# Gender influence on the dose-ranging of a low-dose perindopril–indapamide combination in hypertension: effect on systolic and pulse pressure

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***Background*** **Dose-ranging of antihypertensive agents have been done to optimize diastolic blood pressure (DBP) reduction, but with little information on systolic (SBP), mean (MBP), or pulse (PP) pressures. A low-dose combination of perindopril (Per) and indapamide (Ind) has been shown to reduce more SBP than atenolol for the same DBP reduction. However, the possible influence of gender on this finding has never been tested.**

***Purpose*** **A database of five randomized, double-blind, dose-ranging studies was established to determine the optimal dose of the Per/Ind combination in hypertensive men and women. A total of 2907 patients were treated by either placebo or various combinations associating Per (2, 4, 8 mg) and Ind (0.625, 1.25, 2.5 mg).**

***Results*** **In the overall population, there was a significant dose–response relationship ($P < 0.001$) for doubling the dose of Per 2/Ind 0.625 mg up to Per 8/Ind 2.5 mg with a progressive fall in SBP, DBP, MBP. When men and women were analyzed by dose, SBP, DBP and MBP (but not PP) decreased significantly more in women than in men until the Per 4/Ind 1.25 dosage was reached. Thereafter, with higher dosages, generating a slight but significant hypokalemia, the finding was reversed, resulting in a gender interaction in the overall population.**

***Conclusion*** **In hypertensive subjects, the low-dose combinations Per 2/Ind 0.625 and Per 4/Ind 1.25 are the most effective in reducing blood pressure and avoiding hypokalemia. This effect is more pronounced in women, in which increased SBP and PP are predominant hemodynamic features.** *J Hypertens* **20:1653–1661 © 2002 Lippincott Williams & Wilkins.**

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**See editorial commentary page 1491**

## Introduction

Recent epidemiological studies, as well as recommendations of hypertension guidelines [1–3] have directed attention to systolic blood pressure (SBP) as a better guide than diastolic blood pressure (DBP), for evaluating cardiovascular risk. It has been shown that drug therapy of hypertension frequently results in an adequate control of DBP ($\leq 90$ mmHg), whereas the ability to control SBP ($\leq 140$ mmHg) is achieved less often [4]. Such results have focused attention on hemodynamic factors, such as large artery stiffness and wave reflections, which are important determinants of SBP and pulse pressure (PP), as well as strong independent cardiovascular risk predictors in hypertensive populations. Consequently, the role of drugs or regimen, which may selectively reduce SBP and PP assumes importance.

Very-low-dose combinations involving an angiotensin-converting enzyme (ACE) inhibitor and a diuretic may be suitable for reducing SBP and PP, and at the same time, for facilitating the compliance with long-term drug treatment [5,6]. The use of the diuretic alone would tend to reduce more SBP than DBP, as previously reported in three different studies [7–9]. Combination therapy may be of particular benefit since converting enzyme inhibition may block the diuretic-induced activation of the renin–angiotensin system, thereby contributing to decrease arterial stiffness and consequently to restore a normal SBP and PP [10]. A recent double-blind study has shown that low-dose combinations of perindopril (Per) and indapamide (Ind), i.e., Per 2/Ind 0.625 and Per 4/Ind 1.25, reduces significantly more SBP than the conventional agent atenolol for the same DBP reduction [11]. The Per/Ind association is able to reduce cardiovascular morbidity and mortality significantly, and in particular, to prevent recurrence of stroke or transient ischemic attack [12].

Such information is of special importance in women, a population in which an elevation of SBP and PP are particularly involved in the mechanism of the blood pressure elevation. Indeed, there is a steeper increase of SBP and PP with age in women than in men after 50 years of age [13] and a predominance of systolic hypertension is observed in old women, whether DBP is elevated, normal, or even low [1–3,8,9].

In this study, the dose–response curves of several different combinations of the ACE-inhibitor Per and the sulfonamide diuretic Ind in patients with systolic-diastolic hypertension of middle age in men and women, were examined. A large database composed of five chronic double-blind controlled studies [11,14–18], was constituted to determine the optimal dose of the Per/Ind combination according to gender.

## Material and methods

### Patients

Using the five controlled studies [11,14–18], 2907 men and women with mild to moderate hypertension were eligible to enter a 4-week single-blind placebo run-in period. Hypertension was defined as follows: supine DBP $\geq$ 95 mmHg and $<$ 114 mmHg in Europe or $<$ 109 mmHg in Canada. Age was between 18 and 82 years. If the DBP reading remained within these limits after 4 weeks of placebo, patients were randomly allocated to a 8–12 week treatment period with either a Per/Ind combination, or placebo, being administered using a double-blind, parallel group design.

