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ORIGINAL ARTICLE

Can we identify response markers to antihypertensive drugs? First results from the IDEAL Trial

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Current antihypertensive strategies do not take into account that individual characteristics may influence the magnitude of blood pressure (BP) reduction. Guidelines promote trial-and-error approaches with many different drugs. We conducted the Identification of the Determinants of the Efficacy of Arterial blood pressure Lowering drugs (IDEAL) Trial to identify factors associated with BP responses to perindopril and indapamide. IDEAL was a cross-over, double-blind, placebo-controlled trial, involving four 4-week periods: indapamide, perindopril and two placebo. Eligible patients were untreated, hypertensive and aged 25–70 years. The main outcome was systolic BP (SBP) response to drugs. The 112 participants with good compliance had a mean age of 52. One in every three participants was a woman. In middle-aged women, the SBP reduction from drugs was − 11.5 mm Hg (indapamide) and − 8.3 mm Hg (perindopril). In men, the response was significantly smaller: − 4.8 mm Hg (indapamide) and − 4.3 (perindopril) (*P* for sex differences 0.001 and 0.015, respectively). SBP response to perindopril decreased by 2 mm Hg every 10 years of age in both sexes ($P = 0.01$). The response to indapamide increased by 3 mm Hg every 10 years of age gradient in women ($P = 0.02$). Age and sex were important determinants of BP response for antihypertensive drugs in the IDEAL population. This should be taken into account when choosing drugs *a priori*.

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INTRODUCTION

Some current guidelines[1,2] on drugs for treating hypertension do not recommend the first choice of a specific drug class, although the mechanisms of action and consequences on hemodynamic regulation systems are completely different from one drug class to another. This is because blood pressure (BP) reduction is considered the only acting mechanism in these drugs to reduce cardiovascular risk, and there is no clear *a priori* marker for a class-specific drug effect. This paradigm has tremendous consequences in the management of drug treatment, for example, in giving a major role to the concept of BP control. This concept has been oversimplified, giving the same numerical value to the BP definition of hypertension and to the BP target to be reached with treatment. This has led to recommendations on drugs for treatment of hypertension even in mild or grade I hypertension, only by extrapolating benefits observed in the more severe hypertension of high-risk patients with or without hypertension. This lack of solid evidence to support such treatments in mild hypertensive people has been acknowledged in these same guidelines and confirmed in a recent meta-analysis.[3] This paradigm of BP control also encourages further BP lowering by increasing the antihypertensive drug burden, even if this burden increase has not been associated with a clinical benefit.[4]

Alternative paradigms could be considered, (1) that would distinguish between BP reduction-specific effects and BP-independent, probably class-specific effects; and (2) that would specifically explore response markers to these two components of risk control with BP-lowering drugs. The rationale for such alternatives is that BP control does not explain all the risk reduction observed with treatment,[5,6] that BP-independent mechanisms do have a role in this risk reduction[7] and that class-specific response markers have already been suggested.[8]

Identifying the specific drug-class BP response markers tackles two main methodological issues, namely the high within-individual variability of BP, and the multiplicity of the biomarkers and of their nature (for example, demographic, biological, environmental, behavioral and genetic). This variability is independent of drug response. Physicians and patients do not fully understand it and it is not properly integrated into the management of hypertension. These large random variations may be a source of disappointment for both physicians and patients desperately hoping to control BP, leading to poorly justified

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treatment withdrawal or treatment changes. We set up the Identification of the Determinants of the Efficacy of Arterial blood pressure Lowering drugs (IDEAL) Trial with the specific aim of identifying factors that are associated with different BP responses to two drugs. The trial's methods (including experimental design and statistical analysis) were designed to minimize the consequences of BP variability on the expected results and take the various origins of BP differential responses to drugs into account.

This article explores baseline simple phenotype individual characteristics as markers of BP response to indapamide and perindopril. These two drugs were chosen because they represent two classes with the best level of evidence for the reduction of cardiovascular risk.

MATERIALS AND METHODS

Study design

The study was conducted according to the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects and was funded by public grants from the 2003 Hospital Program for Clinical Research (French Ministry of Health) and the French Society of Hypertension. The study protocol was approved by an institutional ethical review board and the French Data Protection Agency in November 2004. All patients gave signed informed consent before inclusion. Study drugs were donated by SERVIER France (Suresnes, France). The company did not participate in study design, study conduct, data collection, statistical analysis, interpretation of results or manuscript preparation.

