Original Article

Heritability analyses show visit-to-visit blood pressure variability reflects different pathological phenotypes in younger and older adults: evidence from UK twins

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Background: Clinic and long-term average blood pressure (BP) are heritable traits with estimates of heritability ranging from 0.31 to 0.68. Long-term visit-to-visit BP variability (BPV) is emerging as a new cardiovascular risk predictor, though it is unclear if this is completely independent of BP. We hypothesize that BPV should demonstrate the same pattern of additive genetic, shared environmental and unique environmental variance as BP, if both are phenotypic surrogates.

Method: We studied 2889 twin pairs not on any BP-lowering therapy from the Twins UK cohort, and estimated the additive genetic variance for baseline BP, long-term average BP, BP trajectory (rate of change of BP in mmHg/year) and BPV (coefficient of variation and average real variability over an average of 3.2 visits). Heritability estimates were obtained by structural equation modelling adjusting for age, age^2, sex and BMI.

Results: The heritabilities for baseline SBP and DBP were 0.51 (95% confidence interval 0.49, 0.53) and 0.56 (0.54, 0.58); long-term average SBP and DBP were 0.56 (0.53, 0.59) and 0.61 (0.58, 0.64); and systolic and diastolic trajectories over 10 years were 0.49 (0.46, 0.52) and 0.29 (0.27, 0.32), respectively. Both overall systolic and diastolic BPV showed no additive genetic variance contributing to the phenotypic variation, but after stratification by age, the younger subgroup (<51 years) showed heritability estimates of 0.44 (0.38, 0.50) for coefficient of variation and 0.35 (0.29, 0.41) for average real variability.

Conclusion: Age is a major factor that influences heritability estimation of BPV and it is likely that BPV in younger and older age groups may reflect different pathological phenotypes.

Keywords: blood pressure variability, heritability, twins

Abbreviations: A, additive genetic variance; AIC, Akaike information criterion; AVR, average real variability; BP, blood pressure; BPV, blood pressure variability; C, shared/common environmental variance; CKD, chronic kidney disease; E, unique environmental variance; h^2, heritability

INTRODUCTION

Long-term visit-to-visit blood pressure variability (BPV) is emerging as an independent cardiovascular risk predictor from post-hoc analysis of large clinical trials and population cohorts [1–3]. It is well established that blood pressure (BP) is heritable with estimates of heritability ranging from 0.31 to 0.68 [4–8], and high BP is an independent predictor of early mortality [9]. It is unclear whether the predictive value of long-term BPV is independent of clinic or ambulatory BP readings, though there is some evidence that the risk posed by BPV is independent of average BP [1,10]. As BPV correlates with clinic and long-term average BP [3,11], we hypothesize that it should also demonstrate the same pattern of additive genetic (A), shared environmental (C) and unique environmental (E) variance, if it is a phenotypic surrogate of BP. Recently, heritability analysis of short-term BPV from ambulatory BP data showed daytime BPV was not heritable, whereas night-time BPV was 0.33–0.36 heritable [12]. We analysed the heritabilities of BP, long-term average BP, BP trajectory and BPV in a cohort of adult twins to determine if BPV is independent of BP.

METHODS

Study population

Study participants were twins enrolled in the Twins UK registry, a national register of adult twins recruited as volunteers by successive media campaigns without selecting for particular diseases or traits [13]. The registry

Journal of Hypertension 2013, 31:000–000

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Received 4 December 2012 **Revised** 21 May 2013 **Accepted** 16 July 2013

DOI:10.1097/HJH.0b013e32836523c1

incorporates about 12 000 twins, both male and female, studied for a whole range of clinical and behavioural traits. All twin pairs recruited were of the same sex. Of the 12 000 participants in the Twins UK registry, 7118 had BP measurements available. Of these 489 (6.8%) and 1022 (14%) were on BP-lowering treatment at baseline and during follow-up. For the long-term average BP, BP trajectory and BPV analyses, we included only those twins who were not on BP-lowering treatment during the entire follow-up period as this can confound the analyses both in terms of treatment being instituted later or drug non-compliance [3,11]. Also, as the number of singleton twins was modest (240 singletons out of 2889 twin pairs), and as singletons do not contribute to estimation of the covariance, we included in the analysis only complete pairs. There were 2889 twin pairs who had multiple BP measurements during follow-up and were included in the study. Of these, 1304 pairs had at least two BP measurements and were included in the analysis of long-term average BP, whereas 278 twin pairs had at least three BP measurements and were included in the BPV analyses.

