Heterogeneity in Blood Pressure Response to Four Antihypertensive Drugs: A Randomized Repeated Crossover Trial

Johan Sundström,[1,2] MD PhD; Lars Lind,[1] MD PhD; Shamim Nowrouzi,[1] MD; Emil Hagström,[1] MD PhD; Claes Held,[1] MD PhD; Per Lytsy,[1] MD PhD; Bruce Neal,[2] MD PhD; Kerstin Marttala,[1] RN; Ollie Östlund,[3] PhD

[1]Department of Medical Sciences, Uppsala University, Uppsala, Sweden; [2]The George Institute for Global Health, University of New South Wales, Sydney, Australia; [3]Uppsala Clinical Research Center, Uppsala, Sweden

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Correspondence to: Johan Sundström, Department of Medical Sciences, Uppsala University Hospital, Entrance 40, 5th floor, 75185 Uppsala, Sweden, johan.sundstrom@uu.se

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. We estimated that personalized treatment choice would on average lead to 4.4 mmHg 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.

Abstract

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

We hypothesized that there is potential for targeting specific drugs to specific individuals to maximize blood pressure effects; and investigated and quantified that potential.

Design, setting and participants

We conducted a randomized, double-blind, repeated crossover trial in low-risk men and women with grade 1 hypertension. 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 four different classes of blood pressure-lowering drugs - lisinopril, candesartan, hydrochlorothiazide and amlodipine - with repeated treatments for two classes.

Main outcome

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 ($p<0.0001$), 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, we estimated that personalized treatment had the potential to provide an additional 4.4 mmHg systolic blood pressure lowering.

Conclusions and Relevance

These data reveal a substantial heterogeneity in blood pressure response to drug therapy for hypertension. More well-designed trials of personalized therapy are warranted because very large numbers are treated with these therapies and cardiovascular protection is highly dependent on the achieved blood pressure reduction.

Trial registration

ClinicalTrials.gov NCT02774460.

Introduction

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-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 side effects and non-adherence being important clinical problems.[3-5]

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

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

We hypothesized that there is the potential for targeting specific drugs to specific individuals to maximize blood pressure effects and report here the findings of the Precision HYpertenSIon Care (PHYSIC) trial (ClinicalTrials.gov NCT02774460).[14]

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 blood pressure 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 trial followed a protocol pre-registered at ClinicalTrials.gov with the identifier NCT02774460 and the full protocol can be obtained from the authors. 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 gave written informed consent.

Eligibility and consent

Patients were eligible to register for the trial if they: (1) were aged ≥40 years and ≤75 years (male or female); (2) had been previously diagnosed with hypertension, with systolic blood pressure (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 blood pressure-lowering monotherapy at the inclusion visit; (4) willing and able to discontinue current blood pressure 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 blood pressure-lowering medication during the placebo run-in period; and (2) had an office SBP between 140 and 179 mm Hg, and diastolic blood pressure at or below 109 mm Hg at the randomization visit.

Exclusion criteria are listed in Table S1, and involved conditions such as possible secondary hypertension, other serious disease, gout, cardiovascular diseases, renal 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 blood pressure-lowering pharmaceutical monotherapy.[17,18]

Run-in, treatment and washout periods

All registered participants were commenced on a run-in period of 2 weeks using opaque placebo capsules with no background blood pressure-lowering drugs. Participants that completed the run-in period were then assigned to a sequence of six treatment periods administered in random order. Every participant has one treatment period on candesartan 16 mg; lisinopril 20 mg; amlodipine 10 mg; and hydrochlorothiazide 25 mg; in addition, every participant repeated two of the treatment periods selected at random. Each treatment period was of 7–9 weeks duration with half-dose scheduled for weeks 1–2 and full dose for weeks 3–9. There were one week wash-out periods with placebo between each treatment period. Participants were provided with one opaque capsule per day throughout the study. The 7–9 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] Over-encapsulation, and drug packaging and numbering were performed by Apotek Produktion & Laboratorier AB (APL).

