A Systematic Review and Meta-Analysis of the Efficacy and Safety of a Fixed, Low-Dose Perindopril-Indapamide Combination as First-Line Treatment of Hypertension

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ABSTRACT

Background: A low-dose combination of perindopril and indapamide may effectively reduce blood pressure (BP) in hypertensive patients, but some factors related to study design might have contributed to the between-group differences in the rate of reduction of BP observed in some trials.

Objective: The aim of this study was to systematically assess the efficacy and safety profiles (through review of randomized, controlled trials) of the fixed, low-dose combination perindopril 2 mg and indapamide 0.625 mg given as 1 tablet daily as first-line antihypertensive therapy in patients with mild to moderate hypertension.

Methods: We searched MEDLINE (1966–April 2003), EMBASE (1980–March 2003), BIOSIS (1999–December 2002), and the Cochrane Library, using the medical subject headings with the search terms *perindopril, indapamide, hypertension, randomized controlled trials, randomly, random, randomization, perindopril-indapamide, essential hypertension,* and *primary hypertension.* Additional articles were obtained from the reference lists of relevant reviews and papers.

Results: We reviewed 11 trials (5936 individuals). In 5 studies of perindopril-indapamide versus placebo, the between-group weighted mean differences (WMDs) for both systolic and diastolic BP (SBP and DBP, respectively) favored perindopril-indapamide (SBP, –9.03 mm Hg [95% CI, –9.54 to –8.52]; DBP, –5.09 mm Hg [95% CI, –5.42 to –4.77]; both $P < 0.01$ for z score for overall effect). In 6 studies of perindopril-indapamide versus routine antihypertensives, the between-group WMDs for SBP and DBP favored perindopril-indapamide (SBP, –3.72 mm Hg [95% CI, –7.11 to 0.33], $P = 0.03$ for z score for overall effect; DBP, –1.71 mm Hg [95% CI, –2.27 to –1.16], $P < 0.01$ for z score for overall effect). Five studies compared perindopril-indapamide and placebo; in the remaining 3 studies, which assessed perindopril-indapamide versus routine antihypertensives, the between-group WMDs for SBP and DBP favored perindopril-indapamide (SBP, –4.00 mm Hg [95% CI, –6.54 to –1.47], $P < 0.01$; DBP, –1.02 mm Hg [95% CI, –1.73 to –0.31], $P < 0.01$). Adverse events and withdrawals were not significantly different between perindopril-indapamide, placebo, or routine antihypertensive drugs.

Conclusion: The studies in our analysis consistently demonstrated that a fixed, low-dose perindopril-indapamide combination has a favorable safety profile and may be efficacious as first-line treatment for patients with mild to moderate essential hypertension. (*Clin Ther*. 2004;26:257–270) Copyright © 2004 Excerpta Medica, Inc.

Key words: perindopril, indapamide, perindopril-indapamide, antihypertensive, efficacy, safety.

Accepted for publication November 20, 2003.

0149-2918/04/$19.00

INTRODUCTION

Although the sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (BP) in 1997[1] and the 1999 World Health Organization–International Society of Hypertension Guidelines for treatment[2] addressed the use of a combination of an angiotensin-converting enzyme (ACE) inhibitor and a diuretic as initial therapy in patients with essential hypertension, clinical practitioners should take into account the standards of the US Food and Drug Administration when considering the use of combination therapy[3]: (1) therapy with a combination of drugs is superior to monotherapy, (2) each drug component adds to the therapeutic effect, and (3) the dosage forms must be adequate in terms of bioavailability, prevention of unwanted interactions, and the correct dosing of each component.

One fixed, low-dose therapy combines the non-thiazide sulfamoyl chlorobenzamide diuretic indapamide and the ACE inhibitor perindopril, which is active through its metabolite perindoprilat. The use of indapamide as an antihypertensive drug has been well established in the literature.[4] Indapamide is not associated with the major side effects of most diuretics, namely, change in lipid metabolism[5–7] and other biochemical abnormalities (eg, glucose, uric acid), especially when prescribed at lower doses.[8,9] Indapamide has been proposed as the preferred sulfonamide diuretic at lower doses for patients with diabetes mellitus.[10] Regarding the pharmacokinetic characteristics of indapamide and perindopril, their similar half-life justifies administering them in combination as 1 tablet per day.[11] Thus, we can reasonably hypothesize that a fixed, low-dose perindopril-indapamide combination could be a better treatment choice than routine monotherapeutic antihypertensives for many patients with hypertension.

In recent years, a large-population study demonstrated that the perindopril-indapamide combination was more effective than monotherapy in the reduction of BP and the occurrence of stroke.[12] Several reports have shown that a low-dose combination of perindopril-indapamide is efficacious and well tolerated in patients with mild to moderate hypertension and chronic renal failure.[13–15] Population-based studies have shown that the pharmacokinetic profile of a perindopril-indapamide combination is similar to that of each drug as monotherapy in patients with chronic renal failure.[16–18] Also, first-line treatment with a low-dose perindopril-indapamide combination induced a greater decrease in albuminuria in patients with diabetes mellitus than enalapril alone, partially independent of BP reduction.[19] Previous research showed that a perindopril-indapamide combination was efficacious and well tolerated in elderly hypertensive patients.[11,20–25] However, some factors—such as small study samples, nonrandomization, and variations in the formulations and dosages of the perindopril-indapamide combination, the duration of use of the drugs, the dose-response relationship, and the use of placebo or other antihypertensive drugs as controls—might have contributed to the between-group difference in the rate of reduction of BP observed in some trials.[9,12,26] Moreover, trials with small sample sizes were not sufficient to demonstrate a safety profile for the combination therapy.[9,26,27]

We aimed to systematically assess the efficacy and safety profiles of a fixed, low-dose perindopril-indapamide combination (perindopril 2 mg and indapamide 0.625 mg given as 1 tablet daily) as first-line antihypertensive therapy for mild-to-moderate hypertension in randomized, controlled trials, through the use of meta-analysis and sensitivity analysis.

