Personalized antihypertensive treatment guided by pharmacogenomics in China

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Background: The implementation of genotyping for anti-hypertensive drugs in clinical practice remains a challenge. We conducted this study to analyze the distribution of polymorphisms of antihypertensive drug-related genes in Changsha County in China and compare the clinical effectiveness of genotype-guided and clinical experience-guided antihypertensive therapy in hypertensive individuals.

Methods: A total of 9,933 essential hypertensive participants from Changsha County were consecutively enrolled in our study, and 7 genetic polymorphic loci (*CYP2D6*10*, *ADRB1*, *CYP2C9*3*, *AGTR1*, *ACE*, *CYP3A5*3* and *NPPA*) were detected by a polymerase chain reaction (PCR)-fluorescence probe. From an available sample of 660 hypertensive participants, 495 cases were randomly identified by genotype-guided therapy and 165 cases by clinical experience-guided therapy. We performed 24-hour ambulatory blood pressure (BP) monitoring on each of these cases, pre- and post-intervention.

Results: In the enrolled 9,933 cases, the mutation frequencies of *CYP2C9*3*, *ADRB1(1165G>C)*, *AGTR1(1166A>C)*, *CYP2D6*10*, *ACE(I/D)*, *CYP3A5*3* and *NPPA(2238T>C)* were 4.41%, 74.60%, 5.55%, 57.08%, 30.94%, 69.03% and 1.19%, respectively. In both genotype-guided and clinical experience-guided groups, the comparisons of intra-group pre-and post-treatments showed significant decreases in diastolic blood pressure (DBP) ($P<0.01$) and significant increases in the control rate of BP (47.1% *vs.* 38.6% and 37.5% *vs.* 33.9%, $P<0.05$) in response to adjusted antihypertensive agents. Correspondingly, the extent of the reduction of systolic blood pressure (SBP; 3.52±11.72 *vs.* 0.92±9.14 mmHg), the extent of the increase in the rate of BP control (8.5% *vs.* 3.6%) and the percentage rate of decrease of grades 2 and 3 hypertensive individuals were more significant in the genotype-guided group than that in the clinical experience-guided group ($P<0.01$).

Conclusions: While prescribing anti-hypertensive drugs, appropriate dosage and type adjustments should be made according to the gene mutation frequency and individual circumstances. Pharmacogenomics-guided personalized treatment of hypertensive patients is likely to be a more effective strategy, especially in those with significantly elevated SBP.

Keywords: Hypertension; genetic polymorphic loci; pharmacogenomics; personalized treatment; ambulatory blood pressure monitoring (ABPM)

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Introduction

Hypertension is a leading cause of disability and cardiovascular mortality. According to the *China Cardiovascular Disease Report 2018*, hypertension is highly prevalent among Chinese adults, occurring at a rate of 27.9% in the population of 245 million patients, with only 16.8% of patients achieving blood pressure (BP) control (1). Antihypertensive drugs have long been adopted as the main approaches for reducing BP to physiologically normal levels and preventing hypertension-associated target organ damage. Despite the availability of effective antihypertensive drugs, the rate of BP control remains poor due to multiple factors, including irrational prescription of antihypertensive drugs due to insufficient clinical experience and apparent drug resistance (2). Major evidence-based clinical guidelines fundamentally use a standard universal approach to prescribe antihypertensive drugs which, at the individual patient level, are not highly personalized. Clinical practices have shown the heterogeneity of patients' responses to antihypertensive drugs. Genetic polymorphisms and pharmacokinetic characteristics may partially account for the interindividual variability (3,4). Increasing evidence supports the establishment of personalized pharmacotherapeutic treatment based on a patient's genetic background. Personalized pharmacotherapy based on genetic information is therefore expected to become the principal mode of future antihypertensive treatment especially in non-responsive hypertensive patients, in order to distinguish which kind of antihypertensive drug will lower BP most effectively, including economically, for individual patients. To date, the genetic research of hypertension has mainly focused on the causal genes of hypertension and the mechanisms of BP elevation, such as the angiotensin converting enzyme insertion/deletion (*ACE I/D*) (5) polymorphisms and ATPase plasma membrane Ca^{2+} transporting 1 (*ATP2B1*) (6) polymorphisms which were discovered to be associated with high BP. However, there are no currently available clinical tests to guide the choice of antihypertensive drugs, and the association between gene polymorphisms and increased responsiveness to antihypertensive drugs, including angiotensin I-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta blockers, calcium channel blockers (CCBs) and diuretics remains controversial (7). Thus, our study analyzed the distribution of antihypertensive drug-related gene polymorphisms, in the Changsha county of Hunan