Randomization, treatment allocation and masking

All participants received all four drugs and were randomized equally to a second treatment periods for two of the drugs, using a single permuted block of size 300. The order of the six 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 blood pressure monitoring during the last 24 hours of the run-in period and each treatment period. Measurements were sought every 20 min 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 h in duration with at least two measurements per hour and 14 measurements in total between 10:00 and 20:00 h. The primary outcome was daytime (10:00–20:00) ambulatory systolic blood pressure (SBP).[21]

Statistical methods

The statistical analyses were pre-defined in the protocol and in the statistical analysis plan, finalized before unblinding. The sample size was determined as described in Supplementary Methods. 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 two periods in one participant, where the order was accidentally switched without breaking the blinding. The analyses were performed using R v. 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 one 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 three independent treatment contrasts as fixed factors, and the intercept as a random

factor by participant. The null model was compared to the primary 'full' model, which added random effects by participant for the three independent treatment contrasts, allowing unrestricted correlations between the four 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 to the empirical distribution of ratios for the two models fitted to simulated data sets from the fitted null model.

Heterogeneity for individual treatment contrasts was tested by comparing the full model to a restricted model removing only one 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 to a restricted model with one variance parameter value fixed; this method was decided post-hoc when the pre-defined method using the lme4[23] package was found not to work. Results are presented for all six pairwise treatment contrasts, which are correlated since they are determined by the contrast of three 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 SBP 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 two complete crossovers between two 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 two first periods on each treatment were regarded as the first crossover, and the two second treatment periods as the second crossover, although a participant could have both periods on the first treatment before the first period on 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 illustrated in Figure 1 and S1, and adverse events are listed in Table S3 and S4. The primary analysis set comprised 1468 periods (median length, 56 days) in 270 participants.

The randomized participants were on average 64 years old, and half of them were men. The participants had suffered from hypertension for, on average, 3 years, two-thirds had previously used blood pressure-lowering monotherapy, and the office blood pressure after placebo run-in was on average 154/89 mmHg (Table 1 and S5).

Variability in the effects of drug treatments on blood pressure

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

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

In summary, these data show that variation in SBP was large between treatments on average, between participants on average, within participants on 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 blood pressure response showed a preference for the model that allowed one or more treatments to be more effective than other for an individual, compared to a model that assumed no differences in treatment effects between individuals ($p<0.0001$; Table 2). Assuming the fitted model to be true,

personalized treatment using single drug therapy would on average lead to a 4.4 mmHg lower SBP in the trial population than a fixed choice (Table S6). 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 to lisinopril would still lead to a 3.1 mmHg SBP improvement (Table S7). Figure 2, Panel B, illustrates the findings graphically for each of the six treatment comparisons with tight grouping of the datapoints around the diagonals for the comparisons of candesartan vs lisinopril and amlodipine vs hydrochlorothiazide indicating the constancy of treatment responses to these two pairs of drugs. By contrast, the more distributed sets of data points for the other four 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 (Figure S2-S4) and comparisons of predicted model values to observed data (Figure S5-S6). Sensitivity analyses investigating model specification, missing data and targeted population are presented in Table S9 and Figure S7-S12. The heteroscedasticity assumption was seen to be violated, with lower within-participant SBP variation on amlodipine than on the other treatments. We performed a number of sensitivity analyses either excluding the amlodipine arm, or using models allowing heteroscedastic residuals. The results are 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 two crossovers for the treatment pair, we investigated how well a participant's treatment difference at the first crossover between two 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 comparison for all other treatment pairs. This analysis has lower power but is less model-dependent, and the similarity of the results show the robustness of our findings. To further decrease model dependence, we also performed nonparametric tests, giving similar results (Table S10).

Discussion

We provide evidence that widely used antihypertensive drugs vary in effectiveness between individuals, with potential for greater blood pressure reductions with personalized targeting of therapy. The average additional blood pressure reduction achievable is substantial, of a magnitude twice that achieved by doubling the dose of a first blood pressure 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, we were 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 we 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 blood pressure-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 cancer patients 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 our capacity to define the effects of different glucose lowering therapies and to tailor treatment to individuals. Considering non-invasive, wearable blood pressure measurement devices under development, it is possible to imagine a future where continuous blood pressure measurement could differentiate between the effectiveness of multiple drug therapies provided to patients in standardized *n-of-1* testing protocols. Of note, we do 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 that is that it has been 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 illustrated in Figure S13) and has for the first time been used with high fidelity in this project. We think repeated crossover designs are underused, but note that they could be more challenging in other settings. Hypertension is well suited for the repeated crossover design, with four drug class choices in clinical equipoise, and blood pressure is a well-behaved outcome variable; 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, in the current study, we 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 two agents inhibiting the renin-angiotensin aldosterone system provides some reassurance about the validity of the study – these two agents share multiple aspects of their mechanisms of action. In the same way, the benefits of personalization observed for four of the five 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 blood pressure response to therapy.

