Predictors of Antihypertensive Drug Responses: Initial Data from a Placebo-Controlled, Randomized, Cross-Over Study With Four Antihypertensive Drugs (The GENRES Study)

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Background: Only a minority of hypertensive individuals is adequately controlled for their hypertension, partially because reliable predictors for efficient antihypertensive drug therapy are lacking.

Methods: In a prospective, randomized, double-blind, cross-over, placebo-controlled study (The GENRES Study), 208 moderately hypertensive Finnish men (aged 35 to 60 years) were treated for 4 weeks with antihypertensive drugs from four different classes: amlodipine (5 mg), bisoprolol (5 mg), hydrochlorothiazide (25 mg), or losartan (50 mg) daily. Each individual received each of the four monotherapies in a randomized order. Four-week placebo periods were included before and between drug treatment periods. Antihypertensive responses were assessed with 24-h ambulatory and office measurements and analyzed according to age, body mass index, triceps skin fold thickness, waist-to-hip ratio, duration of hypertension, number of previous antihypertensive drugs, number of affected parents, and blood pressure (BP) levels, and profiles during placebo periods.

Results: The median BP responses in 24-h ambulatory recordings (systolic/diastolic) were 11/8 mm Hg for bisoprolol, 9/6 mm Hg for losartan, 7/5 mm Hg for amlodipine, and 5/2 mm Hg for hydrochlorothiazide. The highest pairwise within-subject correlations in BP responses were seen for the combinations of bisoprolol–losartan and amlodipine–hydrochlorothiazide. The BP responses to bisoprolol and losartan did not vary according to the variables. Amlodipine and hydrochlorothiazide responses were positively correlated with age, placebo BP level, and lower night-time dipping on placebo.

Conclusions: Baseline clinical and BP parameters may be used to predict the efficacy of antihypertensive therapies. The GENRES Study material should provide an excellent platform for future pharmacogenetic analyses of antihypertensive drug responsiveness. Am J Hypertens 2007;20:311–318 © 2007 American Journal of Hypertension, Ltd.

Key Words: Hypertension, drug therapy, pharmacogenetics, blood pressure determination.

Risk of cardiovascular and kidney disease associated with hypertension can be alleviated by effective antihypertensive drug therapy.[1] However, less than a third of hypertensive individuals are adequately controlled for their hypertension.[2] In selected cases, clinical algorithms based on the estimation of comorbidity[1] or clinical chemical variables such as plasma renin levels[3] may be helpful for individualization of drug treatment. Molecular genetic analyses are highly accurate to predict tailored drug treatments for specific forms of monogenic hypertension, but until now their performance in guiding the choice of antihypertensive drug treatment in essential hypertension has been disappointing (for recent reviews, Koopmans et al,[4] Turner et al,[5] Mellen and Herrington,[6]

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and Kurland et al[7]). Many individual studies have suffered from significant flaws, such as retrospective study design, small studies with typically less than 100 individuals, lack of randomization, and lack of cross-over comparisons.[4,7]

The GENRES (a randomised double-blind cross-over single-centre placebo-controlled study on molecular GENetics of drug RESponsiveness in essential hypertension) study is the first randomized, double-blind, cross-over single-center study targeted toward molecular genetic prediction of drug responsiveness in essential hypertension. Its aim is to relate the blood pressure (BP)-lowering effects of four different classes of antihypertensive drugs to the genetic variation of the patients. As an initial report of the GENRES study, we describe the general design of the study as well as selected clinical correlates of the individual drug responses.

Methods

Study Design

The clinical part of the GENRES study was conducted in accordance with the Declaration of Helsinki and Guidelines for Good Clinical Practice (1996) at Helsinki University Central Hospital between years 1999 and 2004. The study was approved by the Ethical Committee of Helsinki University Central Hospital and the National Agency for Medicines of Finland. All subjects gave signed informed consent before any study-related activities.

The GENRES study is a randomized, double-blind, placebo-controlled, cross-over study (Fig. 1). The study started with a 4-week run-in placebo period, before which the subjects discontinued their previous antihypertensive medications, if they were on medication. During the 4-week treatment periods, the subjects used one of four antihypertensive drugs in a randomized order. Thus, each individual underwent four separate monotherapy periods. The treatment periods were separated by placebo periods. Randomization to all possible 24 drug sequences was done after the first placebo period in blocks of 24.