province. A polymerase chain reaction (PCR)-fluorescence probe was used to detect the 7 genetic polymorphic loci (*CYP2D6*10*, *ADRB1*, *CYP2C9*3*, *AGTR1*, *ACE*, *CYP3A5*3* and *NPPA*) associated with the effect of antihypertensive drugs, and then the antihypertensive drug doses and type were adjusted based on the gene phenotype and pharmacokinetic characteristics of different patients or based on the clinical experience of the designated doctor. By comparing the difference of curative effect between these 2 groups, we aimed to investigate the value of genotype-based prescribing in clinical antihypertensive therapy, and to provide a potential approach to the personalized management of hypertension.

Methods

Participants

A total amount of 9,933 hypertensive patients aged from 26 to 96 years registered in township hospitals and street health service centers from 2017 to 2018 in the Changsha County of Hunan province were enrolled by the study's investigators, with the patients' written informed consent. The participants comprised 4,015 males and 5,918 females of average age 64.16±8.76 years. The eligibility criteria comprised all of the following: (I) people aged >18 years old, (II) a diagnosis of chronic hypertension (treated or untreated), and (III) according to the *Revised Guidelines for the Prevention and Treatment of Hypertension in China 2010*, having a systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg three times on different days (8). The exclusive criteria included any 1 of the following: (I) secondary hypertension, (II) acute cardiovascular and cerebrovascular events within the previous 3 months, and (III) severe cardiomyopathy, rheumatic heart disease, congenital heart disease, or severe liver and kidney dysfunction. Then, 660 patients with hypertension were recruited from 20 township hospitals and street health service centers using a multistage cluster sampling design and were randomly divided into 2 groups at a ratio of 3:1. The experimental group received antihypertensive drug therapy adjusted according to the gene detection, and the control group received antihypertensive drug therapy according to evidence-based medicine. In the end, 16 patients were lost to follow-up, leaving 484 cases in the experimental group and 160 cases in the control group.
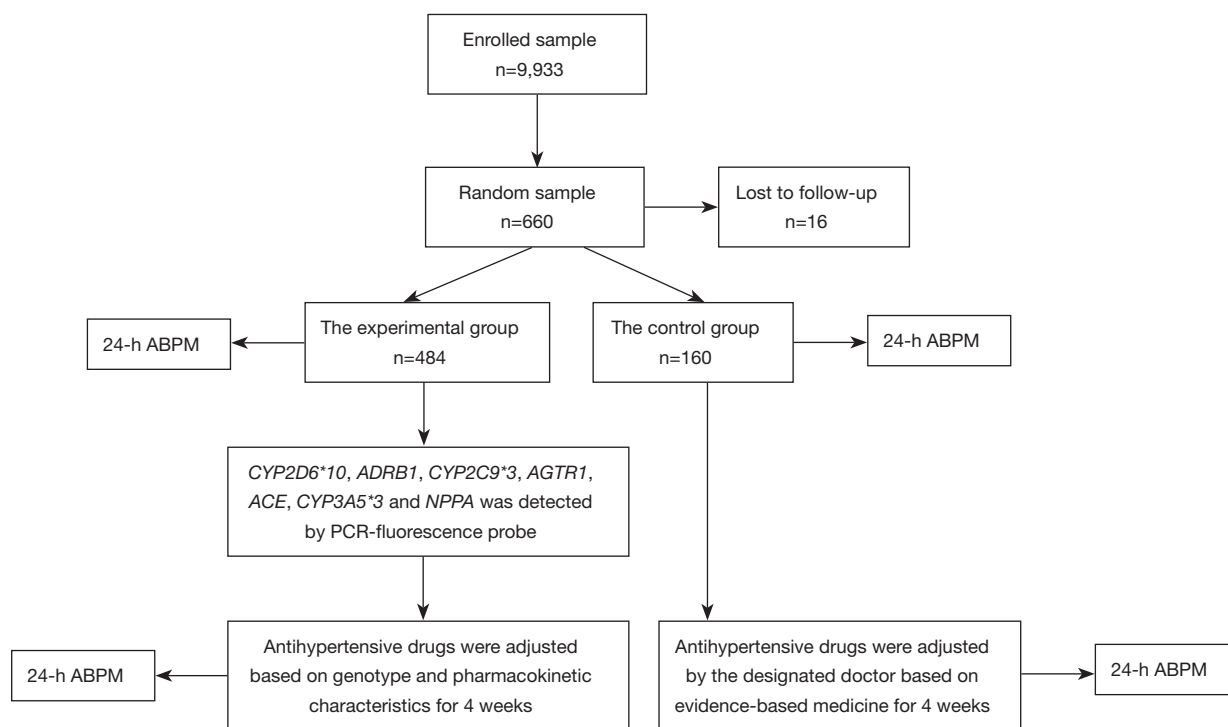
Figure 1 Flow diagram of the study. ABPM, ambulatory blood pressure monitoring; PCR, polymerase chain reaction.