The study excluded secondary hypertension, hypertension complicated by congestive heart failure, myocardial infarction, stroke or other clinically important target organ damage. Subjects with body mass index $>$ 32 kg/m$^2$ and/or plasma creatinine $>$ 150 µmol/l were excluded from the trial. No patient presented hypokalemia ($<$ 4.0 mmol/l), liver disease, previous adverse experience related to ACE-inhibitors or sulfonamide or previously demonstrated non-compliance with drug therapy. Chronic therapy with any drug affecting blood pressure was not permitted.

### Design

We pooled data of five investigations, which were randomized, with double-blind comparison of Per and Ind versus placebo using parallel group design. The studies were conducted in accordance with the principles of both the Declaration of Helsinki and European Good Clinical Practices and also met local regulatory requirements. The protocols were approved by local ethical review committees and all patients provided written informed consent before enrolment.

After the 4-week placebo period, placebo-responders were excluded and patients were assigned to one of the treatments indicated in Table 1. SBP, DBP, mean blood pressure (MBP) and PP, heart rate and possible adverse events were recorded at randomization and after 2, 4 and 8 weeks of drug/placebo therapy. Office blood pressure was evaluated 24 h after the previous dose using a standard mercury sphygmomanometer in the supine position (in triplicate). Standard laboratory tests were performed after 4 and 8 weeks of active treatment. Potassium supplementation was given after week four, if the serum potassium was below 3.4 mmol/l.

### Outcome measures

The primary efficacy parameters was the mean change in office/clinic supine DBP, measured 24 h after the previous dose comparing the final reading with baseline. The average of three consecutive determinations was used for the analysis. Secondary outcome measures included SBP, MBP and PP. MBP was calculated as DBP plus one-third PP. PP was SBP minus DBP. Normal values were considered to be $<$ 90 mmHg for DBP and $<$ 140 mmHg for SBP.

### Statistical analysis

Quantitative data are expressed as means ± standard deviation (SD) or adjusted means ± standard error of means (SE) as $n$ (%) for categorical variables. Analyses were performed with SAS software version 6.7 (Cary, North Carolina, USA) under Windows NT 2000. A value of $P \leq 0.05$ was considered significant. Categorical comparisons were performed by a $\chi^2$ test.

Table 1 **Studies of pooled data: number of patients by dosage**

| Per – Ind (mg) | Study 1 | Study 2 | Study 3 | Study 4 | Study 5 | Total |
|---|---|---|---|---|---|---|
| 0 – 0 | 77 | 0 | 61 | 386 | 0 | 524 (18.0%) |
| 0 – 1.25 | 80 | 540 | 60 | 0 | 0 | 680 (23.4%) |
| 2 – 0.625 | 0 | 0 | 65 | 386 | 229 | 680 (23.4%) |
| 2 – 1.25 | 0 | 0 | 65 | 0 | 0 | 65 (2.2%) |
| 4 – 0.625 | 80 | 0 | 0 | 0 | 0 | 80 (2.8%) |
| 4 – 1.25 | 78 | 542 | 61 | 0 | 0 | 681 (23.4%) |
| 4 – 2.5 | 71 | 0 | 0 | 0 | 0 | 71 (2.4%) |
| 8 – 1.25 | 0 | 0 | 64 | 0 | 0 | 64 (2.2%) |
| 8 – 2.5 | 0 | 0 | 62 | 0 | 0 | 62 (2.1%) |
| Total | 386 (13.3%) | 1082 (37.2%) | 438 (15.1%) | 772 (6.6%) | 229 (7.9%) | 2907 (100.0%) |

Per, perindopril dosages; Ind, indapamide dosages. (%), percentage of the total study population.

Five studies were used in a pooled data analysis. Thus, to ensure that there was no sensible difference between them, first we compared the baseline characteristics and second, the blood pressure changes, using an analysis of variance–covariance with $F$-test after adjustment on pertinent parameters [19–21]. Blood pressure changes were studied using the following formula: [(final value − baseline value)/baseline value] × 100.

In this pooled data analysis, different doses of Per combined with different doses of Ind were investigated. We first evaluated dose–gender interactions by an analysis of variance–covariance with two factors (Per/Ind doses and gender) and adjusted on pertinent parameters of the entire population. Gender comparisons were made using contrast tests in a general linear model SAS procedure when no interaction dose by gender was found. Due to the heterogeneity of Per/Ind dosages, the dose–response curves were obtained by doubling both the doses from Per 2/Ind 0.625 to Per 8/Ind 2.5. Because in some cases the interpretation might appear to be based upon a single aberrant value in the data for each gender across the studied dose range, it was verified that the results of study 3 (which involved different subgroups of the same number of subjects) did not differ from the pooled data analysis. This was done using a 'SAS mixed procedure' to model the unknown variance of within subjects according to each treatment group, and with additional variance of within subjects according to each treatment groups and with additional variance due to gender. Finally, it is important to note that all these procedures require adjustments of mean and standard error of the mean to covariates and blood pressure baseline value.