The four antihypertensive drugs included in the study were a thiazide diuretic (25 mg of oral hydrochlorothiazide; Hydrex semi, Orion Pharma, Espoo, Finland), a β-adrenergic antagonist (5 mg of oral bisoprolol; Emconcor, Merck KGaA, Darmstadt, Germany), an angiotensin II receptor antagonist (50 mg of oral losartan; Cozaar, Merck & Co., Whitehouse Station, NJ), and a calcium channel blocker (5 mg of oral amlodipine; Norvasc, Pfizer, New York, NY). An oral placebo was also used. All preparations were packed in identical gelatin capsules, which were taken between 6 and 9 AM.

Study Population

The number of subjects to complete the study was intended to be 192. At a significance level of .05, the study was calculated to have sufficient power (>90%) to detect a genotype-related difference of 4.5 mm Hg in the antihypertensive effect if the SD of the response is 6.5 to 9 mm Hg[8,9] and the rare allele frequency is 5% or higher.

White men aged 35 to 60 years were included in the study based on the following criteria: the subject was on antihypertensive medication, or three diastolic BP readings ≥95 mm Hg on separate occasions had been measured. Exclusion criteria included treatment with three or more antihypertensive drugs, secondary hypertension, drug-treated diabetes mellitus, congestive heart failure, coronary heart disease, cerebrovascular disease, kidney disease (serum creatinine >115 μmol/L), obstructive pulmonary disease, a disease treated with corticosteroids, clinically significant liver disease, abuse of drugs or alcohol, and body mass index (BMI) ≥32 kg/m^2. During the study, the subject was withdrawn if an exclusion criterion was met, if the BP level increased to ≥200/120 mm Hg or if noncompliance was recorded, defined as uncooperation or underuse of drug/placebo capsules (consumption of <80% of the expected amount). The withdrawn subjects were included in the analysis of treatments they had completed. To compensate for the withdrawals, new subjects were recruited for the study.

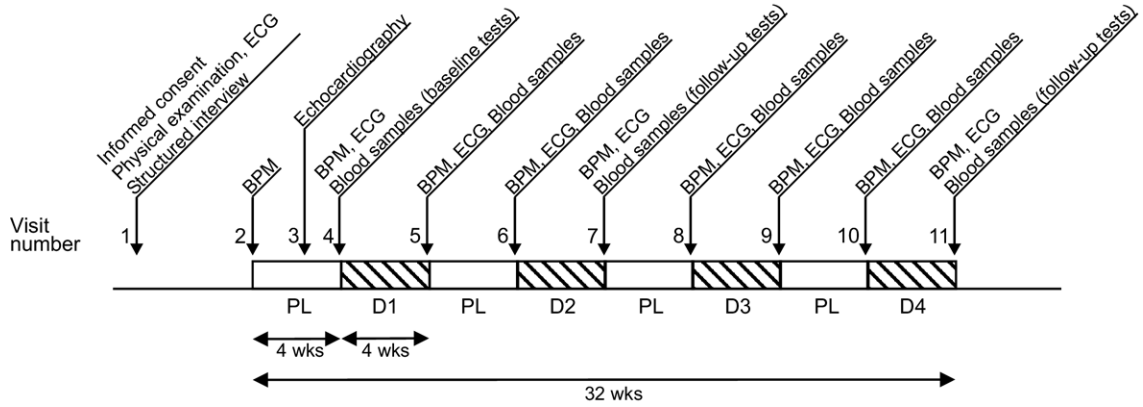

FIG. 1. Study design. BP = blood pressure; BPM = blood pressure measurements; ECG = electrocardiography; D1–D4 = drug periods 1–4; PL = placebo.

Blood Pressure Measurements

The BP measurements were carried out before the first placebo period and after each treatment period (Fig. 1). The visits took place between 7:30 and 11 AM on the same day of the week and within a time interval of 2 h, for each subject. The nondominant arm was used for the measurements.

Office BP measurements were carried out three times with 1-min intervals, after a 30-min rest in the sitting position, using a semiautomated oscillometric device (Omron M4; Omron Healthcare, Tokyo, Japan). The mean of the last two measurements was used in the analyses.

Twenty-four-hour ambulatory BP (ABP) measurements were performed with a device equipped with a QRS complex detector and a position sensor (Diasys Integra; Novacor, Rueil-Malmaison, France). Readings were taken every 15 (standing) or 30 min (recumbent position). Primarily, the auscultatory method was used but an oscillometric measurement was performed if an auscultatory measurement failed. Intensive physical activity was not permitted during the recordings. The ABP recordings were analyzed in a fully blinded fashion. Daytime was defined as hours 7 AM to 10 PM, and night-time as hours 10 PM to 7 AM. The 24-h ABP was calculated as the mean of daytime and night-time values, weighted according to the number of daytime and night-time hours. Single observations were excluded from the analyses due to low pulse pressure ($<$15 mm Hg for systolic pressures $<$120 mm Hg, and $<$20 mm Hg for systolic pressures $\geq$120 mm Hg), high heart rates (HR) ($\geq$110 beats/min), lying down during daytime, standing up or being awake during night-time, or high physical activity. For clinical practice, a recommendation involving $\geq$14 daytime readings and $\geq$7 night-time ABP readings has been published.[10] With the stringent criteria for single readings in this study, $\geq$15 daytime and $\geq$7 night-time readings were required for a recording to be accepted. The mean number of accepted ABP readings during both placebo and drug treatment periods was 67% (52/78) of the theoretical 24-h maximum. The lowest ABP reading count in an accepted recording was 24.