Clinical data collection

Gene samples were collected from the oral mucosa of the 9,933 hypertensive patients, and PCR-fluorescence probe technology was used to detect the 7 genetic polymorphic loci (*CYP2D6*10*, *ADRB1*, *CYP2C9*3*, *AGTR1*, *ACE*, *CYP3A5*3* and *NPPA*) related to the metabolism, transport and target of 5 main kinds of antihypertensive drugs, including ACEIs, ARBs, beta blockers, CCBs and diuretics, which determined the patient's response to antihypertensives. According to the gene phenotype and pharmacokinetic characteristics of different individuals, the most sensitive antihypertensive drugs with the least adverse effects were prescribed in a single-dose regime or combination therapy to the experimental group for 4 weeks, and the dosage adjustment of antihypertensives was based on the following principles: doubling the standard dose when the hypertension was moderately sensitive to certain antihypertensive drugs, and using the minimum dose to start treatment when the hypertension was highly sensitive to certain antihypertensive drugs (as shown in Table S1). In the control group, treatment was prescribed by the designated doctor based on the *Revised Guidelines for the Prevention and Treatment of Hypertension in China 2010* (as

shown in Table S2) for 4 weeks. Several adverse events were reported during the whole process, including mild ankle edema in 5 patients and fatigue in 6 patients. However, the side effects of the antihypertensive drugs disappeared after adjustment of medications and did not cause any cases to withdraw from the study. We used 24-hour ambulatory blood pressure monitoring (ABPM) to assess the BP level of both groups, pre- and post-intervention. The BP treatment target was 24-hour mean BP <130/80 mmHg, daytime mean BP <135/85 mmHg and night mean BP <120/70 mmHg, in accordance with recommendation from the American Heart Association guidelines (9) (*Figure 1*).

24-hour ABPM

Validated 24-hour ABPM (Oscar2; SunTech Medical, Inc., Morrisville, NC, USA) was applied to measure ambulatory BP through a routine day. All individuals were taught to accurately record the time when waking, going to bed, taking medicine and engaging in other activities. Measurements were taken every 30 minutes during the daytime and every 60 minutes during the night-time. Valid recordings were of at least 20 hours duration and a

Table 1 The distribution of polymorphisms of antihypertensive drug-related gene in 9,933 patients

	WW	WM	MM	W (%)	M (%)
CYP2D6*10	2,127	4,259	3,532	42.92	57.08
ADRB1(1165G>C)	640	3,765	5,528	25.4	74.6
CYP2C9*3	9,083	823	27	95.59	4.41
AGTR1(1166A>C)	8,891	977	63	94.45	5.55
ACE(I/D)	4,763	4,193	976	69.06	30.94
CYP3A5*3	962	4,228	4,742	30.97	69.03
NPPA(2238T>C)	9,739	149	44	98.81	1.19

WW, homozygous wildtype; WM, heterozygous mutant; MM, homozygous mutant; W, wild type; M, mutant.

minimum of 70% of the expected 24-hour readings were required to be valid. Means of 24-hour, daytime and night-time ambulatory SBP and DBP were calculated (10).

Statistical analysis

The frequency of each locus was calculated by the frequency counting method and confirmed by the Hardy-Weinberg equilibrium fit test. Quantitative data were expressed as the mean ± standard error ($\bar{x} \pm s$), differences between groups were compared using the independent-sample t-test, and pre- and post-treatment intra-group differences were compared using the paired t-test. Enumeration data were expressed as percentage (%), and the comparison between pre- and post-treatment intra-group was performed by the paired χ^2 test, comparison between groups was performed by the χ^2 test. A value of P<0.05 was considered statistically significant. According to the sample size and BP control rate of the 2 groups, the power calculation that determined the study design was 1, which meant that if there was any difference in the rate of BP control between the 2 group, we were 100% confident of finding it. The software SPSS 22.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analysis.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Board of Xiangya Hospital of Central South University (No. 20170124028) and informed consent was taken from all individual participants.