## Results

### Description of the studied populations of the database

At baseline, there were some slight differences in gender between the five studies ($P = 0.001$), since studies three and five presented more men (57% and 65%) than the three other studies (54% in study one, 51% in study two and 49% in study 4) (Table 2). Differences were also observed for previous antihypertensive drug treatment (PAT): patients of study one (64% of the population against 73% overall) were less likely to have been previously treated than the others ($P = 0.001$). Age, body mass index (BMI) and heart rate were significantly different ($P < 0.0001$) between studies, but these differences were weak: 2 years for age (53.0 to 55.9), 1.3 kg/m$^2$ for BMI and 3.8 beats per minute (bpm) for heart rate. Similar results were found on blood pressures (comparisons were adjusted on all significant parameters), and differences were also weak (1–3 mmHg for SBP; 3 mmHg for DBP; 3 mmHg for MBP and 4 mmHg for PP ($P = 0.0006$). Finally, in the five studies, the analysis of evolution showed no major discrepancy between them (data not shown). SBP,

**Table 2** Studies of pooled data: population description

| | Study 1 | Study 2 | Study 3 | Study 4 | Study 5 | $P$ | Overall means ± SD [Min–Max] |
|---|---|---|---|---|---|---|---|
| PAT (Yes Nb(%)) | 245 (64%) | 818 (76%) | 342 (78%) | 543 (70%) | 169 (74%) | 0.001 | 2117 (73%) |
| Gender (M, W %) | 54 : 46 | 51 : 49 | 57 : 43 | 49 : 51 | 65 : 35 | 0.001 | 53 : 47 |
| Age (years) | 53.0 ± 10.0 | 53.6 ± 10.9 | 55.3 ± 10.7 | 55.9 ± 11.5 | 54.3 ± 12.2 | 0.0001 | 54.4 ± 11.1 [18–82] |
| BMI (kg/m$^2$) | 25.9 ± 2.8 | 26.8 ± 3.2 | 27.2 ± 3.0 | 26.6 ± 3.4 | 26.8 ± 2.8 | 0.0001 | 26.7 ± 3.2 [15.8–36.1] |
| HR (bpm) | 75.8 ± 9.3 | 74.5 ± 9.4 | 75.8 ± 10.2 | 73.4 ± 10.2 | 72.0 ± 9.4 | 0.0001 | 74.4 ± 9.8 [45–123] |
| SBP (mmHg) | 162.8 ± 15.1 | 163.2 ± 15.2 | 161.7 ± 15.4 | 160.0 ± 10.9 | 163.2 ± 13.4 | 0.0001 | 162.1 ± 14.1 [113–218] |
| DBP (mmHg) | 102.1 ± 5.2 | 102.3 ± 5.0 | 101.5 ± 4.8 | 99.3 ± 3.3 | 98.6 ± 6.9 | 0.0001 | 101.1 ± 5.0 [71.3–115.0] |
| MBP (mmHg) | 122.3 ± 7.4 | 122.6 ± 7.1 | 121.6 ± 7.0 | 119.5 ± 4.8 | 120.1 ± 6.4 | 0.0001 | 121.4 ± 6.7 [98.9–147.8] |
| PP (mmHg) | 60.6 ± 13.3 | 60.9 ± 13.9 | 60.2 ± 14.1 | 60.7 ± 10.5 | 64.6 ± 14.9 | 0.0007 | 61.0 ± 13.1 [18.3–108.7] |

Means ± 1 SD. PAT, prior antihypertensive drug treatment; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure; Nb, absolute number.

DBP, MBP and PP decreased in the same way among the five studies with maximum differences varying by 3% for PP. Although such differences were statistically significant, they may be considered as not pertinent, clinically.

### Findings of the data-base

Table 3 indicates the comparison between the groups of men and women of the database. All comparisons were significant except for SBP and MBP, but as comparison studies, clinical differences were not relevant except for PAT, in which women were treated more (76%) than men (70%).

Tables 2 and 3 explain that, due to the heterogeneity of the five studies, the blood pressure changes obtained at the different dosages should be adjusted to age, BMI, PAT, baseline heart rate and baseline values of blood pressure. Note that 1372 patients were older than 55 years (47%) with a gender repartition of 50% men and 50% women. The younger population was composed of 1535 patients (53%) with 55% men and 45% women.

