HHS Public Access

Author manuscript

J Hum Hypertens. Author manuscript; available in PMC 2016 August 15.

Published in final edited form as:

J Hum Hypertens. 2016 September ; 30(9): 549–554. doi:10.1038/jhh.2015.121.

The effects of genes implicated in cardiovascular disease on blood-pressure response to treatment among treatment-naïve hypertensive African Americans in the GenHAT study

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Abstract

African Americans have the highest prevalence of hypertension in the United States. Blood-pressure control is important to reduce cardiovascular disease (CVD)-related morbidity and mortality in this ethnic group. Genetic variants have been found to be associated with BP response to treatment. Previous pharmacogenetic studies of blood-pressure response to treatment in African Americans suffer limitations of small sample size as well as a limited number of candidate genes, and often focused on one antihypertensive treatment. Using 1,131 African-American treatment naïve participants from the Genetics of Hypertension Associated Treatment (GenHAT) Study, we examined whether variants in 35 candidate genes might modulate blood-pressure response to four different antihypertensive medications, including an angiotensin converting enzyme (ACE) inhibitor (lisinopril), a calcium channel blocker (amlodipine), and an α-adrenergic blocker (doxazosin) as compared to a thiazide diuretic (chlorthalidone) after 6 months of follow-up. Several suggestive gene by treatment interactions were identified. For example, among participants with two minor alleles of *REN* rs6681776, diastolic blood-pressure response was much improved on doxazosin compared to chlorthalidone (on average −9.49 mmHg vs. −1.70 mmHg) (P=0.007). Although several suggestive loci were identified, none of the findings passed significance criteria after correction for multiple testing. Given the impact of hypertension and its sequelae in this population, this research highlights the potential for genetic factors to contribute to blood-pressure response to treatment. Continued concerted research efforts focused on genetics are needed to improve treatment response in this high risk group.

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Conflicts of interest

The authors declare no conflicts of interest.

Keywords

African American; antihypertensive drugs; treatment naïve; blood-pressure response; Genetics of Hypertension Associated Treatment Study

1. Introduction

Approximately 43% of African Americans suffer from hypertension, representing a prevalence higher than any other ethnic group in the U.S. The condition contributes to about 44% of cardiovascular disease (CVD) and 38% of all deaths in this ethnic group.[1] Despite the availability of multiple effective antihypertensive agents on the market, including combination preparations, only 45% of African Americans treated for hypertension have controlled blood pressure.[2] Uncontrolled blood pressure in African Americans is strongly linked to cardiovascular and renal complications including stroke, left ventricular hypertrophy, heart failure, and chronic kidney diseases. Consequently, these diseases are more prevalent among African Americans compared to Caucasians.[2] Additionally, the rate of death from hypertension is excessively high among African Americans e.g. 3.3 and 2.7 times higher among African American men and women, respectively compared to Caucasian men and women using data from National Center for Health Statistics.[2] In order to help alleviate these striking health disparities, better control of blood pressure, therefore, remains one of the most important public health priorities for African Americans.

Large clinical trials have demonstrated blood pressure response to antihypertensive medications varies among ethnic groups.[3] African Americans respond better to diuretics and calcium channel blockers (CCBs) as compared to Caucasians and, thus, these drugs remain the recommended first-line agents for this race group.[3] However, variation in response to treatment is still high and blood pressure control remains sub-par at the population level. It has been hypothesized that genetic factors play a role in individual blood-pressure response to antihypertensive medication.[4] Discovery of genetic variants useful for predicting blood-pressure response to pharmacological treatments could improve blood-pressure control and ultimately prevent stroke and CVD, especially in African Americans.

Previous genetic studies have investigated polymorphisms associated with blood-pressure response to treatment in African Americans.[5–17] However, the majority of those studies were small, and/or focused on a limited set of genes for one treatment (e.g. thiazide diuretic). Overall, pharmacogenetic studies of other antihypertensive drugs in African Americans are still limited. To fill this research gap, we evaluated whether variants in 35 candidate genes implicated in CVD modulate blood-pressure response to four different antihypertensive classes including an angiotensin converting enzyme (ACE) inhibitor (lisinopril), a CCB (amlodipine), and an α-adrenergic blocker (doxazosin) compared to a thiazide diuretic (chlorthalidone) in African Americans using data from the Genetics of Hypertension Associated Treatment Study (GenHAT). In order to capture the true blood pressure response to treatment, this study focuses on a subset of 1,131 African Americans who were initially naïve to antihypertensive treatment at study enrollment.

