JAMA | Original Investigation

Heterogeneity in Blood Pressure Response to 4 Antihypertensive Drugs
A Randomized Clinical Trial

Johan Sundström, MD, PhD; Lars Lind, MD, PhD; Shamim Nowrouzi, MD; Emil Hagström, MD, PhD; Claes Held, MD, PhD; Per Lytsy, MD, PhD; Bruce Neal, MD, PhD; Kerstin Marttala, RN; Ollie Östlund, PhD

IMPORTANCE Hypertension is the leading risk factor for premature death worldwide. Multiple blood pressure–lowering therapies are available but the potential for maximizing benefit by personalized targeting of drug classes is unknown.

OBJECTIVE To investigate and quantify the potential for targeting specific drugs to specific individuals to maximize blood pressure effects.

DESIGN, SETTING, AND PARTICIPANTS A randomized, double-blind, repeated crossover trial in men and women with grade 1 hypertension at low risk for cardiovascular events at an outpatient research clinic in Sweden. Mixed-effects models were used to assess the extent to which individuals responded better to one treatment than another and to estimate the additional blood pressure lowering achievable by personalized treatment.

INTERVENTIONS Each participant was scheduled for treatment in random order with 4 different classes of blood pressure–lowering drugs (lisinopril [angiotensin-converting enzyme inhibitor], candesartan [angiotensin-receptor blocker], hydrochlorothiazide [thiazide], and amlodipine [calcium channel blocker]), with repeated treatments for 2 classes.

MAIN OUTCOMES AND MEASURES Ambulatory daytime systolic blood pressure, measured at the end of each treatment period.

RESULTS There were 1468 completed treatment periods (median length, 56 days) recorded in 270 of the 280 randomized participants (54% men; mean age, 64 years). The blood pressure response to different treatments varied considerably between individuals ($P < .001$), specifically for the choices of lisinopril vs hydrochlorothiazide, lisinopril vs amlodipine, candesartan vs hydrochlorothiazide, and candesartan vs amlodipine. Large differences were excluded for the choices of lisinopril vs candesartan and hydrochlorothiazide vs amlodipine. On average, personalized treatment had the potential to provide an additional 4.4 mm Hg–lower systolic blood pressure.

CONCLUSIONS AND RELEVANCE These data reveal substantial heterogeneity in blood pressure response to drug therapy for hypertension, findings that may have implications for personalized therapy.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02774460

JAMA. 2023;329(14):1160-1169. doi:10.1001/jama.2023.3322

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Supplemental content

Author Affiliations: Department of Medical Sciences, Uppsala University, Uppsala, Sweden (Sundström, Lind, Nowrouzi, Hagström, Held, Lytsy, Marttala); The George Institute for Global Health, University of New South Wales, Sydney, New South Wales, Australia (Sundström, Neal); Uppsala Clinical Research Center, Uppsala, Sweden (Östlund).

Corresponding Author: Johan Sundström, MD, PhD, Department of Medical Sciences, Uppsala University Hospital, Entrance 40, Fifth Floor, 75185 Uppsala, Sweden (johan.sundstrom@uu.se).

The number of people with hypertension in the world has doubled in the last 30 years.[1] Despite global access to multiple classes of highly effective blood pressure (BP)-lowering drugs,[2] only 1 in 4 women and 1 in 5 men with hypertension reach treatment targets.[1] While most hypertension guidelines advocate combination pharmacotherapy, many patients in routine care continue to be treated with monotherapy, with adverse effects and nonadherence being important clinical problems.[3-5]

It is unknown whether the optimal choice of BP-lowering therapy varies from one person to another and whether individually targeted BP treatments can maximize clinical benefit. In clinical practice, clinicians and patients misinterpret variation in serial clinic and home measures of BP as indicating treatment effects. In fact, differences due to normal within-person variation in BP are generally much larger than the differences achieved by titrating a BP-lowering drug.[6,7]

To quantify the potential for using personalized medicine strategies to maximize the BP-lowering effects of antihypertensive drugs, a trial design that can control for the large background variability in individuals' BP levels is needed.[8] Designs used hitherto[7,9-13] have not been able to account for this variability.

The Precision Hypertension Care (PHYSIC) Trial (ClinicalTrials.gov NCT02774460) hypothesized that there is the potential for targeting specific drugs to specific individuals to maximize BP effects.[14]

Key Points

Question Is there a potential for personalized drug therapy in hypertension, and, if so, what is the magnitude of the benefit of personalization?

Findings In this randomized, double-blind, repeated crossover trial, the blood pressure response to treatments varied substantially between individuals. It was estimated that personalized treatment choice would on average lead to 4.4 mm Hg–lower systolic blood pressure than a fixed choice.

Meaning There is heterogeneity in blood pressure response to drug therapy for hypertension, of a magnitude that warrants further research.

