

Fixed low-dose combination therapy in hypertension – a dose response study of perindopril and indapamide

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Objective To establish the optimal dose of the perindopril/indapamide combination (Per/Ind) in the treatment of mild or moderate hypertension.

Design This was a randomized, double-blind, placebo-controlled, seven-way parallel-group, dose-ranging study, set in multicenter, outpatient offices/clinics in Europe and Canada.

Patients A total of 438 patients aged between 18 and 75 years whose supine diastolic blood pressure was between 95 and 114 mmHg were randomly assigned to an 8-week double-blind treatment with either placebo, Per 2/Ind 0.625, Per 4/Ind 1.25, Per 8/Ind 2.5, Per 0/Ind 1.25, Per 2/Ind 1.25 or Per 8/Ind 1.25 mg.

Main outcome measures Systolic and diastolic blood pressure measured in the clinic approximately 24 h after dosing.

Results There was a linear 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 supine diastolic blood pressure (–9.3 to –15.0 mmHg). Combining 1.25 mg Ind with increasing doses of Per (0, 2, 4 and 8 mg) also showed a linear dose–response

relationship ($P < 0.001$), with supine diastolic blood pressure falling by –8.0 to –12.0 mmHg compared with a fall of –5.2 mmHg for the placebo group. Similar findings were noted for supine systolic blood pressure, standing blood pressure and ambulatory blood pressure. Hypokalemia was more common (9.7%) in the Per 8/Ind 2.5 mg group than in the groups receiving other doses (0–4.6%).

Conclusion The combinations of Per 2/Ind 0.625 mg and Per 4/Ind 1.25 mg were effective in reducing blood pressure without producing clinically important side effects. *J Hypertens* 2000, 18:317–325 © Lippincott Williams & Wilkins.

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Introduction

During recent years, there has been a trend toward the use of low-dose combination drug therapy in hypertension [1,2]. Although higher doses given as monotherapy may provide some additional antihypertensive effect, dose-related side effects become more common, such as biochemical abnormalities with diuretics and edema with calcium channel blockers. The alternate approach of using smaller doses of two agents in combination generally reduces the likelihood of dose-related side effects while taking advantage of mutually favorable properties of the individual drugs. The recent American JNC (VI) report [3] recommends the use of combination therapy, especially with low-dose diuretics. One logical drug combination that has been recommended is an angiotensin-converting enzyme (ACE) inhibitor with a sulfonamide diuretic. Use of the diuretic alone would provoke the renin–angiotensin–aldosterone system, whereas combining it with an ACE inhibitor would tend to block the resulting cardiovascular effects.

Combination therapy may be of particular benefit in certain patient populations. For example, ACE inhibitors reduce renal and cardiovascular complications in patients with diabetes mellitus [4–7]. Diuretics have also been shown to reduce mortality in hypertensive patients with diabetes as seen with chlorthalidone therapy in the Systolic Hypertension in the Elderly Program [8]. Other reasons for using two agents in a fixed combination are more practical and include achieving better compliance using fewer tablets and reducing the apprehension that some patients experience when taking multiple medications.

If hypertensive patients are to be given a combination therapy, it is important to know the most appropriate dose of each constituent drug in order to maximize the therapeutic response. Accordingly, we have examined the dose–response characteristics of several different combinations of the ACE inhibitor perindopril and the sulfonamide diuretic indapamide in untreated patients

with essential hypertension. The principal objective of this study was to examine the efficacy and safety of these drugs in doses that are likely to be used in clinical practice.

Methods

Patient population and inclusion criteria

Men and women aged 18–75 years with mild to moderate hypertension were eligible to enter a 4-week single-blind placebo run-in period. Hypertension was defined as supine diastolic blood pressure ≥ 95 mmHg and < 114 mmHg in Europe (or < 109 mmHg in Canada in order to satisfy local regulatory and ethical review board requirements). If the diastolic reading remained within these limits after 4 weeks of receiving placebo, patients were randomly allocated to an 8-week treatment period with either a perindopril/indapamide combination or placebo being administered using a double-blind, parallel-group study design.

The major exclusion criteria were secondary hypertension, hypertension complicated by previous myocardial infarction, stroke or other clinically important target organ damage, marked obesity (body mass index > 32 kg/m²), impaired renal function (serum creatinine > 150 μ mol/l), diabetes mellitus, hypokalemia, liver disease, previous adverse experience related to ACE inhibitors or sulfonamides or previously demonstrated noncompliance with drug therapy. Chronic therapy with any drug affecting blood pressure was not permitted.