The complete study design is described elsewhere.[9] The protocol was registered on ClinicalTrials.gov NCT00128518. The IDEAL Trial was a multicenter, randomized, cross-over, double-blind double-placebo-controlled clinical trial that evaluated BP response to perindopril 8 mg and indapamide 1.5 mg slow release. Eligible subjects were included at the selection visit. After inclusion, all patients went through a 2-week single-blind double-placebo run-in phase in order to assess potential treatment compliance. They were further randomized to one of the four sequences, each of them including four 4-week periods: two active treatment periods, separated by placebo wash-out periods. Total study duration for each patient was approximately 22 weeks. Randomization was centralized. Perindopril doses were increased from 4 mg (tert-butylamine salt, equivalent to 5 mg arginine salt) to 8 mg after 1 week. Indapamide 1.5 mg slow release doses were administered each morning over a period of 4 weeks. Placebo tablets were indistinguishable from the active treatment. Urine indapamide and serum *N-acetyl*-Ser-Asp-Lys-Pro dosages were performed systematically to check for patient compliance at the end of each of the four follow-up periods.

Study population

Patients were recruited at eight participating centers in France. Included patients were aged 25–70 years, with no antihypertensive treatment in the past 6 months, a mean (average of the last four measurements) BP $\geqslant$140 mm Hg and $<$180 mm Hg for systolic or $\geqslant$90 mm Hg for diastolic at the inclusion visit. Exclusion criteria were renal insufficiency (defined as serum creatinine higher than 150 μmol l^{-1} or creatinine clearance $<$60 ml min^{-1}) or high cardiovascular risk because of a previous history of vascular disease or uncontrolled or insulin-requiring diabetes, secondary hypertension, an intolerance to ambulatory-BP monitoring or a brachial perimeter of $>$33 cm, potentially increased BP variability (atrial fibrillation, severe sleeping disorders, chronic depression, chronic alcohol consumption or untreated thyroid dysfunction), a treatment that could interfere with BP (like non-steroid anti-inflammatory drugs, corticosteroids, oral estrogens, alpha-blockers and so on), pregnant women or women of childbearing age planning to get pregnant.

Outcomes

The main outcome was office systolic BP (SBP) measured during randomization and at all four follow-up visits in a standardized manner. Seven measurements were taken in the supine position every 5 min, on the dominant arm (determined at the inclusion visit). The same automatic device was used for each patient throughout his or her participation in the study. All seven BP measurements were used in the statistical analysis.

Explanatory variables

The baseline explanatory variables analyzed in this report include age (years), gender (female as reference), body mass index (kg m^{-2}), alcohol consumption (number of glasses per day), smoking (current, former and non-smoker) echocardiography left ventricular hypertrophy (yes/no), duration of hypertension (years), diabetes (yes/no), family history of hypertension (yes/no) and serum creatinine levels (μmol l^{-1}).

Statistical analysis

The inclusion of 400 participants (based on a two-sided alpha risk of 5% with 90% power) would have made the trial powerful enough to detect a difference of 2 mm Hg for SBP between two groups of patients of similar size. We received two grants, but the financial support was less than expected, allowing us to recruit theoretically 200 patients. We stopped recruiting patients before the intended sample size was reached because recruitment was slower than expected and the research grant expired. Hospices Civils de Lyon, the institutional sponsor, decided to stop patient recruitment in June 2009. This decision was only based on administrative grounds, without knowledge of the data.

SBP measurements at baseline and during follow-up were modeled using a linear mixed-effect model. The random part modeled the deviation between the patient's specific mean and the overall mean given the factors included in the fixed part of the model, and hence modeled the variation from patient to patient not explained by the fixed part of the model. The random part included a random SPB mean by patient during the placebo period, and random deviations to this mean during the perindopril and indapamide periods as well as the correlations between these random effects. The hierarchical structure of the model is explained in Figure 1. The fixed part of the model included the center, the visit number and the explanatory variables. Age and all variables with a significance level of $<$0.20 in univariate analyses were kept for the multivariate analyses. The interactions between variables were also introduced in the multivariate model, as well as the third-order interactions between age, gender and variables. The final model was obtained using a backward selection procedure with a significance level of 0.05.