Results

The frequency distribution of each gene locus

Among the 7 genetic polymorphic loci related to the efficacy of 5 main kinds of antihypertensive drugs, CYP2D6*10 and ADRB1(1165G>C) were related to the beta blocker, CYP2C9*3 and AGTR1(1166A>C) were related to the ARBs, ACE(I/D) was related to the ACEIs, and CYP3A5*3 and NPPA(2238T>C) were related to the CCBs and diuretics, respectively. The distribution of these 7 genetic polymorphic loci from 9,933 cases in Changsha County is shown in *Table 1*. There were no significant differences between genders in the mutation rates of the 7 gene loci (*Table 2*; P>0.05). Similarly, there was no significant correlation between genotype and body mass index (BMI), SBP, DBP, and family history of hypertension (*Table 3*; P>0.05). There was a failure to detect certain loci in several samples, probably due to other types of gene mutation carried in these samples.

Baseline characteristics

A total of 660 patients with hypertension were divided into 2 groups: the experimental group consisted of 225 males with an average age of 54.8±7.0 years and 270 females with an average age of 55.0±8.7 years; the control group consisted of 81 males with an average age of 55.3±8.9 years and 84 females with an average age of 56.1±9.5 years. A total of 16 participants were lost to follow-up due to lack of adherence and were excluded from the analysis. Groups were similar for baseline characteristics in terms of age, gender, weight, smoking, blood sugar,

Table 2 Comparison of gene mutation rates between different gender

Gene loci	Male (n=4,015)		Female (n=5,918)		χ²	P
	W (%)	M (%)	W (%)	M (%)		
CYP2C9*3	95.88	4.12	95.39	4.61	0.029	0.865
ADRB1(1165G>C)	24.62	75.38	25.92	74.08	0.045	0.832
AGTR1(1166A>C)	94.60	5.40	94.35	5.65	0.006	0.938
CYP2D6*10	42.11	57.89	43.47	56.53	0.038	0.746
ACE(I/D)	69.03	30.97	69.09	30.91	0.001	0.993
NPPA(2238T>C)	98.89	1.11	98.75	1.25	0.008	0.927
CYP3A5*3	31.16	68.84	30.84	69.16	0.002	0.961

W, wild type; M, mutant.

blood lipids, liver function, kidney function and rate of BP control, but the SBP in the experimental group was slightly higher than that in the control group (*Table 4*; P<0.05).

Analysis of clinical efficacy in pre- and post-treatment groups

In the experimental group and the control group, significant decreases in diastolic pressure (88.51±11.32 mmHg *vs.* 90.95±11.70 mmHg and 86.79±8.46 mmHg *vs.* 88.35±8.55 mmHg, respectively; P<0.01) were observed in response to adjusted antihypertensive agents. Correspondingly, in the genotype-guided group, an overall treatment effect of 3.52±11.72 mmHg in systolic pressure was observed, with pre- and postintervention values of 137.92±13.12 and 134.40±11.37 mmHg (P<0.01), respectively, with no significant difference in the reduction of systolic pressure observed in the clinical experience-guided group (P>0.05; *Table 5*). Pre- and post-treatment intra-group comparisons showed significant increases in the rate of BP control (47.1% *vs.* 38.6% and 37.5% *vs.* 33.9%, respectively; P<0.05; *Table 6*). In the experimental group, there was no significant difference in the number of patients with grade 1of BP before and after treatment, but the number of patients with grade 2 and grade 3 of BP decreased significantly after treatment (P<0.01). No significant decrease in the number of people with a different grade of hypertension was observed in the control group (*Table 7*).

Analysis of clinical efficacy between the 2 groups post-treatment

After 4 weeks of adjusted antihypertensive therapy, the comparisons between the 2 groups showed a significant reduction in systolic pressure (3.52±11.72 *vs.* 0.92±9.14 mmHg, respectively; P<0.01), whereas the reduction of diastolic pressure was not statistically significant (2.44±11.78 *vs.* 1.56±8.50 mmHg, respectively; P>0.05; *Table 5*). The increased rate of BP control and the decreased percentage of people with grade 2 and grade 3 hypertension in the experimental group was more significant than that in the control group (8.5% *vs.* 3.6%, 6.7% *vs.* 1.4% and 3.0% *vs.* 0.5%, respectively; P<0.01; *Tables 6,7*).