The study also has some caveats. 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 blood pressure 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. While we tried to select equipotent doses of the drugs, in some comparisons we did not achieve this. 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. There was some non-adherence 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. 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 non-adherence[5] or side-effects.[4] Despite different names for the same blood pressure strata, current European[18] and American[30] guidelines both recommend initiating treatment at a SBP of 140 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.

In conclusion, these data provide evidence of a substantial heterogeneity in blood pressure 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.

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Author contributions

Authors contributed to the following: conceptualization (JS, LL, OÖ, PL), funding acquisition, resources and supervision (JS, LL), project administration (JS, KM), investigation (JS, LL, SN,

EH, CH, KM), data curation, statistical analysis and visualization (OÖ), writing of original draft (JS, OÖ), review and editing of draft (all authors).

Competing interest declaration

JS reports stock ownership in Symptoms Europe AB and Anagram kommunikation AB, outside of the submitted work. All other authors report no competing interests.

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Data sharing

Data and additional related documents may be available from the corresponding author on reasonable request.

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Tables

Table 1. Participant characteristics

			Randomized participants (N=280)[a]
Demographics		Male sex	152 (54.3)
		Female sex	128 (45.7)
		Age, median (range)	64 (40-76)
Previous medical diagnoses[b]		Pre-eclampsia, 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's phenomenon	4 (1.4)
Anthropometric and blood pressure characteristics		Body mass index (kg/m^2)	29 (15)
		Waist circumference (cm)	99 (12) [n=279]
		Clinic SBP at screening (mmHg)	150 (13)
		Clinic DBP at screening (mmHg)	87 (9)
		Clinic SBP at randomization (mmHg)	154 (9)
		Clinic DBP at randomization (mmHg)	89 (8)
		Ambulatory daytime SBP at end of run-in (mmHg)	145 (11)
		Ambulatory daytime DBP at end of run-in (mmHg)	89 (9)
		Time since hypertension diagnosis (years), median (Q1, Q3)	3 (1, 8) [N=227]
		Previous use of any blood pressure medicine	174 (62.1)
Lifestyle[c]	**Smoking**	Regular	6 (2.1)
		Occasional	10 (3.6)
		Previous	97 (34.6)
		Never smoked	167 (59.6)
		Pack years excluding never smokers, median (Q1, Q3)	9 (4, 18) [n=103]
	Smokeless tobacco (snus)[d]	7 tins or more per week	3 (1.1)
		5-6 tins per week	3 (1.1)
		2-4 tins per week	16 (5.7)
		Up to 2 tins per week	14 (5.0)

		Never used	244 (87.1)
	Alcohol	4 times per week or more	18 (6.4)
		2-3 times per week	86 (30.7)
		2-4 times per month	118 (42.1)
		Up to once per month	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)

[a]Unless specified otherwise, values are shown as mean (standard deviation) or N (%). SBP, systolic blood pressure; DBP, diastolic blood pressure; Q, quartile. [b]These were the five most common diagnoses. [c]The categories presented were those used in the questionnaire. [d]Snus is a Swedish moist snuff variant.

Table 2. Statistical analysis of personal and average treatment contrasts in mean on-treatment daytime ambulatory systolic blood pressure

		A. Descriptive statistics: SBP[a] per medication, and individual SBP crossover differences per comparison			**B. Average effects: estimated mean difference in the trial population**		**C. Personal effects: estimated variation in treatment contrasts between participants[b]**		**D. Personal effects: prediction of new individual crossover contrasts**		
Medications compared	**Number of measurements**	**First[c] medication, SBP[d] (mmHg), mean (SD[e])**	**Second[c] medication, SBP[d] (mmHg), mean (SD)**	**Observed[f] crossover differences, SBP (mmHg), mean (SD)**	**Adjusted treatment differences[g], SBP (mmHg), mean (95% CI[h])**	**p-value**	**Variation in treatment differences between participants[i], SBP (mmHg), SD (95% CI)**	**p-value**	**Differences in crossover differences for individuals with two periods for both medications[j], SBP (mmHg), mean (SD)**	**Predicted treatment difference at second crossover from difference at first crossover[k], SBP (mmHg), mean (95% CI)**	**p-value**
Amlodipine–candesartan	737 periods in 263 participants	130.9 (8.6) [N=244]	131.8 (12.8) [N=250]	–1.2 (12.3) [N=232]	-0.8 (-1.9; 0.4)	.18	8.6 (7.1; 10.3)	<.001	–0.7 (11.6) [N=37]	0.40 (0.18; 0.62)	<.001
Amlodipine–lisinopril	722 periods in 262 participants	130.9 (8.6) [N=244]	129.7 (12.7) [N=241]	0.9 (12.3) [N=225]	1.4 (0.2; 2.5)	.018	8.9 (7.5; 10.6)	<.001	–0.09 (11.6) [N=34]	0.71 (0.36; 1.05)	<.001