Blood pressure measurement

Clinic BP was measured by a trained nurse using either the Marshall mb02, the Omron Mx3 or the Omron HEM713C Digital Blood Pressure Monitors performed with the patient in the sitting position for at least 3 min. At each visit, the cuff was placed on the patient's arm so that it was approximately 2–3 cm above the elbow joint of the inner arm, with the air tube lying over the brachial artery. The patient arm was placed on the table or supported with the palm facing upwards, so that the tab of the cuff was placed at the same level of the heart. Three measurements were taken with an interval of approximately 1 min between each reading. The second and third measures were subsequently recorded.

Finally, we defined those with estimated glomerular filtration rate (eGFR) below 60 to suffer from chronic kidney disease (CKD), and those who had either a myocardial infarction, or a stroke, or ischemic heart disease to suffer from cardiovascular disease.

Statistical analyses

The baseline characteristics of study participants were compared using analysis of variance (ANOVA) or *t*-test for continuous variables and chi-square test for categorical variables. To estimate correlations amongst different BP traits, we calculated Pearson's correlation coefficients. For each individual with two or more BP longitudinal reading, we calculated long-term average BP across all repeated measures. BPV was estimated by calculating for each individual both the coefficient of variation and the average real variability (ARV; $\mathrm{AVR}_{BP}\frac{1}{n-1}\sum_{i=1}^{n-1}|\mathrm{BP}_{i+1}-\mathrm{BP}_i|$) [1] of three or more readings obtained over 10 years. Only twin pairs with measurements taken at similar time points were included in the analysis.

As BPV is known to increase with age, we have calculated heritability both in the overall population and stratifying by the median age.

Trajectories of change in BP over 10 years were estimated using empirical Bayes predictions to estimate the rate of change in mmHg/year [14]. This method predicts point estimates and calculates, based on these point estimates, the slope of change.

Repeatability of BP in each patient was calculated using the intra-class correlation of BP, taking one member of the twin pair with repeat measurements.

To estimate the heritability of BP and longitudinal changes in BP, we used structural equation modelling to decompose the observed phenotypic variance into three latent sources of variation: additive genetic variance (A), shared/common environmental variance (C) and non-shared/unique environmental variance (E) [15]. Additive genetic influences are indicated when monozygotic twins are more similar than dizygotic twins. The common environmental component estimates the contribution of family environment which is assumed to be equal in both monozygotic and dizygotic twin pairs [16], whereas the unique environmental component does not contribute to twin similarity; rather it estimates the effects that apply only to each individual and includes measurement error. Any greater similarity between monozygotic twins than dizygotic twins is attributed to greater sharing of genetic influences. Heritability is defined as the proportion of the phenotypic variation attributable to genetic factors, and is given by the equation: $h^2=(\mathrm{A})/(\mathrm{A}+\mathrm{C}+\mathrm{E})$. The Akaike information criterion (AIC) was used to determine the best-fitting model (among ACE, AE, CE and E models). The model with the lowest AIC reflects the best balance of goodness of fit and parsimony [15]. The maximum likelihood method of model fitting was applied to the raw data using OpenMX. We adjusted BP measurements for age, age^2, sex and BMI.

RESULTS

The study cohort comprised of 1454 monozygotic and 1435 dizygotic twin pairs, and the baseline characteristics are presented in Table 1. The overall demographics of the monozygotic and dizygotic twin pairs are presented in Table 1. Both twin groups were predominantly female (10% of monozygotic twins and 4% of dizygotic twins were males). Monozygotic twin pairs were on average 1 year older than dizygotic twin pairs, had slightly lower BMI (0.27 kg) and lower DBP, but similar SBP. Nine hundred and forty-one monozygotic and 988 dizygotic twin pairs had either SBP greater than 140 or DBP greater than 90. There were 628 monozygotic and 676 dizygotic twin pairs with multiple longitudinal BP measurements, and were included in the long-term average BP and the BP trajectories over 10-year analyses, whereas 99 monozygotic and 179 dizygotic twin pairs were included in the BPV analysis with an average of 3.2 (0.4) readings. Stratifying the