Study design

The study was a multinational, randomized, double-blind comparison of perindopril and indapamide versus placebo using a seven-way parallel-group study design. The study was conducted in accordance with the principles of both the Declaration of Helsinki and European Good Clinical Practices and also met local regulatory requirements. The protocol was approved by each local ethical review committee and all patients provided written informed consent before enrollment.

After the 4-week placebo period, eligible patients were assigned to one of the following treatments: placebo, 2 mg perindopril and 0.625 mg indapamide (Per 2/Ind 0.625), 4 mg perindopril and 1.25 mg indapamide (Per 4/Ind 1.25), 8 mg perindopril and 2.5 mg indapamide (Per 8/Ind 2.5), 0 mg perindopril and 1.25 mg indapamide (Per 0/Ind 1.25), 2 mg perindopril and 1.25 mg indapamide (Per 2/Ind 1.25), 8 mg perindopril and 1.25 mg indapamide (Per 8/Ind 1.25). These combinations provide data on the dose–response characteristics for doubling of the dose Per 2/Ind 0.625 up to Per 8/Ind 2.5 mg daily and of increasing doses of perindopril from 0 to 8 mg daily in combination with 1.25 mg indapamide daily.

Blood pressure, heart rate and possible side effects were recorded at randomization and after 2, 4 and 8 weeks of drug or placebo therapy. Supine and standing clinic blood pressures were evaluated approximately 24 h after the previous dose using a standard mercury sphygmomanometer as recommended by American Society of Hypertension and World Health Organization guidelines. Readings were taken in triplicate after 10 min supine and after 1 min standing. A 24-h ambulatory blood pressure recording was also performed using a SpaceLabs model 90207 device (SpaceLabs Inc, Redmond Washington, USA) before the first randomized dose and during the final 24 h of the 8-week treatment period. Standard laboratory tests were performed after 4 and 8 weeks of active treatment. Potassium supplementation was permitted after 4 weeks if the serum potassium was below 3.4 mmol/l.

Outcome measures

The primary efficacy parameter was the mean change in clinic supine diastolic blood pressure measured 24 h after the previous dose comparing the final reading with baseline. The average of three consecutive supine diastolic blood pressure determinations was used for the analysis. Secondary outcome measures included supine systolic blood pressure and standing blood pressure, ambulatory blood pressure and the responder rate (decrease from baseline supine diastolic blood pressure of at least 10 mmHg and/or a final supine diastolic blood pressure of ≤ 90 mmHg). The primary safety criteria included serum potassium below 3.4 mmol/l and any serious side effect requiring urgent intervention.

Statistical methods

An intent-to-treat analysis was performed for efficacy and safety in which the last available endpoint values were carried forward [9]. The dose–response relationship for changes in blood pressure was evaluated using linear regression analysis for (a) increasing doses of perindopril (0–8 mg daily) with a fixed dose of indapamide (1.25 mg daily) and (b) for a doubling of the perindopril/indapamide combination. An extended ‘test of trend’ version of the Cochran–Mantel–Haenszel test was used to evaluate the dose–response relationship in terms of the percentage of responders. A pair-wise comparison between increasing doses of perindopril/indapamide and placebo was performed for each analysis using a Student’s *t* test. Bonferroni adjustment was used for continuous variables and Fisher exact test for discrete variables to compare all active groups with placebo.

Descriptive statistics were used for quantitative variables (mean \pm SEM) and for qualitative variables (frequency and rates) The type I error was set at 5%. A Cochran–Mantel–Haenszel test assessed the responder

rate and frequency of patients with low serum potassium in each treatment group.

Results

Population

Four hundred and ninety-six patients were enrolled into the run-in period and received placebo therapy. Of these, 438 were assigned for randomization to one of the six combinations of perindopril and indapamide or to placebo. Fifty-eight patients were excluded for the following reasons (number of patients in parentheses): patient's choice (12), supine diastolic blood pressure < 95 mmHg (19), side effects (9), supine diastolic blood pressure (Europe) > 114 or (Canada) > 109 mmHg (6), abnormal laboratory parameter (4), investigator decision (3), protocol violation (3). Baseline characteristics of the remaining 438 patients in each subgroup are shown in Table 1. There were no significant differences in the characteristics of the treatment subgroups. A preponderance of patients was male and most were of middle age (40–65 years). Supine and standing clinic blood pressure and 24-h, daytime and night-time ambulatory blood pressure values at baseline for each treatment subgroup are listed in Table 2. There were no significant differences in baseline values. No patient was lost to follow-up and there were no deaths in the study. Four hundred and twenty-one patients completed the 8-week double-blind treatment phase and were available for the efficacy analysis.