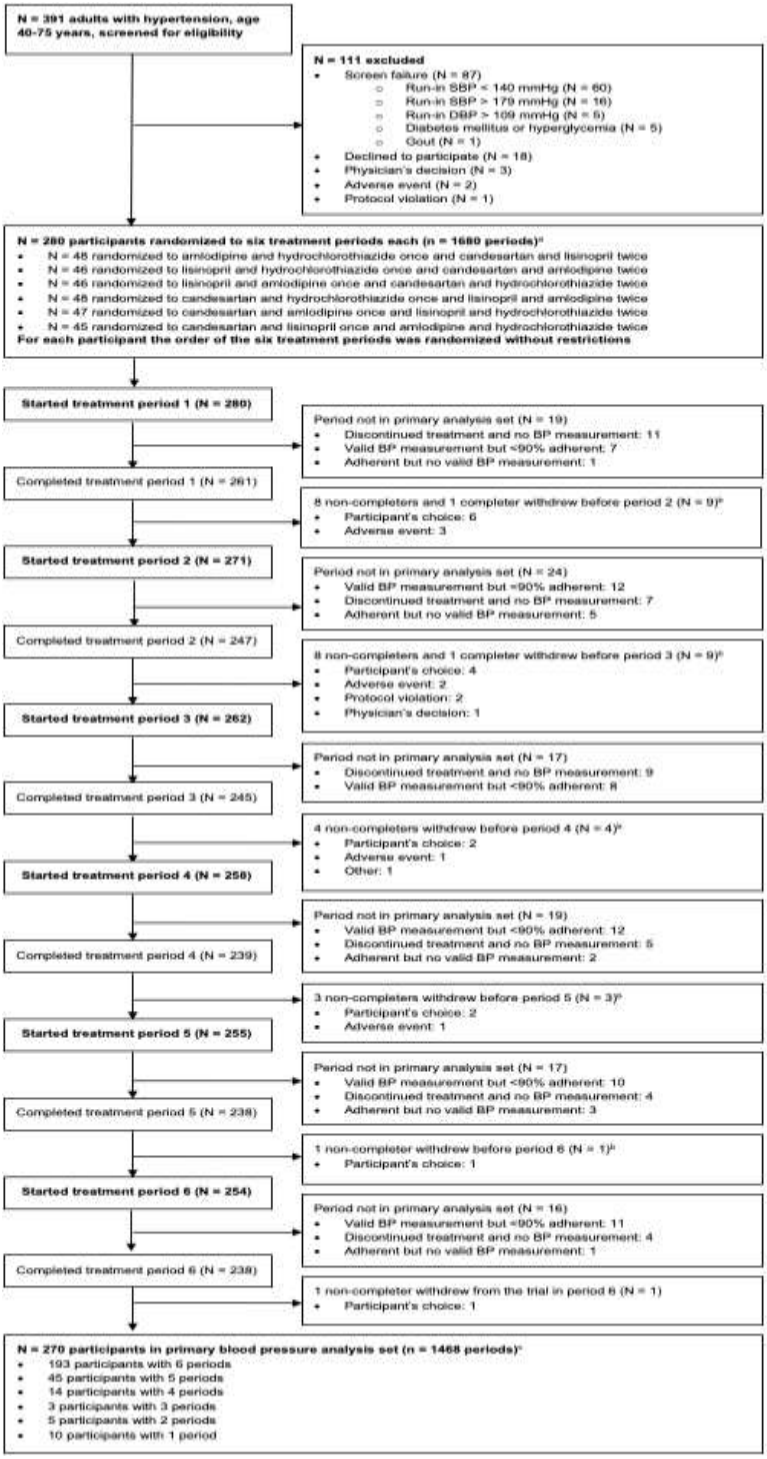
Hydrochlorothiazide –amlodipine	731 periods in 266 participants	136.1 (10.3) [N=253]	130.9 (8.6) [N=244]	5.6 (8.3) [N=231]	5.1 (3.9; 6.2)	<.001	2.4 (1.1; 3.9)	<.001	–0.4 (10.8) [N=33]	0.33 (-0.07; 0.73)	.10
Hydrochlorothiazide –candesartan	746 periods in 265 participants	136.1 (10.3) [N=253]	131.8 (12.8) [N=250]	4.4 (12.0) [N=238]	4.3 (3.2; 5.4)	<.001	7.2 (5.9; 8.8)	<.001	–0.08 (10.8) [N=36]	0.44 (0.05; 0.82)	.027
Hydrochlorothiazide –lisinopril	731 periods in 264 participants	136.1 (10.3) [N=253]	129.7 (12.7) [N=241]	6.6 (11.6) [N=230]	6.4 (5.3; 7.6)	<.001	7.9 (6.3; 9.5)	<.001	–1.0 (10.6) [N=36]	0.40 (0.19; 0.60)	<.001
Lisinopril–candesartan	737 periods in 262 participants	129.7 (12.7) [N=241]	131.8 (12.8) [N=250]	–2.0 (9.6) [N=232]	-2.1 (-3.3; -1.0)	<.001	3.6 (0.0; 5.4)	0.15	–2.1 (14.0) [N=39]	0.11 (-0.18; 0.40)	.46
Global hypothesis test	**1468 periods in 270 participants**					**<.001**		**<.001**			

