Thérapie 2012 Mai-Juin; 67 (3): 195–204
DOI: 10.2515/therapie/2012031

The IDEAL Study: Towards Personalized Drug Treatment of Hypertension

Theodora Bejan-Angoulvant[1], *Jean-Philippe Baguet*[2], *Sylvie Erpeldinger*[3], *Jean-Marc Boivin*[4], *Alain Mercier*[5], *Georges Leftheriotis*[6], *Jean-Pierre Gagnol*[7], *Jean-Pierre Fauvel*[8], *Céline Giraud*[9], *Giampiero Bricca*[10] *and François Gueyffier*[11] *for the IDEAL Study Group*[⋆]

1 Department of Clinical Pharmacology, Hospices Civils de Lyon, Lyon, France; UMR 5558, CNRS, Villeurbanne, France; Claude Bernard Lyon 1 University, Lyon, France
2 Department of Cardiology, Centre Hospitalier Universitaire, Grenoble, France; INSERM 1039, Bioclinic Radiopharmaceutics Laboratory, Joseph Fourier University, Grenoble, France
3 Department of General Practice, Claude Bernard Lyon 1 University, Lyon, France
4 Plurithematic Clinical Investigation Centre, CIC-P-Inserm CHU de Nancy, Lorraine Institute of Heart and Vessels Louis Mathieu, Vandœuvre-lès-Nancy, France; Henri Poincaré Nancy University, France
5 Department of General Practice, Faculty of Medicine, Rouen University, Rouen, France; CIC Inserm 0204, CHU of Rouen, Rouen, France
6 Vascular Functionnal Exploration Laboratory, CHU Angers, Angers, France
7 Arnaud de Villeneuve Hospital, CHU Montpellier, Montpellier, France
8 Department of Nephrology and Hypertension, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France
9 Clinical Investigation Center, CIC 201, INSERM, Lyon, France
10 Endocrine and Metabolic Function Exploration, Centre of Biology North, Croix-Rousse Hospital, Hospices Civils de Lyon, Lyon, France
11 Clinical Investigation Centre, CIC 201 Inserm and Department of Clinical Pharmacology, Hospices Civils de Lyon, Lyon, France; UMR 5558, CNRS, Villeurbanne, France; Claude Bernard Lyon 1 University, Lyon, France

Text received 18th November 2011; accepted 8th December 2011

Keywords:
hypertension;
drug treatment;
treatment response biomarkers; responders;
pharmacogenetics

Abstract – Objective. To identify markers (phenotypic, genetic, or environmental) of blood pressure (BP) response profiles to angiotensin converting enzyme inhibitors (ACEIs) and diuretics. **Methods.** IDEAL was a crossover (two active and two wash out phases), double-blind, placebo-controlled trial. Eligible patients were untreated hypertensive, aged 25 to 70. After two visits, patients were randomized to one of four sequences. The main outcome was BP differences between the active treatment and placebo. **Results.** One hundred and twenty-four patients were randomised: mean age 53, men 65%, family history of hypertension 60%. Average BP fall at each visit before randomisation was about 2% of the initial level reflecting both a regression to the mean and a placebo effect. **Conclusion.** The results are expected to improve knowledge in drug's mechanisms of action and pathophysiology of hypertension, and to help in personalizing treatment. The estimation of BP responses to each drug in standardized conditions provided a benefit to each participant.

⋆ **the IDEAL Study Group.** Yishi Li (Key Laboratory of Clinical Trial Research in Cardiovascular Drugs, Ministry of Health, Fuwai Cardiovascular Hospital, Beijing, PR. China); Calin Pop (Faculty of Medicine, Arad, Western University Vasiel Goldis; Cardiology, Regional Hospital, Baie Mare, Romania); Salam Farhat (Claude Bernard Lyon 1 University, Lyon, France); Alain Richet (Claude Bernard Lyon 1 University, Lyon, France); Yves Zerbib (Claude Bernard University Lyon 1, Lyon, France); Marie-France Le Goaziou (Claude Bernard Lyon 1 University, Lyon, France); Rojee Neguib (Claude Bernard Lyon 1 University, Lyon, France); Marie Flori (Claude Bernard Lyon 1 University, Lyon, France); Pierre Lantelme (Cardiology, Croix Rousse Hospital, Lyon, France); Denis Angoulvant (Cardiology, Louis Pradel Hospital, Lyon, France); Pierrette Darchy (Cardiology, Louis Pradel Hospital, Lyon, France); Stéphane Laurent (Pharmacology, Pompidou European Hospital, Inserm and Paris Descartes University, Paris, France); Faiez Zannad (Cardiology Departement, Nancy University, Nancy, France); Patrick Rossignol (Nancy University and Inserm CIC, Nancy, France); Anne-Françoise Cailleux (Rouen University Hospital, Inserm CIC, Rouen, France); Christian Libersa (CIC, Inserm and CHU, Lille, France); Atul Pathak (Clinical Pharmacology, Toulouse University; Inserm; Federation of Cardiology, Toulouse, France); Jean-Michel Halimi (Nephrology, Bretonneau Hospital, Tours, France); Jacques Amar (Inserm, Faculty of Medicine, Toulouse, France); Xavier Jeunemaitre (Department of Genetics, Pompidou European Hospital, Inserm-PARCC, Paris, France); Michel Azizi (Clinical Center of Investigations, Pompidou European Hospital, Paris, France); Florent Boutitie (Department of Biostatistics, Hospices Civils de Lyon; CNRS, Villeurbanne, France).