Methods

Study Design and Setting

We used a repeated crossover design, in which some of the treatments were repeat tested within a participant, to enable us to quantify both within-patient and between-patient differences in BP response to different antihypertensive treatments.[8,15,16] In particular, the repeat testing of the same treatments within an individual separates the treatment effects from the period effects and make it possible to quantify robustly the constancy of the response to a treatment and the likely magnitude of the benefit achievable with personalization of therapy. The full protocol is in Supplement 1. The study site was the outpatient research clinic of the Department of Medicine at Uppsala University Hospital. The study was approved by the Uppsala ethics committee (2016-135) and all participants provided written informed consent.

Eligibility and Consent

Patients were eligible to register for the trial if they (1) were aged between 40 years and 75 years (male or female); (2) had been previously diagnosed with hypertension, with systolic BP (SBP) between 140 and 159 mm Hg within a 5-year period prior to the start of the trial; (3) were pharmacologically untreated or used BP-lowering monotherapy at the inclusion visit; (4) willing and able to discontinue current BP-lowering therapy for the trial duration; and (5) gave written informed consent to participate in the study. Subsequent randomization was done only if participants also (1) did not take any BP-lowering medication during the placebo run-in period and (2) had an office SBP between 140 and 179 mm Hg and diastolic BP at or below 109 mm Hg at the randomization visit. Exclusion criteria are listed in eTable 1 in Supplement 2 and involved conditions such as possible secondary hypertension, other serious disease, gout, cardiovascular diseases, kidney failure, diabetes, or contraindications to the trial drugs. Data on medical history were based on electronic medical records and patient self-reports.

Overall, the participants reflected a low-risk primary prevention sample with an indication for BP-lowering pharmaceutical monotherapy.[17,18]

Run-in, Treatment, and Washout Periods

All registered participants started a run-in period of 2 weeks using opaque placebo capsules with no background BP-lowering drugs. Participants who completed the run-in period were then assigned to a sequence of 6 treatment periods administered in random order. Every participant had 1 treatment period with candesartan, 16 mg (angiotensin-receptor blocker); lisinopril, 20 mg (angiotensin-converting enzyme inhibitor); amlodipine, 10 mg (calcium channel blocker); and hydrochlorothiazide, 25 mg (thiazide); in addition, every participant repeated 2 of the treatment periods selected at random. Each treatment period was of 7 to 9 weeks' duration, with half doses scheduled for weeks 1 and 2 and full doses for weeks 3 through 9. There were 1-week washout periods with placebo between each treatment period. Participants were provided with 1 opaque capsule per day throughout the study. The 7 to 9 weeks' treatment duration, titration schedules, and selected doses were based on relevant guidelines[17,19] and evidence that carryover effects are negligible after 4 weeks of treatment.[20] Overencapsulation and drug packaging and numbering were performed by Apotek Produktion & Laboratorier AB.

Randomization, Treatment Allocation, and Blinding

All participants received all 4 drugs and were randomized equally to a second treatment period for 2 of the drugs, using a single permuted block of size 300. The order of the 6 treatment periods for each participant was then randomized without restrictions. A research nurse dispensed the investigational product as numbered blister packs of identical opaque capsules, according to a computer-generated list programmed by an independent study statistician.

Outcomes

Participants underwent 24-hour ambulatory BP monitoring during the last 24 hours of the run-in period and each treatment period. Measurements were sought every 20 minutes during the day and every hour during the night with monitors fitted during the morning and removed 24 hours later. Successful registrations were at least 22 hours in duration with at least 2 measurements per hour and 14 measurements in total between 10:00 and 20:00 hours. The primary outcome was daytime (10:00-20:00) ambulatory SBP.[21]

Statistical Methods

The statistical analyses were predefined in the protocol and in the statistical analysis plan, and finalized before unblinding (Supplement 1). The sample size was determined as described in the eMethods in Supplement 2. The targeted estimand was biologic efficacy variation among adherent trial participants, and the primary analysis population, determined before unblinding, comprised all treatment periods with at least 90% adherence and recorded SBP. Adherence was assessed by recording dispensed and returned capsules.

Analysis was performed by allocated treatment, defined as randomized treatment except for 2 periods in 1 participant, for whom the order was accidentally switched without breaking the blinding. We used 2-sided tests with a .05 significance threshold. The analyses were performed using R version 4.1.2,[22] and packages lme4,[23] lmerTest,[24] pbkrtest,[25] nloptr,[26] and MASS.[27]

The primary hypothesis was tested by comparing models that did and did not allow 1 or more treatments to be more effective than other treatments on an individual basis. The null model without participant-specific benefits was a linear mixed model for SBP, with treatment period and 3 independent treatment contrasts as fixed factors, and the intercept as a random factor by participant. The null model was compared with the primary full model, which added random effects by participant for the 3 independent treatment contrasts, allowing unrestricted correlations between the 4 participant-level random effects. All models were fitted using the maximum likelihood approach. The *P* values were obtained by parametric bootstrap with 10 000 iterations, where the likelihood ratio between the fitted full and null models was compared with the empirical distribution of ratios for the 2 models fitted to simulated data sets from the fitted null model.