All analyses are based on the primary blood pressure analysis set. [a] SBP, mean daytime (10:00–20:00) ambulatory systolic blood pressure. [b] Pre-defined primary analysis. The columns in the table are ordered from descriptive to increasingly complex models. [c] First and second medication 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. [d] Descriptive statistics for the first period allocated the medication. Half the participant had each treatment allocated also to a second period. The primary blood pressure analysis set comprises all periods with at least 90% adherence and a valid blood pressure measurement. Second period means are given in Table S8.[e] SD, standard deviation. [f] Descriptive statistics for the individual observed treatment differences at the first crossover. 1/6 of the participants also were allocated a second crossover between the same treatments. Second crossover differences are given in Table S8. [g] Estimated treatment contrasts under the assumption that the treatment contrasts are the same for all participants. If the actual contrasts are heterogeneous, these estimates can be interpreted as the average treatment

contrasts in the trial population. A negative value indicates that the average SBP among participants was lower on the first medication than on the second medication in the comparison. Linear mixed effect model with treatment as a factor and intercept as a random effect by participant, using Satterthwaite degrees of freedom. [h] CI, Confidence interval. [i] Primary analysis: Estimated standard deviation of the treatment contrasts, when treatment contrasts are allowed to vary by individual. The global test is for non-zero standard deviation of any of the six treatment contrasts. Larger values indicate more heterogeneous treatment effects. Linear mixed effect model with intercept and treatment as random effects by participant, with unstructured correlations between intercept and three independent treatment contrasts. Confidence intervals are taken from p-value curves constructed using likelihood ratio tests with reference distributions calculated by parametric bootstrap. [j] 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. [k] Estimated expected difference in treatment difference in a second crossover, for two individuals that differed by 1 mmHg in treatment difference in the first crossover, also presented as a regression line in Figure 3. Larger values indicate more heterogeneous treatment contrasts. The six analyses are based on the disjoint sets of patients with two crossovers for a contrast, presented in the first column as the difference between the two 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.