The main efficacy outcome, SPB response to drug exposure, was defined as the opposite of the difference between mean treatment SPB and mean placebo SPB, as estimated from the model. A response to a drug marker was defined as a covariate that had significant interaction with one of the drugs.

The analysis was restricted to patients who completed all four treatment periods with coherent drug dosages at the end of the two active periods. A carry-over effect of treatments was tested as an interaction term between study visit and treatment effect.

RESULTS

Study population

In the IDEAL Trial, 139 patients were included between March 2005 and May 2010. One hundred twenty-four patients were randomized and 115 of them completed all four periods. The main reason for withdrawal between the inclusion visit and randomization was consent withdrawal (9 out of 15 patients) and 1 patient for an adverse event during one of the placebo run-in phases. Six patients experienced serious adverse events after randomization: one was hospitalized for a pulmonary infection

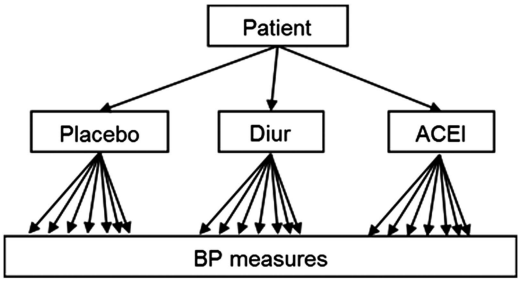

Figure 1. Hierarchical model structure for the statistical analysis. ACEI, angiotensin-converting enzyme inhibitors; Diur, diuretics.

Table 1. Baseline (randomization) characteristics of patients included in the final analysis

	Final analysis (N = 112)
Age, mean (s.d.) years	52 (9)
Men/women (sex ratio)	75/37 (2)
Systolic BP (s.d.) mm Hg	145.0 (11.6)
Diastolic BP (s.d.) mm Hg	89.0 (8.8)
BMI, mean (s.d.) kg m^{-2}	27.3 (4.1)
Hip circumference, mean (s.d.) cm	104 (9)
Brachial circumference, mean (s.d.) cm	29 (3)
Waist circumference, mean (s.d.) cm	96 (13)
Serum cholesterol, mean (s.d.) mmol l^{-1}	5.5 (1.0)
Serum triglycerides, mean (s.d.) mmol l^{-1}	1.3 (0.7)
Serum HDL-cholesterol, mean (s.d.) mmol l^{-1}	1.4 (0.4)
Serum creatinine, mean (s.d.) μmol l^{-1}	80 (15)
Known diabetes (%)	7 (6%)
Smokers (%)	23 (21%)
Regular alcohol consumption (%)	46 (41%)
History of hypercholesterolemia (%)	45 (39%)
History of hypertriglyceridemia (%)	21 (18%)
Family history of hypertension	68 (61%)
Echocardiographic LVH	16 (14%)
% Framingham 10-year cardiovascular risk score (median, IQR)	15 ((9–24)

Abbreviations: BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; IQR, interquartile range; LVH, left ventricular hypertrophy.

with hyponatremia, one had hypokaliemia, one had a benign cutaneous allergic reaction from indapamide, one suffered chest pain with a surge in hypertension (this was the only case in these six patients who did not stop the study treatment and contributed to the final analysis), one had an ankle sprain and one died suddenly. This death occurred in a 55-year-old man without any known risk factors (body mass index 22 kg m^{-2}, non-smoker, normal echocardiogram without left ventricular hypertrophy) except hypercholesterolemia (untreated, with a total cholesterol/high-density lipoprotein ratio of 4.7 at inclusion), with a family history of hypertension and moderate BP levels measured with a 24 h. Ambulatory-BP monitoring was 135/80 mm Hg. He was found dead after the third follow-up visit, a few hours after beginning the last treatment period (indapamide).

One patient was excluded from analysis because of a lack of adherence (no pills returned, no indapamide detected after the indapamide phase and no increase in *N-acetyl*-Ser-Asp-Lys-Pro after the perindopril phase). Two other patients were excluded from analysis because of incoherent data on compliance. The final analysis was based on 112 patients that completed all four periods and had complete and coherent data.