Clinic blood pressure

There was a progressive fall in blood pressure for increasing doses of perindopril/indapamide, both for increasing doses of perindopril with the dose of indapamide kept constant at 1.25 mg daily and for a repeated doubling of the perindopril/indapamide combination (Figs 1 and 2). A significant ($P = 0.007$) linear relationship (coefficient of determination: $r^2 = 0.030$, slope: $b = -0.48$, intercept: $a = -8.36$) was present between indapamide 1.25 mg daily in combination with increasing doses of perindopril (0, 2, 4 and 8 mg daily) and the change in supine diastolic blood pressure from baseline to the final visit at week 8.

Per 0/Ind 1.25 mg daily altered supine diastolic blood pressure by -8 ± 1 mmHg versus -12 ± 1 mmHg for the Per 8/Ind 1.25 mg daily combination (Fig. 1). Similar findings were noted for supine systolic blood pressure, with values decreasing progressively ($P = 0.002$; $r^2 = 0.43$, $b = -0.95$, $a = -12.82$) from -12 ± 2 mmHg for Per 0/Ind 1.25 mg daily to -18 ± 2 mmHg for Per 8/Ind 1.25 mg daily. A repeated doubling of the Per/Ind combination from 2/0.625 mg to 8/2.5 mg daily resulted in a progressive reduction ($P < 0.001$) in both supine systolic ($r^2 = 0.20$, $b = -2.15$, $a = -7.46$) and diastolic ($r^2 = 0.17$, $b = -1.16$, $a = -5.99$) blood pressure between baseline and week

Table 1 The demographic characteristics of patients in each treatment subgroup at baseline

	Placebo	Per 2/Ind 0.625	Ind 1.25	Per 2/Ind 1.25	Per 4/Ind 1.25	Per 8/Ind 1.25	Per 8/Ind 2.5	Total
Patients (n)	61	65	60	65	61	64	62	438
Age (years)	56 ± 1	55 ± 1	56 ± 1	54 ± 1	54 ± 1	57 ± 1	55 ± 1	55 ± 1
M/F (n)	32/29	40/25	33/27	37/28	35/26	40/24	34/28	251/187
Weight (kg)	77 ± 2	78 ± 1	80 ± 2	79 ± 1	78 ± 2	79 ± 1	76 ± 2	78 ± 1
Duration of hypertension (months)	84 ± 10	88 ± 10	75 ± 10	83 ± 9	68 ± 7	84 ± 9	104 ± 11	84 ± 4
Previous antihypertensive treatment (n)	49	56	44	51	47	47	43	337

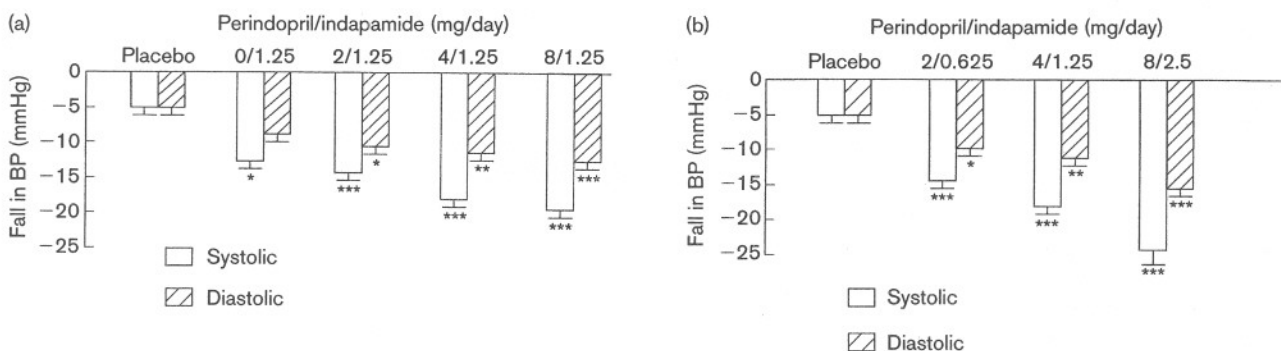
Data shown are mean ± SEM. Baseline is week 0. Drug doses are mg/day.