Heterogeneity for individual treatment contrasts was tested by comparing the full model vs a restricted model removing only 1 of the random effects. Confidence intervals for individual treatment contrast variance parameters were estimated from *P* value curves obtained using parametric bootstrap for selected parameter values, comparing the full model vs a restricted model with 1 variance parameter value fixed. This method was decided post hoc when the predefined method using the lme4[23] package was found not to work. Results are presented for all 6 pairwise treatment contrasts, which are correlated because they are determined by the contrast of 3 of the treatments to the fourth. The pairwise contrasts are considered separate research questions and no multiplicity adjustment was used. Average treatment contrasts were obtained from the primary null model using Satterthwaite degrees of freedom. Predicted mean SBPs for the participants were obtained as conditional means from the primary analysis model at the maximum likelihood fit.

An estimate of theoretical maximum mean gain from personalization in the trial population was calculated by parametric bootstrap from the primary model. Theoretical maximum mean gain from optimal choice between pairs of treatments were obtained by dividing the estimates of standard deviations with the square root of 2π, as follows from standard formulae for the half-normal distribution.

As a secondary analysis of participant-specific treatment contrasts, the data from each set of participants with 2 complete crossovers between 2 treatments were analyzed using linear regression of the treatment contrast in the second crossover on the first crossover. This directly indicated whether a participant's individual treatment difference when switching treatment on one occasion could predict the individual difference if switching again, without which there would be no potential for person-level treatment adaptation. For this analysis, the 2 first periods on each treatment were regarded as the first crossover, and the 2 second treatment periods as the second crossover, although a participant could have both periods with the first treatment before the first period with the second treatment.

Results

We screened 391 participants between February 20, 2017, and May 25, 2020. After placebo run-in, 280 participants were eventually randomized to a total of 1680 scheduled treatment periods. The last participant visit was on June 11, 2021. Participant flow and SBP trajectories are shown in **Figure 1** and eFigure 1 in Supplement 2, respectively, and adverse events are listed in eTables 3 and 4 in Supplement 2. The primary analysis set comprised 1468 periods (median length, 56 days) in 270 participants.

The randomized participants had a mean age of 64 years, and half of them were men (54.3%). The participants had hypertension for a mean of 3 years, 62.1% had previously used BP-lowering monotherapy, and the mean office BP after placebo run-in was 154/89 mm Hg (**Table 1**; eTable 5 in Supplement 2).

Variability in the Effects of Drug Treatments on Blood Pressure

The selected treatment doses were on average not equipotent, with participants having higher BP when taking hydrochlorothiazide than when taking other treatments, when taking amlodipine compared with lisinopril, and when taking candesartan compared with lisinopril (**Table 2**). This is showed graphically in **Figure 2**A, where the blue line illustrates the mean difference in achieved BP for each of the 6 comparisons. The black line is where the line would lie if the doses were equipotent.

Figure 2A also illustrates the large between-patient variability in mean BP, illustrated by the spread of the data points along the diagonals of the plots. Substantial within-patient variability in BP is also showed by the horizontal and/or vertical error bars plotted for the subset of data points that represent patients with 2 intervention periods taking the same treatment. Further, the panel also shows the between-treatment variability in the SBP response within individuals to one treatment vs another. Participants lying above the diagonal black line had higher BP values on the first listed treatment, and participants below the black line had higher BP values on the second listed treatment.

These data showed that variation in SBP was large between treatments on average, between participants on average, within participants taking the same treatment, and between treatments in the same participant.

Evidence of the Potential for Personalized Treatment

The primary assessment of the potential for personalized treatment choices to maximize BP response showed a preference for the model that allowed 1 or more treatments to be more effective than others for an individual compared with a model that assumed no differences in treatment effects between

Figure 1. Participant Flow and Analyzed Treatment Periods in the Precision Hypertension Care (PHYSIC) Trial

[a] Each treatment period consisted of a 1-week placebo washout period, a 2-week dose increase period, and at least 4 weeks at target dose. For each participant, the order of the 6 treatment periods was randomized without restrictions.

[b] Participants who did not complete a treatment period continued with the next period unless withdrawn.

[c] Ten of the 280 randomized participants contributed to zero periods. A participant-level graphic overview of adherence and missing data per treatment period is given in eTable 2 in Supplement 2.