Article published by EDP Sciences

Mots clés :
hypertension ;
médicament ;
marqueurs de réponse ;
répondeurs ;
pharmacogénétique

Résumé – Étude IDEAL : vers la personnalisation du traitement médicamenteux de l'hypertension. Objectif. Identifier les marqueurs (phénotypiques, génétiques, environnementaux) des profils de réponse pressionnelle à un inhibiteur de l'enzyme de conversion de l'angiotensine et un diurétique. **Méthodes.** IDEAL est un essai en plan croisé (2 phases actives et 2 phases de désimprégnation) en double-insu *versus* placebo. Les patients étaient des hypertendus non traités de 25 à 70 ans. Deux visites précédaient la randomisation des patients. Le critère principal était la différence de PA traitement actif *versus* placebo. **Résultats.** Cent vingt-quatre patients ont été randomisés d'âge moyen 53, hommes 65 %, histoire familiale d'hypertension 60 %. La baisse moyenne de PA à chaque visite pré-randomisation était d'environ 2 % du niveau initial traduisant une régression vers la moyenne et un effet placebo. **Conclusion.** IDEAL permettra d'améliorer les connaissances sur les mécanismes d'action des médicaments dans l'hypertension, étape indispensable vers la personnalisation du traitement. L'estimation de la réponse pressionnelle dans des conditions standardisées a représenté un bénéfice réel pour chaque participant.

List of abbreviations: see end of article.

1. Background

Several classes of blood pressure (BP) lowering drugs have been shown to reduce cardiovascular morbidity and mortality for the primary and secondary prevention of hypertension as well as in high-risk patients.[1,2] Most randomised controlled trials (RCTs) used an adaptive intensification strategy based on BP response in order to achieve a predefined arbitrary BP target.[3] However, some large RCTs demonstrated the benefit of a fixed-dose strategy in primary prevention,[4,5] in secondary post-stroke prevention,[6,7] and in high-risk patients.[8,9]

The clinical benefit of the usual adaptive strategy has not been evaluated nor quantified when compared with the fixed-dose strategy or to an alternative adaptive strategy based on patients' pre-therapeutic characteristics such as BP level or medium-term risk. Several RCTs have suggested that the benefit associated with intensified BP-lowering treatment was either lower than the benefit of basic treatment[10] or absent in low-risk individuals.[11] In older or oldest individuals the intensification of BP-lowering treatment was also debatable.[12,13] The proportion of risk reduction explained by BP reduction varies between 20% to 70% depending on the criteria and methods used.[14–16] Yet efforts used to control BP ignore other potential mechanisms involved in drug effects.

The average BP reduction under treatment is about 5 to 6 mmHg for diastolic BP (DBP) and 12 to 15 mmHg for systolic BP (SBP),[17] which is about 6 to 10% of initial BP. The magnitude of this BP reduction is just as important as the standard deviation of the within-individual BP distribution during 24-hour ambulatory measurements.[18] It is easy to demonstrate BP reduction in therapeutic trials of tens or hundreds of participants with standardised procedures. However, it is impossible to show this in standard clinical practice. It is therefore an illusion to adjust drug treatment based on a patient's BP response, because BP varies considerably without any treatment administration. This has been recently illustrated in a meta-analysis of angiotensin-converting enzyme inhibitors (ACEIs) based on individual patient data.[19] The consequences of BP measurement errors have also been shown in simulation studies, with a 75% misclassification rate after four years.[20]

Several trials assessed the individual markers of BP response, through parallel groups or crossover designs. Materson *et al.* compared 6 drugs and a placebo in parallel groups in 1,292 patients.[21] Their trial showed that diltiazem, a calcium antagonist, was the most efficient at reducing BP. Diltiazem response was correlated to Afro-American ethnic origin, while the response to ACEIs and beta-blockers was correlated to age. The existence of BP response profiles to various drug classes was confirmed in a crossover, double-blinded trial.[22] Fifty-six participants received sequentially each of the four main drug groups, ACEIs (A), beta-blockers (B), calcium-channel antagonists (C), and diuretics (D). The authors observed a correlation of the specific response following the AB/CD rule. There were significant correlations between the BP responses to A and B, and between C and D, but not between the other four pairings of treatments. Attwood and his team applied a similar experimental design to a population of 72 participants (68 completed the study) with three drugs (a calcium-channel antagonist, a beta-blocker, and an ACEI).[23] They observed a stronger correlation of BP response between the beta-blocker and the ACEI. The response to the calcium-channel antagonist and to the beta-blocker was also significantly correlated. The activation level of the renin-angiotensin-aldosterone system offered an explanation to the AB/CD rule because beta-blockers and ACEIs depress the system, whereas diuretics and calcium-channel antagonists activate it. This was recently illustrated in a parallel group study evaluating atenolol and hydrochlorothiazide.[24,25]

The determinants of BP response patterns are not completely understood. In the above mentioned studies, Attwood and Dikerson sought to identify factors explaining the different BP responses between drugs. Active renin and initial BP levels were some of the factors that explained BP differences. The failure of both studies to determine whether age, body mass index, and

plasma noradrenaline were related to class-specific BP response could be attributed to the lack of power or to a somewhat imprecise phenotypic measurement. More recently, another study conducted by Morgan *et al*. with a similar crossover design in 60 elderly patients with previously untreated hypertension suggested a better BP response to diuretics or calcium-channel antagonists than to ACEIs and beta-blockers.[26]

Genetic polymorphisms have been associated with differences in response to certain BP-lowering drugs.[27–29] These observations were mostly based on observational, uncontrolled trials. Recently, an open-label, crossover, controlled trial suggested that ethnicity, low sodium intake, and ADD1 614G→T polymorphism were independent predictors of BP response. In addition, a number of genetic variants contributed significantly (9%) to the total variance of the SBP response.[30] Another double-blind, crossover study[31] evaluated the 24-hour ambulatory blood pressure (AMBP) monitoring response to four drug classes. The authors found that: i) plasma renin activity was positively correlated with the response to losartan, bisoprolol, but negatively correlated with the response to hydrochlorothiazide (HCTZ); ii) total serum calcium and 24-hour urinary sodium excretion were negatively correlated with the amlodipine response; and iii) ADRB1 Ser49Ser homozygote genotype was significantly correlated with the SBP response to bisoprolol.[32,33] The other genotypes tested (ADRB1 Arg389Gly, ADRB2 Gly16Arg, and ADRB2 Gln27Glu) were not associated with any drug BP response.