These adjusted blood pressure changes (%) are presented in Table 4. In the overall population, all blood pressure changes were statistically different from zero, except in the placebo group for PP. As an example, the dose-ranging indicated a significant dose-response relationship ($P < 0.001$) for doubling the dose of Per 2/Ind 0.625 mg up to Per 8/Ind 2.5 mg with a progressive fall in SBP, DBP and MBP (Fig. 1). For all blood pressures (SBP, DBP, MBP) except PP, an interaction gender by dose was found significant. As shown on Figure 1, this interaction became evident after the Per 4/Ind 1.25 dosage had been reached and was observed even in aged people (Fig. 2). The same findings were observed when SBP changes (expressed in mmHg) were studied either in the pooled data analysis or using the homogeneous repartition of subgroups of study three (Fig. 3).

**Table 3** Database: comparison between men and women

| | Men | Women | *P* |
|---|---|---|---|
| *n* (%) | 1537 (53%) | 1370 (47%) | |
| PAT Yes(%) | 70% | 76% | 0.001 |
| Variables (Mean ± SD) | | | |
| Age (years) | 53.8 ± 11.1 | 55.2 ± 11.0 | 0.0005 |
| BMI (kg/m$^2$) | 27.0 ± 2.8 | 26.3 ± 3.5 | 0.0001 |
| HR (bpm) | 73.4 ± 9.9 | 75.5 ± 9.6 | 0.0001 |
| SBP (mmHg) | 161.8 ± 14.7 | 162.4 ± 13.4 | 0.2040 |
| DBP (mmHg) | 101.3 ± 5.2 | 100.8 ± 4.8 | 0.0090 |
| MBP (mmHg) | 121.4 ± 7.0 | 121.3 ± 6.4 | 0.7110 |
| PP (mmHg) | 60.4 ± 13.6 | 61.6 ± 12.5 | 0.0188 |

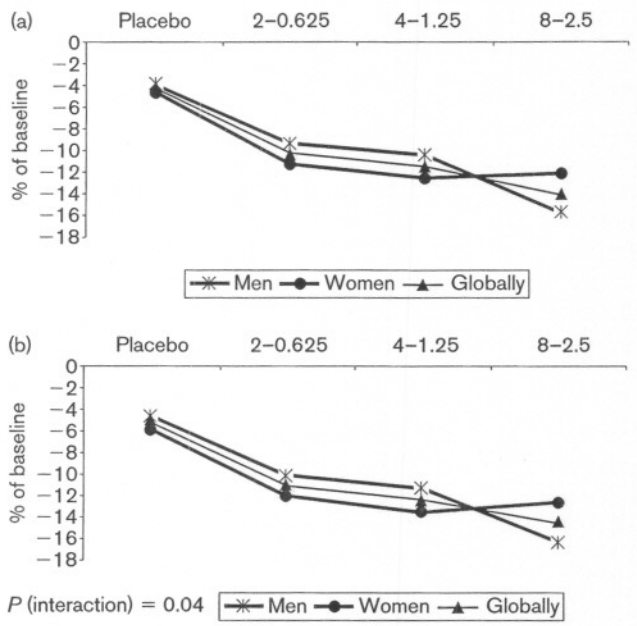
PAT, prior antihypertensive drug treatment; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure.

**Table 4** Blood pressure changes (%) according to dose groups and gender and adjusted on age, BMI, PAT, heart rate and blood pressures baseline values