METHODS

We searched MEDLINE (1966–April 2003), EMBASE (1980–March 2003), BIOSIS (1999 to December 2002), and the Cochrane Library. We combined the medical subject headings with the search terms *perindopril, indapamide, hypertension, randomized controlled trials, randomly, random, randomization, perindopril-indapamide, essential hypertension*, and *primary hypertension*. Additional articles were obtained from the reference lists of relevant reviews and papers. Two of the authors (S.K. and N.A.) reviewed all 168 abstracts identified by the search and found 58 studies with primary data. To limit the association between perindopril-indapamide and hypertension, we excluded studies that were animal experiments, were nonrandomized controlled trials or clinical controlled trials, focused on the protection of target organs (eg, heart, brain, kidneys) without BP data, included only monotherapy, or were not written in English. Most studies in our analysis were conducted with patients with mild to moderate systolic and dia-

stolic hypertension or isolated systolic hypertension, and the combination of perindopril-indapamide was administered as initial treatment or after a 4- to 8-week placebo run-in period, or as first-line therapy. Two studies[12,27] compared nonhypertensive and hypertensive patients. If 2 studies were performed using the same population, the study with the most recent data was included.

Fourteen relevant studies were included. However, 2 studies[28,29] included only the data for diastolic BP (DBP); in 1 trial, the results of reduction of BP were described only as change of mean BP, without systolic BP (SBP) and DBP data.[9] We were unable to obtain further data through correspondence with the authors.

Finally, 11 relevant studies were entered into our analysis. We employed a 2-step method of analysis of data: first, we analyzed the efficacy and safety profile of the different dosages of perindopril-indapamide combination in antihypertensive treatment; second, we examined the efficacy and safety profile of the fixed, low-dose combination therapy.

Jadad scores[30] were used to measure the quality of the randomized controlled trials (**Table I**). Two reviewers (S.K. and N.A.) rated study quality independently, and there was 90% agreement on their recorded Jadad scores. If the reviewers disagreed, a final score was reached through consensus by a third reviewer.

Statistical analysis was performed with use of Review Manager software (RevMan 4.1, Cochrane Collaboration, Oxford, United Kingdom). The analysis was stratified by control group status: placebo or routine antihypertensive drugs. In each study, the size of the change in BP was calculated as the difference between the mean BP of the treatment and control groups at the end of the intervention. The difference in mean BP was weighted according to the inverse of the sum of variances within studies and between studies. The weighted mean difference (WMD) in each study was pooled with the fixed-effects model[31]; if the result of the χ^2 test for heterogeneity was statistically significant ($P < 0.05$), the analysis was repeated using a random-effects model.[31] A funnel plot was performed to detect publication bias.[32]

Table I. Criteria for grading the quality of randomized controlled trials using the Jadad scoring system.[30] Each study received 1 point for each "yes" or 0 for each "no" per question.*

1. Was the study described as randomized, such as using the words "randomly," "random," and "randomization"?†
2. Was the study described as "double blind"?‡
3. Was there a description of withdrawals and dropouts?

*The maximum number of points was 5.
† An additional point was given if the method of randomization was described and it was appropriate (eg, table of random numbers, computer generated). A point was deducted if the method of randomization was inappropriate (eg, patients were allocated alternately by birth date or hospital number).
‡ A point was given if the method of blinding was described and it was appropriate (eg, identical placebo). An additional point was deducted if the method of blinding was inappropriate (eg, comparing placebo tablet with injection).

RESULTS

Study Design, Demographics, and Efficacy

The literature search identified 11 randomized, controlled trials with a total of 5936 patients (**Table II**), in which 2 studies were given a Jadad score of 5,[12,26] another 8 reports were each given a Jadad score of 3,[19,21–24,33–35] and 1 study was given a Jadad score of 1 because its abstract gave no description of the method of masking or details regarding withdrawals and dropouts.[27] The methods of randomization and masking were not described in detail in 7 studies,[19,22–24,33–35] and details regarding withdrawals and dropouts and the method of masking were described incompletely in 1 study.[21] The randomized, controlled trials were dissimilar in several ways. One employed a factorial design.[26] In 9 studies, the predose SBP of perindopril-indapamide ranged from 140 to 210 mm Hg and the predose DBP ranged from 90 to 115 mm Hg.[19,21–24,26,33–35] In 1 study[27] with a daytime mean ambulatory BP measurement, the predose SBP was >135 mm Hg and DBP was >85 mm Hg, and in another study,[12] there were no BP entry criteria. The age of the study patients ranged from 65 to 85 years in 4 studies,[21–24] 40 to 75 years in 3 studies,[12,19,35] 18 to 84 years in 2 trials,[26,34] and 18 to 75 years in 1 trial.[33] The ages of the participants were not described in detail in 1 abstract.[27]

In all studies, perindopril and indapamide were combined as 1 tablet taken once per day. In 8 studies, the dose was perindopril 2 mg and indapamide 0.625 mg.[21–24,27,33–35] In 1 study,[26] the dose was perindopril 4 mg and indapamide 1.25 mg; in another,[12] the dose was perindopril 4 mg and indapamide 2.5 mg; and in a third study,[19] the dose was initially perindopril

Table II. Randomized, controlled trials of a low-dose combination of perindopril-indapamide (PI) as first-line therapy in hypertension.