Taking into account all the established sources of variability of BP response before the beginning of treatment would increase the efficiency of BP-lowering drugs in clinical practice. In this paradigm, monitoring would essentially involve checking the tolerability and safety of drugs and the stability of target-organ damage. Identifying response factors is a complex and multidimensional problem, involving phenotypic, genetic, and environmental conditions. It requires optimal experimental design, modern resources for genetic and biological exploration, and efficient standardized individual measurements of BP response. The principal objective of the Identification of the Determinants of the Efficacy of Arterial blood pressure Lowering drugs (IDEAL) trial was to identify phenotypic, environmental, and genetic markers of BP response to two major classes of antihypertensive drugs: ACEIs and diuretics.

2. Methods

This study was funded by public grants from the 2003 Hospital Program for Clinical Research (French Ministry of Health) and the French Society of Hypertension, and was sponsored by Hospices Civils de Lyon. Study medication, NACSDKP peptid and indapamide urinary dosages were provided by Servier Laboratory France. The pharmaceutical firm was not involved in protocol writing, study management, monitoring, data collection, data analysis, or the interpretation of results. Data management was performed by ClinInfo using electronic case report forms. Data analysis was carried out by the Biostatistics and the Clinical Pharmacology Departments of Hospices Civils de Lyon.

Table I. The four different sequences including two active periods (D or A) and two placebo periods (PD + PA).

Sequence 1: D+PA • PD+PA • A+PD • PD+PA
Sequence 2: PD+PA • D+PA • PD+PA • A+PD
Sequence 3: A+PD • PD+PA • D+PA • PD+PA
Sequence 4: PD+PA • A+PD • PD+PA • D+PA

A: ACE (angiotensin-converting enzyme) inhibitor; **D**: diuretic; **PD**: placebo of diuretic; **PA**: placebo of ACE inhibitor.

2.1. Design

IDEAL was a randomised, crossover, double-blind, placebo-controlled clinical trial. Included patients were followed up for 22 weeks. Two drugs were evaluated: perindopril 8 mg and indapamide 1.5 mg slow release (SR). Patients were included at the selection visit (V-2), then came to a second visit (V-1) and participated in a two-week double placebo run-in phase. The aim of this period was to assess treatment compliance. Patients were randomised at the third visit (V0) to a sequence including two four-week active treatment phases, separated by two placebo wash-out phases. Phase order and drug choice (sequence) were determined by randomisation. The sequence guaranteed that the two active periods were separated by a placebo period, each participant being his/her own control. There were four different groups of treatment sequences (table I).

Tested drugs were chosen based on the following criteria: i) they represented major classes of BP-lowering drugs that are recommended as the first-line therapy in a wide range of patients; ii) they represented the two groups of the AB/CD rule; iii) they were prescribed at a standard dose in the treatment of hypertension and iv) they could be administered in a double-blind manner. The treatment formulation and presentation was: perindopril 4 mg (tert-butylamine salt, equivalent to 5 mg arginine salt) for the ACEI and indapamide 1.5 mg SR for the diuretic. Daily doses of perindopril and indapamide were 8 mg, which was reached after 1 week of 4 mg, and 1.5 mg SR respectively. Each dose was administered in the morning over a period of four weeks. Placebo tablets were identical to the active treatment. Oral oestrogens (contraceptive or hormone substitution therapy), corticosteroids, non-steroidal anti-inflammatory drugs, aspirin at anti-inflammatory dose ⩾500 mg/d, alpha-blockers for urological

conditions, and all other medication likely to interfere with BP were prohibited during the study.

2.2. Study setting and participants

2.2.1. Inclusion criteria

Eligible subjects were men or women aged 25-60, with no antihypertensive treatment in the past six months, had a recommendation for antihypertensive treatment from their family doctor, mean systolic BP of ⩾140 mmHg and <180 mmHg or mean diastolic BP ⩾90 mmHg at the inclusion visit (average of the last four measurements), and gave informed written consent. Cardiovascular risk according to the Framingham equation, serum creatinine clearance (Cockroft and Gault formula), and compliance to treatment were calculated for all patients before randomisation. Exclusion criteria ensured investigators that patients did not have target-organ damage or excessive cardiovascular risk. We did not include patients with: i) high cardiovascular risk because of previous history of vascular disease (myocardial infarction, angina pectoris, stroke, peripheral arterial disease, a history of angioplasty, or vascular surgery), uncontrolled (HbA1c >8%) or insulin-requiring diabetes, serum creatinine higher than 150 μmol/l or creatinine clearance <60 mL/min; ii) secondary hypertension; iii) intolerance to ambulatory blood pressure monitoring (ABPM) or a brachial perimeter above 33 cm; iv) potentially increased BP variability because of paroxysmal or permanent atrial fibrillation, severe sleeping disorders including sleep apnoea, chronically treated depression, chronic excessive consumption of alcohol, thyroid dysfunction (with the exception of patients receiving stable substitution therapy for at least six months prior to screening), or any treatment that could possibly interfere with BP (non-steroidal anti-inflammatory drugs including aspirin at anti-inflammatory dose, corticosteroids, or oestrogens); v) pregnant women or those of childbearing age planning to have a child (pregnancy tests were conducted at each visit); vi) the use of any antihypertensive treatment in the past six months; vii) a life expectancy of less than five years. The use of treatment required for preventing cardiovascular complications was encouraged but had to be stable during trial follow-up (low dose aspirin, statins, and antidiabetic agents except insulin). After the inclusion of the first nine patients in August 2006, the scientific committee of the trial discussed and agreed to raise the maximum age of inclusion from 60 to 70. This amendment to the protocol was approved by the ethics committee and regulatory authorities. We did not include very old patients because cardiovascular risk steeply increases with age and we considered the placebo treatment for eight weeks as unethical. Essential hypertension in patients under 25 is quite rare in France and therefore would not have changed the characteristics of our included population.