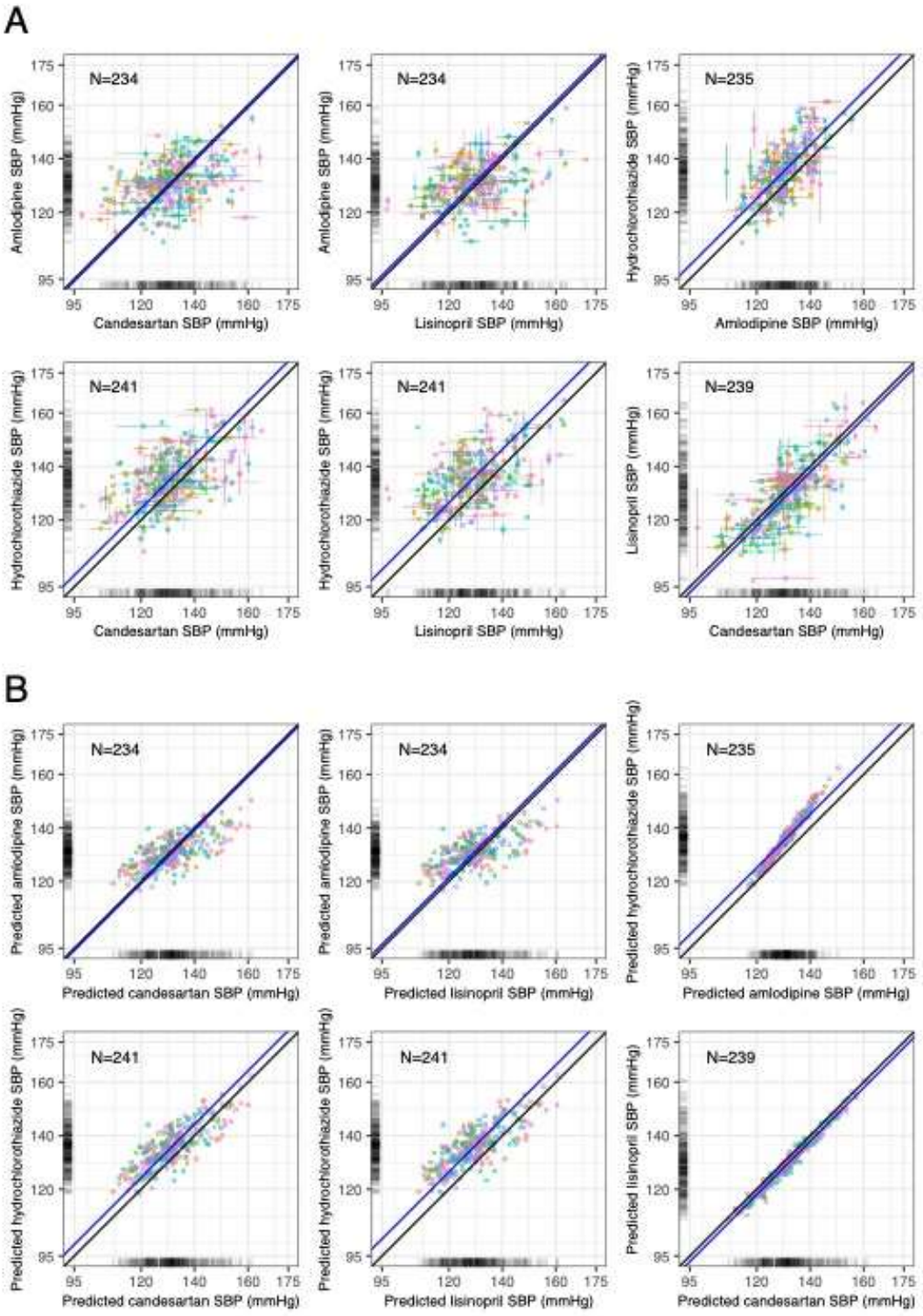
Figures

Figure 1. Participant flow and analyzed treatment periods



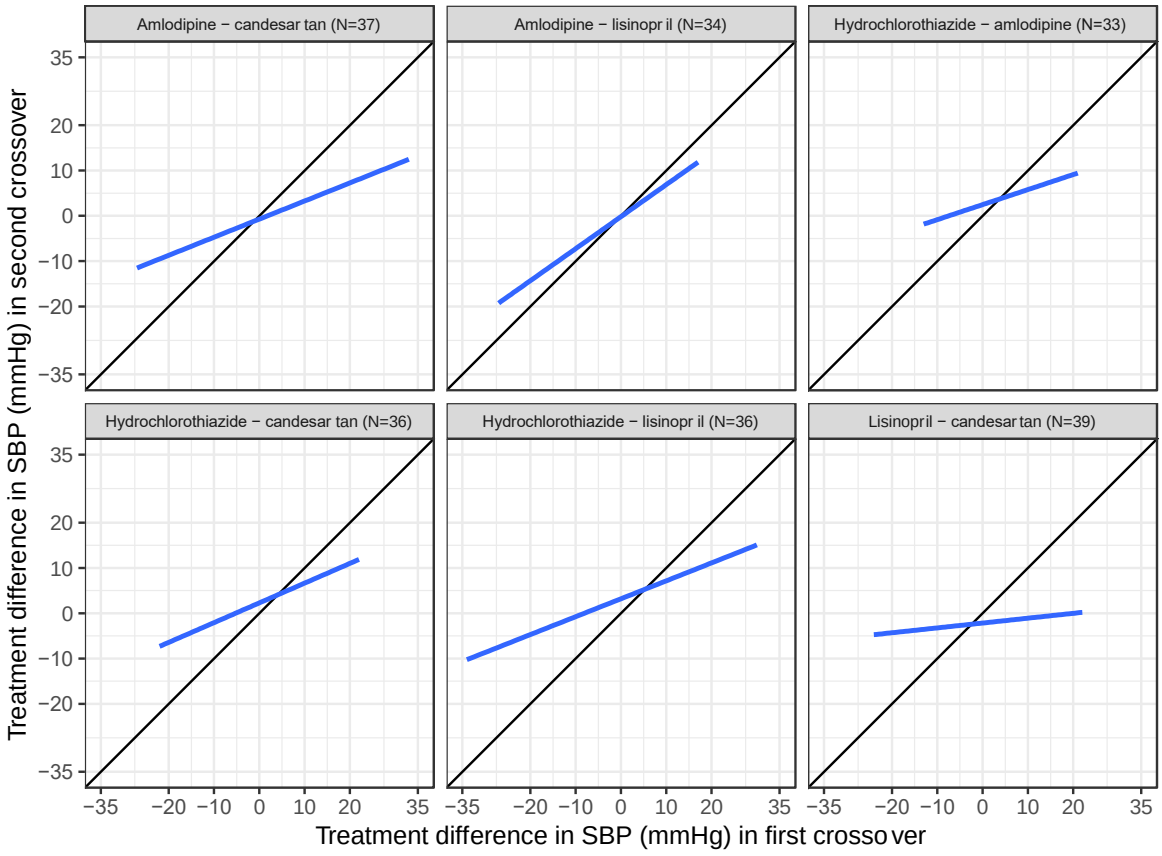
[a]Each treatment period consisted of a 1-week placebo wash-out period, a 2-week dose increase period, and at least 4 weeks at target dose. [b]Participants that did not complete a treatment period continued with the next period in the trial unless withdrawn. [c]Ten of the 280 randomized participants contributed with zero periods. A participant-level graphic overview of adherence and missing data per treatment period is given in Table S2.

Figure 2. Observed (panel A) and model estimates of (panel B) mean on-treatment daytime ambulatory systolic blood pressure, comparisons between pairs of treatments



Different (arbitrary) colors are used to distinguish participants. For each panel, N refers to the number of participants with at least one data point on both treatments. Panel A: Each dot shows observed mean daytime ambulatory systolic blood pressures (SBP) at the end of treatment periods for one participant. For participants with data from two periods on a treatment, the individual period values are given by the error bar end points, while the dot is at the participant mean. For participants with only one period, the dot is at the single period value without a bar. Participants with two periods on both treatments are shown as dots with both horizontal and vertical error bars. The black line signifies the plot of no difference between treatments; participants above the line had higher SBP on the treatment on the y axis than on the treatment on the x axis. The blue line is shifted by the average treatment contrast in the trial population. Note that to show all (six) pairwise comparisons, the same on-treatment blood pressure values for each treatment appear in three panels, either on the x- or y-axis. The hash marks on the axes show the marginal distributions. Panel B: Conditional mean SBP from the fitted primary model, described in Statistical Methods. Each dot represents best estimates of the unknown "real" mean SBP for each individual participant on each treatment, underlying the measured SBP values presented in Panel A. The estimates include the average difference between treatments, person-specific overall SBP, and person-specific treatment contrasts. Dots close to the blue line of average treatment difference indicate participants with low estimated gain from personalization between those two treatments.

Figure 2. Crossover differences in mean on-treatment daytime ambulatory systolic blood pressure, second difference by first difference



Each dot denotes a participant with two 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 are from the analyses presented rightmost in Table 2, and the shaded area the pointwise 95% confidence interval. The hash marks on the axes show the marginal distributions. If there is a potential for personalized treatment choice, a better than average result of one drug vs the other at the first crossover should

be associated with the same participant having a better than average result also at the second crossover. Conversely, absence of such a pattern indicates lack of potential for personalization.