Discussion

Up to now, the choices of antihypertensive drugs have been based on clinical experience and relevant hypertension guidelines. A lack of expert consensus and guidelines on dosing, antihypertensive drug validity, and side effects as well as balancing clinical benefit with cost remain crucial challenges in antihypertensive therapy (11). How to prescribe the most effective antihypertensive drugs with the least amount of side effects for each hypertensive patient is a major issue for clinicians. It has been found that the heterogeneity of patients' responses to antihypertensive drugs is, to a large extent, genetically determined (12-14). However, personalized pharmacotherapy based

Table 3 Correlation between genotype and clinical features

Gene loci	Genotype	BMI (kg/m^2)	SBP (mmHg)	DBP (mmHg)	Family history of hypertension (n)
CYP2C9*3	WW	23.90±3.19	138.77±12.32	84.11±6.96	1,029
	WM	23.98±3.03	138.95±12.82	84.41±7.21	86
	MM	23.47±2.76	138.74±11.45	83.74±6.42	3
	F/χ^2	0.453	0.073	0.722	0.585
	P	0.636	0.929	0.486	0.747
ADRB1(1165G>C)	WW	23.91±3.16	138.98±12.84	83.97±7.09	79
	WM	23.94±3.21	138.96±12.43	84.08±7.06	411
	MM	23.89±3.14	138.65±12.25	84.20±6.91	628
	F/χ^2	0.372	0.765	0.550	1.253
	P	0.689	0.465	0.577	0.534
AGTR1(1166A>C)	WW	23.92±3.19	138.73±12.26	84.16±6.96	1,017
	WM	23.76±2.96	139.17±13.13	83.86±7.13	98
	MM	24.28±3.20	140.37±14.15	85.16±7.61	3
	F/χ^2	1.521	1.049	1.441	4.424
	P	0.219	0.350	0.237	0.109
CYP2D6*10	WW	23.90±3.27	138.81±12.78	84.13±6.88	234
	WM	23.93±3.14	138.80±12.25	84.26±6.97	478
	MM	23.90±3.15	138.78±12.24	84.02±7.06	406
	F/χ^2	0.140	0.004	1.102	0.341
	P	0.870	0.996	0.332	0.843
ACE(I/D)	WW	23.93±3.23	138.83±12.34	84.19±6.93	568
	WM	23.90±3.12	138.76±12.31	84.10±7.03	448
	MM	23.84±3.11	138.71±12.67	84.05±7.01	102
	F/χ^2	0.355	0.053	0.264	4.140
	P	0.701	0.949	0.768	0.126
NPPA(2238T>C)	WW	23.90±3.17	138.78±12.37	84.13±6.98	1,106
	WM	24.18±3.61	139.52±11.36	84.65±7.10	9
	MM	24.20±2.80	136.08±14.32	83.28±7.83	3
	F/χ^2	0.740	0.850	0.581	5.023
	P	0.477	0.427	0.560	0.081
CYP3A5*3	WW	23.82±3.18	138.74±11.86	83.79±6.45	116
	WM	23.85±3.16	138.80±12.50	84.09±6.99	474
	MM	23.98±3.18	138.79±12.33	84.25±7.08	528
	F/χ^2	2.119	0.011	1.819	0.698
	P	0.120	0.989	0.162	0.705

WW, homozygous wildtype; WM, heterozygous mutant; MM, homozygous mutant; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 4 Comparison of baseline data between two groups

	Experimental group (n=495)	Control group (n=165)	P
Age (y)	54.90±8.04	55.71±7.11	0.118
Gender (M/F)	225/270	81/84	0.225
Weight (kg)	62.56±9.24	64.12±10.08	0.143
Smoking (n)	202	53	0.134
FBS (mmol/L)	5.43±1.05	5.60±2.31	0.090
TC (mmol/L)	4.47±0.90	4.28±1.27	0.416
TG (mmol/L)	1.66±1.68	1.66±1.04	0.990
LDL-C (mmol/L)	3.02±0.99	2.90±1.20	0.572
BUN (mmol/L)	5.95±1.79	5.92±2.10	0.941
Scr (µmol/L)	83.59±23.55	91.58±45.62	0.323
SUA (mmol/L)	369.10±114.17	364.89±95.58	0.823
ALT (U/L)	32.56±0.83	29.88±1.53	0.092
SBP (mmHg)	137.92±13.12*	133.12±9.94	0.027
DBP (mmHg)	90.95±11.70	88.35±8.55	0.173
BP control rate (%)	38.6±6.5	33.9±4.9	0.115