Table 1. Participant Characteristics in a Trial of Antihypertensive Drugs

	Randomized participants (N = 280)[a]
Demographics	
Sex	
Male	152 (54.3)
Female	128 (45.7)
Age, median (range), y	64 (40-76)
Previous medical diagnoses[b]	
Preeclampsia among participants who have been pregnant	13/120 (10.8)
Erection problems among male participants	16/152 (10.5)
Cancer	19 (6.8)
Sleep apnea	16 (5.7)
Raynaud phenomenon	4 (1.4)
Anthropometric and blood pressure characteristics	
Body mass index[c]	29 (15)
Waist circumference, cm	99 (12)
No.	279
Clinic blood pressure at screening, mm Hg	
Systolic	150 (13)
Diastolic	87 (9)
Clinic blood pressure at randomization, mm Hg	
Systolic	154 (9)
Diastolic	89 (8)
Ambulatory daytime blood pressure at end of run-in, mm Hg	
Systolic	145 (11)
Diastolic	89 (9)
Time since hypertension diagnosis, median (IQR), y	3 (1-8)
No.	227
Previous use of any blood pressure medicine	174 (62.1)
Lifestyle[d]	
Smoking	
Regular	6 (2.1)
Occasional	10 (3.6)
Previous	97 (34.6)
Never smoked	167 (59.6)
Pack-years excluding those who never smoked	
No.	103
Median (IQR)	9 (4-18)
Smokeless tobacco (snus), tins or more/wk[e]	
7	3 (1.1)
5-6	3 (1.1)
2-4	16 (5.7)
Up to 2	14 (5.0)
Never used	244 (87.1)
Alcohol	
≥4 times/wk	18 (6.4)
2-3 times/wk	86 (30.7)
2-4 times/mo	118 (42.1)
Up to once/mo	39 (13.9)
Never used	19 (6.8)
Physical activity	
Regular training	38 (13.6)
Regular leisure time physical exercise	97 (34.6)
Moderate leisure time physical activity	128 (45.7)
Sedentary leisure time	17 (6.1)

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure;
[a] Unless specified otherwise, values are shown as mean (SD) or No. (%).
[b] These were the 5 most common diagnoses.
[c] Calculated as weight in kilograms divided by height in meters squared.
[d] The categories presented were those used in the questionnaire.
[e] Snus is a Swedish moist snuff variant.

individuals ($P < .001$; Table 2). Assuming the fitted model to be true, personalized treatment using single-drug therapy would on average lead to a 4.4 mm Hg-lower SBP in the trial population than a fixed choice (eTable 6 in Supplement 2). Taking into consideration that lisinopril was found to be on average most efficacious of the drugs at the selected doses (Table 2), personalized treatment compared with lisinopril would still lead to a 3.1 mm Hg SBP improvement (eTable 7 in Supplement 2). Figure 2B illustrates the findings graphically for each of the 6 treatment comparisons with tight grouping of the data points around the diagonals for the comparisons of candesartan vs lisinopril and amlodipine vs hydrochlorothiazide indicating the constancy of treatment responses to these 2 pairs of drugs. By contrast, the more distributed sets of data points for the other 4 comparisons illustrate the marked differences in responses to treatment between individuals and the corresponding potential for getting a greater treatment effect by selecting one drug instead of the other.

The assumptions of the primary model were checked by normal distribution plots (eFigures 2-4 in Supplement 2) and comparisons of predicted model values to observed data (eFigures 5-6 in Supplement 2). Sensitivity analyses investigating model specification, missing data, and targeted population are presented in eTable 9 and eFigures 7 through 12 in Supplement 2. The homoscedasticity assumption was seen to be violated, with lower within-participant SBP variation with amlodipine than with the other treatments. We performed a number of sensitivity analyses either excluding the amlodipine periods or using models allowing heteroscedastic residuals. The results were close to those from the primary model, with somewhat larger hydrochlorothiazide-amlodipine variation estimates from the heteroscedasticity model. In the primary analysis, 212 of 1680 potential SBP values were unobtained. We repeated the primary analysis only including participants with full adherence and no missing data in any period, and performed analyses including all valid SBP measurements regardless of adherence, by randomized treatment. Both these analyses agreed well with the primary analyses.

In a complementary analysis in only those with 2 crossovers for the treatment pair, we investigated how well a

Table 2. Statistical Analysis of Personal and Mean Treatment Contrasts in On-Treatment Daytime Ambulatory Systolic Blood Pressure (SBP)[a]