2.2.2. Recruitment and randomisation

Subjects were recruited from eight participating centres across France. Several sources of recruitment were considered, including family doctors, ABPM exploration departments, and advertising. All eligible patients were given an oral and written description of the study. A written informed consent form was signed after the patient agreed to enter the study protocol. Randomisation was performed centrally, following a pre-established randomisation list with several sizes of blocks unknown by investigators, and stratified by centre.

2.3. Assessments performed during trial visits

Patients were included in the study (V-2) after clinical examination, standardized BP measures, height, weight, brachial, and abdominal perimeter measurements (table II). The investigator checked inclusion and exclusion criteria, informed the patient, and obtained informed written consent. The dominant arm was determined at this time by measuring BP simultaneously on both arms with two automatic devices. The highest mean SBP or DBP defined the dominant arm. All measures afterwards were made on the same arm using the same automatic device during the patient's participation in the study. The second visit (V-1) had to be done within one month and included standardised BP measures, transthoracic echocardiography, electrocardiogram (ECG), ABPM, and blood sampling (local and centralised). Patients began a placebo simple-blind period for two to three weeks, until the next visit when randomisation had to be performed (V0). Compliance was checked by counting the returned pills. Study exclusion criteria were checked again and BP was measured following standard procedure. Results from standardised BP measures at V-1 and V0 were recorded, but were no longer considered as inclusion criteria. Blood and urine samples were collected, including genetic samples. Patients were followed every four to five weeks (V1 to V4). At each follow-up visit V1 to V4, BP was measured, blood and urine samples were collected, and all adverse events were recorded. Serum potassium was checked at the beginning of each period.

2.3.1. ABPM sub-study

Patients were asked to participate in the ABPM sub-study. This involved an ABPM recording at randomisation and each follow-up visit, in order to evaluate the impact of drug classes on 24-hour BP variability (main objective) and the effect of drug classes on the dipper/non-dipper profile (secondary objective).

Table II. Patient follow-up (FU) and assessments performed during trial visits.

	V-2 Inclusion	V-1 Run-in	V0 Randomisation	V1 FU	V2 FU	V3 FU	V4 End
Supine BP measures over 30 minutes	X	X	X	X	X	X	X
Clinical examination	X						
Randomisation			X				
Pregnancy test [1]	X	X	X	X	X	X	X
Echocardiography		X					
ECG		X					
ABPM [2]		X	X	X	X	X	X
Fasting blood check-up [3]		X					
Local urinaire check-up [4]		X	X	X	X	X	X
Genetic samples			X				
Centralised blood and urine samples [5]		X	X	X	X	X	X
Safety assessement		X	X	X	X	X	X
Compliance (pill count)			X	X	X	X	X
Urinary dosages [5]			X	X	X	X	X

[1] systematically in women of childbearing age;
[2] systematic at the V-1 visit; only if patient accepted to participate to the ABPM sub-study afterwards;
[3] routine recommended check-up in hypertensive patients: serum glucose, sodium, potassium, cholesterol, triglycerides, HDL-c, plasma creatinine and uric acid;
[4] urinary sodium, potassium, creatinine, proteinuria;
[5] centralised samples for biological biomarkers regarding the renin-angiotensin-aldosterone system, inflammation, natriuretic peptides, nitro-oxidative stress;
[6] urinary indapamide and NACSDKP.
ABPM: ambulatory blood pressure monitoring; **BP**: blood pressure; **ECG**: electrocardiogram.

2.3.2. Evaluation outcomes

The main efficacy outcome was the difference of BP throughout each active phase compared to the previous placebo phase. BP measurements were all standardised. Seven measurements were taken in the supine position every five minutes on the same arm (dominant arm) and with the same automatic device throughout the study. Safety was assessed by recording all adverse events and serious adverse events at each follow-up visit. Compliance was assessed by counting returned pills at each visit.

2.3.3. Candidate markers

The candidate markers (table III) were morphological characteristics, echocardiographic data, environmental parameters, and biological parameters.

Both candidate gene and genome-wide approaches were considered. At the time of inception, the most relevant candidate genes were: i) alpha-adducin Gly 460 Trp and the response to diuretics; ii) ACE I/D and the response to ACEIs. Since then, several polymorphisms were studied mostly in prospective uncontrolled studies or in retrospective studies with different numbers of patients ranging from 40 to 40,000: ADRB1 and ADRB2, AGT, AGTR1, NOS3. They had inconsistent results regarding associations with either BP or risk reduction.[34–36] To our knowledge, only a few studies assessed the impact of genetic polymorphisms in double-blind, crossover studies.[30,37]

2.3.4. Quality Control

At least three monitoring visits were performed in each participating centre: at the beginning of the study, after enrolling at least one patient, and at the end of the study. Case report forms were monitored at regular intervals by a clinical research assistant to ensure data consistency and adherence to the protocol and good clinical research practices.

2.3.5. Amendments to the protocol

All major changes to the protocol had to be made in agreement with the scientific committee of the study and the sponsor. The ethics committee was notified if any of the planned amendments affected the ethical or medical aspects of the study (inclusion criteria, addition of a new centre, etc.)

Table III. Candidate markers assessed in the study.