Table 2 Clinic and ambulatory blood pressure values at baseline for each treatment subgroup

	Placebo	Per 2/Ind 0.625	Ind 1.25	Per 2/Ind 1.25	Per 4/Ind 1.25	Per 8/Ind 1.25	Per 8/Ind 2.5
Patients (n)	61	65	60	65	61	64	62
Supine BP							
systolic	164 ± 2	163 ± 2	161 ± 2	159 ± 2	160 ± 2	164 ± 2	162 ± 2
diastolic	102 ± 1	102 ± 1	101 ± 1	101 ± 1	101 ± 1	102 ± 1	101 ± 1
Standing BP							
systolic	166 ± 2	165 ± 2	160 ± 2	159 ± 2	159 ± 2	163 ± 2	162 ± 2
diastolic	104 ± 1	105 ± 1	103 ± 1	104 ± 1	103 ± 1	104 ± 1	103 ± 1
24-h ambulatory BP							
systolic	151 ± 2	151 ± 2	148 ± 2	150 ± 2	150 ± 2	152 ± 2	150 ± 2
diastolic	93 ± 1	95 ± 1	92 ± 1	95 ± 1	93 ± 1	94 ± 1	92 ± 1
Daytime ambulatory BP							
systolic	155 ± 2	156 ± 2	152 ± 2	155 ± 2	154 ± 2	156 ± 2	154 ± 2
diastolic	96 ± 1	99 ± 1	96 ± 1	98 ± 1	96 ± 1	97 ± 1	96 ± 1
Night-time ambulatory BP							
systolic	138 ± 2	136 ± 2	135 ± 2	136 ± 2	137 ± 2	139 ± 2	137 ± 2
diastolic	82 ± 1	83 ± 1	81 ± 1	83 ± 1	83 ± 1	83 ± 1	82 ± 1

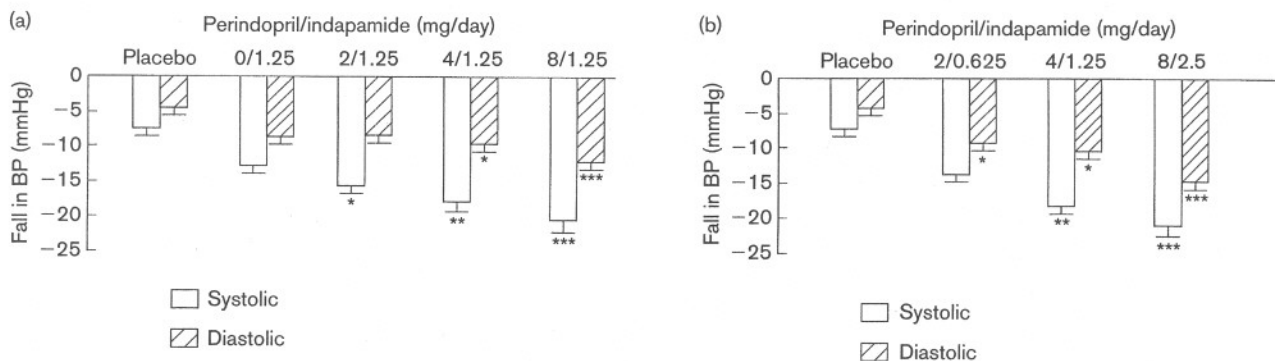
Values (mmHg) are means ± SEM. Baseline is week 0. Drug doses are mg/day. BP, blood pressure.

Fig. 1



Changes in supine blood pressure (BP) from week 0 (baseline) to week 8 for (a) increasing doses of perindopril in combination with 1.25 mg indapamide daily and (b) doubling of the perindopril/indapamide combination. Data presented as means ± SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ versus placebo.

Fig. 2



Changes in standing blood pressure (BP) from week 0 (baseline) to week 8 for (a) increasing doses of perindopril in combination with 1.25 mg indapamide daily and (b) doubling of the perindopril/indapamide combination. Data presented as means ± SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ versus placebo.

8 with the reductions decreasing from $-14 \pm 2/ -9 \pm 1$ mmHg (Per 2/Ind 0.625) and $-23 \pm 2/ -15 \pm 1$ mmHg (Per 8/Ind 2.5) at week 8 (Fig. 1). In the placebo group, supine blood pressure fell by $-5 \pm 2/ -5 \pm 1$ mmHg at week 8.