TABLE 1. Baseline demographic characteristics of the study population

Phenotype	MZ	DZ	*P*-value
N	2908	2870	
M : F	288 : 2620	118 : 2752	0.04
Age (years)	47.85 (14.01)	46.96 (12.64)	0.01
BMI (kg/m^2)	25.24 (4.55)	25.51 (4.58)	0.02
SBP (mmHg)	121.14 (15.47)	121.26 (15.13)	0.68
DBP (mmHg)	75.73 (10.21)	76.56 (10.47)	0.002

DZ, dizygotic; MZ, monozygotic.

TABLE 2. Heritability of baseline BP, long-term average BP, BP trajectory and BPV measured both as CV and ARV

Phenotype	MZ			DZ			Best model	A [95% CI]	C [95% CI]	E [95% CI]
	N pairs	Mean (SD)	ICC [95% CI]	*N* pairs	Mean (SD)	ICC [95% CI]				
Baseline SBP (mmHg)	1454	121.14 (15.47)	0.50 [0.46, 0.54]	1435	121.26 (15.13)	0.27 [0.22, 032]	AE	0.51 [0.49, 0.53]	–	0.49 [0.47, 0.51]
Long-term average SBP (mmHg)	628	121.78 (13.31)	0.56 [0.50, 0.61]	676	122.31 (12.92)	0.27 [0.20, 0.34]	AE	0.56 [0.53, 0.59]	–	0.44 [0.41, 0.47]
SBP trajectory (mmHg/year)	628	0.81 (0.31)	0.60 [0.55, 0.65]	676	0.80 (0.35)	0.40 [0.33, 0.46]	ACE	0.49 [0.46, 0.52]	0.14 [0.12, 0.16]	0.37 [0.34, 0.40]
SBP variability, CV	99	0.07 (0.04)	0.29 [0.10, 0.46]	179	0.07 (0.04)	0.21 [0.07, 0.35]	CE	–	0.25 [0.20, 0.31]	0.75 [0.70, 0.80]
SBP variability, ARV	99	10.42 (6.73)	0.31 [0.12, 0.48]	179	10.58 (6.54)	0.23 [0.09, 0.36]	CE	–	0.26 [0.21, 0.31]	0.74 [0.69, 0.79]
Baseline DBP (mmHg)	1454	75.73 (10.21)	0.55 [0.50, 0.58]	1435	75.56 (10.47)	0.29 [0.24, 0.34]	AE	0.56 [0.54, 0.58]	–	0.44 [0.42, 0.46]
Long-term average DBP (mmHg)	628	75.89 (8.20)	0.61 [0.56, 0.66]	676	76.36 (8.28)	0.24 [0.17, 0.31]	AE	0.61 [0.58, 0.64]	–	0.39 [0.36, 0.42]
DBP trajectory (mmHg/years)	628	0.10 (0.34)	0.52 [0.46, 0.57]	676	0.12 (0.38)	0.43 [0.37, 0.49]	ACE	0.29 [0.27, 0.32]	0.26 [0.24, 0.28]	0.45 [0.43, 0.48]
DBP variability, CV	99	0.07 (0.04)	0.13 [−0.07, 0.32]	179	0.08 (0.04)	0.13 [−0.02, 0.32]	CE	–	0.13 [0.09, 0.17]	0.87 [0.83, 0.91]
DBP variability, ARV	99	6.84 (4.31)	0.04 [−0.16, 0.23]	179	6.85 (4.20)	0.10 [−0.05, 0.24]	CE	–	0.07 [0.05, 0.09]	0.93 [0.91, 0.95]

ARV, average real variability; CV, coefficient of variation; DZ, dizygotic; MZ, monozygotic; ICC, intra-class correlation coefficient.
Values in the three rightmost columns indicate the amount of variance attributed to the compartment of additive genetic factors (A or heritability), common/shared environmental factors (C) and unique environmental factors (E). 95% confidence intervals for both ICC and ACE are reported.

population by the median age (51.34 years), there were 795 monozygotic and 859 dizygotic pairs in the younger age group and 659 monozygotic and 576 dizygotic pairs in the older age group for baseline BP; 309 monozygotic and 423 dizygotic pairs in the younger age group and 319 monozygotic and 253 dizygotic pairs in the older age group for long-term average BP and the BP trajectories over 10 years. Finally, 37 monozygotic and 103 dizygotic pairs in the younger age group and 62 monozygotic and 76 dizygotic pairs in the older age group were included in the age-stratified BPV analysis.