Assessments for Safety

Safety was assessed with standard visit procedures, BP measurements, and electrocardiogram (ECG). Laboratory tests (blood hemoglobin, white blood cells and platelets, and serum sodium, potassium, and alanine aminotransferase) were taken after treatment periods 1, 4, and 8 (Fig. 1). Echocardiography was done at the end of the first treatment period (see Results section).

Statistical Analyses

In the analysis of BP levels and responses, explanatory variables included age, duration of hypertension, number of previous antihypertensive drugs, number of affected parents, BMI, waist-to-hip ratio (WHR), weight, and triceps skinfold thickness. Statistical SPSS software (version 11.01, SPSS Inc., Chicago, IL) was used. The data are presented as mean ($\pm$ SD) or median (interquartile range). Because most of the variables were non-normally distributed, pairwise correlations were analyzed using Spearman's rho. When the explanatory variable was categorical or ordinal, Mann-Whitney U or Jonckheere-Terpstra test was used.

All significant findings in the initial analyses were subjected to multivariate analysis using stepwise regression. In the analysis of drug responses, the corresponding BP value on placebo periods was also included. Non-normally distributed response variables were transformed by the Blom method to approximate normal distribution in multivariate analysis. Collinearity of the explanatory variables was considered during the analysis. The antihypertensive responses between the study drugs were compared first with Friedman and then pairwise with Wilcoxon signed ranks tests. Within-subject correlations between BP responses to different study drugs were analyzed with Pearson's correlation using normalized z scores. Because high HR was an exclusion criterion for single observations in ABP recordings, HR in ABP recordings was not analyzed.

Results

Characteristics of Subjects

Altogether 313 subjects were screened for the study. At least one placebo period was completed by 244 subjects (Table 1), and at least one active drug period by 233 subjects. All four placebo periods were completed by 211 subjects and all four active drug periods by 208 subjects. The number of completed treatment periods was 214 for amlodipine, 218 for bisoprolol, 217 for hydrochlorothiazide, and 219 for losartan. Younger age was associated with increasing number of affected parents ($P < .001$). Thus, the mean age of subjects with two affected parents was 48.3 years, 3.7 years younger than the mean age of subjects with no affected parents. Younger age was also associated with fewer antihypertensive drugs before the study ($P < .05$).

Safety and Withdrawals

No life-threatening adverse events were recorded during the study. Withdrawals occurred for the following reasons: high BP level (12 subjects), aortic dilatation in echocardiography (7 subjects), clinically significant left ventricular hypertrophy (1 subject), echocardiographic findings suggesting past myocardial infarction (2 subjects), angina pectoris (3 subjects), atrial fibrillation (4 subjects), asthma (2 subjects), normotension (7 subjects), noncompliance (8 subjects), kidney disease (4 subjects), and miscellaneous medical causes (6 subjects). Other withdrawals were due to personal reasons (49 subjects) and occurred mostly before the first placebo period.

Table 1. Characteristics of the GENRES study population

Parameter	Mean ± SD
Age (y)	50.5 ± 6.4
Body mass index (kg/m^2)	26.8 ± 2.7
Triceps skinfold thickness (mm)	11.2 ± 5.2
Waist-to-hip ratio	0.99 ± 0.05
Duration of hypertension (y)	11.2 ± 8.5
Number of previous antihypertensive drugs (*n*/%)	
0	47/19%
1	123/50%
2	74/30%
Number of parents with hypertension (*n*/%)	
0	90/37%
1	110/45%
2	44/18%
BP levels and HR during placebo periods (mm Hg)	
Office measurements (sitting values)	
Systolic	153 ± 14
Diastolic	100 ± 8
Heart rate	70 ± 8
Ambulatory recordings	
24 h	
Systolic	135 ± 11
Diastolic	93 ± 6
Heart rate	73 ± 8
Daytime	
Systolic	145 ± 11
Diastolic	100 ± 6
Heart rate	79 ± 9
Night-time	
Systolic	119 ± 11
Diastolic	82 ± 7
Heart rate	64 ± 8
Nocturnal dipping of BP (mm Hg)	
Systolic	26 ± 8
Diastolic	18 ± 6
Repeatability of BP measurements during the placebo periods (CV%)	
Office	
Systolic	5.4 ± 2.7
Diastolic	5.2 ± 2.4
Ambulatory, 24-h	
Systolic	3.6 ± 1.9
Diastolic	3.5 ± 1.7
Ambulatory, daytime	
Systolic	3.9 ± 1.9
Diastolic	3.8 ± 1.5
Ambulatory, night-time	
Systolic	4.9 ± 2.4
Diastolic	5.2 ± 2.7