2. Materials and methods

2.1. Study population

Data were derived from the GenHAT study, an ancillary pharmacogenetic study of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[18] Both studies have been described.[4, 18] Briefly, ALLHAT was a randomized, double-blind, clinical trial that was conducted from February 1994 to March 2002 in 623 North American centers in both the US and Canada. A total of 42,418 hypertensive participants at least 55 years of age were randomized to one of four classes of antihypertensive medications including chlorthalidone, lisinopril, amlodipine, and doxazosin, in a ratio of 1.7:1:1:1, respectively.[18] Randomization drugs were titrated to meet the study treatment goal of systolic blood pressure less than 140 mmHg, and diastolic blood pressure less than 90 mmHg. Treatment was given once daily: chlorthalidone (12.5 mg for the first and second titration and 25 mg for the third), lisinopril (10, 20, or 40 mg), amlodipine (2.5, 5, or 10 mg), or doxazosin (2, 4, or 8 mg). At the 6 month visit, the average dose of chlorthalidone, lisinopril and amlodipine were 16.5, 23.1, and 5.8, respectively according to data from ALLHAT.[19] If blood pressure control was not achieved on the maximum study medication dose, a second-step, open-label agent (reserpine, clonidine, or atenolol) and then a third-step open-label agent (hydralazine) was added.[19] Medication adherence was simply assessed in ALLHAT as the percent of visits a participant responded “yes” via questionnaire that they took their study drug at least 80% of the time prior to that particular visit.[19]

2.2. Sample for current analysis

Our study hypothesis states that genes involved in the development and progression of CVD modulate blood-pressure response to 6 months of antihypertensive treatment with lisinopril, amlodipine, and doxazosin vs. chlorthalidone among treatment-naïve hypertensive participants belonging to the GenHAT study. Among the available 39,114 eligible GenHAT participants 1,131 African Americans were randomized to one of the four drugs and reported no current antihypertensive treatment at study initiation. Overall treatment naïve African-Americans participants in GenHAT study are slightly younger, more likely male, have lower BMI, and lower frequency of type 2 diabetes, and higher baseline blood pressure level compared to the rest of the African American cohort from GenHAT (see Supplemental Table 1).

This research was approved by the institutional review boards at the University of Alabama at Birmingham, the University of Texas Health Science Center, and the University of Minnesota. Informed written consent was collected from all ALLHAT participants. Anonymity of GenHAT participants has been described.[20]

2.3. Study outcome

The study outcome was systolic blood pressure (SBP), and diastolic blood pressure (DBP) change from baseline to the 6-month follow-up visit (i.e., SBP_{6month}-$SBP_{baseline}$, and DBP_{6month}-$DBP_{baseline}$). Blood pressure at each time point was the average of 2 seated blood-pressure measurements at each visit. Specifically, blood pressure was measured two times for each participant at each visit with a standard mercury sphygmomanometer, and

participants were required to sit quietly with both feet flat on the floor, in an erect but comfortable posture for more than 5 minutes (ALLHAT protocol). For a more detailed description of blood pressure measurement, see Davis et al.[18]