The baseline characteristics of the individuals included in the long-term average BP and BP trajectory analysis and in both the BPV analyses are presented in the supplementary material (Table S1 and Table S2, http://links.lww.com/HJH/A276).

In the 99 monozygotic and 179 dizygotic twin pairs, SBP coefficient of variation and ARV increased with increasing age, whereas only DBP coefficient of variation showed an increase with age. DBP coefficient of variation and ARV were significantly higher in individuals with SBP above 140 mmHg compared to those with SBP below 140 mmHg. Smoking, alcohol use and BMI did not show any association with BPV (Table S3, http://links.lww.com/HJH/A276).

The heritability analyses for baseline BP, long-term average BP, BP trajectories over 10 years and BPV measured both as coefficient of variation and ARV are presented in Table 2. The best-fitting model for both baseline SBP and DBP was the AE model with heritability estimates of 0.51 [95% confidence interval (CI) 0.49, 0.53] and 0.56 (0.54, 0.58), respectively. The AE model was also the best fitting model for long-term average SBP and DBP with heritability estimates of 0.56 (0. 53, 0.59) and 0.61 (0.58, 0.64), respectively. The ACE model was the best-fitting model for both SBP and DBP trajectories over 10 years with heritability estimates of 0.49 (0.46, 0.52) and 0.29 (0.27, 0.32), respectively. In contrast, BPV, measured as either coefficient of variation or ARV, for both SBP and DBP, showed no clear genetic influence and appeared to be primarily due to unique environmental factors. Only 0.25 (0.20, 0.31) of SBP variability and 0.13 (0.09, 0.17) of DBP variability measured as coefficient of variation were due to shared environmental factors. Similarly, only 0.26 (0.21, 0.31) of SBP variability and 0.07 (0.05, 0.09) of DBP variability measured as ARV were due to shared environmental factors. When we stratified the population by age, the best-fitting model for baseline BP, long-term average BP and DBP trajectories over 10 years was the same as that identified in the overall analysis, with the exception of SBP trajectories for which in both age groups, the best-fitting model was the AE model, instead of the ACE model as reported in Table 3. Heritability estimates in the older age group tended to be lower than in the younger age group (Table 3). The best-fitting model for SBP variability in the younger age group was the AE model with heritability estimates of 0.44 (0.38, 0.50) for coefficient of variation and 0.35 (0.29, 0.41) for AVR. The best-fitting model for SBP variability in the older age group was the CE model in line with the overall results. Similarly, the best-fitting model for DBP variability in the younger age group was the AE model with heritability estimates of 0.18 (0.14, 0.23) for coefficient