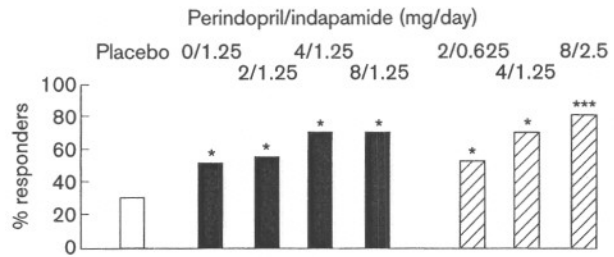
Similar linear relationships were seen for both standing systolic and diastolic clinic blood pressures (Fig. 2). For example, treatment with Per 0/Ind 1.25 mg daily for 8 weeks decreased standing blood pressure by $-12 \pm 2/ -7 \pm 1$ mmHg, whereas adding perindopril caused a progressive fall of up to $-20 \pm 2/ -11 \pm 1$ mmHg for the Per 8/Ind 1.25 mg daily dose ($P < 0.001/ < 0.001$; $r^2 = 0.33/0.03$, $b = -0.92/ -0.52$, $a = -12.74/ -6.89$). Doubling the Per/Ind combination also progressively decreased ($P < 0.001$) standing systolic ($r^2 = 0.097$, $b = -1.55$, $a = -9.23$) and diastolic ($r^2 = 0.13$, $b = -1.08$, $a = -4.97$) blood pressure changes at week 8 from $-13 \pm 2/ -9 \pm 1$ mmHg for Per 2/Ind 0.625 to $-20 \pm 2/ -14 \pm 1$ mmHg for Per 8/Ind 2.5 mg daily (Fig. 2). In the placebo group, standing blood pressure fell by $-4 \pm 1/ -4 \pm 1$ mmHg at week 8.

The responder rate for the primary outcome measure (supine diastolic blood pressure) also showed a progressive increase for increasing doses of perindopril up to 4 mg combined with 1.25 mg indapamide daily and for doubling of the Per/Ind combination as seen in Figure 3.

Ambulatory blood pressure

Both systolic and diastolic 24-h ambulatory blood pressures decreased progressively (Fig. 4) with increasing doses of perindopril combined with 1.25 mg indapamide daily or with a doubling of the Per/Ind combination. However, increasing the dose from Per 4/Ind 1.25 to Per 8/Ind 1.25 did not produce a clinically relevant (≤ 1 mmHg) reduction in blood pressure

Fig. 3



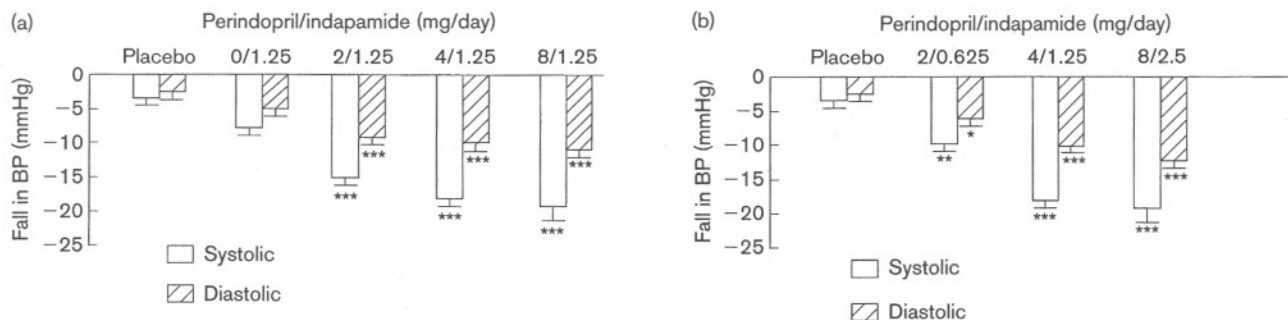
Responder rates for patients in each treatment subgroup achieving a decrease from baseline supine diastolic blood pressure of ≥ 10 mmHg and/or a final supine diastolic blood pressure ≤ 90 mmHg. Data are shown for a) increasing doses of perindopril in combination with 1.25 mg indapamide daily and (b) doubling of the perindopril/indapamide combination. Data presented as means \pm SEM. * $P < 0.05$, *** $P < 0.001$ versus placebo.

whereas a greater change was noted at lower dosage increments. Similarly, the greatest reduction associated with the doubling of the Per/Ind dose combination occurred between Per 2/Ind 0.625 and Per 4/Ind 1.25 mg daily, with little additional fall being achieved by increasing to the maximum Per 8/Ind 2.5 mg daily dose (Fig. 4). The same pattern was observed when ambulatory blood pressure was subdivided into mean daytime (0700–2200 h; Fig. 5) and mean night-time (2200–0700 h; Fig. 6) periods.