2.4. Genotyping

The DNA of GenHAT participants was extracted from stored blood using Gentra Purgene Kits (Minneapolis, MN).[4] The current study considered 78 single nucleotide polymorphisms (SNPs) belonging to 38 genes which were genotyped by using amplified DNA products of a multiplex PCR. The linear immobilized probe assay was used to detect multiple candidate markers (Roche Molecular Systems, Alameda, CA, USA).[4] These SNPs were selected by Roche for inclusion on the assay because their biochemical pathways were found to be involved in the development and progression of atherosclerotic plaques including lipid metabolism, homocysteine metabolism, blood pressure regulation, thrombosis, and leukocyte adhesion.[21] Of the 78 genotyped SNPs, 13 (beta-2 adrenergic receptor (*ADRB2*) rs1800888, cystathionine-beta-synthase (*CBS*) rs5742905, coagulation factor II (*F2*) rs1799963, coagulation factor V (*F5*) rs6025, intercellular adhesion molecule 1 (*ICAM1*) rs1799969, matrix metalloproteinase 12 (*MMP12*) rs2276109, nitric oxide synthase 3 (*NOS3*) rs3918226, phosphodiesterase 4D (*PDE4D*) rs10074908, sodium channel, nonvoltage-gated 1, alpha subunit (*SCNN1A*) rs5742912, selectin E (*SELE*) rs5361, *SELE* rs5355, tumor necrosis factor (*TNF*) rs361525, *TNF* rs1800750) had minor allele frequency <5% and were excluded in the analyses presented due to insufficient sample size to test gene by treatment interaction. Five SNPs with missing rate ≥5% including lipoprotein lipase (*LPL*) rs328, matrix metalloproteinase 7 (*MMP7*) rs11568818, *MMP7* rs11568819, phosphodiesterase 4D (*PDE4D*) rs153031, and *PDE4D* rs6450512 were excluded from the analyses. Furthermore, each of the 60 SNPs was also tested for Hardy Weinberg Equilibrium (HWE). SNPs with HWE p-value < 0.01 were excluded similarly to a previous GenHAT publication.[20] Three SNPs including angiotensin I-converting enzyme (*ACE*) rs1799752, angiotensin II receptor, type 1 (*AGTR1*) rs1492078, and methylenetetrahydrofolate reductase (*MTHFR*) rs1801133 ($P=9*10^{-16}$, $4.5*10^{-6}$, 0.008; respectively) were excluded, leaving 57 SNPs for the current gene-by-treatment study (Supplemental Table 2).

2.5. Statistical methods

ANOVA and chi-square tests were used to test for baseline differences between treatment groups for continuous and categorical variables, respectively. Linear regression was used to test for gene-by-treatment effects comparing lisinopril, amlodipine, and doxazosin to chlorthalidone separately, with SBP and DBP response after 6 months as the dependent variable, and the genotype, treatment and genotype-by-treatment interaction term considered as independent variables. Since other covariates were balanced by the randomization scheme, our main models were not adjusted for other covariates. However, our top findings were additionally adjusted for age in sensitivity analysis. For each SNP, we tested an additive genetic model where the common allele was considered as the referent group. A P-value of 0.05 was considered suggestive evidence for an association. A Bonferroni correction was used to adjust for multiple testing of 57 independent SNPs and 3 treatment comparisons; therefore α was adjusted to 0.05/(57*3)=0.0003. SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

3. Results

Table 1 shows the baseline characteristics of the 1,131 subjects included in this analysis. There were no significant differences between the four medication arms in baseline characteristics including sex, blood pressure at baseline, body mass index, type 2 diabetes, smoking, HDL-cholesterol, LDL-cholesterol, fasting triglyceride level, prevalent left ventricular hypertrophy, and estimated glomerular filtration rate or medication adherence. African Americans in the chlorthalidone arm were slightly older than participants in other the treatment groups. Additionally, the allele frequency of the 57 SNPs was not significantly different between the four medication arms except for *ACE* rs4343 and matrix metalloproteinase 12 (*MMP12*) rs652438 (both P=0.03) (Data not shown).

No gene by treatment interaction was statistically significant after correction for multiple testing (Supplemental Tables 3A–3F). However, several suggestive (P<0.05) gene-by-treatment interactions for angiotensinogen (*AGT*) r5051, coagulation factor VII (*F7*) rs6046, *F7* rs762637, and renin (*REN*) rs6681776 for SBP, and *AGTR1* rs275653, *F7* rs6046, coagulation factor XIII A1 subunit (*F13*) rs5985, matrix metalloproteinase 3 (*MMP3*) rs3025058 and *REN* rs6681776 for DBP were observed (Table 2A and 2B).