TABLE 3. Heritability of BPV measured both as CV and ARV by age groups

Phenotype	Age <51.34					Age >51.34				
	MZ : DZ pairs	Best model	A [95% CI]	C [95% CI]	E [95% CI]	MZ : DZ pairs	Best model	A [95% CI]	C [95% CI]	E [95% CI]
Baseline SBP (mmHg)	795 : 859	AE	0.52 [0.50, 0.54]	–	0.48 [0.46, 0.50]	659 : 576	AE	0.50 [0.48, 0.52]	–	0.50 [0.48, 0.52]
Long-term average SBP (mmHg)	309 : 423	AE	0.62 [0.59, 0.64]	–	0.38 [0.35, 0.41]	319 : 253	AE	0.53 [0.50, 0.56]	–	0.47 [0.44, 0.50]
SBP trajectory (mmHg/year)	309 : 423	AE	0.61 [0.58, 0.64]	–	0.39 [0.36, 0.42]	319 : 253	AE	0.38 [0.35, 0.41]	–	0.62 [0.59, 0.65]
SBP variability, CV	37 : 103	AE	0.44 [0.38, 0.50]	–	0.56 [0.50, 0.62]	62 : 76	CE	–	0.16 [0.10; 0.23]	0.84 [0.77, 0.90]
SBP variability, ARV	37 : 103	AE	0.35 [0.29, 0.41]	–	0.65 [0.59, 0.71]	62 : 76	CE	–	0.19 [0.13; 0.26]	0.81 [0.74, 0.87]
Baseline DBP (mmHg)	795 : 859	AE	0.56 [0.54, 0.58]	–	0.44 [0.42, 0.46]	659 : 576	AE	0.55 [0.53, 0.57]	–	0.45 [0.43, 0.47]
Long-term average DBP (mmHg)	309 : 423	AE	0.64 [0.61, 0.66]	–	0.36 [0.34, 0.39]	319 : 253	AE	0.57 [0.54, 0.60]	–	0.43 [0.40, 0.46]
DBP trajectory (mmHg/year)	309 : 423	ACE	0.29 [0.27, 0.31]	0.12 [0.10, 0.14]	0.59 [0.56, 0.62]	319 : 253	ACE	0.29 [0.26, 0.32]	0.19 [0.17,0.21]	0.54 [0.51, 0.57]
DBP variability, CV	37 : 103	AE	0.18 [0.14, 0.23]	–	0.82 [0.77, 0.86]	62 : 76	CE	–	0.18 [0.12; 0.26]	0.82 [0.74, 0.88]
DBP variability, ARV	37 : 103	AE	0.12 [0.08, 0.17]	–	0.88 [0.83, 0.91]	62 : 76	CE	–	0.09 [0.05; 0.15]	0.91 [0.85, 0.95]

ARV, average real variability; CV, coefficient of variation; DZ, dizygotic; MZ, monozygotic.
Values in the three rightmost columns indicate the amount of variance attributed to the compartment of additive genetic factors (A or heritability), common/shared environmental factors (C) and unique environmental factors (E). 95% confidence intervals for ACE are reported.

of variation and 0.12 (0.08, 0.17) for AVR, whereas the best-fitting model for DBP variability in the older age group was the CE model (see Table 3). Table S4 (http://links.lww.com/HJH/A276) shows the Pearson's correlation coefficients within each BP trait. The intra-class correlation coefficient of longitudinal SBP measurements was 0.6 (0.57, 0.63; $P < 0.0001$) and of DBP measurement was 0.56 (0.53, 0.59; $P < 0.0001$) over 10 years.

DISCUSSION

In a large adult twin cohort not on any BP-lowering treatment, we show that measures of BPV (namely coefficient of variation and ARV) show different additive genetic variance when stratified by age. The contribution of additive genetic variance to systolic and diastolic BPV in the younger population was 0.25–0.50 and 0.08–0.23, respectively, whereas in the older age group, more than 80% of the population variance in BPV was due to random environmental effects with no additive genetic variance. This finding is in contrast to the heritability estimates of baseline BP, long-term average BP and BP trajectory, all of which show heritabilities ranging from 0.29 to 0.56, comparable with previous studies [4–6], and no substantial differences when stratified by age. Visit-to-visit BPV correlates with factors that increase arterial stiffness [1], and increasing age is associated with greater arterial stiffness. In the older subgroup, it is likely that increased arterial stiffness will have amplified variation in clinic BP due to random environmental factors, and this may have obscured any underlying additive genetic variation. The additive genetic variance of BPV in the younger subgroup was lower than that for BP, with over 50% of the variance due to random environmental factors. This implies that the genetic architecture of BPV is different from BP, insofar as the BPV phenotype actively captures the environmental effect, which other BP measurement methods actively try to minimize. For example, in addition to age-related arterial stiffening, behavioural changes, seasonal changes in temperature and non-adherence to treatment (in those on treatment with BP-lowering medications) are random environmental effects that affect BP measurements and consequently BPV. Our results are supported by two recent publications – one showed a heritability of 0.08 for SBP variability and 0.21 for DBP variability using 24-h BP data in young adults. In this study, though heritability estimates were low, the best-fitting model for both was the ACE model, indicating that BPV could not be explained by environment alone [17]. The second study showed lack of heritability of daytime BPV from ambulatory BP-monitoring data [12], which is similar to our results in the overall analysis. We have not found any suggestion of dominance component in our analysis of BPV that could reduce additive variance.