| Perindopril (mg/day) | 0 | | 2 | | 4 | | 8 | |
|---|---|---|---|---|---|---|---|---|
| Indapamide (mg/day) | 0 | 1.25 | 0.625 | 1.25 | 0.625 | 1.25 | 2.5 | 1.25 | 2.5 |
| SBP(%) | | | | | | | | | |
| Men | −3.93 ± 0.49 | −8.47 ± 0.42 | −9.42 ± 0.40 | −9.62 ± 1.29 | −11.36 ± 1.24 | −10.42 ± 0.42 | −12.46 ± 1.24 | −9.75 ± 1.24 | −15.68 ± 1.34 |
| *P* = 0.0368 | NS | 0.05 | 0.003 | NS | NS | 0.0003 | NS | 0.009 | NS |
| Women | −4.58 ± 0.48 | −9.84 ± 0.44 | −11.24 ± 0.46 | −9.58 ± 1.48 | −10.37 ± 1.24 | −12.57 ± 0.43 | −12.47 ± 1.41 | −15.23 ± 1.60 | −12.08 ± 1.48 |
| DBP(%) | | | | | | | | | |
| Men | −5.00 ± 0.52 | −9.87 ± 0.44 | −10.13 ± 0.43 | −9.36 ± 1.36 | −10.94 ± 1.31 | −11.46 ± 0.44 | −14.20 ± 1.31 | −10.25 ± 1.31 | −16.41 ± 1.42 |
| *P* = 0.0408 | 0.15 | 0.05 | 0.001 | NS | NS | 0.0001 | 0.10 | 0.10 | 0.09 |
| Women | −6.43 ± 0.51 | −11.23 ± 0.46 | −12.23 ± 0.49 | −10.24 ± 1.57 | −10.83 ± 1.31 | −13.78 ± 0.46 | −11.39 ± 1.49 | −14.34 ± 1.69 | −12.50 ± 1.57 |
| MBP(%) | | | | | | | | | |
| Men | −4.51 ± 0.46 | −9.30 ± 0.39 | −9.89 ± 0.38 | −9.37 ± 1.22 | −11.19 ± 1.17 | −11.04 ± 0.40 | −13.56 ± 1.17 | −10.14 ± 1.17 | −16.06 ± 1.27 |
| *P* = 0.0228 | 0.14 | 0.03 | 0.0008 | NS | NS | 0.0001 | 0.22 | 0.02 | 0.09 |
| Women | −5.65 ± 0.46 | −10.67 ± 0.41 | −11.86 ± 0.43 | −9.96 ± 1.40 | −10.72 ± 1.17 | −13.32 ± 0.41 | −11.98 ± 1.33 | −14.87 ± 1.51 | −12.41 ± 1.40 |
| PP(%) | | | | | | | | | |
| Men | −1.46 ± 1.01 | −5.06 ± 0.87 | −6.81 ± 0.84 | −10.52 ± 2.68 | −11.40 ± 2.58 | −7.52 ± 0.87 | −6.77 ± 2.58 | −7.59 ± 2.58 | −14.27 ± 2.79 |
| *P* = 0.1848 | NS | NS | 0.25 | NS | 0.24 | 0.14 | 0.13 | 0.07 | NS |
| Women | −0.42 ± 1.00 | −6.45 ± 0.91 | −8.10 ± 0.95 | −7.11 ± 3.08 | −8.15 ± 2.58 | −9.40 ± 0.90 | −13.89 ± 2.93 | −15.10 ± 3.32 | −10.69 ± 3.08 |

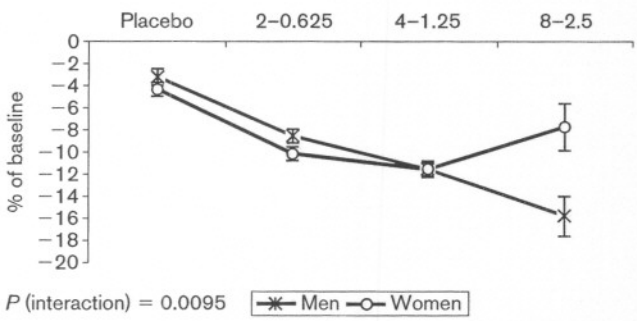
*P* = result of interaction gender by dose test. Means ± SE are presented. Results (*P*) of variance analysis with covariate between gender are presented between means of men and women for each dose. BMI, body mass index; PAT, prior antihypertensive drug treatment; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure. The *P* values in the left column represent the overall value of the men/women interaction for SBP, DBP, MBP and PP. The other *P* values, on the same horizontal line, correspond to the *P* value of each dosage.