REN rs6681776 modified DBP response when comparing doxazosin to chlorthalidone (P=0.007). Among participants with the homozygous wild-type allele (G) of *REN* rs6681776, doxazosin and chlorthalidone response were similar. However, among participants with two minor alleles (A) at rs6681776, DBP response was markedly increased on chlorthalidone (on average −9.49mmHg for chlorthalidone vs. −1.70 mmHg for doxazosin). DBP response was also increased for heterozygotes at rs6681776 on chlorthalidone versus doxazosin (on average −9.51mmHg vs. −5.85 mmHg). Similar trends for the minor allele were observed for DBP response for *AGTR1* rs275653 and *F7* rs6046 when comparing amlodipine to chlorthalidone (P=0.02 and 0.01, respectively), and *F13* rs5985 when comparing doxazosin to chlorthalidone (P=0.03) (Table 2A).

Gene-by-treatment effects associated with SBP response with P<0.05 are described in Table 2B. The minor allele at *AGT* rs5051 and *REN* rs6681776 was associated with smaller response to lisinopril as compared to chlorthalidone (P=0.04 for both). Another marginally significant gene by treatment interaction for SBP response was observed for *F7* rs762637 when comparing lisinopril to chlorthalidone (P=0.02). In particular among participants homozygous for the wild-type allele (G) of *F7* rs762637, there was an increased response to chlorthalidone compared to lisinopril (on average −20.91 mmHg vs. −14.67 mmHg). However, among participants with two minor alleles (A) of rs762637, SBP response was, on average, markedly increased on lisinopril compared to chlorthalidone (on average −22.53 mmHg vs. −15.67 mmHg). There was little difference in the SBP response for heterozygotes at rs762637. Similar trends were observed for *F7* rs762637 for SBP response when comparing doxazosin to chlorthalidone (P=0.01). In sensitivity analyses, all findings for DBP and SBP response were consistent when models were additionally adjusted for age.

4. Discussion

Discovery of genetic variants that modify blood-pressure response to common antihypertensive agents may improve blood-pressure control and treatment outcomes among individuals with hypertension. In the current analysis, we evaluated the interaction between multiple candidate variants and antihypertensive treatment on SBP and DBP response to common antihypertensive agents among African Americans newly initiating antihypertensive treatment as part of the Genetics of Hypertension Associated Treatment Study. Our results suggest that variants involved in the renin-angiotensin-aldosterone system (RAAS) and coagulation may be associated with inter-individual differences in SBP and DBP response to common antihypertensive treatments among this understudied racial group.

We have extensively reviewed the literature for blood pressure response to antihypertensive treatment. Overall, African Americans have been considerably underrepresented in the published literature. According to our review of 37 studies, fewer than half included African Americans. Among the 14 studies that included African Americans, the average sample size was 210.[5–17, 22] Twelve of them were candidate gene studies with an average of 6 genes considered, and two were genome wide association studies (GWAS). One of the GWAS found a statistically significant association between three SNPs near *LYZ, YEATS4*, and *FRS2* and DBP response in participants using a thiazide diuretic.[12] The other GWAS failed to report any SNPs associated with response to thiazide diuretic.[17] All of the 14 studies included previously treated hypertensive subjects with less than a 9-week washout period, which may not be sufficient to avoid background noise for antihypertensive treatment response caused by previous treatments.[23] In candidate genes studies, variants in *GNB3, ACE, AGTR1, ADRBK1, GPR83, FGF5, SH2B3,* and *EBF1* were found to be associated with blood-pressure response mostly to thiazide diuretic treatment. Overall we cannot compare our results to these studies since we examined different loci. Still our research builds upon these studies by shedding light on the potential for pharmacogenetic markers that may prove useful to optimize antihypertensive treatment in African Americans.