Reference	Inclusion Criteria	PI/Control, no. of patients	Daily Dose	Duration of Use	Results	Quality Score*
Laurent[21]	Outpatients aged 68–85 years with uncomplicated essential hypertension	386/386	P: 2 mg, I: 0.625 mg; control: PBO	12 wk	Normalization and response rates: 67% and 74%, respectively ($P < 0.05$); 79.8% of patients sustained normalization over 1 year	3‡‡
Chalmers et al[22]	Outpatients aged 68–85 years with uncomplicated mild to moderate essential hypertension or ISH (DBP <95 mm Hg and SBP 160–183 mm Hg)	125/135	P: 2 mg, I: 0.625 mg; control: PBO	12 wk	Initial normalization of BP: 96.2% ($P < 0.05$); 79.8% of patients sustained normalization over 1 year	3‡§
Myers et al[33]	Men and women aged 18–75 years with mild to moderate hypertension entering a 4-week, single-masked PBO run-in	65/61	P: 2 mg, I: 0.625 mg; control: PBO	18 wk	Decrease of supine SBP ($P < 0.001$), DBP ($P < 0.001$), and ambulatory BP ($P < 0.001$)	3‡§
Castaigne et al[23]	Patients aged 65–85 years with satisfactory PBO compliance and persistent mild or moderate SDH or ISH	68/55	P: 2 mg, I: 0.625 mg; control: PBO	12 wk	SBP and DBP reductions in ISH: –23 mm Hg and –9.8 mm Hg, respectively (both $P < 0.01$ vs PBO)	3‡§
Castaigne et al[24]	Patients aged 68–85 years with mild to moderate essential hypertension	193/190	P: 2 mg, I: 0.625 mg; control: PBO	12 wk	PBO vs PI: responders, 48.9% vs 81.3% ($P < 0.05$); normalization, 42.1% vs 74.1% ($P < 0.05$)	3‡§
Asmar et al[34]	Patients aged 18–84 years with uncomplicated hypertension (excluded the presence of antidiabetic, hypocholesterolemic, or CV drug intake)	204/202	P: 2 mg, I: 0.625 mg; control: atenolol 50 mg	1 y	PI normalized SBP (but not DBP) and BP significantly more than did atenolol ($P < 0.01$)	3‡§
PROGRESS[12]	Patients aged 55–75 years with a history of stroke and TIA within the previous 5 years (no BP entry criteria)	1770/1281	P: 4 mg, I: 2.5 mg; control: perindopril 4 mg	4 y	PI resulted in larger reduction of SBP/DBP (12/5 mm Hg) and stroke than control (5/3 mm Hg; $P < 0.05$)	5
Chanudet and De Champvallins[35]	Men and women aged 47–70 years with SBP 160 to 209 mm Hg and/or DBP 95 to 114 mm Hg (excluded secondary hypertension, previous CV events, and renal or hepatic impairment)	146/131	P: 2 mg, I: 0.625 mg; control: losartan 50 mg	12 wk	PI vs losartan: responders, 91.7% vs 81.8% ($P < 0.05$); normalization, 76.0% vs 60.0% ($P < 0.05$)	3‡§
Wing et al[26]	Patients aged 18–80 years with DBP ≥95 and <115 mm Hg (excluded secondary or malignant hypertension, CAD, stroke, or TIA)	17/17	P: 4 mg, I: 1.25 mg; control: perindopril 4 mg + low-salt diet (<100 mmol/d)	30 wk	Goal BP reached: PI, 40%; control, 50% ($P < 0.05$). No response: PI, 17%	5

(continued)

Table II. (Continued)

Reference	Inclusion Criteria	PI/Control, no. of patients	Daily Dose	Duration of Use	Results	Quality Score*
Morgan et al[27]	After a 4-week PBO run-in, patients with daytime mean ambulatory SBP >135 mm Hg, mean DBP >85 mm Hg	24/23	P: 2 mg, I: 0.625 mg; control: irbesartan 150 mg	8 wk	PI more effective than irbesartan in essential hypertension ($P < 0.001$)	1†‡
Mogensen et al[19]	Patients aged 40–75 years with type 2 diabetes, SBP 140 to 179 mm Hg, DBP <110 mm Hg, and AER 20 to 499 μg/min in ≥2 of 3 assays	233/224	P: 2 mg, I: 0.625 mg, with dosage doubling in 2 steps at 12 intervals; control: enalapril 40 mg/d	1 y	Mean (SD) SBP/DBP change: PI, −14.8 (15.8)/8.8 (9.3) mm Hg; enalapril, −12.3 (15.5)/7.3 (9.0) mm Hg. AER change: PI, −42%; enalapril, −27%.	3‡§

PBO = placebo; ISH = isolated systolic hypertension; BP = blood pressure; DBP = diastolic BP; SBP = systolic BP; SDH = mild to moderate systolic and diastolic hypertension; CV = cardiovascular; TIA = transient ischemic attack; CAD = coronary artery disease; AER = albumin excretion rate.
*Jadad quality score[30] (see Table I). Highest total score was 5.
†Points deleted from quality score because there was no description of withdrawals or losses to follow-up.
‡Points deleted from quality score because method of blinding was either not described or not appropriate.
§Points deleted from quality score because method of randomization was either not described or not appropriate.

2 mg and indapamide 0.625 mg, but could be adjusted (if needed, based on BP or BP response after weeks 12 and 24) to a maximum dose of perindopril 8 mg and indapamide 2.5 mg or enalapril 40 mg. The duration of intervention in 6 studies was 8 to 12 weeks[21–24,27,35]; in 1 study, 18 weeks[33]; and in 4 studies, 30 weeks to 4 years.[12,19,26,34] In 5 studies, the control group was given placebo,[21–24,33] and in the other 6 studies, the control groups were given atenolol,[34] perindopril,[12] losartan,[35] perindopril with low-salt diet,[26] irbesartan,[27] or enalapril.[19]

Results of the meta-analysis are shown in **Figure 1** to **Figure 3**. In 5 studies of perindopril-indapamide versus placebo (Figure 1), the BP values were consistently significantly different between the treatment group and the placebo group.[21–24,33] The z score for overall effect on SBP was 34.74 ($P < 0.001$), the between-group WMD for SBP was –9.03 mm Hg (95% CI, –9.54 to –8.52), and the χ^2 test value for heterogeneity of SBP was 1.42 (P = NS); the z score for overall effect on DBP was 30.93 ($P < 0.001$), the between-group WMD for DBP was –5.09 mm Hg (95% CI, –5.42 to –4.77), and the χ^2 test value for heterogeneity of DBP was 3.21 (P = NS). In 6 reports of perindopril-indapamide versus routine antihypertensive drugs (Figure 2),[12,19,26,27,34,35] the z score for overall effect on SBP was 2.15 (P = 0.03), the between-group WMD for SBP was –3.72 mm Hg (95% CI, –7.11 to –0.33), and the χ^2 test value for heterogeneity of SBP was 165.13 ($P < 0.01$); the z score for overall effect on DBP was 6.01 ($P < 0.01$), the between-group WMD for DBP was –1.71 mm Hg (95% CI, –2.27 to –1.16), and the χ^2 test value for heterogeneity of DBP was 12.75 ($P < 0.01$); the χ^2 test values for heterogeneity of SBP and DBP were significantly different ($P < 0.05$) in these 6 studies.