Medications compared	No. of measurements	Descriptive statistics: SBP per medication and individual SBP crossover differences per comparison, mean (SD), mm Hg[b]			Average effects: estimated mean difference in the trial population		Personal effects: estimated variation in treatment contrasts between participants[c]		Personal effects: prediction of new individual crossover contrasts		
		First medication[d,e]	Second medication[d,e]	Observed crossover differences[f]	Adjusted treatment differences, SBP, mean (95% CI), mm Hg[g]	*P* value	Variation in treatment differences between participants, SBP, SD (95% CI), mm Hg[h]	*P* value	Differences in crossover differences for individuals with 2 periods for both medications, SBP, mean (SD), mm Hg[i]	Predicted treatment difference at second crossover from difference at first crossover, SBP, mean (95% CI), mm Hg[j]	*P* value
Amlodipine-candesartan	737 Periods in 263 participants	130.9 (8.6)	131.8 (12.8)	-1.2 (12.3)	−0.8 (−1.9 to 0.4)	.18	8.6 (7.1 to 10.3)	<.001	-0.7 (11.6)	0.40 (0.18 to 0.62)	<.001
No.		244	250	232					37		
Amlodipine-lisinopril	722 Periods in 262 participants	130.9 (8.6)	129.7 (12.7)	0.9 (12.3)	1.4 (0.2 to 2.5)	.02	8.9 (7.5 to 10.6)	<.001	-0.09 (11.6)	0.71 (0.36 to 1.05)	<.001
No.		244	241	225					34		
Hydrochlorothiazide-amlodipine	731 Periods in 266 participants	136.1 (10.3)	130.9 (8.6)	5.6 (8.3)	5.1 (3.9 to 6.2)	<.001	2.4 (1.1 to 3.9)	<.001	-0.4 (10.8)	0.33 (−0.07 to 0.73)	.10
No.		253	244	231					33		
Hydrochlorothiazide-candesartan	746 Periods in 265 participants	136.1 (10.3)	131.8 (12.8)	4.4 (12.0)	4.3 (3.2 to 5.4)	<.001	7.2 (5.9 to 8.8)	<.001	-0.08 (10.8)	0.44 (0.05 to 0.82)	.03
No.		253	250	238					36		
Hydrochlorothiazide-lisinopril	731 Periods in 264 participants	136.1 (10.3)	129.7 (12.7)	6.6 (11.6)	6.4 (5.3 to 7.6)	<.001	7.9 (6.3 to 9.5)	<.001	-1.0 (10.6)	0.40 (0.19 to 0.60)	<.001
No.		253	241	230					36		
Lisinopril-candesartan	737 Periods in 262 participants	129.7 (12.7)	131.8 (12.8)	-2.0 (9.6)	−2.1 (−3.3 to -1.0)	<.001	3.6 (0.0 to 5.4)	.15	-2.1 (14.0)	0.11 (−0.18 to 0.40)	.46
No.		241	250	232					39		
Global hypothesis test	1468 Periods in 270 participants					<.001		<.001			

[a] All analyses are based on the primary blood pressure analysis set.

[b] Mean daytime (10:00-20:00) ambulatory SBP.

[c] Predefined primary analysis. The columns are ordered from descriptive to increasingly complex models.

[d] First and second medications as given in the first column, that is, for the lisinopril-candesartan comparison, "first" refers to lisinopril and "second" to candesartan. This does not indicate the order in which participants were given the treatments, which was randomized.

[e] Descriptive statistics for the first period allocated the medication. Half the participants had each treatment allocated also to a second period. The primary blood pressure analysis set comprised all periods with at least 90% adherence and a valid blood pressure measurement. Second period means are given in eTable 8.

[f] Descriptive statistics for the individual observed treatment differences at the first crossover. One-sixth of the participants also were allocated a second crossover between the same treatments. Second crossover differences are given in eTable 8 in Supplement 2.

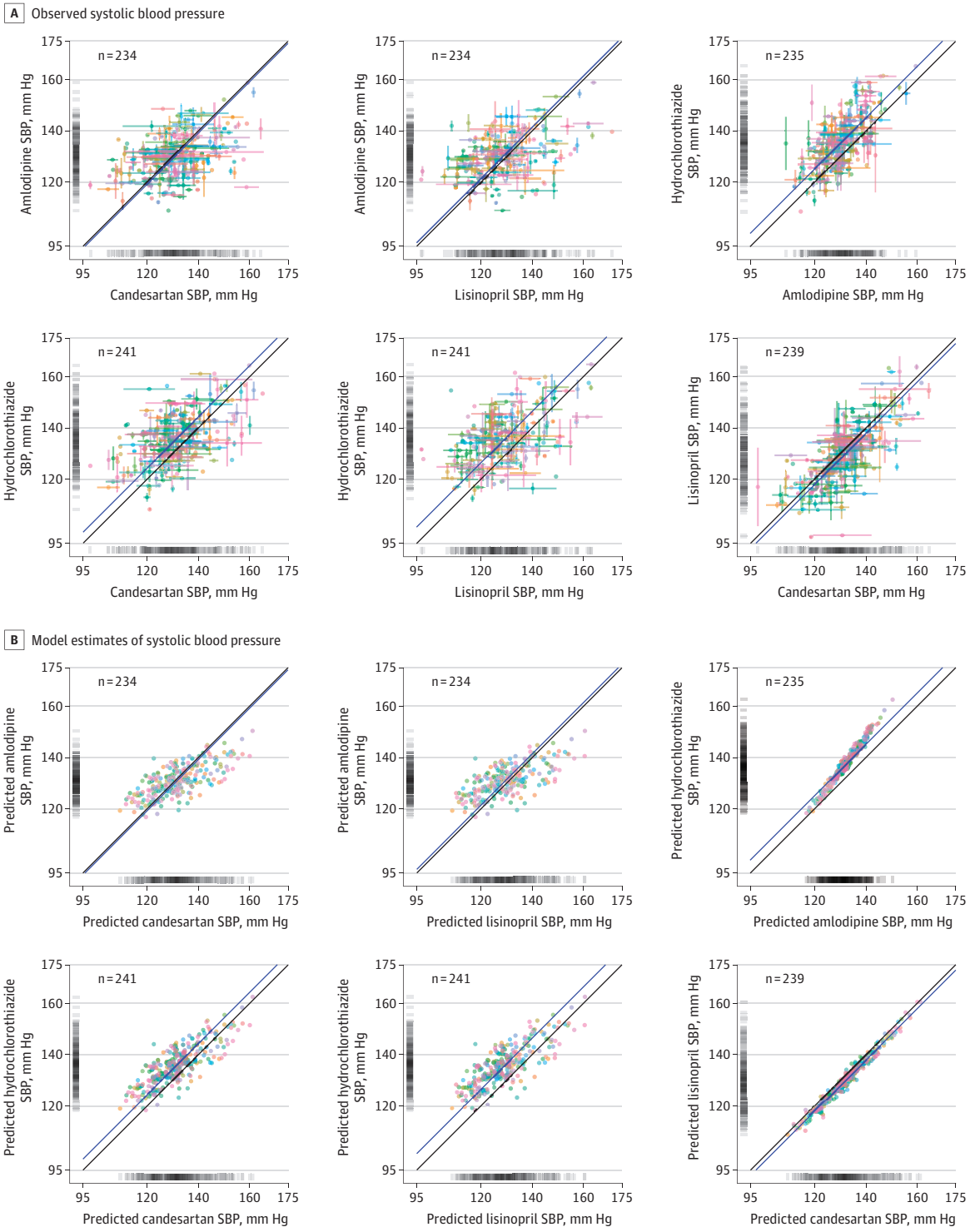
[g] Estimated treatment contrasts under the assumption that the treatment contrasts were the same for all participants. If the actual contrasts were heterogeneous, estimates could be interpreted as the mean treatment contrasts in the trial population. A negative value indicated that the mean SBP among participants was lower with the first medication than with the second medication in the comparison. Linear mixed-effect model with treatment contrasts, and with period as a fixed factor and intercept as a random effect by participant, using Satterthwaite degrees of freedom.