In this study, we observed suggestive evidence that *AGT* rs5051, *AGTR1* rs275653 and *REN* rs6681776 (all belonging to the RAAS) may modify blood pressure response to common treatments among African Americans. That we know of, *AGTR1* rs275653 and *REN* rs6681776 have not been linked to hypertension, CVD outcomes, or blood-pressure response to antihypertensive treatment previously. Association between *AGT* rs5051 and blood pressure or related outcomes has been previously reported.[7, 24] A randomized trial with 130 African American females assigned hydrochlorothiazide (a thiazide diuretic) for four weeks found that participants with two minor alleles (G) of rs5051 had smaller SBP response compared to those carrying at least one common allele (A) at rs5051 (p=0.032).[7] We found no similar main effect of that SNP on SBP response in GenHAT (data not shown). Another study of 509 Chinese hypertensive participants randomized to imidapril or benazepril (ACE inhibitors) for six weeks found that participants with two minor alleles (G) of rs5051 had a larger SBP and DBP response compared to those carrying at least one common allele (A) (p=0.007, 0.014, respectively).[24] Additionally, an additive association between the minor allele of rs5051 and increased left ventricular mass indexed by height was reported in a study with 102 African Americans after adjusting for potential confounders (p=0.006).[25]

It is highly biologically plausible that *REN, AGT* and *AGTR1* may modify antihypertensive treatment response. The RAAS plays a major role in maintaining salt-water balance and blood pressure. *REN* encodes renin, an enzyme released from the kidney which converts angiotensinogen, encoded by *AGT*, to angiotensin I.[26] Angiotensin I is further cleaved by ACE to form the biologically active form, angiotensin II.[26] In the kidney, angiotensin II binds to the AT1 receptor encoded by the *AGTR1* gene. Activated AT1 receptor promotes the secretion of aldosterone which precipitates vasoconstriction in vascular cells and increased water reabsorption in the proximal tubules.[26] ACE inhibitors block the conversion of angiotensin I to the active form, angiotensin II, and disrupt the RAAS.[26] Thiazide diuretics inhibit Na^+ reabsorption in the renal distal tubule and reduce plasma volume.[27] SNP rs5051 is in the 5' untranslated region of *AGT*. Both SNPs rs275653 and rs6681776 are promoter variants located about 120 bp and 1.2 kb upstream of the transcription start sites of *AGTR1* and *REN*, respectively. Given the importance of this pathway for blood-pressure regulation, the mechanics of antihypertensive drug action, and the suggested associations reported in this study, pharmacogenetic studies of these genes and other genes belonging to RAAS continue to be warranted in AAs.

Our results also suggest that genes involved in coagulation (*F7* and *F13*) and tissue remodeling (*MMP3*) may be important for variation in blood pressure response to common antihypertensive treatments. Previous studies have highlighted *F7* as being associated with CVD outcomes. In particular, the minor allele at *F7* rs6046 has been linked with decreased risk of myocardial infarction, and coronary artery disease in Caucasian, Japanese, and Indian populations.[28–30] Additionally, the minor allele at *F7* rs6046 was reported to be associated with a 27% lower risk of incident ischemic stroke (HR=0.73, p= 0.002) among over 4000 Caucasians followed for up to 16 years.[31] Additionally, *MMP3* rs3025058 has been associated with myocardial infarction and stroke in the literature stroke.[32, 33]

Variants in *MMP3, F7* and *F13* are also biologically plausibly related to differences in blood pressure response to treatment.[34, 35] Specifically, *F7* encodes coagulation factor VII which is vitamin K-dependent and important for blood clotting. F7 is the initiator of the extrinsic (e.g. injury-induced) coagulation pathway. *F13* encodes the A1 subunit of the coagulation factor XIII which is the last factor in the blood clotting cascade. *MMP3* encodes matrix metalloproteinase-3, an extracellular protease which reduces the level of plasminogen, the initiator of the fibrinolysis cascade.[35] MMP3 can also cleave plasminogen activator inhibitor-1 (PAI-1) and α-2-antiplasmin (α-2-AP).[35] Interestingly, angiotensin II and aldosterone are known to increase the expression of PAI-1.[34]

Our study has several strengths. First, the GenHAT study is ancillary to the largest randomized controlled clinical trial (ALLHAT) of antihypertensive agents funded by the NIH to date. In the context of this rich data resource, we were able to accrue a sizable population of treatment naïve hypertensive subjects for this pharmacogenetic study, where the blood-pressure response was not affected by previous treatment. Additionally, our study investigated potential pharmacogenetic effects of four different antihypertensive drug classes, two of which had not been previously considered (doxazosin, and amlodipine) in this ethnic group. Importantly, GenHAT includes the largest number of African Americans

in a clinical trial of antihypertensive treatment to date that allowed us to focus this study on this historically underrepresented population.