The results of the sensitivity analysis in 6 trials of perindopril-indapamide versus routine antihypertensive drugs[12,19,26,27,34,35] were not materially changed after the fixed-effects model and random-effects model were used. However, after exclusion of 3 trials[12,19,26] in which the doses of perindopril-indapamide were higher to test the effect of a fixed low-dose combination, the results were significantly changed (Figure 3): the z score for overall effect on SBP for perindopril-indapamide versus routine antihypertensive drugs[27,34,35] was 3.10 (P = 0.002), the between-group WMD for SBP was –4.00 mm Hg (95% CI, –6.54 to –1.47), and

Reference	Perindopril-Indapamide No. of Patients	Perindopril-Indapamide Mean (SD)	Control No. of Patients	Control Mean (SD)	Weight, %	WMD (95% CI Random) Data
SBP						
Castaigne et al[24]	193	–22.50 (13.90)	190	–12.30 (15.20)	8.9	–10.20 (–13.12 to –7.28)
Castaigne et al[23]	68	–23.00 (11.80)	55	–13.20 (16.40)	5.5	–9.80 (–14.96 to –4.64)
Chalmers et al[22]	125	–22.20 (14.90)	135	–12.00 (14.80)	7.7	–10.20 (–13.81 to –6.59)
Myers et al[33]	65	–13.00 (2.00)	61	–4.00 (1.00)	12.4	–9.00 (–9.55 to –8.45)
Laurent[21]	386	–15.20 (12.90)	386	–6.70 (13.90)	10.7	–8.50 (–10.39 to –6.61)
Subtotal	837		827		45.3	–9.03 (–9.54 to –8.52)
Heterogeneity: $\chi^2 = 1.42$, $df = 4$, $P = 0.84$						
Overall effect: $z = 34.74$, $P < 0.01$						
DBP						
Castaigne et al[24]	193	–13.20 (8.00)	190	–7.30 (9.00)	11.0	–5.90 (–7.61 to –4.19)
Castaigne et al[23]	68	–9.70 (7.90)	55	–4.10 (8.60)	8.9	–5.60 (–8.55 to –2.65)
Myers et al[33]	65	–9.00 (1.00)	61	–4.00 (1.00)	12.5	–5.00 (–5.35 to –4.65)
Chalmers et al[22]	125	–15.00 (7.40)	135	–8.50 (8.90)	10.6	–6.50 (–8.48 to –4.52)
Laurent[21]	386	–10.80 (7.90)	386	–5.60 (9.10)	11.7	–5.20 (–6.40 to –4.00)
Subtotal	837		827		54.7	–5.09 (–5.42 to –4.77)
Heterogeneity: $\chi^2 = 3.21$, $df = 4$, $P = 0.52$						
Overall effect: $z = 30.93$, $P < 0.01$						

Forest Plot

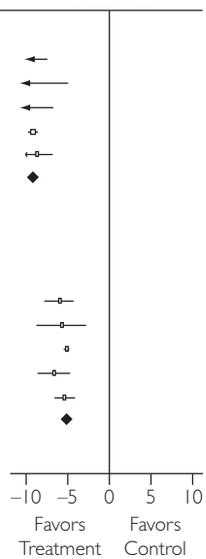

Figure 1. Weighted mean difference (WMD) in systolic and diastolic blood pressure (SBP and DBP) in 5 studies of perindopril-indapamide versus placebo.

Reference	Perindopril-Indapamide No. of Patients	Perindopril-Indapamide Mean (SD)	Control No. of Patients	Control Mean (SD)	Weight, %	WMD (95% CI Random) Data
SBP						
Wing et al[26]	17	–5.00 (2.00)	17	–5.00 (2.00)	8.6	0.00 (–1.34 to 1.34)
Chanudet and De Champvallins[35]	134	–22.20 (12.80)	123	–19.80 (16.10)	7.2	–2.40 (–5.98 to 1.18)
Morgan et al[27]	24	–17.00 (2.30)	23	–14.00 (2.90)	8.6	–3.00 (–4.50 to –1.50)
PROGRESS[12]	1770	–12.30 (0.50)	1281	–4.90 (0.60)	9.0	–7.40 (–7.44 to –7.36)
Asmar et al[34]	204	–23.10 (15.60)	202	–16.20 (16.00)	7.6	–6.90 (–9.97 to –3.83)
Mogensen et al[19]	233	–14.80 (15.80)	135	–12.30 (15.50)	7.4	–2.50 (–5.81 to 0.81)
Subtotal	2382		1781		48.3	–3.72 (–7.11 to –0.33)
Heterogeneity: $\chi^2 = 165.13$, $df = 5$, $P < 0.01$						
Overall effect: $z = 2.15$, $P = 0.03$						
DBP						
Wing et al[26]	17	–1.00 (1.00)	17	1.00 (1.00)	8.9	–2.00 (–2.67 to –1.33)
Chanudet and De Champvallins[35]	134	–14.90 (8.40)	123	–12.90 (8.60)	8.3	–2.00 (–4.08 to 0.08)
Asmar et al[34]	204	–13.30 (8.60)	202	–12.90 (9.60)	8.4	–0.40 (–2.17 to 1.37)
Morgan et al[27]	24	–8.00 (1.30)	23	–7.00 (1.60)	8.8	–1.00 (–1.84 to –0.16)
PROGRESS[12]	1770	–5.00 (0.30)	1281	–2.80 (0.30)	9.0	–2.20 (–2.22 to –2.18)
Mogensen et al[19]	233	–8.80 (9.30)	135	–7.30 (9.00)	8.3	–1.50 (–3.43 to 0.43)
Subtotal	2382		1781		51.7	–1.71 (–2.27 to –1.16)
Heterogeneity: $\chi^2 = 12.75$, $df = 5$, $P = 0.026$						
Overall effect: $z = 6.01$, $P < 0.01$						