[h] Primary analysis: estimated SD of the treatment contrasts, when treatment contrasts were allowed to vary by individual. The global test was for nonzero SD of any of the 6 treatment contrasts. Larger values indicated more heterogeneous treatment effects. Linear mixed-effect model with intercept and treatment as random effects by participant, with unstructured correlations between intercept and 3 independent treatment contrasts, and with period as a fixed factor. Confidence intervals were taken from *P* value curves constructed using likelihood ratio tests with reference distributions calculated by parametric bootstrap.

[i] Descriptive statistics of the differences between the observed treatment difference at the first crossover for a participant, and the observed treatment difference at the second crossover for the same participant.

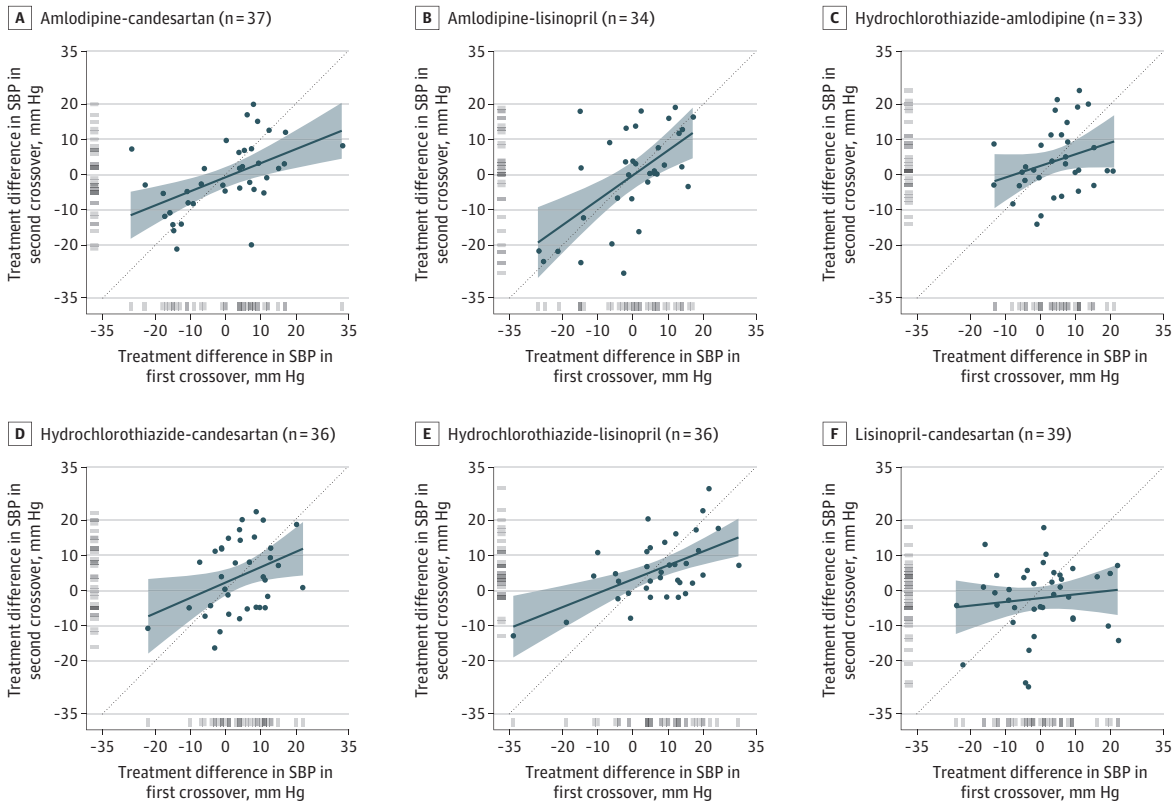
[j] Estimated expected difference in treatment difference in a second crossover, for 2 individuals who differed by 1 mm Hg in treatment difference in the first crossover, also presented as a regression line in Figure 3. Larger values indicated more heterogeneous treatment contrasts. The 6 analyses were based on the disjoint sets of patients with 2 crossovers for a contrast, presented in the first column as the difference between the 2 crossovers, and graphically in Figure 3. Linear regression with the treatment difference at the second crossover as dependent variable, and the treatment difference at the first crossover as independent variable.

