td>1.04 (0.85,1.27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined CHD</td>
<td>257 (6.0)</td>
<td>1239 (5.1)</td>
<td>1.20 (1.05,1.37)</td>
<td>1.19 (1.03,1.36)</td>
<td>1.15 (1.00,1.32)</td>
<td>1.13 (0.98,1.30)</td>
<td>1.13 (0.98,1.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>100 (2.4)</td>
<td>279 (1.2)</td>
<td>2.08 (1.65,2.61)</td>
<td>1.79 (1.42,2.27)</td>
<td>1.66 (1.31,2.11)</td>
<td>1.55 (1.22,1.97)</td>
<td>1.54 (1.21,1.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined CVD</td>
<td>538 (12.6)</td>
<td>2273 (9.4)</td>
<td>1.38 (1.26,1.52)</td>
<td>1.34 (1.22,1.48)</td>
<td>1.27 (1.15,1.40)</td>
<td>1.23 (1.11,1.36)</td>
<td>1.23 (1.11,1.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>132 (3.1)</td>
<td>418 (1.7)</td>
<td>1.84 (1.51,2.23)</td>
<td>1.76 (1.44,2.15)</td>
<td>1.54 (1.25,1.89)</td>
<td>1.45 (1.18,1.78)</td>
<td>1.45 (1.18,1.78)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Model 1: baseline SBP
† Model 2: model 1 + age, sex, race/ethnicity, region of residence, treatment assignment
‡ Model 3: model 2 + smoking, body mass index, education, estimated glomerular filtration rate, diabetes, fasting glucose, total cholesterol, low high-density lipoprotein cholesterol (HDL), HDL, triglycerides, history of myocardial infarction/stroke, history of coronary revascularization, history of other atherosclerotic CVD, major ST depression or T-wave, left ventricular hypertrophy, aspirin use, use of antihypertensive medications before randomization
§ Model 4: model 3 + adherence 0-6 months
Figure S1.
Hazard ratios (HR) of 6-24 month combined cardiovascular disease (CVD), stroke, and heart failure associated with systolic blood pressure (SBP) trajectory classes in selected subgroups. HRs are adjusted by covariates in model 4 (Table S5). All p-values for interaction >0.1 except for age (p=0.033) and sex (p<0.001) of stroke, sex (p=0.009) of combined CVD, and sex (p=0.043) and treatment (doxazosin vs chlorthalidone, p=0.064) of heart failure.
Figure S2.
Hazard ratios (HR) of 6-24 month combined cardiovascular disease (CVD), stroke, and heart failure associated with systolic blood pressure (SBP) trajectory class posterior probability by using natural splines. HRs are adjusted by covariates in model 4 (Table S5).
Figure S3.
Discriminant power of systolic blood pressure (SBP) trajectory classes, compared with other classification strategies: difference of the first follow-up SBP and randomization SBP, SBP at 6 months and average SBP during the first 6 months compared with 140 mm Hg. HR: hazard ratio. HRs are the fully adjusted hazard ratio shown in Model 4 (See Table S7).