Forest Plot

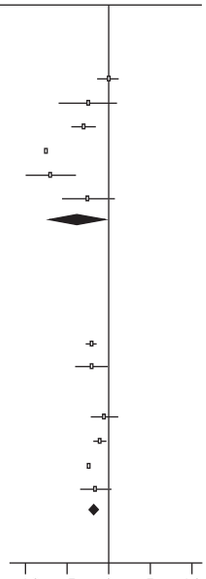

Figure 2. Weighted mean difference (WMD) in systolic and diastolic blood pressure (SBP and DBP) in 6 studies of perindopril-indapamide versus routine antihypertensive drugs.

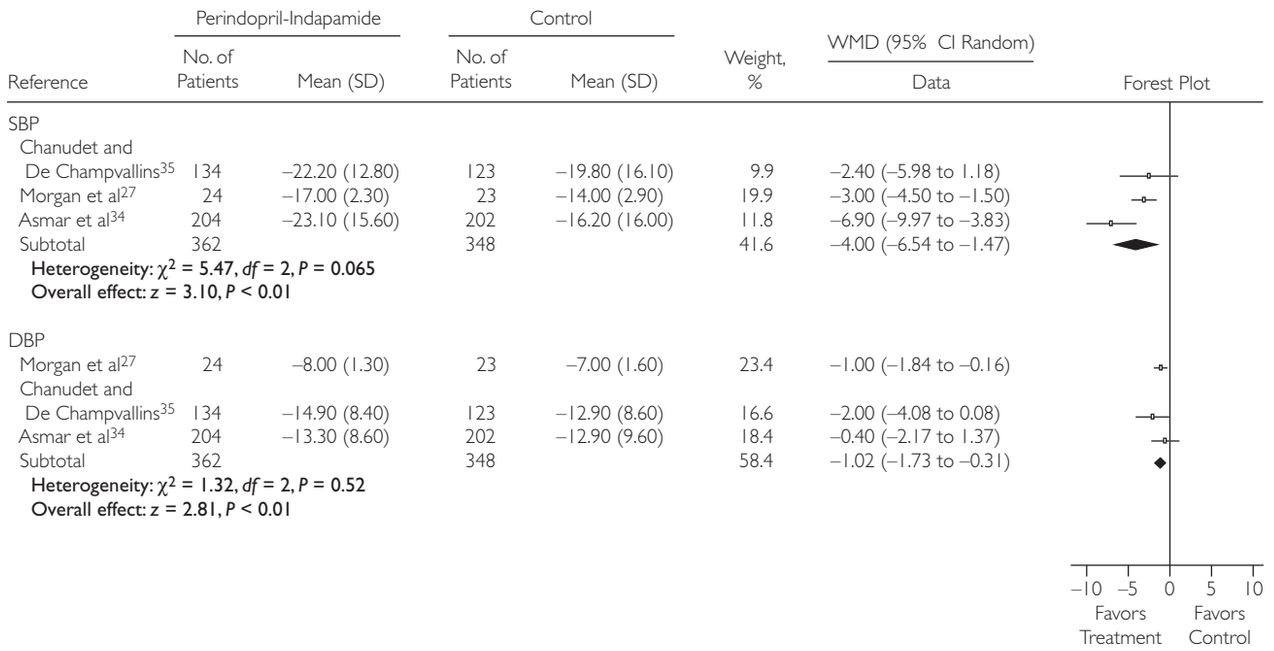

Figure 3. Sensitivity analysis of weighted mean difference (WMD) in systolic and diastolic blood pressure (SBP and DBP) in 3 studies of perindopril-indapamide versus routine antihypertensive drugs.

the χ^2 test value for heterogeneity of SBP was 5.47 (P = NS); the z score for overall effect on DBP for perindopril-indapamide versus routine antihypertensive drugs was 2.81 (P = 0.005), the between-group WMD for DBP was –1.02 mm Hg (95% CI, –1.73 to –0.31), and the χ^2 test value for heterogeneity of DBP was 1.32 (P = NS). There was little evidence of funnel-plot asymmetry (P = NS).

In a test of power of analysis, the sample needed for reaching significance for each group in the 8 trials[21–24,27,33–35] of a fixed, low-dose combination of perindopril 2 mg and indapamide 0.625 mg daily was estimated with use of the following formulas[36]:

$$N = 2(z_\alpha + z_\beta)^2 \cdot (\delta^2/d^2)$$
$$\delta^2 = (\delta_1^2 + \delta_2^2)/2$$

where

N = estimated number of cases in each group;
z_α = standard normal deviation that corresponds to α (probability of type-I error);
z_β = standard normal deviation that corresponds to β (probability of type-II error);
δ = SD of BP;
d = difference of mean BP between the 2 groups.

The mean SDs of SBP in the treatment and control groups were 10.77 and 12.04 mm Hg, respectively. The mean SDs of DBP in the treatment and control groups were 6.31 and 7.05 mm Hg, respectively. If α were 0.05, β were 0.10, and the difference of mean BP (SBP or DBP) between 2 groups were 2 mm Hg, then the sample of each group according to the mean SD of SBP derived with the above formula would be 685.71, and the sample of each group according to the mean SD of DBP derived with the above formula would be 235.23. If the difference of mean SBP between 2 groups were 10 mm Hg and the difference of mean DBP between 2 groups were 5 mm Hg, then the sample of each group according to the mean SD of SBP derived with the formula would be 27.43, and the sample of each group according to the mean SD of DBP derived with the above formula would be 37.64. Our treatment group and control group samples from the 8 trials were 1199 and 1175 patients, respectively; therefore, our pool of data was sufficient to test our hypothesis.