Baseline characteristics of patients included in the analysis are described in Table 1.

The randomized patients were young (mean age 52), with a men-to-women ratio of 2 and moderately overweight (body mass index 27 kg m^{-2}). Twenty-one percent of them were current smokers, 6% had known diabetes and 61% had a family history of hypertension. Mean supine BP measured over 30 min was 145.0 (s.d. 11.6)/89.0 (s.d. 8.8) mm Hg at randomization visit.

Response to drugs and other determinants of BP

Observed mean placebo-adjusted BP reductions under indapamide and perindopril in the 112 patients considered for the final analysis were of similar magnitude: −7.2 (s.d. 9.8)/−4.0 (s.d. 6.2) mm Hg and −6.6 (s.d. 11.0)/−4.2 (s.d. 6.7) mm Hg, without significant difference.

In univariate analyses, male sex, body mass index and both treatments were significant predictors of SBP (*P* 0.003, 0.02, <0.0001 and <0.0001, respectively). The carry-over effect of treatments was nonsignificant ($P = 0.49$). Study visits and study centers were significantly associated with SBP ($P < 0.0001$ and 0.02, respectively). Alcohol consumption and left ventricular hypertrophy were weak predictors of SPB (*P*-values < 0.20). Using estimates from the multivariate model, the response to indapamide was a decrease in 29 of the 37 women (78%), with a decrease of up to 10 mm Hg and more for 22/37 (59%) of them. Twenty-two men (29%) had an increase in SBP and 26/75 (35%) had a 10 mm Hg or more decrease while taking indapamide. In all, 28/37 (76%) women had a decreased SBP and for 17/37 (46%) this decrease was of 10 mm Hg or more while taking perindopril. Twenty-four men (32%) had an increased SBP and 22/75 (29%) had a >10 mm Hg decrease on perindopril (Figure 2).

Markers of BP responses to drugs

The final model included selected variables and interaction terms, to identify the individual characteristics associated with BP responses to drugs (Table 2). Once the effect of sex (for indapamide) and sex and age (for perindopril) on the SPB response were taken into account, the remaining between-individual variability in SBP response was of 7.40 (95% confidence interval (CI) (6.28, 8.71)) for indapamide and 6.98 (95% CI (5.91, 8.24)) for perindopril. No significant correlation was found between the individual BP responses to indapamide and to perindopril (correlation = 0.23, 95% CI (−0.03, 0.46)). A positive correlation was observed between SBP and the response to indapamide (correlation = 0.36, 95% CI (0.15, 0.54)), which can be interpreted as an increase in the response to indapamide of about 1 mm Hg for every 3 mm Hg of the SBP. The respective correlation for perindopril was not statistically significant (correlation = −0.05, 95% CI (−0.21, 0.29)). Two markers were identified in the interaction approach: gender and age (Figure 3). The women's responses were significantly greater for the two drugs, approximately twice of that observed in men ($P < 0.001$ for indapamide and $P = 0.015$ for perindopril). Age was significantly negatively associated with perindopril response, with a 2 mm Hg lesser response every 10 years of age ($P = 0.010$). Age was not associated with response to indapamide when women and men were examined together. As this association was expected from literature, we conducted a complementary subgroup analysis, and found that this association was present in women, with an increase of the response by 3 mm Hg every 10 years of age ($P = 0.024$), but not in men (see Figure 3). The mean decrease in SBP observed in men with age did not explain the lack of association between age and response to indapamide.

Gender explained 19% of the response changes observed for indapamide and 11% for perindopril. With perindopril, age explained 13% of the response changes; age and sex together explained 24% of these changes.

DISCUSSION

IDEAL Trial methodology (experimental design and statistical analysis) was specifically set up to explore individual markers of BP response to drugs. The design was defined to neutralize the impact of placebo effect and to minimize the effect of regression to the mean. The placebo effect was controlled by having placebo periods between active periods. Regression to the mean was reduced by keeping patients whose BP did not reach the required level at randomization in the study population. All seven BP measurements taken during follow-up were included in a mixed-effects regression model.