Withdrawals and side effects

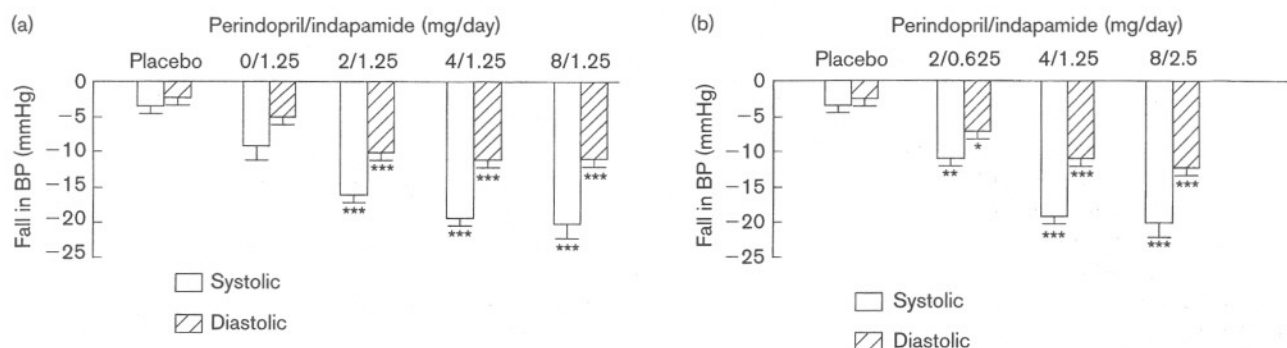
Treatment was stopped prematurely in 17 patients before the scheduled end of week 8: 12 for adverse events (dizziness, headache and nausea), four for lack of efficacy and one for non-medical reasons. No patients were withdrawn for a major protocol violation. A nonfatal myocardial infarction occurred on day

Fig. 4



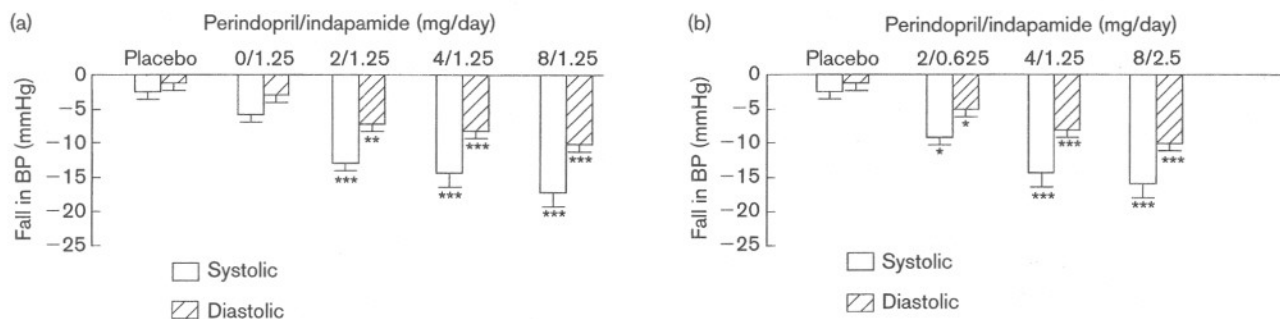
Changes in 24-h ambulatory blood pressure (BP) from week 0 (baseline) to week 8 for (a) increasing doses of perindopril in combination with 1.25 mg indapamide daily and (b) doubling of the perindopril/indapamide combination. Data presented as means \pm SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ versus placebo.

Fig. 5



Changes in daytime 24-h ambulatory blood pressure (BP) from week 0 (baseline) to week 8 for (a) increasing doses of perindopril in combination with 1.25 mg indapamide daily and (b) doubling of the perindopril/indapamide combination. Data presented as means \pm SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ versus placebo.

Fig. 6



Changes in night-time 24-h ambulatory blood pressure (BP) from week 0 (baseline) to week 8 for (a) increasing doses of perindopril in combination with 1.25 mg indapamide daily and (b) doubling of the perindopril/indapamide combination. Data presented as means \pm SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ versus placebo.

16 in a 67-year-old woman receiving Per 8/Ind 2.5 mg daily. Her blood pressure on day 14 had been 159/82 mmHg. The event was considered 'unlikely' to be related to study medication by the local investigator.

Angina developed in a 63-year-old man on day 35 of therapy with Per 8/Ind 2.5 mg daily. His blood pressure on the previous visit was 150/83 mmHg. The relationship between this adverse event and the study medication was designated as 'doubtful' by the local investigator.

Cough did not occur in any patients in the placebo group and was present in 5% of patients on Per 0/Ind

1.25, 4.6% in Per 2/Ind 1.25 and 8.2–9.7% with the other Per/Ind combinations.