Safety

The reporting of the numbers of patients who withdrew from the study or were lost to follow-up and of

the details regarding adverse events was inconsistent (**Table III**). It was not possible to assess the size of the total pool of patients from which subjects were lost to follow-up in any included study. The reasons for withdrawals may be attributed to the occurrence of a serious adverse event unrelated to study drugs (eg, acute edema, retinal or renal impairment), a nonmedical reason, the development of a cough or rash, or a major protocol violation. Common adverse events included cough, headache, peripheral vertigo, hypokalemia, and asthenia. In all 11 trials, the occurrences of drug-related adverse events during follow-up and the numbers of withdrawals and losses to follow-up were not significantly different between the perindopril-indapamide and control groups.

DISCUSSION

Recent multicenter trials have shown that monotherapy normalized BP in <67% of hypertensive patients.[37,38] Low-dose combination therapy has been proposed as appropriate initial therapy for hypertension.[39]

Theoretical advantages of a fixed, low-dose perindopril-indapamide combination have been posited. The compensatory activation of the renin-angiotensin system in response to indapamide is inhibited by the activity of perindopril; thus, perindopril limits the potassium loss observed with indapamide.[40] The combination of the 2 drugs may be given at a substantially reduced dose with respect to the usual monotherapy doses, and may produce additional antihypertensive efficacy and minimal adverse events.[2,21] The perindopril-indapamide combination may also prevent damage to target organs.[11,12,25,41–43] A fixed, low-dose combination may be administered as 1 tablet once per day, which simplifies the dosage and thus may improve compliance. Finally, the low-dose combination may offer an efficacy/tolerability ratio that is suitable for first-line treatment in hypertension.[21,26,35]

In our study, the results of meta-analysis of 5 studies of perindopril 2 mg/indapamide 0.625 mg versus placebo showed that the WMD of SBP (–9.03 mm Hg [95% CI, –9.54 to –8.52], $P < 0.001$) and the WMD of DBP (–5.09 mm Hg [95% CI, –5.42 to –4.77], $P < 0.001$) were in favor of treatment (Figure 1). In the 5 studies[21–24,32] with perindopril 2 mg/indapamide 0.625 mg, the rates of normalization and response of BP were 64.7% to 90% and 74% to 81.3%, respectively, with treatment but only 42.1% to 44.4% and 48.9%, respectively, with placebo. Comparison with other antihypertensive drugs also demonstrated that the reductions in SBP and DBP were greater with perindopril-indapamide therapy (Figure 2)[12,19,26,27,34,35]; the between-group WMD for SBP was –3.72 mm Hg (95% CI, –7.11 to –0.33; $P < 0.03$) and for DBP, –1.71 mm Hg (95% CI, –2.27 to –1.16; $P < 0.001$). However, heterogeneity was statistically significant between the different studies ($P < 0.05$), and the differences of design of randomized controlled trials may contribute to their heterogeneity. In addition, differences in measurement methods such as ambulatory BP monitoring may result in heterogeneity.[26,27]

We also found that the rates of normalization and response of BP were higher with perindopril 2 mg/indapamide 0.625 mg than with losartan 50 mg daily (76.0% vs 60% normalization and 91.7% vs 81.8% response, respectively; both $P < 0.05$),[35] and the rates of normalization and response of BP were higher with perindopril 2 to 4 mg/indapamide 0.625 to 1.25 mg than with irbesartan 150 to 300 mg daily (66.6% vs 34.8% normalization and 79.2% vs 43.5% response, respectively; both $P < 0.05$).[27] In another study, the rates of response of BP were 83% with perindopril 4 mg/indapamide 1.25 mg and 50% with perindopril 4 mg plus low-salt diet (defined as <100 mmol/d).[26] In a study of perindopril 2 to 8 mg/indapamide 0.625 mg versus enalapril 10 to 40 mg daily, the rates of response of BP were 68% and 60%, respectively ($P < 0.05$).[19] Thus, in these studies, low-dose or higher-dose perindopril-indapamide combination therapy resulted in better BP control rates than placebo or monotherapy (conventional dosage of perindopril [plus low-salt diet], losartan, irbesartan, or enalapril).

It was hypothesized that differences in dosage may contribute to the heterogeneity of randomized controlled trials. When we excluded from our sensitivity analysis 1 report[12] of perindopril 4 mg/indapamide 2.5 mg daily, 1 report[26] of perindopril 4 mg/indapamide 1.25 mg daily, and 1 report[19] with a dose adjustment of perindopril-indapamide, the results were changed in favor of the combination treatment (statistical significance not assessed). Also, in the other 8 randomized, controlled trials of perindopril 2 mg/indapamide 0.625 mg daily (5 studies of

Table III. Randomization, loss to follow-up, and reported adverse events (AEs) in randomized, controlled trials of a low-dose combination of perindopril-indapamide (PI) as first-line therapy in hypertension.