BP = blood pressure; HR = heart rate.

The 244 subjects with at least one placebo period completed are included.

Blood Pressure Levels During Placebo Periods

The subjects of this study were moderately hypertensive. During the placebo periods, the mean office BP was 153/100 mm Hg and the mean 24-h ABP 135/93 mm Hg (Table 1). There were two subjects with a mean placebo systolic 24-h ABP <130 mm Hg concomitantly with diastolic 24-h ABP <80 mm Hg. During the placebo periods, 24-h ABP recording showed the best repeatability, with coefficients of variation of 3.6% (systolic) and 3.5% (diastolic pressure) (Table 1). There was a marked within-subject correlation between the two types of BP measurements. Thus, the Spearman's correlation coefficients between office BP and 24-h ABP values were 0.70/0.67 (systolic/diastolic), between office BP and daytime ABP values 0.68/0.64, and between office BP and night-time ABP values 0.63/0.56.

The number of preceding antihypertensive drugs was associated with both office BP and ABP levels during the placebo periods (Table 2). Age was positively correlated with systolic and diastolic office BP (but not ABP) values and BMI with diastolic office BP values. No significant associations with BP levels were found for the duration of hypertension or the number of affected parents.

The mean nocturnal dipping (difference between daytime and night-time ABP values) during the placebo periods was 26 mm Hg for systolic BP and 18 mm Hg for diastolic BP (Table 1) and the lowest 2.5th percentiles were 10 and 8 mm Hg, respectively. The diastolic dipping value was negatively correlated with age and positively with BMI (Table 2).

Antihypertensive Responses

Comparison of the Four Study Drugs In both ABP and office BP measurements, 5 mg of bisoprolol had the best antihypertensive effect, followed by 50 mg of losartan, 5 mg of amlodipine, and 25 mg of hydrochlorothiazide, in that order (Fig. 2). The daytime ABP responses were higher than the night-time responses for bisoprolol, losartan, and amlodipine. In contrast, hydrochlorothiazide showed better responses during night-time than daytime ($P = .15$ for systolic and $P = .003$ for diastolic response).

The within-subject similarity of BP responses between different study drugs was analyzed using pairwise correlation matrixes. The highest similarity in all measurement modes was obtained for responses to bisoprolol and losartan, with correlations ranging from 0.32 to 0.39, followed by responses to amlodipine and hydrochlorothiazide, with correlations ranging from 0.20 to 0.35 (Table 3). The lowest correlations were seen for the treatment pairs of bisoprolol–amlodipine and bisoprolol–hydrochlorothiazide. The correlations were in most cases higher in the ABP than in the office BP responses.

Relation to Baseline Subject Characteristics The BP responses to study drugs were analyzed using a number of variables (Table 4). For losartan, no significant associations of the explanatory variables with BP responses were found. There was a negative correlation of HR in office BP measurements during placebo periods with 24-h ABP responses to bisoprolol.

Table 2. Correlation matrix of blood pressure levels during the placebo periods with basic subject characteristics

	Age	Duration of hypertension	Number of previous antihypertensive drugs	Number of affected parents	BMI	WHR	Triceps skinfold thickness
Office measurements							
Systolic BP	0.36‡	0.06	0.24‡	−0.08	0.04	0.15*	−0.07
Diastolic BP	0.16*	0.03	0.24‡	−0.03	0.18†	0.14*	−0.01
Ambulatory 24-h recording							
Systolic BP	0.11	−0.06	0.24‡	0.07	−0.01	0.07	−0.06
Diastolic BP	−0.03	−0.06	0.26‡	0.10	0.02	0.02	−0.01
Nocturnal dipping of BP							
Systolic	−0.05	0.06	−0.04	−0.02	0.12	0.17†	0.05
Diastolic	−0.18†	0.05	−0.04	−0.02	0.15*	0.08	0.12

BMI = body mass index; BP = blood pressure; WHR = waist-to-hip ratio.
The values shown are Spearman's correlation coefficients (r).
* $P < .05$, † $P < .01$, ‡ $P < .001$.