**Fig. 1**



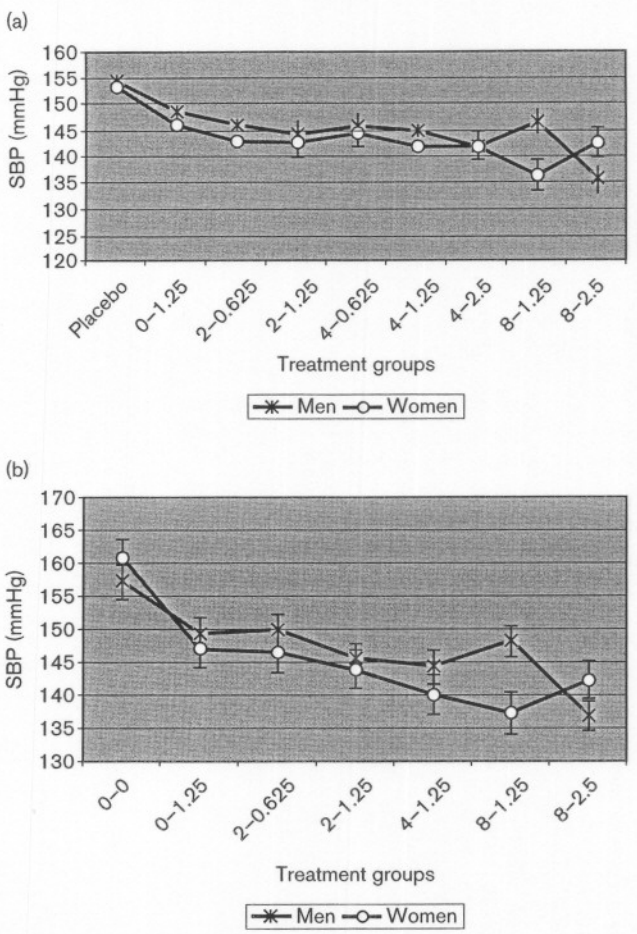

Percentage of (a) SBP and (b) MBP changes according to gender and Per/Ind doses by doubling the dose of Per 2/Ind 0.625 up to Per8/Ind 2.5 mg. The same result is observed when the Per 8/Ind 1.25 mg group is added (data not shown). Per, perindopril dosages; Ind, indapamide dosages.

**Fig. 2**




Systolic blood pressure (SBP) change (%) according to gender and Per/Ind doses in pooling data analysis in subjects > 55 years. Per, perindopril dosages; Ind, indapamide dosages.

**Fig. 3**




Systolic blood pressure (SBP) (mmHg) mean values according to (a) gender and Per/Ind dose in the overall population (pooling data analysis) and (b) study three. The same results were observed in both populations. Per, perindopril dosages; Ind, indapamide dosages.

All means were statistically different according to dose–response groups in each gender. However, because of the presence of interactions, gender differences were studied in each dose. The *P*-values of tests are presented for each dose in Table 4. For Per 2/Ind 0.625 and Per 4/Ind 1.25, the blood pressure reduction (%) was significantly more pronounced in women than in men, except for PP. In the higher dosage of the Per/Ind combination (Per 4/Ind 2.5 mg and Per 8/Ind 1.25 and 2.5), the difference in behavior between men and women was reversed, explaining the significance of the interaction (Fig. 1). Table 4 clearly shows that the interaction was mainly due to the higher dosages (Per 4 mg/Ind 2.5 mg and Per 8/Ind 1.25 and 2.5 mg) and could completely disappear when these high dosages are removed from the analysis.

Table 5 summarizes the results of gender comparisons for the two low dose combinations (Per 2/Ind 0.625 and Per 4/Ind 1.25) and placebo. The BP reduction (%) was significantly higher for women than for men, the difference approximating 2%. The level of significance was reached only for SBP, DBP and MBP but not for PP. Table 6 indicates the main factors influencing the SBP and PP changes, whatever the gender. These factors were: for SBP, mainly treatment groups

Table 5 **Blood pressure changes (%) (mean ± SE) according to dose groups and gender, adjusted on age, BMI, PAT, heart rate and blood pressures baseline values**

| | | Placebo | *P* | Per 2/Ind 0.625 | *P* | Per 4/Ind 1.25 | *P* |
|---|---|---|---|---|---|---|---|
| SBP | Men | −3.84 (0.49) | 0.32 | −9.33 (0.41) | 0.002 | −10.34 (0.42) | 0.0003 |
| | Women | −4.52 (0.49) | | −11.21 (0.46) | | −12.52 (0.44) | |
| DBP | Men | −4.92 (0.51) | 0.04 | −10.02 (0.43) | 0.0007 | −11.37 (0.44) | 0.0002 |
| | Women | −6.38 (0.51) | | −12.20 (0.48) | | −13.72 (0.46) | |
| MBP | Men | −4.42 (0.46) | 0.07 | −9.77 (0.38) | 0.0004 | −10.97 (0.40) | 0.0001 |
| | Women | −5.57 (0.46) | | −11.81 (0.43) | | −13.28 (0.41) | |
| PP | Men | −1.47 (1.02) | 0.5 | −6.82 (0.84) | 0.28 | −7.54 (0.87) | 0.12 |
| | Women | −0.50 (1.01) | | −8.20 (0.95) | | −9.50 (0.90) | |

*P*, mean comparison between gender; Per, perindopril; Ind, indapamide; BMI, body mass index; PAT, prior antihypertensive drug treatment; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure.