Morphological	Age, sex, height, weight, body mass index, body surface area	
Environmental	Alcohol, tobacco, caffeine, salt consumption	
LV hypertrophy	ECG, echocardiogram	
Biological	*Plasma*	*Urine*
Standard	Creatinine, total cholesterol, HDL-c, triglycerides, fasting glucose, sodium, potassium	Creatinine, sodium, potassium
RAAS activity	Renin, prorenin and its soluble receptor, aldosterone, angiotensinogen	Renin, aldosterone, angiotensinogen
Natriuretic peptides	ANP, NT proBNP	/
Inflammatory markers, collagen remodelling	CRP, TNFalpha, IL6, CCL22, collagene peptides, soluble receptor of CD14	/
Nitro-oxidative stress	Nitroalbumin	/
Pharmacokinetic and pharmacodynamics	/	Indapamide, NACSDKP

ANP: atrial natriuretic peptide; **CCL22**: chemokine (C-C motif) ligand 22; **CD14**: cluster of differentiation 14; **CRP**: C reactive protein; **ECG**: echocardiogram; **IL6**: interleukin 6; **NT proBNP**: N terminal pro Brain natriuretic peptide; **RAAS**: renin-angiotensin-aldosetrone system; **TNF-alpha**: tumor necrosis factor-alpha.

2.3.6. Ethical and organisational review

The study protocol was approved by an institutional ethical review board (CPP [*Centre de Protection des Personnes*], Centre Léon Bérard, Lyon, France) and the French Data Protection Agency (*Commission nationale informatique et libertés* [CNIL]) in November 2004. The study was conducted according to the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. All data were collected anonymously and confidentiality was maintained at all levels of data management.

2.4. Analysis

2.4.1. Power calculation

Based on an alpha risk of 5%, a beta risk of 10% (or a power of 90%) the inclusion of 400 participants was considered to make the trial powerful enough to detect a difference of 2 mmHg for SBP.

2.4.2. Analysis plan

The main efficacy outcome was the difference of BP (systolic, diastolic, and pulse pressure) measured at the end of each active phase compared to the previous placebo phase. BP variation under double-blind placebo, without any previous drug exposure, was assessed on behalf of the included patients, i.e. those who took placebo during the first period after randomisation. Some subgroups of participants were identified according to their response to the two studied drugs. Four subgroups (non-responders to both, responders to both, responders to one of the two treatments) were described by: population size, demographic and phenotypic characteristics. The markers, including genetic markers, associated with a specific group response were analyzed by univariate and multivariate statistics through a mixed effect model taking period and carry-over effects into account.

3. Results

The protocol was registered on ClinicalTrials.gov as NCT00128518. We included 139 patients between March 2005 and May 2010. We stopped recruiting patients before the intended sample size was reached because recruitment was slower than expected and the research grant expired. The decision to stop patient recruitment was made in June 2009, by the trial's academic sponsor (Hospices Civils de Lyon). It was based purely on administrative grounds without knowledge of the data. We randomised 124 patients (figure 1) and 115 of them completed all four periods. The main reason for withdrawal between the inclusion visit and randomisation was consent withdrawal (nine patients out of 15).

Randomised patients (table IV) were young (mean age 53), with a sex ratio men-to-women of 1.8, and moderately overweight. Twenty-one percent of patients were current smokers, 6% had known diabetes, and 60% had a family history of hypertension. Mean supine BP measured over 30 minutes was 152/93 mmHg at inclusion visit (V-2), 148/91 mmHg at second visit (run-in V-1) and 145/89 mmHg at the third visit (randomisation V0). Because active treatment could only start after randomisation, a regression to the mean phenomenon was responsible for the BP decrease between visits V-2 and V0, with the

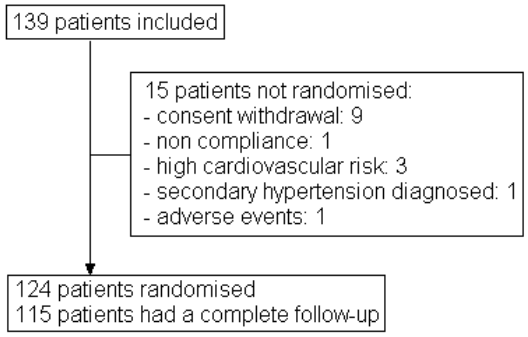

Fig. 1. Patients flow-chart.

Table IV. Baseline characteristics of randomised patients (N=124) expressed as mean (SD) or median (IQR) for continuous variables, and percentage for categorical variables.

Baseline characteristics	N=124 patients
Age, mean (SD) years	53 (9)
Men/Women (sex ratio)	80/44 (1.8)
BMI, mean (SD) Kg/m^2	27 (4)
Hip circumference, mean (SD) cm	104 (9)
Brachial circumference, mean (SD) cm	29 (3)
Abdominal circumference, mean (SD) cm	96 (13)
Serum cholesterol, mean (SD) mmol/L	5.5 (1)
Serum triglycerides, mean (SD) mmol/L	1.3 (0.7)
Serum HDL-cholesterol, mean (SD) mmol/L	1.4 (0.4)
Serum creatinine, mean (SD) µ mol/L	79 (15)
Known diabetes (%)	7 (6)
Smokers (%)	29 (21)
Regular alcohol consumption (%)	48 (39)
History of hypercholesterolemia (%)	47 (38)
History of hypertriglyceridemia (%)	21 (17)
Familial history of hypertension	74 (60%)
Echocardiographic LVH	19 (15%)
% Framingham risk score (median, IQR)	16 (9–24)

BMI: body mass index; **IQR**: inter-quartile range; **LVH**: left ventricular hypertrophy; **SD**: standard deviation.

addition of a possible single blind placebo-effect between visits V-1 and V0 (simple-blind run-in placebo) [figure 2]. Mean BP reductions under indapamide and perindopril in 115 patients that completed all periods, were of similar magnitude: -7.2/-4.0 mmHg and -6.6/-4.3 mmHg respectively (not statistically significant).