The IDEAL Trial has successfully achieved this objective and confirms that response markers do exist and can be identified, even in size-limited trials. In this study population, 19% of SBP response changes were from indapamide and 24% from

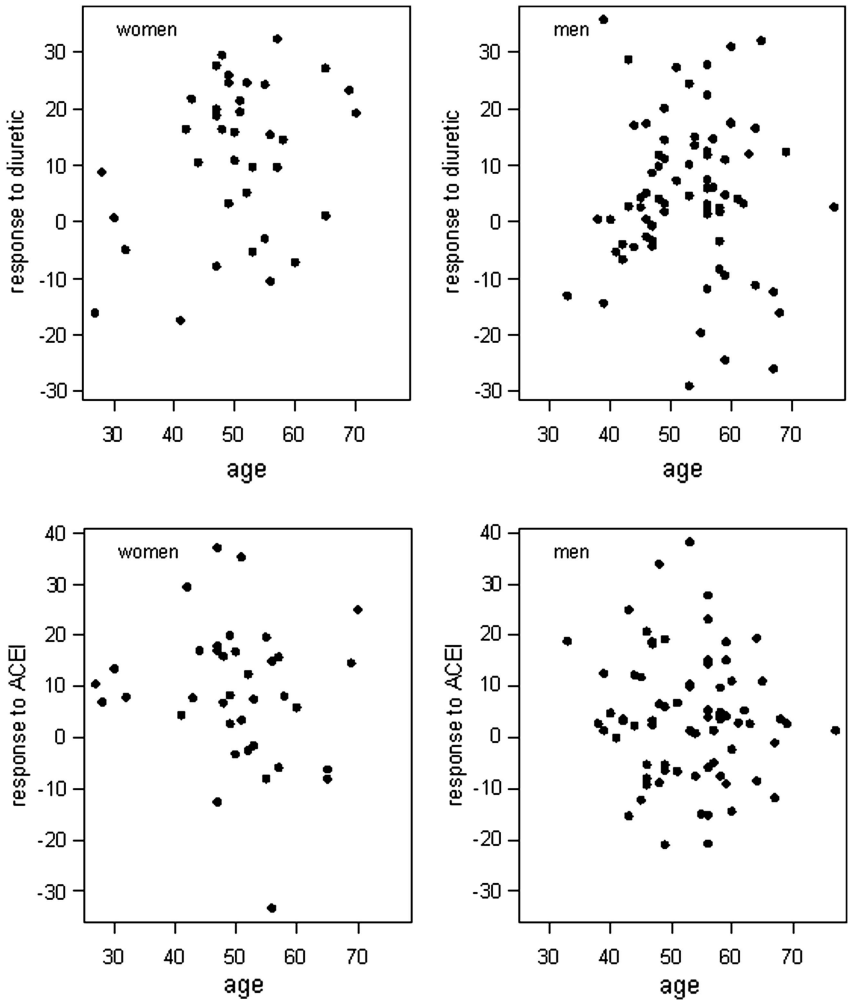

Figure 2. Distribution of adjusted SBP responses to indapamide (top panel) and perindopril (bottom panel) by age and sex. BP response is in mm Hg. Age is in years. ACEI, angiotensin-converting enzyme inhibitors.

Table 2. Fully adjusted multivariate mixed-effect model on the total IDEAL population

Variables[a]	*Mean effect (mm Hg)*	*s.e.m.*	P-*value*
Intercept	145.43	2.03	<0.001
Indapamide in 55-year-old women	−11.54	1.36	<0.001
Perindopril in 55-year-old women	−8.25	1.31	<0.001
Age in women	0.18	0.15	0.244
Male gender	2.94	2.01	0.145
LV hypertrophy	5.25	2.58	0.045
Age–male gender interaction	−0.47	0.20	0.018
Interactions with BP responses to drugs			
Perindopril–age	0.21	0.08	0.010
Indapamide–male gender	6.76	1.65	0.001
Perindopril–male gender	3.93	1.60	0.015

Abbreviations: BP, blood pressure; IDEAL, Identification of the Determinants of the Efficacy of Arterial blood pressure Lowering drugs; LV, left ventricular; s.e.m., standard error of the mean parameter estimate. [a]Results for center and study visits were not included in this table.