Our study also has some limitations. First, ALLHAT recruited hypertensive patients aged 55 years and older with a large proportion affected with diabetes mellitus and/or at high risk of cardiovascular disease. Therefore, generalizing our findings to healthier and younger populations may not be valid. Second, the 57 SNPs examined do not fully cover the candidate genes considered in this study. Finally, our findings need to be replicated in an external population before any assessment of clinical utility can be made. However, at this time we are unable to identify an existing data set of African Americans with comparable genotype and phenotype data. With the increasing availability of genotype and phenotype data from publically available sources we hope that additional clinical trial and or electronic medical record linked genomic database studies will become available.

Given the significant burden of high blood pressure in this ethnic group and the availability of effective blood pressure lowering treatments, strategies to improve blood-pressure control among African Americans are needed. Genetic studies may prove useful for treatment optimization. In the current study, we report that *F7* rs6046, *F7* rs762637, *F13* rs5985, *MMP3* rs3025058 and variants in genes belonging to RAAS (*AGT* rs5051, *AGTR1* rs275653 and *REN* rs6681776) may modify SBP and DBP-response to common antihypertensive agents among African Americans. However, no variant was statistically significant given the large number of tests performed. Still our findings paired with evidence that this group has been underrepresented in the literature support continued research. Collaborations with other study populations and expansion into more comprehensive genomic coverage will be necessary to further discovery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This study was supported in part by grant HL63082 (GenHAT) from the NIH/NHLBI and grant N01-HC-35130 (ALLHAT) from the NIH/NHLBI.

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What is known about this topic

In the U.S, hypertension is most prevalent among African Americans.

Discovery of genetic variants could help predict blood-pressure response to pharmacological treatments and improve blood-pressure control for African-American hypertensive patients.

Previous pharmacogenetic studies of blood-pressure response to treatment in African Americans suffer limitations of small sample size as well as a limited number of candidate genes and often focused on only one antihypertensive treatment.

What this study adds

The study had the largest number of treatment-naive hypertensive African Americans to date.

The study investigated the pharmacogenetic effects of four different antihypertensvie drug classes, two of which have been understudied (doxazosin, and amplodipine) in African Americans.

The study suggested that *F7 rs6046, F7 rs762637, F13 rs5985, MMP3 rs3025058* and variants in genes belonging to the *RAAS (AGT rs5051, AGTR1 rs275653 and REN rs6681776)* may modify SBP and DBP-response to common antihypertensive agents among African Americans.

Table 1

Baseline characteristic for African-American treatment naive participants by treatment group (N=1,131)

	Chlorthalidone	Lisinopril	Amlodipine	Doxazosin	p-value
Sample size (n,%)	412 (36.4)	240 (21.2)	225 (19.9)	254 (22.5)	
AT BASELINE					
Age, mean (SD)	66.7 (8.7)	65.0 (8.1)	65.0 (7.5)	65.4 (8.1)	**0.02**
Women, n (%)	191 (46.4)	128 (53.3)	111 (49.3)	127 (50)	0.39
SBP in mmHg, mean (SD)	156.9 (12.2)	157.1 (13.4)	157.6 (12.9)	157.2 (13.2)	0.93
DBP in mmHg, mean (SD)	90.7 (9.6)	91.0 (9.3)	90.9 (10.1)	91.0 (9.5)	0.98
Eligibility risk factors:					
BMI, mean (SD), kg/m^2	29.1 (6.4)	30.1 (7.7)	29.5 (6.1)	29.2 (5.8)	0.22
Type 2 diabetes, n (%)	117 (28.4)	57 (23.8)	62 (27.6)	74 (29.1)	0.53
Current cigarette smoker, n (%)	149 (36.2)	91 (37.9)	83 (36.9)	86 (33.9)	0.95
HDL cholesterol <35 mg/dL, n (%)	16 (3.9)	14 (5.8)	9 (4.0)	7 (2.8)	0.38
LVH by electrocardiogram, n (%)	133 (32.3)	62 (25.8)	64 (28.4)	63 (24.8)	0.14
Fasting glucose, mg/dL	125.0 (72.2)	120.1 (60.3)	114.6 (49.0)	124.1 (64.7)	0.41
Total cholesterol, mg/dL	218.9 (50.2)	218.6 (44.2)	216.5 (47.0)	215.9 (41.8)	0.84
HDL cholesterol, mg/dL	52.9 (16.0)	51.5 (17.4)	52.2 (14.4)	52.7 (16.2)	0.75
LDL cholesterol, mg/dL	139.9 (45.4)	140.5 (39.1)	139.6 (42.2)	138.8 (38.0)	0.98
Fasting triglyceride, mg/dL	127.6 (88.3)	135.2 (134.2)	112.9 (69.7)	126.4 (78.2)	0.20
Glomerular filtration rate, mean (SD), mL/min/1.73 m^2	83.4 (22.2)	86.2 (20.8)	87.8 (22.2)	85.4 (19.5)	0.09
AT 6 MONTH VISIT					
SBP in mmHg, mean (SD)	137.1 (16.2)	141.0 (17.7)	141.0 (15.9)	142.3 (16.9)	**0.0003**
DBP in mmHg, mean (SD)	81.2 (10.7)	82.8 (10.4)	82.1 (10.0)	82.7 (11.3)	0.18
Adherence percentage, mean (SD)	69.0 (29.5)	65.0 (8.1)	68.3 (27.7)	64.3 (30.6)	0.20