4. Discussion

A precise estimate of individual BP responses to different drug classes is needed for a more rational choice of antihypertensive treatment. During the IDEAL trial, BP response to the two drugs tested were established using seven BP measurements taken

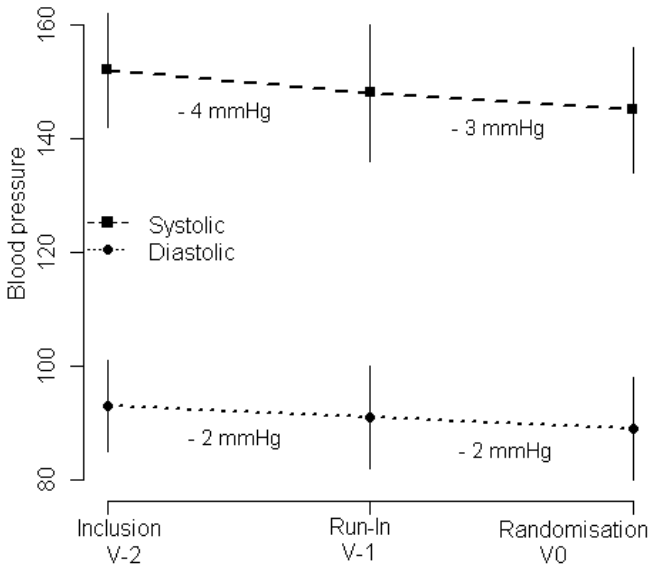

Fig. 2. Mean blood pressure reductions at the first 3 visits for the 124 randomised patients.

under standardised conditions: on the same arm, with the same automatic device against double-blind placebo control. This level of information is usually not obtainable in ambulatory medical practice. Study participants benefited from this BP response assessment. Our data collection system was designed to deliver the estimate of patient BP response to each drug at the last follow-up visit, as soon as the last BP measurements were recorded on the electronic case report form. The decision to treat and the choice of drug after the end of the trial was left to the patient's general practitioner, who was informed of his patient's BP response to the trial drugs. Some patients stopped antihypertensive medications because their BP was low without active treatment, and/or their cardiovascular risk was low. For the participants, the counterpart of this benefit was the risk related to the exposure to 10 weeks of placebo. This risk was reduced by inclusion criteria. The inclusion of participants with an estimated 10-year risk of cardiovascular events above 20% by the Framingham equation was possible. Investigators were informed of this risk level and asked to make sure other cardiovascular prevention drugs were prescribed correctly.

An interesting point of methodology has been illustrated in the conduct of the IDEAL trial. The BP criterion for hypertension was verified only at the first (inclusion) visit. Once this BP inclusion criterion was met at the first visit, patients were not excluded thereafter, even when their BP fell below the level required at the first screening visit. We adopted this rather unusual procedure to decrease the impact of the regression to the mean phenomenon on BP changes after randomisation. So the regression to the mean was observed mainly before randomisation, and was not considered a confusion factor in the BP response to the study drugs. This

potential source of bias has been reduced by 7/4 mmHg thanks to this simple procedure (figure 2).

The results are expected to contribute to the identification of biomarkers related to class-specific BP response and to promote personalized care of hypertension. In addition, identifying markers of class-specific BP response will improve the understanding of mechanisms at stake in the development of hypertension. Clinical pharmacology is a powerful tool for exploring pathophysiology. These results will also contribute to the development of integrated systems biology models like the quantitative x-modelling database (QxDB)[38], along with research projects granted by the French National Research Agency (especially the SAPHIR Project: a Systems Approach for PHysiological Integration of Renal, cardiac and respiratory function [SAPHIR][38,39] and Building the public health Impact Model for Blood pressure-lowering drugs: from gene to pOpulation [BIMBO] available on http://lbbe-dmz.univ-lyon1.fr/spip_bimbo/) and the European Commission (Virtual Physiome in Human).[40,41] This could be achieved in two ways: 1) by taking into account new biomarkers as key elements of integrated models; 2) by using trial databases as validation datasets, allowing comparisons between model predictions and observed data in order to optimise model parameters.

This study presents some limitations. IDEAL relied on the hypothesis that a single drug treatment is appropriate when treating hypertension in some patients. Using more than one drug class to control hypertension is required in a large proportion of participants in clinical trials. For example, in ALLHAT, the largest clinical trial to date, two thirds of participants only took the trial's first-line drug at five years.[42] In addition, we have to emphasize that 1) BP "targets" are generally based on expert consensus rather than on evidence based data; 2) BP "control" has never been shown to be mandatory to get benefit from BP-lowering drugs; 3) large trials that evaluated a fixed dose of one drug have shown similar benefits as trials that evaluated escalating doses of BP-lowering drugs adjusted to BP targets; 4) the intensification of BP-lowering drug treatment is not associated with a well demonstrated benefit.[43] The gain associated with an *a priori* rational choice of drugs is another hypothesis of IDEAL and it has not been demonstrated yet. Determining class-specific BP response to explain a significant part of the variation of BP response will be crucial to discussing the validity of this hypothesis. IDEAL will provide an important piece of knowledge, with a well-defined phenotype of BP response because of its double-blind placebo controlled design. The lack of power is the main limitation of IDEAL. The French Ministry of Health research grant allowed the recruitment of 200 patients. Several methods used to optimize patient recruitment (advertising directed at the general population through the press or the Internet, hospitals, research organisations, and outpatient clinics) did not produce significant results. The best method was to collaborate with a network of general practitioners and ABPM facilities. We optimised this system in the Clinical Investigation Centre of Lyon by hiring a GP to be in charge of network management. To compensate for reduced recruitment, we set up sister studies with the same experimental design in China and Romania. Our partners in these countries committed themselves to recruit 200 Chinese and 200 Romanian participants based on the same inclusion criteria. Differences in the genetic background of the samples will allow us to explore the general value of the results by testing the reproducibility of the results between samples. Contacts with other trial investigators have been taken to insure international collaboration and conduct a meta-analysis on individual patient data for all trials that explored BP response markers including genetic ones.