Reference	No. of Patients		AEs and/or Reasons for Withdrawal	Other AEs
	Randomized	Withdrawn or Lost to Follow-up		
Laurent[21]	772	0	≥1 EAE: PI, 18 (12.3%); losartan, 11 (8.4%)	Cough: losartan, 8.2%; PI, 6.5%. Potassium-sparing: PI, 0.3%.
Chalmers et al[22]	383	28	Serious AEs: PBO, 2 (acute edema, retinal detachment); PI, 2 (renal impairment, syncope with collapse); no explanation given for other withdrawals	Overall: PBO, 23%; PI, 20%. Cough: PBO, 8.2%; PI, 1.5%. Headache: PBO, 3.3%; PI, 6.4%. Peripheral vertigo: PBO, 6.5%; PI, 2.2%.
Myers et al[33]	438	17	Withdrawals: AEs, 12 (dizziness, headache, and nausea); lack of efficacy, 4; nonmedical reason, 1	Cough: PBO, 0%; PI, 8.2%–9.7%. Hypokalemia: PI, 4.6%. Mean uric acid increased significantly with PI compared with PBO (35.1–55.7 μmol/L vs 10.8 μmol/L; $P < 0.01$).
Castaigne et al[23]	125	8	Withdrawals: PI, 3; PBO, 5 (cough, burning sensation of mouth, and hyperglycemia). EAEs: PI, 2 (cough); PBO, 8 (6 cough, 1 edema, 1 headache).	Cough: PI, 13; PBO, 8. Headache: PI, 2; PBO, 13.
Castaigne et al[24]	380	21	Withdrawals: PBO, 15; PI, 6 (3 for AEs). 60% took only P 2 mg/I 0.625 mg at end of study.	Kalemia <3.4 mmol/L: PBO, 1 pt (0.5%); PI, 4 pts (2.1%)
Asmar et al[34]	406	39	Withdrawals, PI vs atenolol: nonmedical reasons, 12 vs 6; AEs, 19 vs 20; lack of efficacy, 10 vs 24; major protocol deviation, 3 vs 2	Headache, dizziness, asthenia, cough, and potassium <3.4 mmol/L: PI, 7 (3.0%); atenolol, 3 (1.3%; P = NS)
PROGRESS[12]	6105	PI, 714 (23%); PBO, 636 (21%)	AEs, PI vs PBO: nonmedical reasons, 232 (7.6%) vs 250 (8.2%); cough, 47 (2.2%) vs 69 (0.4%); hypertension, 64 (2.1%) vs 29 (0.9%); and heart failure, 47 (2.2%) vs 69 (2.3%)	Angioedema: PI, 3 (no AEs with PI were fatal or required intubation)
Chanudet and De Champvallins[35]	277	20	Withdrawals, PI vs losartan: AEs, 6 vs 4; unsatisfactory therapeutic effect, 1 vs 1; nonmedical reason, 3 vs 2; major protocol violation, 2 vs 1. EAEs, PI vs losartan: 33.6% vs 25.2% (P = 0.128).	Total: losartan, 8.4%; PI, 12.3%. Cough: PI, 4.1%. Dizziness/giddiness: losartan, 2.7%; PI, 0.7%. Asthenia: losartan, 0.9%; PI, 1.4%. Hypokalemia: losartan, 1.5%; PI, 1.4%.
Wing et al[26]	19	2	Withdrawals: PI, 3 (adverse symptoms [eg, cough, rash], patient concerns about high BP readings, and cough and palpitation)	Most pts had ≥1 symptom in all phases; the most commonly reported were lethargy, dizziness, headache, and cough
Morgan et al[27]	47	0	NA	Both drugs well tolerated with slightly fewer AEs with low-dose PI vs irbesartan (13 vs 17; P = NS)
Mogensen et al[19]	481 (PI, 244; enalapril, 237)	111	Withdrawals, PI vs enalapril: AEs, 19 vs 21; nonmedical reasons, 12 vs 10; major protocol deviations, 6 vs 4 of 237; lack of efficacy, 13 vs 25 (P = 0.03). 1 pt lost to follow-up. EAEs, PI vs enalapril: 6 (2.5%) vs 15 (6.3%; P = 0.036).	Hyperkalemia (>5.5 mmol/L): PI, 8 (3.3%); enalapril, 13 (5.5%). Kalemia (<3.4 mmol/L): PI, 6 (2.5%); enalapril, 4 (1.7%)

EAE = emergent adverse events; PBO = placebo; pts = patients; NA = not available.

perindopril-indapamide versus placebo[21–24,33] and 3 studies of perindopril-indapamide versus routine antihypertensive drugs[27,34,35]) significant reduction of BP was consistently seen in the perindopril-indapamide treatment group ($P < 0.05$). The results of sensitivity analysis of the 5 studies with placebo as the control showed that the fixed, low-dose perindopril-indapamide combination consistently reduced SBP and DBP significantly more than placebo ($P < 0.05$).[21–24,33] The overall effect of perindopril-indapamide versus other antihypertensive drugs[27,34,35] was in favor of perindopril-indapamide. These results also indicated that a fixed, low-dose perindopril-indapamide combination decreased SBP more significantly than did other antihypertensive drugs (conventional dosage of atenolol, losartan, or irbesartan; $P < 0.05$). However, in 11 selected trials, perindopril-indapamide was compared with antihypertensive monotherapy. One trial[9] found that the perindopril-hydrochlorothiazide combination was more effective in the reduction of BP (14%) than the perindopril-indapamide (9.6%) after 4 weeks of treatment ($P < 0.05$) and, subsequently, the addition of hydrochlorothiazide caused a greater increase in serum uric acid levels compared with that observed after indapamide administration ($P < 0.01$). Therefore, it is necessary to compare perindopril-indapamide with other combinations of antihypertensive drugs in future study.

With respect to the protection of target organs, in 1 study,[34] perindopril-indapamide contributed more to the maintenance of pulse pressure amplification than did atenolol ($P < 0.05$), and the antihypertensive effects of the combination were observed only at the site of the central arteries, whereas brachial BP appeared to remain within the normal range. Thus, perindopril-indapamide may be able to reduce cardiovascular risk through its action on larger-artery stiffness and wave reflection. Chanudet and De Champvallins[35] demonstrated that the decrease in nighttime SBP was significantly higher in the perindopril-indapamide group than in the losartan 50 mg/d group ($P < 0.05$), and better control of nighttime SBP may be relevant to prevention of acute cardiovascular events.[44,45] In terms of its efficacy and tolerability ratio, the low-dose perindopril-indapamide combination appears to be appropriate for first-line hypertensive management.