Figure 2. Observed and Model Estimates of Mean Daytime Ambulatory Systolic Blood Pressure (SBP): Comparisons Between Pairs of Treatments



Arbitrary colors distinguish participants. The n refers to participants with at least 1 data point with both treatments. A, Dots show observed mean daytime ambulatory SBP at the end-of-treatment periods for 1 participant. For participants with data from 2 periods, individual period values are given by error bars; the dot is at the participant mean. The black line signifies no difference between treatments; participants above the line had higher SBP on the y-axis than on the x-axis treatment. The blue line is shifted by the mean treatment contrast in the trial population. To show all 6 pairwise comparisons, the same BP values for each treatment appear in 3 panels. Hash marks on the axes show marginal distributions. B, Conditional mean SBP from the fitted primary model. Each dot represents best estimates of the unknown real mean SBP for each participant with each treatment underlying the measured SBP values in panel A. Estimates include the mean difference between treatments, person-specific overall SBP, and person-specific treatment contrasts. Dots close to the blue line indicate participants with low estimated gain from personalization.

Figure 3. Crossover Differences in Mean On-Treatment Daytime Ambulatory Systolic Blood Pressure (SBP): Second Difference by First Difference



Each dot denotes a participant with 2 crossovers for that pair of treatments. In each panel, both axes show a difference in SBP on the first listed drug minus the second listed drug, for example, SBP on amlodipine minus SBP on candesartan. The x-axis shows the difference in the first crossover, and the y-axis the difference in the second crossover, in the same participant. The order of treatments in each crossover was randomized. The regression lines (blue lines) are from the analyses presented rightmost in Table 2, and the shaded areas the pointwise 95% CIs. The dotted diagonal lines represent identical treatment differences at the first and second crossovers. The hash marks on the axes show the marginal distributions. If there is a potential for personalized treatment choice, a better than mean result of one drug vs the other at the first crossover should be associated with the same participant having a better than mean result also at the second crossover. Conversely, absence of such a pattern indicates lack of potential for personalization.

participant's treatment difference at the first crossover between 2 treatments predicted the same difference at a repeated crossover (**Figure 3** and Table 2). Once again, there was no evidence of personalized effects for the comparisons of candesartan vs lisinopril or amlodipine vs hydrochlorothiazide, but there were significant correlations across the first and second comparisons for all other treatment pairs. This analysis had lower power but was less model-dependent, and the similarity of the results showed the robustness of our findings. To further decrease model dependence, we also performed nonparametric tests, giving similar results (eTable 10 in Supplement 2).

Discussion

This study provided evidence that widely used antihypertensive drugs vary in effectiveness between individuals, with potential for greater BP reductions with personalized targeting of therapy. The mean additional BP reduction achievable was substantial, of a magnitude twice that achieved by doubling the dose of a first BP-lowering drug, and more than half that of adding a second drug[28] on average.

Using the robust repeated crossover design that separates time period from treatment effects, this study was able to rule out large differences in response to some therapies—candesartan vs lisinopril and amlodipine vs hydrochlorothiazide—showing that within these pairs the choice of therapy was unimportant for most. However, for all other comparisons tested, the choice was important with particularly large gains to be made by personalizing the choice between candesartan vs amlodipine and for choosing between lisinopril vs amlodipine.

The potential for large BP-lowering gains from personalizing antihypertensive therapy highlights the need for a mechanism that can be used to identify which individuals will benefit most from which treatments. Broadly, personalizing therapy could be achieved either by identifying the phenotypic characteristics that are associated with enhanced response to one treatment vs another or by directly measuring the individual's responses to a series of treatments to ascertain which is most effective. The first is a method

widely used to tailor therapies to patients with cancer where treatment selection is targeted, for example, to the expression of specific receptors. An example of the latter is continuous blood glucose monitoring, which has transformed the capacity to define the effects of different glucose-lowering therapies and to tailor treatment to individuals. Considering noninvasive, wearable BP measurement devices under development, it is possible to imagine a future where continuous BP measurement could differentiate between the effectiveness of multiple drug therapies provided to patients in standardized n-of-1 testing protocols. Of note, this study does not propose the year-long process for each patient used in this trial to identify an individual's optimal treatment.