*, compared with the control group, $P<0.05$. FBS, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; BUN, serum urea nitrogen; Scr, serum creatinine; SUA, serum uric acid; ALT, alanine aminotransferase; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 5 Effect of adjusted treatment on BP in each group

Groups	n	SBP (mmHg)	DBP (mmHg)
Experimental group			
Pre-	495	137.92±13.12	90.95±11.70
Post-	484	134.40±11.37**	88.51±11.32**
D-value	8	3.52±11.72[#]	2.44±11.78
Control group			
Pre-	165	133.12±9.94	88.35±8.55
Post-	160	132.20±8.76	86.79±8.46**
D-value	6	0.92±9.14	1.56±8.50

**, comparisons of intra-group pre- and post-treatment, $P<0.01$. [#], comparisons between two groups post-treatment, $P<0.01$. BP, blood pressure; SBP, mean values of 24-h systolic blood pressure; DBP, mean values of 24-h diastolic blood pressure.

on genetic information has not yet been established in the field of hypertension research. To our knowledge, this was the first study to compare the value of genotype-based prescribing and clinical experience-based prescribing in antihypertensive therapy. Several hypertension studies have focused on the association between genetic polymorphic loci and the effect of different antihypertensive drugs, particularly diuretics and beta blocker (2,7). Patients with the *NPPA T2238C* gene mutation were more sensitive to diuretics and experienced a better therapeutic effect when treated with diuretics than other hypertensive patients (15). A genome-wide association study (GWAS)

Table 6 Effect of adjusted treatment on the rate of BP control in each group

Groups	Controlled (n)	Uncontrolled (n)	Totaled (n)	Rate of BP control	Δ
Experimental group					
Pre-	191	304	495	38.6%	
Post-	228	256	484	47.1%*	8.5%#
Control group					
Pre-	56	109	165	33.9%	
Post-	60	100	160	37.5%*	3.6%

*, comparisons of intra-group pre- and post-treatment, P<0.05. #, comparisons between groups post-treatment, P<0.01. BP, mean values of 24-h blood pressure.

Table 7 Effect of adjusted treatment on BP grade in two groups

Groups	n	Grade of BP	Pre- (n/%)	Post- (n/%)	Δ
Experimental group					
Pre-	495	Grade 1	210/42.4	211/43.6	1.2%
Post-	484	Grade 2	75/15.2	41/8.5**	6.7%#
		Grade 3	19/3.8	4/0.8**	3.0%#
Control group					
Pre-	165	Grade 1	79/47.9	74/46.3	1.6%
Post-	160	Grade 2	25/15.2	22/13.8	1.4%
		Grade 3	5/3.0	4/2.5	0.5%

**, comparisons of intra-group pre- and post-treatment, P<0.01. #, comparisons between two groups post-treatment, P<0.01. BP, mean values of 24-h blood pressure.

involving over 60,000 cases identified polymorphisms of *ADRB1* and *CYP2D6* associated with hypertension and the response to beta blockers, and the most common gene mutations of *ADRB1* and *CYP2D6* in the Asian population are *G1165C* and *CYP2D6*10*, respectively (16,17). The CCBs were mainly metabolized by *CYP3A4* and *CYP3A5* enzymes, and the polymorphic *CYP3A5* genotypes have been shown to cause a different response to CCBs, such as amlodipine (18). Most data are highly conflicting such that no candidate gene shows a positive association with responses to ACEI and ARBs (19). However, genes encoding key enzymes that are involved in the metabolism, transport and targets of drugs have provided a basis for pharmacogenomics, which may also contribute to BP control in humans. For example, losartan is biotransformed into its active metabolite, EXP-3174, mediated by the metabolizing enzyme, *CYP2C9*. A relationship between *CYP2C9* polymorphisms and the pharmacokinetics of ARBs have also been observed,

although the clinical impact in terms of BP was modest (20). It has been shown that *AGTR1* mediates the function of ARBs by association with G proteins that activate a phosphatidylinositol-calcium second messenger system (21). Further, ACE is a key enzyme in the enzyme/substrate cascade reaction of RAS, the polymorphism of which has been associated with the activity of ACE (3). Among the polymorphic ACE genotypes, the DD genotype has the highest level of activity, and II genotype has the lowest level of activity, with the level of activity of the ID genotype sitting in the middle. The higher activity of ACE has, the more significant antihypertensive role ACEI plays (22).