Authors' contributions

Theodora Bejan-Angoulvant, Jean-Philippe Baguet, Jean-Pierre Fauvel, Céline Giraud, Denis Angoulvant, François Gueyffier were involved in drafting the manuscript.

Theodora Bejan-Angoulvant, Jean-Philippe Baguet, Sylvie Erpeldinger, Jean-Marc Boivin, Jacques Amar, Georges Leftheriotis, Jean-Pierre Gagnol, Jean-Pierre Fauvel, François Gueyffier were investigators in the study and made a substantial contribution to data acquisition. Florent Boutitie and Céline Giraud were in charge of statistical analysis. Yishi Li and Calin Pop were the main investigators for the IDEAL sister studies in China and Romania. Giampierro Bricca was involved in protocol design and the biological sample analysis plan.

Members of the IDEAL study Group were either clinical investigators (Salam Farhat, Alain Richet, Yves Zerbib, Marie-France Le Goaziou, Rojee Neguib, Marie Flori, Anne-Françoise Cailleux, Christian Libersa, Atul Pathak, Jean-Michel Halimi, Pierre Lantelme), members of the scientific board (Stéphane Laurent, Faiez Zannad, Patrick Rossignol, Jacques Amar, Xavier Jeunemaître, Michel Azizi), or contributed to patient enrolment (Denis Angoulvant, Pierrette Darchy). All authors have given final approval of the version to be published.

Acknowledgements

IDEAL was made possible thanks to a grant from the French Society of Hypertension and from the 2003 French Hospital Program for Clinical Research (D50327). Its results contribute to the success of the BIMBO ANR project (SYSCOMM 2008-002).

We are grateful to Servier who offered the drugs and the dosages of indapamide and NACSDKP, without being involved in study conduct and data analysis.

The authors would like to thank Kent Neal (supported by the French Cochrane Centre) for proofreading the manuscript.

Competing interests. None.

List of abbreviations. ABPM: ambulatory blood pressure monitoring; ACEIs: angiotensin-converting enzyme inhibitors; ACE I/D: insertion/deletion polymorphism of ACE; ADD1: α-adducin gene; ADRB1 and ADRB2: beta-1 and beta-2 adrenoreceptor; AGT: angiotensinogen; AGTR1: angiotensin II receptor 1; AMBP: ambulatory blood pressure; BP: blood pressure; CNIL: *Commission nationale informatique et libertés* (French Data Protection Agency); CPP: Comité de protection des personnes (French institutional ethical review board); DBP: diastolic BP; ECG: electrocardiogram; HbA1c: glycosilated haemoglobin; HCTZ: hydrochlorothiazide; IDEAL: Identification of the Determinants of the Efficacy of Arterial blood pressure Lowering drugs; NOS3: nitic oxyde synthase 3; RCTs: randomised controlled trials; SBP: systolic BP; SR: slow release.

References

1. Gueyffier F, Froment A, Gouton M. New meta-analysis of treatment trials of hypertension: Improving the estimate of therapeutic benefit. J Hum Hypertens 1996; 10(1): 1-8
2. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: Meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009; 338: b1665
3. Gueyffier F, Boutitie F, Boissel JP, *et al*. Indana: A meta-analysis on individual patient data in hypertension. Protocol and preliminary results. Therapie 1995; 50: 353-62
4. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm hg. JAMA 1970; 213: 1143-52
5. Veterans administration cooperative study group on antihypertensive agents. Effects of treatment on morbidity in hypertension: results in patients with diastolic blood pressures averaging 115 through 129 mm hg. JAMA 1967; 202: 1028-34
6. Post-stroke antihypertensive treatment study. A preliminary result. Pats collaborating group. Chin Med J (Engl) 1995; 108: 710-7
7. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 2001; 358: 1033-41
8. Yusuf S, Sleight P, Pogue J, *et al*. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The heart outcomes prevention evaluation study investigators. N Engl J Med 2000; 342: 145-53
9. Patel A, MacMahon S, Chalmers J, *et al*. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): A randomised controlled trial. Lancet 2007; 370: 829-40
10. Neal B, MacMahon S, Chapman N. Effects of ace inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood pressure lowering treatment trialists' collaboration. Lancet 2000; 356: 1955-64
11. Hansson L, Zanchetti A, Carruthers SG, *et al*. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the hypertension optimal treatment (HOT) randomised trial. Hot study group. Lancet 1998; 351: 1755-62
12. Principal results of the japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). Hypertens Res 2008; 31: 2115-27
13. Bejan-Angoulvant T, Saadatian-Elahi M, Wright JM, *et al*. Treatment of hypertension in patients 80 years and older: The lower the better? A meta-analysis of randomized controlled trials. J Hypertens 2010; 28: 1366-72
14. Collins R, Peto R, MacMahon S, *et al*. Blood pressure, stroke, and coronary heart disease. Part 2, short-term reductions in blood pressure: Overview of randomised drug trials in their epidemiological context. Lancet 1990; 335: 827-38
15. Boissel JP, Gueyffier F, Boutitie F, *et al*. Apparent effect on blood pressure is only partly responsible for the risk reduction due to antihypertensive treatments. Fundam Clin Pharmacol 2005; 19: 579-84
16. Staessen JA, Wang JG, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. Lancet 2001; 358: 1305-15
17. MacMahon S, Peto R, Cutler J, *et al*. Blood pressure, stroke, and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990; 335: 765-74
18. Gueyffier F, Boutitie F, Cornu C, *et al*. Presentation of octave II. A current epidemiologic study in france of the added prognostic value of ambulatory blood pressure monitoring. Arch Mal Coeur Vaiss 1996; 89: 1381-8
19. Bell KJ, Hayen A, Macaskill P, *et al*. Monitoring initial response to angiotensin-converting enzyme inhibitor-based regimens: an individual patient data meta-analysis from randomized, placebo-controlled trials. Hypertension 2010; 56: 533-9
20. Turner MJ, van Schalkwyk JM. Blood pressure variability causes spurious identification of hypertension in clinical studies: A computer simulation study. Am J Hypertens 2008; 21: 85-91
21. Materson BJ, Reda DJ, Cushman WC, *et al*. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. The department of veterans affairs cooperative study group on antihypertensive agents. N Engl J Med 1993; 328: 914-21
22. Dickerson JE, Hingorani AD, Ashby MJ, *et al*. Optimisation of antihypertensive treatment by crossover rotation of four major classes. Lancet 1999; 353: 2008-13
23. Attwood S, Bird R, Burch K, *et al*. Within-patient correlation between the antihypertensive effects of atenolol, lisinopril and nifedipine. J Hypertens 1994; 12: 1053-60
24. Johnson JA, Boerwinkle E, Zineh I, *et al*. Pharmacogenomics of antihypertensive drugs: Rationale and design of the pharmacogenomic evaluation of antihypertensive responses (PEAR) study. Am Heart J 2009; 157: 442-9
25. Turner ST, Schwartz GL, Chapman AB, *et al*. Plasma renin activity predicts blood pressure responses to beta-blocker and thiazide diuretic as monotherapy and add-on therapy for hypertension. Am J Hypertens 2010; 23: 1014-22
26. Morgan TO, Anderson AI, MacInnis RJ. Ace inhibitors, beta-blockers, calcium blockers, and diuretics for the control of systolic hypertension. Am J Hypertens 2001; 14: 241-7
27. Cusi D, Barlassina C, Azzani T, *et al*. Polymorphisms of alpha-adducin and salt sensitivity in patients with essential hypertension. Lancet 1997; 349: 1353-7
28. Kurland L, Melhus H, Karlsson J, *et al.* On behalf of the Swedish Irbesartan Left Ventricular Hypertrophy Investigation versus Atenolol (SILVHIA) Trial. Angiotensin converting enzyme gene polymorphism predicts blood pressure response to angiotensin II receptor type 1 antagonist treatment in hypertensive patients. J Hypertens 2001; 19: 1783-7
29. Sofowora GG, Dishy V, Muszkat M, *et al*. A common beta1-adrenergic receptor polymorphism (arg389gly) affects blood pressure response to beta-blockade. Clin Pharmacol Ther 2003; 73: 366-71