We tried to resolve the environmental component by measuring the correlation between repeated measurements in the same individual (intra-class correlation, repeatability). Stability of repeated measures in the same individual can be considered to be expressions of the same genotype or of environmental factors, and any variation in this reflects the variation within individuals caused by measurement errors and other random environmental factors [18]. The

intra-class correlation of repeated BP measures is modest and the calculated heritability of baseline BP is very similar to the heritability of long-term average BP; taken together, these indicate only a minor influence of random environmental factors affecting single BP measurements at each visit.

There are many factors that affect visit-to-visit BPV, including behavioural changes, seasonal changes in temperature, large artery stiffening associated with ageing and in those on treatment with BP lowering medications – non-adherence to treatment. Whereas all these may have an effect on BPV, in the twin population, we show that the heritability of BPV is similar to BP in the younger subgroup, but environmental effects predominate in the older subgroup. This would suggest that arterial stiffening due to ageing, increases BPV due to environmental influences and BPV in different age groups may reflect different pathological processes.

The main strength of this study is the availability of a very large twin population not on any BP-lowering treatment with longitudinal data and the ability to analyse heritability for multiple BP traits simultaneously. Our study cohort is not on any BP-lowering medication, which excludes the possibility of drug-adherence issues confounding BPV. We have used two metrics of BPV – coefficient of variation and ARV. Coefficient of variation provides a normalized measure of variability and ARV takes the order of the BP measurements into account and quantifies variability between adjacent readings.

Our study also has some limitations. First, the sample size for BPV analysis is small (278 twin pairs). However, we estimate that this sample of 99 monozygotic pairs and 179 dizygotic pairs has 80, 70 and 60% power to detect heritabilities of 0.38, 0.35 and 0.30, respectively [19,20]. Using the same dataset, we have shown striking differences in the additive genetic variance component of long-term average BP and BPV which use the same longitudinal measures. Moreover, BP trajectory, which is the rate of change of BP over time, also shows higher heritability. Second, with an average of 3.2 readings, the number of BP measurements was limited. This could impact the capacity of modelling BPV which ideally requires 7–10 readings. Finally, there is a female preponderance in our study sample and the BPV analysis includes only female twins. Our results on BPV, however, are in line with those previously reported by Fava *et al*. [12], which are based on a cohort of both males and females.

Our study indicates that the underlying pathological processes for BPV is dependent on the context – for example, age. This means interpretation of outcome data associated with BPV also needs to take into account these factors in order to determine the clinical utility of this trait.

ACKNOWLEDGEMENTS

Source of funding: The Twins UK study was funded by the Wellcome Trust; European Community's Seventh Framework Programme (FP7/2007–2013), ENGAGE project grant agreement (HEALTH-F4-2007-201413). The study also receives support from the Department of Health via the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy's & St Thomas' NHS Foundation Trust in partnership with King's College London. T.D.S. is an NIHR Senior Investigator and is holder of an ERC Advanced Principal Investigator award.

Conflicts of interest

The authors declare no conflict of interest.

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Reviewers' Summary Evaluations

Reviewer 1

This novel study uses an unusually large dataset of twins with repeated BP measurements to determine the genetic contribution to BP variability. The coefficient of variation is used in untreated patients, avoiding confounding by mean BP and medication adherence. However, its power was limited by the relatively few, solely female, eligible twins with limited measurements, showing no significant heritability due to a greater environmental contribution in older participants. However, in an important hypothesis-generating subgroup analysis, BP variability was significantly heritable in younger participants, suggesting a physiological and genetic basis that may be independent of the genetic contribution to mean BP.

Reviewer 2

Given the recent interest in blood pressure variability as a predictor of outcomes it is topical to study the extent to which this trait is influenced by heredity and by environment. The major conclusion for clinicians that blood pressure variability seems to have a significant heritable component in the young but less so in older subjects as environmental factors come into play will surprise no-one. The use of the twin registry and the sophisticated analysis are strengths of this study. Unfortunately the cohort has some limitations beyond the control of the investigators. There would also be greater confidence in the fidelity of the blood pressure variables if more measurements were available. Overall this is a useful contribution which supports the findings of a similar study recently published in the Journal on short-term BP variability. Reference: Xu X, Ding X, Zhang X, *et al. J Hypertens* 2013; 31:690–697.