perindopril. Several placebo-controlled trials with the same objective were performed in the past. In the US Department of Veterans Affairs parallel-group trial on 1292 men, being African American was a better response marker to calcium antagonists than to drugs acting on the renin–angiotensin system (angiotensin-converting enzyme (ACE) inhibitors, angiotensin 2 antagonists inhibitors and beta-blockers). In this same study, aging was a response marker to diuretics.[10] Two cross-over trials explored correlations between BP response to drugs. In the first trial, 72 patients received a beta-blocker (B), an ACE inhibitor (A) and a calcium antagonist (C).[11] In the second trial, 56 patients received these three drug classes plus a diuretic (D).[12] Plasma renin levels, which decrease on average with age, were associated with a response to the beta-blocker in the first trial. The second trial led to the Cambridge AB/CD rule for optimization of antihypertensive treatment because there was a significant correlation between the responses to A and B on the one hand and C and D on the other hand, without any other significant correlations. This suggests that renin levels and their variation with age could be the main determinants of class-specific responses. The more recent ROTATE Trial with 97 patients tested the four previous drug classes plus an angiotensin 2 antagonist. The authors concluded that phenotype (such as ethnic origin), environmental (such as sodium consumption) and genetic (ADD1 614G→T polymorphism) biomarkers were significantly

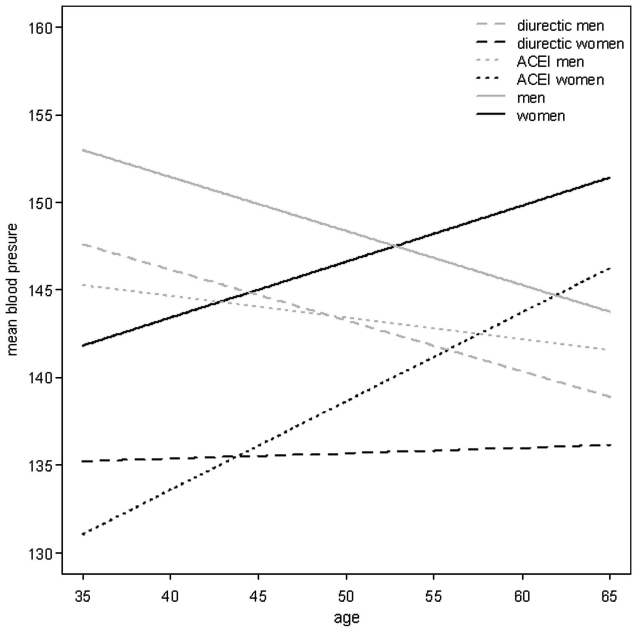

Figure 3. Modeled SBP according to age, sex and treatment. The SBP model represents interactions for women and men. ACEI, angiotensin-converting enzyme inhibitors.

associated with drug response. The GENRES trial included 208 men and evaluated the same drug classes except for ACE inhibitors. Its authors concluded that age and initial BP were associated with BP response,[13] confirming the correlations observed previously with plasma renin levels.[14] It failed to confirm the correlation of response to beta-blockers with beta-adrenergic receptor polymorphisms.[15]

With a full-analysis population of 112 patients displaying an average placebo-controlled BP response of $-7.2/-4.0$ mm Hg on indapamide and $-6.6/-4.2$ mm Hg on perindopril, the IDEAL Trial allowed us to confirm the role of two important markers for SBP response to drugs. This average placebo-adjusted BP reduction is about 25% less than that expected from the average estimate of a standard dose of an antihypertensive drug, estimated at around 9 mm Hg from a systematic review of 354 trials by Law *et al.*[16] This may be explained by the short-term exposure to treatment and the make-up of the study population because there were relatively less responders than in other trials. In the same paper, Law *et al.* observed an association between pre-treatment BP and BP response without separating drug classes. We noticed this for indapamide, but not perindopril. These associations were observed between trials and were more subject to ecological and publication biases. The slope of the regression line estimated by Law *et al.* was about 1 for every 10, whereas the association we observed for indapamide was steeper (about 1 mm Hg response increase for every 3 mm Hg SBP increase). This steeper slope could also be explained by the modeling process, which decreases the deleterious impact of noise on the association estimates.