Table 6 **Stepwise regressions of factors influencing blood pressures changes: SBP or PP**

| | Reg. coeff. ± SE | Part $R^2$ | *P* |
|---|---|---|---|
| SBP changes (%) in entire population $R^2 = 18.25\%$ | | | |
| Treatment groups* | −0.19 ± 0.01 | 9.58% | 0.0001 |
| SBP pre-treatment (mmHg) | 1.61 ± 0.43 | 5.53% | 0.0001 |
| Age (years) | 0.09 ± 0.02 | 1.29% | 0.0001 |
| PAT | −1.51 ± 0.38 | 0.64% | 0.0002 |
| Gender | 0.11 ± 0.06 | 0.67% | 0.0001 |
| HR pre-treatment (bpm) | 0.05 ± 0.02 | 0.39% | 0.0027 |
| BMI (kg/m$^2$) | −1.02 ± 0.08 | 0.16% | 0.0556 |
| Part of $R^2$ due to treatment groups | | 52.49% | |
| PP changes (%) in entire population $R^2 = 20.68\%$ | | | |
| PP pre-treatment (mmHg) | −0.66 ± 0.03 | 15.31% | 0.0001 |
| Age (years) | 0.30 ± 0.04 | 3.31% | 0.0001 |
| Treatment groups* | −1.04 ± 0.15 | 1.91% | 0.0001 |
| HR pre-treatment (bpm) | 0.07 ± 0.04 | 0.15% | 0.0594 |
| Part of $R^2$ due to treatment groups | | 12.48% | |

*Treatment groups are placebo, Per 2 mg/Ind 0.625 mg and Per 4 mg/Ind 1.25 mg. SBP, systolic blood pressure; PAT, prior antihypertensive drug treatment; HR, heart rate; BMI, body mass index; PP, pulse pressure.

(explaining 9.58% of the total variance of SBP changes) and baseline SBP (5.53%); for PP, mainly baseline PP (explaining: 15.31% of the total variance of PP changes). Finally, it is noteworthy that baseline PP was a more sensitive predictor than baseline SBP and that PP did not differ significantly between the two dosages, Per 2/Ind 0.625 and Per 4/Ind 2.5.

## Discussion

The present data have examined several different combinations of Per and Ind in comparison with placebo in order to determine, in hypertensive subjects, the optimum doses in men and women for use in clinical practice. This study complements our earlier reports on the dose–response characteristics of various combinations of Per and Ind, in which we provided a complete placebo-controlled 4 × 4 factorial dose–response data set for doses of Per 0, 2, 4 and 8 mg/day and Ind at 0, 0.625, 1.25 and 2.5 mg/day [11,14–18]. This comprehensive approach to determine the dose–response characteristics of two complementary antihypertensive medications not only provides a basis for regulatory approval, but also offers practising clinicians some data enabling them to base treatment decisions to reduce blood pressure in each particular gender. In the present study, it has been identified that the Per/Ind combination was even more effective in women than in men, but that this difference affected SBP, DBP, and MBP, but not PP.

### Limits of the study

The present results represent a *post-hoc* analysis of the individual data of several double-blind, already published clinical trials [11,14–18]. The major weakness of this approach might be principally that, (1) the pooling of results from different centers usually conceals subtle differences in methodology conditions, and (2) reliance on blood pressure changes from baseline introduces additional 'noise' because of the placebo effect and the inherent variability of conventional single-time point blood pressure measurements. Nevertheless, it is noteworthy that all these criticisms have been taken into consideration for a long time in several published meta-analysis of the literature [19–21], particularly related to antihypertensive therapy. The present study took into account most of the usual basis of such meta-analysis. More specifically, to ensure that there was no substantial difference between the various populations, first the baseline characteristics of each trial were compared and second, the blood pressure changes were compared, by an analysis of variance–covariance with an *F*-test in adjusting pertinent parameters.

One difficulty of this study was that the interpretation might potentially appear to be based upon a single 'aberrant' value of the data for each gender across the studied dose-range. However, along the investigation, evidence was provided that the results did not differ, whether the totality of data were pooled or the statistical evaluation was limited to study three (in which homogeneous subgroups of subjects were investigated; see Table 1) or to the dose–response curves obtained

by doubling the dose of the Per/Ind combination (Fig. 1). These statistical evaluations were based on a three way analysis of variance indicating that: (1) the first interaction, which was significant, means that the SBP changes under treatment differ according to the dosage studied, (2) the second interaction, which was not significant, means that the SBP changes did not differ according to gender, but (3) the third interaction, which was significant, means that the SBP changes differed according to gender, in addition to differences before and after treatment. Such findings also observed with DBP and MBP, clearly validated the main results of the present investigation.