A key strength of this study was that it was designed explicitly to assess the potential for personalized medicine in a complex multifactorial disease.[8] The repeated crossover design is recognized as the gold standard approach[8,15,16] (limitations of other trial designs are shown in eFigure 13 in Supplement 2) and has for the first time been used with high fidelity in this study. Repeated crossover designs are underused, but they could be more challenging in other settings. Hypertension is well suited for the repeated crossover design, with 4 drug class choices in clinical equipoise, and BP is a well-behaved outcome variable because it is continuous and normally distributed on a clinically relevant scale. A specific benefit of a well-powered repeated crossover trial is the ability to not only detect the potential for benefits from personalized treatment, but also to exclude effects. For example, the current study found that little would be gained by personalizing the choices of lisinopril vs candesartan or hydrochlorothiazide vs amlodipine. The absence of any potential benefit from choosing between the 2 agents inhibiting the renin-angiotensin-aldosterone system provides some reassurance about the validity of the study—these 2 agents share multiple aspects of their mechanisms of action. In the same way, the benefits of personalization observed for 4 of the 5 other comparisons between drugs with quite different mechanisms of action aligns with expectations,[10] though the reason for the absence of a potential for benefit from personalizing hydrochlorothiazide vs amlodipine therapy is unclear. The consistency of the findings across the primary analyses based on all participants, as well as the analyses restricted to the repeat comparisons, also provides support for the primary conclusions about the importance of heterogeneity in BP response to therapy.

Limitations

The study also had some limitations. First, the study was done in a specific patient group and with a specific set of drugs. The run-in period and the single-center design could lead to a more homogenous sample than general grade 1 hypertension populations, which could lead to an underestimation of heterogeneity in treatment effects, although between-person BP variability in this study was very similar to that in a large population-based sample.[29] Whether the results are generalizable to other individuals and across the drug classes is uncertain.

Second, while this study tried to select equipotent doses of the drugs, in some comparisons this was not achieved. However, this does not invalidate the study of the research question because the analysis is focused on the constancy of within-person and between-person responses, and this evaluation does not depend on the drugs being equipotent.

Third, there was some nonadherence to scheduled treatment regimens, and this may have attenuated the statistical power of the study. On average, though, adherence to the trial protocol was very high.

Fourth, the study evaluated effects of monotherapy for practical reasons, but it is likely that there would also be benefits from personalization of the dual combination therapies recommended for initial treatment by most guidelines. Optimizing monotherapy also has significant potential value in its own right because many patients still use single-drug therapy because of nonadherence[5] or adverse effects.[4] Despite different names for the same BP strata, current European[18] and American[30] guidelines both recommend initiating treatment at an SBP of 140 mm Hg for all with low risk of cardiovascular events; while the European guidelines have a place for monotherapy in these persons, the American guidelines recommend combination therapy for them. Calculation of risk was not possible in this study due to a lack of lipid assessments.

Conclusions

The data from this study provide evidence of a substantial heterogeneity in BP response to drug therapy for hypertension. Given the size of the likely benefits, additional studies to confirm these findings, to test for the potential of personalization of combination antihypertensive therapy, and to identify mechanisms to enable the personalization of antihypertensive therapy in routine clinical practice should be a priority.

ARTICLE INFORMATION

Accepted for Publication: February 21, 2023.

Author Contributions: Dr Östlund had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Sundström, Lind, Nowrouzi, Lytsy, Marttala, Östlund.
Acquisition, analysis, or interpretation of data: Sundström, Nowrouzi, Hagström, Held, Neal, Östlund.
Drafting of the manuscript: Sundström, Nowrouzi, Östlund.
Critical revision of the manuscript for important intellectual content: Lind, Nowrouzi, Hagström, Held, Lytsy, Neal, Marttala, Östlund.
Statistical analysis: Östlund.
Obtained funding: Sundström.
Administrative, technical, or material support: Sundström, Lind, Nowrouzi, Neal, Marttala.
Supervision: Sundström, Nowrouzi.
Other - Data collection: Held.

Conflict of Interest Disclosures: Dr Sundström reported owning stock in Symptoms Europe AB and Anagram Kommunikation AB. Dr Hagström reported receiving grants from Pfizer and Amgen and personal fees from Amgen, Novo Nordisk, Bayer, AstraZeneca, Amarin, and Novartis. Dr Östlund reported fees from Uppsala University paid to his institution, Uppsala Clinical Research Center, for its participation in the PHYSIC trial during the conduct of the study. No other disclosures were reported.

Funding/Support: This study was supported by the Swedish Research Council (grant 921-2014-7126), Kjell and Märta Beijer Foundation, and Anders Wiklöf.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and

interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We thank Lars Lindhagen, PhD, Uppsala Clinical Research Center, for reviewing the statistical analysis and suggesting valuable improvements for numerical optimization. He did not receive compensation.

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