Female gender was the most powerful marker of BP response in the IDEAL Trial, associated with both drugs tested, but more importantly with indapamide. The difference in response between women and men for indapamide (7 mm Hg) was the same magnitude as the average response for the trial population. This better response in women was already observed in a large database analysis, both within and between trials.[17] This large database came from collecting individual data from randomized controlled trials that explored to what extent BP-lowering drugs decreased cardiovascular risk. This sex–treatment interaction was not noted in the previous trials cited,[10–15] but the two most powerful of them[10,13] were conducted in men only. This interaction is obviously an easy marker to take into account in clinical practice, which should also be systematically adjusted for in clinical trials. Understanding why women respond better than men to BP-lowering drugs could improve significantly the management of drugs against the risks associated with hypertension. This will be explored in next steps of the IDEAL trial analyses, focused in particular to markers of the activity of renin–angiotensin–aldosterone system, and genetic markers.

Age, which was already identified as a response marker and its use recommended in the NICE-BHS guidelines, http://www.nice.org.uk/nicemedia/live/13561/56008/56008.pdf, is usually negatively correlated with drugs acting against the renin–angiotensin–aldosterone system, and positively correlated with calcium antagonist and thiazide diuretic response. We observed a 2 mm Hg decrease in response to perindopril for every 10 years of age gradient, but the corresponding expected positive association was only significant for women taking indapamide, with a slope of the same magnitude but reversed, with a 3 mm Hg increase for every 10 years of age gradient.

The remaining between-individual variability of BP response was 7.40 for diuretics and 6.98 mm Hg for ACE inhibitors in the fully adjusted model. This contradicts findings from an individual patient data meta-analysis of parallel group trials comparing ACE inhibitors with placebo, where this variability was estimated at 2.6 mm Hg.[18] If this was true, such minor variability between individuals would prevent us from adjusting treatments to BP measurements and searching for BP response determinants. This discrepancy illustrates the limits of the parallel group approach and strongly supports the idea of exploring differences within individuals of BP response to drugs.

Information on ethnicity was not collected during the trial, the main reason being that this collection is forbidden by default in France in medical files. This is a remarkable limitation because of the knowledge that African-American people respond differentially to BP-lowering drugs. From an informal survey of investigators, black people were not or very little represented in each center, leading to a figure of 1 or 2% of the overall study population, so not susceptible to have significantly influenced the presented results.

The IDEAL Trial has a relative lack of power, compared with the sample size (400 patients) that we had initially hoped for. The selection process led to an over-representation of men, who displayed a significantly reduced response to both drugs on average. This shows how difficult it is to explore determinants of drug response, because this determination cannot result from a totally controlled experiment. Response markers are represented differently in different trial populations. Exploring the reproducibility of the results from one clinical trial is really important, and could and should be achieved by comparing these results to other trial results in the form of a meta-analysis on individual patient data. More powerful trials have to be set up and will benefit from the hypothesis generated formerly in smallest trials such as IDEAL and others,[10–15] as well as from the results of an ongoing meta-analysis of trials with similar objectives (http://www.pharmgkb.org/page/icaps). Industry sponsors have no reason to be motivated by discovering BP response markers, because of the potential negative impact on the market, which could result from such a discovery. However, owing to the potential impact of these discoveries, trial results should be pooled at the individual patient data level regardless of trial results and sponsor. We believe these results should be completed by further biological and genetic analyses to obtain a satisfactory set of response markers and then be assembled within predictive scores useful in orienting the choice of the first-line drug to be used. This would result in better BP control, and in turn better cardiovascular risk control, at a lesser cost with fewer drugs and medical visits. Furthermore, these

scores could be useful for identifying different types of hypertension and understand how hypertension develops.

The next steps of the IDEAL research program include exploring response markers further: genetic and biological markers of the renin–angiotensin–aldosterone system. This would allow us to understand why women respond better than men on average, and especially in the IDEAL population. These results are expected to contribute to a worldwide network to set up response scores specific to antihypertensive drug mechanisms of action.

What is known about topic

- BP reduction is considered the only acting mechanism in antihypertensive drugs to reduce cardiovascular risk.
- Individual characteristics are not taken into account in current treatment strategies.
- Antihypertensive drugs are currently chosen at random.

What this study adds

- The IDEAL trial confirmed two important response markers in antihypertensive drugs: gender and age.
- Being female was the most powerful marker of BP response.
- This study strongly supports the idea that class-specific responses to BP-lowering drugs could be predicted *a priori.*

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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