Hypokalemia defined as a serum potassium concentration below 3.4 mmol/l was noted in nine patients at week 4 before any potassium supplementation. Five of these patients were receiving the maximum dosage of Per 8/Ind 2.5 mg daily. Seven out of the nine hypokalemic patients received potassium supplements after week 4 and all nine patients completed the study to the end of week 8. The incidence of hypokalemia at any time during the randomization period varied between 0 and 4.6% for all drug combinations with the exception of Per 8/Ind 2.5 mg, which had a 9.7% incidence.

Mean serum potassium concentrations (mmol/l) showed little change between baseline and week 4 after which potassium supplementation was permitted. Mean (SEM) changes from baseline varied from -0.08 (0.05) to -0.26 (0.06) with the exception of the Per 8/Ind 2.5 mg subgroup, which showed a change ($P < 0.005$) in mean serum potassium of -0.39 (0.05). Mean serum potassium values at week 4 remained ≥ 4.10 mmol/l with the exception of the Per 8/Ind 2.5 subgroup (3.92 ± 0.05).

There were minor changes in serum creatinine, glucose and cholesterol, with the maximum mean increases from baseline in any of the treatment subgroups being $3.3 \mu\text{mol/l}$, 0.66 mmol/l and 0.18 mmol/l , respectively. The maximum decrease in mean serum sodium was -0.20 mmol/l for 1.25 mg indapamide alone and -1.3 mmol/l for Per 8/Ind 1.25. Hyponatremia (serum sodium level $< 130 \text{ mmol/l}$) occurred only in the Per 8/Ind 1.25 subgroup ($n = 3$, 1.5%). Mean uric acid increased significantly for all treatment groups (range of increase 35.1 – $55.7 \mu\text{mol/l}$) compared with an increase of $10.8 \mu\text{mol/l}$ with placebo ($P < 0.01$).

Discussion

This study examined several different combinations of perindopril and indapamide in comparison with placebo in order to determine the optimum doses for use in clinical practice. There was a linear progression in the fall in blood pressure for both increasing doses of perindopril with indapamide maintained at 1.25 mg daily and for three different multiples of 2 mg perindopril and 0.625 mg indapamide daily. The net change in supine blood pressure after correcting for the response to placebo was $-9/-4$ and $-13/-5 \text{ mmHg}$ for the Per 2/Ind 0.625 and Per 4/Ind 1.25 mg daily, respectively. Although Per 8/Ind 2.5 mg daily produced a placebo-corrected net change in blood pressure of $-18/-10 \text{ mmHg}$, this combination was also associated with more hypokalemia. Even though adding 8 mg perindopril may reduce the likelihood of developing hypokalemia with 2.5 mg indapamide alone, this dose of the ACE inhibitor/diuretic combination may still require adjunctive therapy in order to maintain a normal serum potassium. It is also noteworthy that the highest doses of perindopril and indapamide did not produce much additional fall in ambulatory blood pressure ($\leq 1 \text{ mmHg}$) compared with lower doses in contrast to changes seen with the clinic blood pressure. Similar discrepancies between clinic and ambulatory readings have been reported in other dose-response studies [10] but the underlying explanation for the difference remains an enigma. In balancing efficacy against safety, it would appear that combinations of Per 2/Ind 0.625 mg and Per 4/Ind 1.25 mg daily are most appropriate for patients with

uncomplicated mild to moderate essential hypertension.

In a previous study [11], 2 and 4 mg perindopril once daily for 12 weeks reduced the placebo-corrected supine clinic blood pressure at 24 h by $-2/-3$ and $-4/-4 \text{ mmHg}$, respectively. In the present study, the combination of perindopril with indapamide resulted in a greater reduction in blood pressure than that achieved with perindopril alone. The apparent additive effect of the ACE inhibitor/diuretic combination should provide additional benefits in reducing cardiovascular outcomes in clinical practice.

This study complements an earlier one [12] on the dose-response characteristics of other combinations of perindopril and indapamide in which a similar design and methodology were used. In this previous study, the mean reduction in diastolic blood pressure after 8 weeks of therapy was evaluated for 4 mg perindopril combined with increasing daily doses of indapamide from 0.625 mg to 2.5 mg. Supine diastolic blood pressure fell by -10.9 , -12.2 , -13.5 and -14.1 mmHg for Per 4/Ind 0, Per 4/Ind 0.625, Per 4/Ind 1.25 and Per 4/Ind 2.5 mg daily, respectively, compared with -6.1 mmHg for placebo. Responder rates for these doses were 64, 64, 73 and 81%, respectively compared with 29% for placebo. Thus the addition of 0.625 mg indapamide to 4 mg perindopril does not increase the incidence of responders and produces only a small net change in diastolic blood pressure (-1.3 mmHg) compared with 4 mg perindopril monotherapy. The data confirm Per 2/Ind 0.625 and Per 4/Ind 1.25 mg daily as optimum doses for clinical practice.