For amlodipine, age was significantly associated with its BP responses in both ABP (Table 4) and office BP measurements. For example, the median 24-h systolic response was 5 mm Hg higher in the highest (>55.7 years) than in the lowest age quartile (<45.7 years). The BMI was negatively correlated with systolic and diastolic ABP responses to amlodipine.

Age was positively correlated with systolic BP response to hydrochlorothiazide in office BP and 24-h ABP measurements; the association with diastolic 24-h ABP response became statistically significant only after multivariate analysis. Although the duration of hypertension was positively correlated with age ($r = 0.15$, $P = .02$), their associations with BP responses to hydrochlorothiazide were opposite (Table 4).

Relation to Blood Pressure Levels During Placebo Periods When analyzed in corresponding placebo BP quartiles, the antihypertensive drug responses were higher in the highest than in the lowest quartile. In 24-h ABP

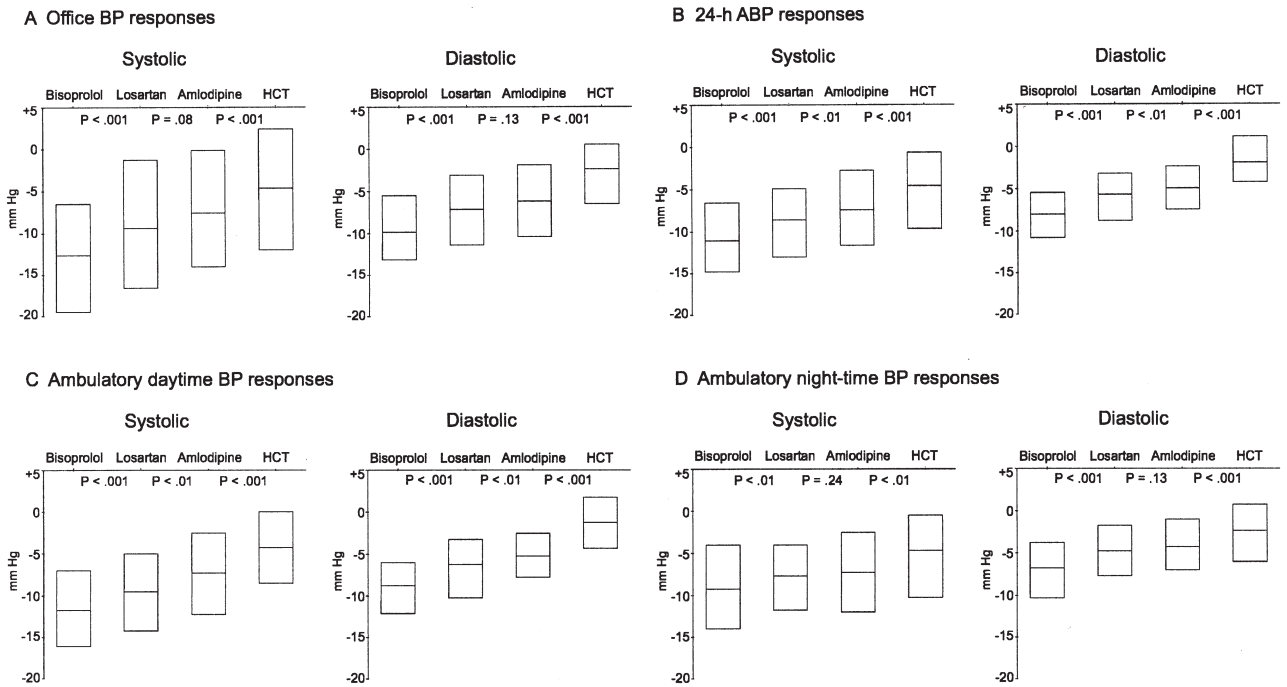

FIG. 2. Antihypertensive responses. (**A**) Office sitting BP; (**B**) 24-h ABP; (**C**) ambulatory daytime BP; (**D**) ambulatory night-time BP. Medians and interquartile ranges are shown. Statistical significance between adjacent medications was calculated with Wilcoxon signed rank test. BP = blood pressure; HCT = hydrochlorothiazide.