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; LVH, left ventricular hypertrophy.

* test of differences between treatment groups: ANOVA for continuous variables, chi-square for categorical variables.

Table 2

A. Pharmacogenetic effect of genetic variants to diastolic blood-pressure response by treatment groups

	Estimated diastolic blood pressure response (mmHg)		
Variant	**Amlodipine (N=225)**	**Chlorthalidone (N=412)**	**p-value**
AGTR1 rs275653			
AA	−9.83	−8.69	0.02
AG	−7.95	−10.25	
GG *	−6.07	−11.81	
F7 rs6046			
GG	−9.70	−9.17	0.01
GA	−6.45	−10.55	
AA *	−3.20	−11.93	
Variant	Doxazosin (N=254)	Chlorthalidone (N=412)	p-value
F13 rs5985			
CC	−9.55	−9.52	0.03
CT	−5.96	−9.58	
TT *	−2.37	−9.64	
MMP3 rs3025058			
6A/6A	−7.05	−9.41	0.02
5A/6A	−11.82	−10.01	
5A/5A *	−16.59	−10.61	
REN rs6681776			
GG	−9.99	−9.53	0.007
GA	−5.85	−9.51	
AA *	−1.70	−9.49	

B. Pharmacogenetic effect of genetic variants to systolic blood-pressure response by treatment groups

	Estimated systolic blood pressure response (mmHg)		
Variant	**Lisinopril (N=240)**	**Chlorthalidone (N=412)**	**p-value**
AGT rs5051			
AA	−16.85	−19.1	0.04
AG	−13.84	−21.47	
GG *	−10.83	−23.84	
F7 rs762637			
GG	−14.67	−20.91	0.02
GA	−18.60	−18.29	

B. Pharmacogenetic effect of genetic variants to systolic blood-pressure response by treatment groups

	Estimated systolic blood pressure response (mmHg)		
Variant	**Lisinopril (N=240)**	**Chlorthalidone (N=412)**	**p-value**
AA *	−22.53	−15.67	
REN rs6681776			0.04
GG	−17.43	−19.63	
GA	−12.75	−20.62	
AA *	−8.07	−21.61	
Variant	Amlodipine (N=225)	Chlorthalidone (N=412)	p-value
F7 rs6046			
GG	−17.98	−19.65	
GA	−12.35	−20.19	0.03
AA *	−6.72	−20.73	
Variant	Doxazosin (N=254)	Chlorthalidone (N=412)	p-value
F7 rs762637			
GG	−13.54	−20.91	
GA	−17.38	−18.29	0.01
AA *	−21.22	−15.67	
REN rs6681776			
GG	−16.97	−19.63	
GA	−12.09	−20.62	0.02
AA *	−7.21	−21.61	

* Homozygous for minor allele