Based on the above, we performed PCR-fluorescence probe technology to detect the distribution frequency of these genetic polymorphic loci from 9,933 patients with hypertension in the Changsha County of Hunan province, and found that the mutation frequencies of *CYP2C9*3*, *AGTR1(1166A>C)*, *ADRB1(1165G>C)*, *CYP2D6*10*, *ACE(I/*

D), *CYP3A5*3* and *NPPA(2238T>C)* were 4.41%, 5.55%, 74.60%, 57.08%, 30.94%, 69.03% and 1.19%, respectively. It has been shown that the mutation of these 7 genes could decrease enzyme activity, slow down the drug metabolism and increase blood drug concentration, increasing the sensitivity to drugs (15,22-25). Our results suggested that a large group of hypertensive patients seem to exhibit more sensitivity to beta blockers and CCBs, poor sensitivity to diuretics, and normal sensitivity to ARB and ACEI. While prescribing the above drugs, appropriate dosage adjustment should be made according to the gene mutation frequency associated with responses to anti-hypertensive drugs and individual circumstances.

The 24-hour ABPM has been widely used as the most informative measurement of BP behavior because it can more accurately and comprehensively reflect a patient's overall BP. Recently, ABPM was recommended in English, Canadian and American guidelines (9,26,27) for diagnosing hypertension, especially for identifying white-coat and masked hypertension, determining the efficacy of treatment, and assessing the long-term control of hypertension (28,29). It has been shown that clinical BP monitoring alone is inadequate for optimizing BP control because of BP variability, and ABPM should be used more routinely to confirm BP control (30). Besides, ABPM is a stronger predictor of all-cause and cardiovascular mortality than clinical BP monitoring (31). The 2017 AHA Hypertension Guidelines pointed out that the evaluation of antihypertensive efficacy should be carried out at least 2 weeks after drugs adjustment (13). Therefore, we used ABPM to detect the patients' responses to adjusted antihypertensive drugs, and a mean 24-hour SBP of ≤130 mmHg and a 24-hour DBP of ≤80 mmHg was considered the standard.

According to the results of gene detection (as shown in Table S1), the most sensitive antihypertensive drugs with the least adverse effects were prescribed to each patient in the experimental group. If a patient's genotype was *ADRB1(1165C/C)*, which is highly sensitive to beta blocker, a beta-blocker was the preferred drug and a starting minimum dose was deemed appropriate. On the contrary, if a patient's genotype is determined as *ADRB1(1165G/G)*, which is insensitive to beta blocker, a beta-blocker should not be prescribed for antihypertensive therapy. For example, the genetic polymorphic loci associated with the effect of antihypertensive drugs of case 36 was *CYP2C9*1/*1*, *AGTR1(1166A/A)*, *ADRB1(1165C/C)*, *CYP2D6*1/*1*, *ACE(I/D)*, *CYP3A5*3/*3* and *NPPA(2238T/T)*, which showed high sensitivity to CCBs and beta blocker, middle sensitivity to ARB, ACEI and diuretics. The 24-hour mean BP of this patient with a long-term use of indapamide (diuretics) as antihypertensive drug was 151/79 mmHg. Considering the antihypertensive effect of diuretics was relatively weak, therefore, indapamide was adjusted to L-amlodipine (CCB) for this patient. After 4 weeks, the 24-hour mean BP was decreased to 136/82 mmHg (up to standard). Additionally, the treatment was prescribed by the designated doctor based on the *Revised Guidelines for the Prevention and Treatment of Hypertension in China 2010* in the control group. As the prescription of the control group was affected by the doctor's clinical experience and medication preference, in order to reduce the risk of antihypertensive drugs and high test costs, the allocation ratio of the experiment group to the control group was set at 3:1. After 4 weeks of adjusted antihypertensive therapy, significant decreases in DBP were observed in both groups, while a significant difference in SBP reduction was observed in the experimental group but not in the control group. The reason for this may be that the failure to reach the standard in the control group was mainly due to high DBP, while antihypertensive drugs adjusted according to clinical experience mainly reduced DBP, hence there was no significant difference in the reduction of SBP. In addition, a significant increase in the rate of BP control was observed in both groups, and the increase of BP control rate in the experimental group was more significant than that in the control group. Only in the experimental group the number of patients with grade 2 and grade 3 of BP decreased significantly after treatment. These results indicated that genotype-guided, personalized treatment is more likely to be effective in hypertensive patients, especially in those with significantly elevated SBP.