Mogensen et al[19] indicated that increased urinary albumin excretion is associated with worsened renal and cardiovascular outcomes. A cost-benefit analysis suggested that therapies that reduce the albumin excretion rate (AER) by ≥10% save money.[46] A mean estimated treatment effect of 24% greater reduction in the AER in those treated with perindopril-indapamide compared with enalapril would have significant benefits in terms of cost savings,[47] and the 42% reduction in AER demonstrated in their study with perindopril-indapamide therapy[19] was greater than that previously reported in ACE inhibitor studies.[48] First-line treatment with a low-dose perindopril-indapamide combination induces a greater decrease in albuminuria than does treatment with enalapril, partially independent of BP reduction. The fixed, low-dose perindopril-indapamide combination as first-line treatment has a good tolerability/efficacy ratio in hypertensive patients with renal failure.[43] In addition, there was no difference in the need to modify diabetic therapy between the groups during the study,[19] suggesting that changes in metabolic and lipid profile were small. Morgan et al[27] also proved that the trough/peak BP ratios for the low-dose perindopril-indapamide combination were systolic 1.31 and diastolic 0.92, and for irbesartan, 1.07 and 0.67, respectively. In 1 trial,[12] in participants treated with the combination therapy (in whom BP was lowered by a mean 12/5 mm Hg), relative risk reduction of stroke was 43% (95% CI, 30%–54%), and relative risk reduction of major vascular events was 40% (95% CI, 29%–49%), but in participants treated with perindopril alone (in whom BP was lowered by a mean 5/3 mm Hg), relative risk reduction of stroke was 5% (95% CI, –19% to 23%) and relative risk reduction of major vascular events was 4% (95% CI, –15% to 20%). These findings of our meta-analysis have shown that the perindopril-indapamide combination may be more beneficial for the protection of target organs than certain antihypertensive drugs with monotherapy (conventional dosage of atenolol, losartan, and irbesartan, and adjusted dosage of enalapril).[19,27,34,35]

Interestingly, we found the effects of a decrease in BP and protection of target organs occurred in nonhypertensive patients with management of BP with the perindopril-indapamide combination. The mean (SD) 24-hour SBP/DBP of these patients fell by 17 (2.3)/8 (1.3) mm Hg ($P < 0.01$) with low-dose combination perindopril-indapamide therapy in

patients with a daytime mean ambulatory SBP >135 mm Hg and/or DBP >85 mm Hg.[27] Combination therapy seemed to confer similar advantages over single-drug therapy for both hypertensive and nonhypertensive participants[12]: the reduction in stroke risk with combination therapy was 44% (95% CI, 28%–57%) among hypertensive individuals (93/948 treated vs 159/955 control group) and 42% (95% CI, 19%–58%) among nonhypertensive individuals (57/822 vs 96/819), whereas the reductions with single-drug therapy were 10% (95% CI, –25% to 35%) among hypertensives (70 treated vs 76 control) and 1% (95% CI, –34% to 26%) among nonhypertensives (87 treated vs 89 control).

Each 10-mm Hg reduction in SBP was associated with a mean (SE) 28% (8%) lower risk of stroke recurrence, demonstrated in a larger study with 2435 patients,[49] and sustained DBP reductions of 5 to 6 mm Hg subsequently reduced the risk of initial stroke by ~33% in a systematic review.[50] On the basis of the size of the overall BP reduction achieved in the PROGRESS study[12] (SBP/DBP, –9/–4 mm Hg), the observed mean (SE) reduction in stroke risk was 28% (3%). The results of our meta-analysis of 5 studies showed that a fixed, low-dose perindopril-indapamide combination consistently reduced SBP (–9.03 mm Hg) and DBP (–5.09 mm Hg) significantly more than placebo.[21–24,33] Thus, our evidence confirms the benefit of a fixed, low-dose perindopril-indapamide combination as being effective antihypertensive therapy that is protective of the target organs.

A few trials showed a significant dose-response relationship with doubling of the dose of perindopril 2 mg/indapamide 0.625 mg up to perindopril 8 mg/indapamide 2.5 mg, with a corresponding progressive fall in SBP, DBP, and mean BP,[23,28] and when the data were analyzed by patient sex and dose, the SBP, DBP, and mean BP (but not pulse pressure) decreased significantly more in women than in men until the dosage perindopril 4 mg/indapamide 1.25 mg was reached ($P < 0.05$),[51] but these trials also proved that the fixed, low-dose perindopril 2 mg/indapamide 0.625 mg was efficacious and well tolerated in antihypertensive therapy.

We also concluded that serious adverse events and withdrawals in the low-dose perindopril-indapamide combination group were not different from those seen with placebo or routine antihypertensive drugs in the selected 11 trials. Common adverse events were headache, dizziness, asthenia, cough, and hypokalemia (Table III). Only 1 report[32] showed that mean uric acid was increased significantly in the perindopril-indapamide combination group (35.1–55.7 µmol/L) compared with an increase of 10.8 µmol/L in placebo group ($P < 0.01$). The perindopril-indapamide combination did not produce significant signs of increasing renal impairment, lipid abnormalities, or glucose intolerance. Emergent adverse events (eg, acute cardiac infarction, serum potassium <3.4, headache, asthenia) were not different between the perindopril-indapamide and control groups during follow-up.

Although our results favored a fixed, low-dose perindopril-indapamide combination as first-line, short-term antihypertensive therapy in mild to moderate essential hypertension, few studies with long-term efficacy and tolerability data were found. Therefore, research is needed on the long-term efficacy and tolerability of the perindopril-indapamide combination as first-line antihypertensive therapy, particularly with regard to protection of target organs. In addition, the cost-effectiveness of the fixed, low-dose perindopril-indapamide combination should be compared with that of other antihypertensive therapies.

CONCLUSION

The studies in our analysis consistently demonstrated that a fixed, low-dose perindopril-indapamide combination has a favorable safety profile and may be efficacious as first-line treatment for patients with mild to moderate essential hypertension.

ACKNOWLEDGMENTS

The authors wish to thank the staff of the Fu Wai Heart Hospital Library who provided additional data and the staff of the Chinese Academy of Medical Sciences and Peking Union Medical College Library for help with the literature search.

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