30. van Rijn-Bikker PC, Mairuhu G, van Montfrans GA, *et al*. Genetic factors are relevant and independent determinants of antihypertensive drug effects in a multiracial population. Am J Hypertens 2009; 22: 1295-302
31. Hiltunen TP, Suonsyrja T, Hannila-Handelberg T, *et al*. Predictors of antihypertensive drug responses: Initial data from a placebo-controlled, randomized, cross-over study with four antihypertensive drugs (the GENRES study). Am J Hypertens 2007; 20: 311-8
32. Suonsyrja T, Hannila-Handelberg T, Paavonen KJ, *et al*. Laboratory tests as predictors of the antihypertensive effects of amlodipine, bisoprolol, hydrochlorothiazide and losartan in men: Results from the randomized, double-blind, crossover GENRES study. J Hypertens 2008; 26: 1250-6
33. Suonsyrja T, Donner K, Hannila-Handelberg T, *et al*. Common genetic variation of beta1- and beta2-adrenergic receptor and response to four classes of antihypertensive treatment. Pharmacogenet Genomics 2010; 20: 342-5
34. Mellen PB, Herrington DM. Pharmacogenomics of blood pressure response to antihypertensive treatment. J Hypertens 2005; 23: 1311-25
35. Arnett DK, Claas SA, Lynch AI. Has pharmacogenetics brought us closer to 'personalized medicine' for initial drug treatment of hypertension? Curr Opin Cardiol 2009; 24: 333-9
36. Johnson JA. Pharmacogenomics of antihypertensive drugs: Past, present and future. Pharmacogenomics 2010; 11: 487-91
37. Suonsyrja T, Donner K, Hannila-Handelberg T, *et al*. Common genetic variation of beta1- and beta2-adrenergic receptor and response to four classes of antihypertensive treatment. Pharmacogenet Genomics 2010; 20: 342-5
38. Ribba B, Tracqui P, Boix JL, *et al*. QxDB: A generic database to support mathematical modelling in biology. Philos Transact A Math Phys Eng Sci 2006; 364: 1517-32
39. Thomas SR, Baconnier P, Fontecave J, *et al*. Saphir: A physiome core model of body fluid homeostasis and blood pressure regulation. Philos Transact A Math Phys Eng Sci 2008; 366: 3175-97
40. Fenner JW, Brook B, Clapworthy G, *et al*. The EuroPhysiome, STEP and a roadmap for the virtual physiological human. Philos Transact A Math Phys Eng Sci 2008; 366: 2979-99
41. Hunter P, Coveney PV, de Bono B, *et al*. A vision and strategy for the virtual physiological human in 2010 and beyond. Philos Transact A Math Phys Eng Sci 2010; 368: 2595-614
42. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). JAMA 2002; 288: 2981-97
43. Arguedas JA, Perez MI, Wright JM. Treatment blood pressure targets for hypertension. Cochrane Database Syst Rev 2009: CD004349

Correspondence and offprints: *François Gueyffier*, Clinical Investigation Centre, Louis Pradel Cardiologic Hospital, 28 avenue Doyen Lépine, 69677 Bron Cedex, France.
E-mail: francois.gueyffier@chu-lyon.fr