In clinical practice, high SBP, low DBP and large pulse pressure are the characteristics of elderly patients with hypertension, and systolic pressure is independently related to cardiovascular and cerebrovascular events (32); therefore, the genotype-guided antihypertensive therapy can not only provide a new scientific basis for clinically individualized medication but also significantly reduce the side effects of antihypertensive drugs. It is also expected that genotype-guided antihypertensive therapy will reduce the incidence of hypertensive complications by reducing SBP, and ultimately reduce the economic burden on patients and society, which is worthy of application and promotion in clinical work. Notably, due to the short observation time of only 4 weeks, more clinical benefits of gene-guided

individualized therapy may need to be determined by extending the observation time, expanding the sample size and using more AMBP indexes such as BP variability and circadian BP rhythm. Furthermore, the different treatments in the control group were based on age and other individual circumstances, whereas in the experimental group, prescription was exclusively based on genotype. Therefore, the analysis of curative effects should be according to age stratification in consideration of the wide age range of participants. In addition, the kinds and doses of antihypertensive drugs prescribed based on the gene phenotype and pharmacokinetic characteristics or evidence-based medicine were different between different individuals, so data on antihypertensive medication in the 2 groups were not presented. Further research will focus on the efficacy of gene-guided clinical medication in patients with very high BP, such as refractory hypertension, or on the efficacy and adverse outcomes of a specific antihypertensive drug under the guidance of genotyping for individual patients.

Acknowledgments

Footnote

Data Sharing Statement: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-22-154/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-22-154/coif). MFC reports that the study materials of this manuscript were provided by Changsha County Government. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Board of Xiangya Hospital of Central South University (No.

20170124028) and informed consent was taken from all individual participants.

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Table S1 Genotyping of gene loci and its clinical significance

Gene loci	Genotype	Phenotype	Dose recommendations	Drug types	Representative drugs
CYP2C9*3	*1/*1	Strong metabolism	Standard dose	Angiotensin II receptor blocker	Losartan (adverse); telmisartan; candesartan; valsartan; irbesartan
	*1/*3	Normal metabolism	A lower dose		
	*3/*3	Weak metabolism	Very low dose		
AGTR1(1166A>C)	1166A/A	Normal sensitivity	Standard dose	–	Losartan; telmisartan; candesartan; valsartan; irbesartan
	1166A/C	Decreased sensitivity	Slightly higher dose		
	1166C/C	Very low sensitivity	High dose or other drugs		
ADRB1(1165G>C)	1165G/G	Decreased sensitivity	High dose or other drugs	β adrenergic receptor blocker	Metoprolol; carvedilol; atenolol; bisoprolol; labetalol
	1165G/C	Normal sensitivity	Standard dose		
	1165C/C	Increased sensitivity	A lower dose		
CYP2D6*10	*1/*1	Strong metabolism	Standard dose or high dose	–	Metoprolol; carvedilol; atenolol; bisoprolol; labetalol
	*1/*10	Normal metabolism	Standard dose		
	*10/*10	Weak metabolism	A lower dose		
ACE(I/D)	I/I	Decreased enzyme activity	Enalapril and imidapril	Angiotensin converting enzyme inhibitors	Benazepril; fosinopril; enalapril; perindopril; ramipril
	I/D	Normal enzyme activity	Applicable to all ACEI		
	D/D	Increased enzyme activity	Benazepril and fosinopril		
NPPA(2238T>C)	T/T	Normal sensitivity	Standard dose	Diuretic	Chlorothiazide; hydrochlorothiazide; chlortalidone
	T/C	Slightly higher sensitivity	A lower dose		
	C/C	High sensitivity	Very low dose		
CYP3A5*3	*1/*1	Normal metabolism	Standard dose	Calcium channel blockers	Nifedipine; felodipine; lacidipine; amlodipine; benidipine
	*1/*3	Slightly lower metabolism	A lower dose		
	*3/*3	Weak metabolism	Very low dose		

Table S2 Antihypertensive drugs used in the control group

Drug types	Prescribed drugs
Angiotensin II receptor blocker	Telmisartan; valsartan
β-adrenergic receptor blocker	Metoprolol
Angiotensin converting enzyme inhibitors	Captopril; enalapril
Diuretic	Indapamide
Calcium channel blockers	Nitrendipine; amlodipine; extended release nifedipine
Others	Beijing hypotensive No. 0; Zhenju Jiangya tablet; compound kendir leaves tablets; reserpine