Table 3. Comparison of intraindividual ambulatory 24-h blood pressure responses (systolic/diastolic) between study drugs

	Amlodipine	Bisoprolol	Hydrochlorothiazide	Losartan
Amlodipine	—	0.12/0.14	0.35‡/0.35‡	0.22†/0.13
Bisoprolol	0.12/0.14	—	0.15*/0.16*	0.32‡/0.39‡
Hydrochlorothiazide	0.35‡/0.35‡	0.15*/0.16*	—	0.23†/0.14*
Losartan	0.22†/0.13	0.32‡/0.39‡	0.23†/0.14*	—

Pearson's correlation coefficients with normalized values are shown.
* $P < .05$, † $P < .01$, ‡ $P < .001$.

recordings, this trend was especially pronounced for amlodipine (both systolic and diastolic BP) and hydrochlorothiazide (systolic BP) (Fig. 3).

The responses to bisoprolol and losartan were similar on different levels of night-time BP dipping on placebo (Table 4). In contrast, the ABP responses to amlodipine and the office BP responses to hydrochlorothiazide were negatively correlated with night-time dipping on placebo.

Discussion

The GENRES study is the first prospective, double-blind, cross-over, single-center, placebo-controlled pharmacogenomic study in essential hypertension, and considering its clinical part only, the GENRES study is the second, but the largest study so far, that involves systematic cross-over treatment with drugs from four major antihypertensive drug classes in a double-blind, placebo-controlled manner. The first comparable study with drugs from five antihypertensive classes (angiotensin-converting enzyme [ACE] inhibitor, β-blocker, calcium channel blocker, diuretic, and α-blocker) included 43 patients, but did not have placebo periods between active treatment periods, and did not include ABP recordings after all treatment periods.[11] Other cross-over studies have been open and nonrandomized in their design, or have involved smaller patient populations or fewer drug classes.[12–19]

The present study was limited because it included only male subjects. This decision was based on hypothesis-generating nature of the GENRES study, which would benefit of all attempts to diminish the effect of intrinsic or extrinsic factors causing avoidable variation in BP levels. First, epidemiologic surveys indicate marked sex-dependent differences in BP levels, which vary at different ages (for reviews, see Reckelhoff,[20] Os et al,[21] and Safar and Smulyan[22]). Second, there is a marked sexual dimorphism in the regulation of genes controlling BP, those influencing the activity of the renin-angiotensin system in particular.[20,21] Third, the casual use of oral contraceptive pills by the volunteers may have increasing effects on BP levels,[23] and there is evidence that even the phase of the menstrual cycle[24] or use of postmenopausal hormone replacement therapy[25] may in occasional subjects influence BP.

The drugs selected for the study were considered to be representative of their classes, and the dosages sufficient but well tolerated. Considering the ultimate pharmacogenetic goal of the GENRES study, its design did not necessitate the use of equipotent doses of the various agents, as comparison of their antihypertensive effectiveness was not an objective. The study was done in a university hospital setting, and included 4755 visits and 2022 ABP recordings, all performed in the same outpatient clinic room by a committed study personnel. Administration of placebos to the patients did not violate ethical considerations, as these periods were relatively short and the study provided useful patient-specific data for subsequent tailoring of drug treatment. The ABP recordings had a better repeatability than office BP measurements, confirming earlier results.[26]

Nocturnal dipping values were, on average, 18% for both systolic and diastolic BP during the placebo periods. The lowest 2.5th percentiles were 7% and 8%, respectively. This corresponds to the general view that nondipping is present when there is a less than 10% decrease in nocturnal pressure.[27]

Within-subject correlations of the drug-to-drug effects indicated that the most concordant responses were seen with bisoprolol and losartan, and with amlodipine and hydrochlorothiazide. These data are in harmony with previous results from less well-controlled or smaller studies, but the r values for intraindividual responses to different drug classes are lower than those reported previously (for review, see Stergiou et al[28]). Collectively, the data indirectly support the ideas of Laragh[3] who recommends classification of hypertensive patients into sodium volume-mediated (postulated to be sensitive to diuretics and calcium channel blockers) and renin-angiotensin-mediated vasoconstrictor (postulated to be sensitive to β-blockers and ACE inhibitors/angiotensin II blockers) categories. In fact, systematic cross-over comparisons of different classes of drugs support the "AB/CD scheme" (in which A stands for ACE inhibitor, B for β-blocker, C for calcium channel blocker, and D for diuretic) for choosing antihypertensive therapy, maintaining that the first drug should be selected from one of these pairs and poorly responding patient should be switched to the other pair.[11,17] This strategy has been raised as a treatment algorithm in the guidelines published by the British Hypertension Society.[29]

Data from the BP levels during placebo administration showed interesting associations with the BP responses to amlodipine and, to some extent, to hydrochlorothiazide.