#### Antihypertensive effect of Per/Ind in men and women

The antihypertensive effect of a given combination between a diuretic and a converting enzyme inhibitor is traditionally due to the association of salt and water depletion, together with blockade of the renin–angiotensin system. This mechanism is certainly operating with the higher dosages of the Per/Ind combination (above Per 4/Ind 1.25), with which a significant hypokalemia is observed, indicating the presence of salt and water depletion [15]. The antihypertensive effect of the two low dosages, Per 2/Ind 0.625 and Per 4/Ind 1.25, which do not cause substantial hypokalemia [15,22], is more difficult to interpret and might suggest that, independently of the diuretic (Ind)-induced salt and water depletion, a subtle synergistic effect between Per and Ind at low doses should be observed at the cellular level. It has been shown that in SHRs, reduced sodium intake and/or diuretics given at low doses are able to translate vascular smooth muscle cells from a secretory to a contractile phenotype, a situation which is known to favor the antihypertensive effect of renin–angiotensin inhibition [23–28]. Whatever the mechanisms involved, it appears clear that, when studying the dose–response curve of the Per/Ind combination, the most effective dose in reducing blood pressure corresponds to the highest one but that, in terms of risk-benefit, the most appropriate dosages enabling both to reduce blood pressure and to avoid hypokalemia are the Per 2/Ind 0.625 and Per 4/Ind 1.25 dosages.

One particularity of this study was that the Per/Ind effectiveness differed significantly in men and women. For the low dosages of the combination, the percentage decrease of SBP, DBP and MBP was higher in women than in men. This result was reversed for the higher dosages, resulting in a significant gender-interaction for SBP, DBP and MBP in the overall population. As shown in Table 4 and Figure 1, this interaction resulted exclusively from a difference in the effect of the higher dosages of Ind ($>$ 1.25 mg), and Per (8 mg). This result further validates the choice of the two low-dose combinations, Per 2/Ind 0.625 and Per 4/Ind 1.25, as the most appropriate dosages for the drug treatment in hypertension.

Studies of pulsatile hemodynamics have recently shown that the hemodynamic profile of women differs substantially from that of men, with a prominent role of the pulsatile component of blood pressure (PP) over its steady component (MBP), in relation to the short stature of women and its consequences on arterial stiffness and wave reflections [29]. Because Per 2/Ind 0.625 and Per 4/Ind 1.25 have been shown to reduce significantly SBP and PP more than atenolol for the same DBP reduction, and because this difference was due to specific effects of the Per/Ind combinations on arterial stiffness and wave reflections [11], it seems logical that the low doses of Per/Ind combinations might be more effective in women. Higher dosages, which are associated with a significant salt and water depletion, result in a reduced compliance of the totality of the vascular system including mostly the large compartment of veins [30].

#### Per/Ind combination and pulse pressure

An important finding of the present study was that, irrespective of gender, both Per 2/Ind 0.625 and Per 4/Ind 1.25 reduced equally PP. Because PP is the difference between SBP and DBP and because SBP and PP are strongly correlated [9,31–34], it is often difficult to determine unequivocally the particular effects of the decrease of SBP and PP during chronic drug treatment of hypertension. However, the present data gave some important information in this respect. First, along the statistical evaluation, there was evidence that, in the present large populations of hypertensive subjects, PP remained unmodified under placebo. This finding contrasts with the decrease in SBP, DBP and MBP, usually observed under placebo and has been recently reported by Asmar *et al.* [35,36], pointing to the interest to evaluate SBP and PP separately, in order to better determine the severity of the hypertensive vascular disease. Second, over 50 years of age, brachial PP is a more powerful independent marker of cardiovascular risk than SBP itself. This finding has been observed both in untreated and treated hypertensive subjects, particularly regarding the prediction of myocardial infarction [9,13,32–34,37,38].

In the recent findings of the Hypertension Optimal Treatment (HOT) study, in which the exclusive goal of the trial was to normalize DBP, subjects with the higher risk at the end of the follow-up were those in which DBP was adequately controlled, whereas SBP, and hence PP, still remained elevated [39]. These findings (Table 6) clearly indicate that subjects with the higher SBP and PP are those who respond best to the Per 2/Ind 0.625 and Per 4/Ind 1.25 low-dose combinations. For this purpose, PP is a more adequate

tool than SBP for optimizing drug treatment, since this parameter is independent on gender and highly reproducible under placebo. Furthermore, the baseline value of PP represents 15–31% of the total variance of its changes under the Per/Ind combination (Table 6). However, in this line of evidence, a limit of caution should be given on the present results. The data of the present study were limited to subjects with mild to moderate systolic–diastolic hypertension in middle-age, and cannot be extrapolated to subjects with severe hypertension or with isolated systolic hypertension, particularly in the elderly.

### Conclusion

The low-dose combinations Per 2/Ind 0.625 and Per 4/Ind 1.25 are the most effective to reduce blood pressure and both to avoid hypokalemia in hypertensive subjects. Their effect is more impressive in women, in which increased SBP and PP are predominant hemodynamic features.

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