These results, together with the present findings, provide a placebo controlled, factorial dose-response data set for doses of perindopril 0, 2, 4 and 8 mg per day and indapamide at 0, 0.625, 1.25 and 2.5 mg per day. This comprehensive approach to determining the dose-response characteristics of two complementary antihypertensive medications not only provides a basis for regulatory approval, but also offers practicing clinicians sound data upon which to base treatment decisions in routine clinical practice.

The placebo-corrected reductions in clinic blood pressure seen with Per 2/Ind 0.625 and Per 4/Ind 1.25 are similar to changes noted in clinical outcome studies [13] in which decreases in diastolic blood pressure of 4 – 5 mmHg have been associated with significant improvements in the rate of stroke (-40%) and coronary heart disease (-15 to -20%). Similar benefits have been noted in clinical trials in older patients with systolic hypertension [13] in whom changes in systolic blood pressure of -12 to -13 mmHg compared with placebo resulted in signifi-

cant reductions in the incidence of stroke and myocardial infarction. The benefit of achieving a fall of this magnitude with minimal side effects is important if long-term compliance with therapy is taken into consideration.

It may be possible to maintain drug therapy in 75% of patients participating in long-term efficacy studies but similar success rates have not always been achieved in clinical practice. Indeed, a substantial proportion of patients who are prescribed monotherapy discontinue treatment possibly because of apparent side effects to their antihypertensive medications [14]. The combination of low doses of two agents into a single tablet should enhance compliance by reducing the number of tablets and perceived number of medications being taken, thus achieving a clinically useful reduction in blood pressure with fewer side effects over the long term. This approach is now recommended in the latest JNC (VI) report [3].

The side-effect profile for the perindopril/indapamide combination was similar to placebo with one exception. Cough appeared to be more frequent when perindopril was used and this is consistent with other studies on ACE inhibitor therapy in hypertension [15]. However, there were no signs of increasing renal impairment, lipid abnormalities or glucose intolerance with any of the combinations of perindopril or indapamide. There was a significant increase in serum uric acid in all treatment groups and serum potassium was generally lower with indapamide, although mean values remained well within the normal range. Indapamide has been associated with fewer biochemical abnormalities than some of the commonly used thiazide diuretics, especially when prescribed at lower doses, although good comparative studies in the same large patient population have yet to be done [16].

Indapamide has been proposed as the preferred sulfonamide diuretic for patients with diabetes mellitus because of the drug's purported minimal effects on lipids and glucose intolerance at lower doses [17]. Recently, ACE inhibitors have been recommended for diabetic patients with microalbuminuria [3]. The combination of perindopril and indapamide would be a logical choice for most diabetic patients with hypertension. Consequently, it would be useful to examine the dose-response characteristics of the perindopril/indapamide combination, such as Per 2/Ind 0.625 mg and Per 4/Ind 1.25 mg daily in hypertensive patients with diabetes mellitus to see whether the findings in uncomplicated hypertension can be extrapolated to this subpopulation.

In summary, the combinations of Per 2/Ind 0.625 mg and Per 4/Ind 1.25 mg daily effectively reduced blood

pressure in patients with uncomplicated mild to moderate essential hypertension without producing serious side effects. The recent trend toward low-dose combinations with these and other agents should help improve long-term drug therapy by maintaining antihypertensive efficacy and maximizing patient compliance in the clinical setting.

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Appendix

The following co-investigators participated in the study:

in the UK – Charles Barber, Anthony Burgess, Howard Duncane, James Gray, Christopher Kyle, Ian Longhorn, Peter Maksimcsyk, Graham Martin, Mickael Pimm, Peter Saul and Barry Silvert;

in the Netherlands – Theodor Erwterman, Cees Oldenbroek and Johan Smilde;

in Germany – Constantin Baran, Peter Eckert, Christian Klein, Ludwig Kredel, Dieter Landers, Reimund Pieske, Volker von Behren and Klaus Zitzman;

in Canada – Allan Bell, Douglas Bishop, Rafael Charzyk, Stephen Chris, Sheldon Filkenstein, John Buller, Mickael Ingber, Ben Lasko, Lawrence Lerner, Kim-Weng Tan, David Vanderhout, Bernita Young and Preston Zuliani.