Table 4. Correlation matrix of blood pressure responses to study drugs in ambulatory 24-h recording with several variables

	Age	Duration of hypertension	Number of previous antihypertensive drugs	Number of affected parents	BMI	WHR	Triceps skinfold thickness	Night-time dipping	HR
Blood pressure response to									
Amlodipine	0.24‡/0.26‡	−0.07/−0.04	0.14*/0.13	0.08/0.02	−0.14*/−0.14*	−0.04/−0.04	0.03/0.02	−0.17+/−0.21†	−0.08/−0.06
Bisoprolol	0.10/0.02	0.09/0.06	−0.02/0.08	−0.04/−0.00	−0.09/−0.03	−0.02/0.02	−0.08/−0.12	−0.00/−0.00	−0.16*/−0.13
Hydrochlorothiazide	0.19‡/0.08	−0.13/−0.19‡	0.04/0.02	−0.02/0.00	−0.01/0.07	−0.03/0.06	0.17*/0.09	−0.03/−0.04	−0.06/0.01
Losartan	0.10/−0.10	−0.03/−0.01	0.01/−0.05	0.12/0.09	−0.10/−0.05	0.03/0.04	−0.07/−0.10	0.00/−0.01	−0.11/−0.07

BMI = body mass index; BP = blood pressure; HR = heart rate in office BP measurements during placebo periods; night-time dipping = night-time dipping (systolic/diastolic) during placebo periods; WHR = waist-to-hip ratio. The values shown are Spearman's correlation coefficients (r) for systolic / diastolic responses, and a positive coefficient indicates a better drug response with increasing value of the explanatory variable.
* $P < .05$, † $P < .01$, ‡ $P < .001$.

FIG. 3. Antihypertensive drug responses in relation to the corresponding placebo BP quartiles. Medians and interquartile ranges are shown. (**A**) Office systolic BP; (**B**) office diastolic BP; (**C**) 24-h ambulatory systolic BP; (**D**) 24-h ambulatory diastolic BP. BP = blood pressure; B = bisoprolol; L = losartan; A = amlodipine; H = hydrochlorothiazide.

Thus, antihypertensive responses to these two drugs increased markedly with placebo BP levels. Moreover, lower nocturnal dipping was also associated with better response to these drugs. These results were not explained by age. We are not aware of similar data from previous studies. If confirmed, determination of the extent of nocturnal dipping may serve as an adjunct in individualization of antihypertensive drug treatment.

The BP responses to bisoprolol and losartan were rather stable, independent of the age of the subjects. In contrast, age predicted significantly the efficiencies of amlodipine and hydrochlorothiazide, as reported earlier.[30]

There are important limitations in the present study. It was limited to white, male, and relatively young individuals. Therefore, the data may not be valid as such for women, older subjects, and other ethnic groups.

In conclusion, we have designed a carefully controlled study of human essential hypertension that permits association of carefully phenotyped BP responses of 200 male patients with their genomic variation. Our first report validates the clinical portion of the GENRES study. Our data demonstrate wide interindividual variation in responses to four main classes of antihypertensive drugs. We here show that the responses to a calcium channel blocker best correlate to those of a diuretic, and the responses to a β-blocker best correlate to those of an angiotensin receptor blocker. The GENRES study material should provide an excellent platform for future studies on putative associations between common variants of hypertension candidate genes and antihypertensive drug responsiveness.

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References

1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, for the the National High Blood Pressure Education Program Coordinating Committee: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206–1252.
2. Kaplan NM, Opie LH: Controversies in hypertension. Lancet 2006; 367:168–176.
3. Laragh J: Laragh's lessons in pathophysiology and clinical pearls for treating hypertension. Am J Hypertens 2001;14:491–503.
4. Koopmans RP, Insel PA, Michel MC: Pharmacogenetics of hypertension treatment: a structured review. Pharmacogenetics 2003;13: 705–713.
5. Turner ST, Boerwinkle E: Genetics of blood pressure, hypertensive complications, and antihypertensive drug responses. Pharmacogenomics 2003;4:53–65.
6. Mellen PB, Herrington DM: Pharmacogenomics of blood pressure response to antihypertensive treatment. J Hypertens 2005;23:1311–1325.
7. Kurland L, Lind L, Melhus H: Using genotyping to predict responses to anti-hypertensive treatment. Trends Pharmacol Sci 2005; 26:443–447.
8. Hingorani AD, Jia H, Stevens PA, Hopper R, Dickerson JE, Brown MJ: Renin-angiotensin system gene polymorphisms influence blood pressure and the response to angiotensin converting enzyme inhibition. J Hypertens 1995;13:1602–1609.
9. Hunt SC, Cook NR, Oberman A, Cutler JA, Hennekens CH, Allender PS, Walker WG, Whelton PK, Williams RR: Angiotensinogen genotype, sodium reduction, weight loss, and prevention of hypertension: trials of hypertension prevention, phase II. Hypertension 1998;32:393–401.
10. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P, for the European Society of Hypertension Working Group on Blood Pressure Monitoring: European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. J Hypertens 2003;21:821–848.
11. Deary AJ, Schumann AL, Murfet H, Haydock SF, Foo RS, Brown MJ: Double-blind, placebo-controlled crossover comparison of five classes of antihypertensive drugs. J Hypertens 2002;20:771–777.
12. Bidiville J, Nussberger J, Waeber G, Porchet M, Waeber B, Brunner HR: Individual responses to converting enzyme inhibitors and calcium antagonists. Hypertension 1988;11:166–173.
13. Chalmers J, Wing L, Taylor S: Analysis of time trends, individual subject responses and background variation in crossover factorial studies with antihypertensive drugs. J Hypertens 1990;8(Suppl 4): S27–S35.
14. Niutta E, Cusi D, Colombo R, Pellizzoni M, Cesana B, Barlassina C, Soldati L, Bianchi G: Predicting interindividual variations in antihypertensive therapy: the role of sodium transport systems and renin. J Hypertens 1990;8(Suppl 4):S53–S58.
15. Cappuccio FP, Markandu ND, Singer DR, MacGregor GA: Amlodipine and lisinopril in combination for the treatment of essential hypertension: efficacy and predictors of response. J Hypertens 1993; 11:839–847.
16. Attwood S, Bird R, Burch K, Casadei B, Coats A, Conway J, Dawes M, Ebbs D, Farmer A, Robinson J: Within-patient correlation between the antihypertensive effects of atenolol, lisinopril and nifedipine. J Hypertens 1994;12:1053–1060.
17. Dickerson JEC, Hingorani AD, Ashby MJ, Palmer CR, Brown MJ: Optimisation of anti-hypertensive treatment by crossover rotation of four major classes. Lancet 1999;353:2008–2013.
18. Falconnet C, Bochud M, Bovet P, Maillard M, Burnier M: Gender difference in the response to an angiotensin-converting enzyme inhibitor and a diuretic in hypertensive patients of African descent. J Hypertens 2004;22:1213–1220.
19. Stergiou GS, Efstathiou SP, Roussias LG, Mountokalakis TD: Intraindividual blood pressure responses to angiotensin-converting enzyme inhibition and angiotensin receptor blockade. J Clin Hypertens 2005;7:18–23.
20. Reckelhoff JF: Gender differences in the regulation of blood pressure. Hypertension 2001;37:1199–1208.
21. Os I, Oparil S, Gerdts E, Hoieggen A: Essential hypertension in women. Blood Press 2004;13:272–278.
22. Safar ME, Smulyan H: Hypertension in women. Am J Hypertens 2004;17:82–87.
23. Curtis KM, Mohllajee AP, Martins SL, Peterson HB: Combined oral contraceptive use among women with hypertension: a systematic review. Contraception 2006;73:179–188.
24. Pechere-Bertschi A, Burnier M: Female sex hormones, salt, and blood pressure regulation. Am J Hypertens 2004;17:994–1001.
25. Mueck AO, Seeger H: Effect of hormone therapy on BP in normotensive and hypertensive postmenopausal women. Maturitas 2004; 49:189–203.
26. Bottini PB, Carr AA, Rhoades RB, Prisant LM: Variability of indirect methods used to determine blood pressure: office vs mean 24-hour automated blood pressures. Arch Intern Med 1992;152: 139–144.
27. Staessen JA, Asmar R, De Buyzere M, Imai Y, Parati G, Shimada K, Stergiou G, Redon J, Verdecchia P: Task Force II: blood pressure measurement and cardiovascular outcome. Blood Press Monit 2001; 6:355–370.
28. Stergiou GS, Skeva II, Baibas NM, Kalkana CB, Roussias LG, Mountokalakis TD: Does the antihypertensive response to angiotensin converting enzyme inhibition predict the antihypertensive response to angiotensin receptor antagonism? Am J Hypertens 2001; 14:688–693.
29. Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, Sever PS, McG Thom S, for the British Hypertension Society: Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. J Hum Hypertens 2004;18:139–185.
30. Materson BJ, Reda DJ, Cushman WC, Massie BM, Freis ED, Kochar MS, Hamburger RJ, Fye C, Lakshman R, Gottdiener J, Ramirez EA, Henderson WG, for The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents: Single-drug therapy for hypertension in men: a comparison of six antihypertensive agents with placebo: the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. N Engl J Med 1993;328:914–921.