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Abstract—Microalbuminuria in diabetes is a risk factor for early death and an indicator for aggressive blood pressure (BP) lowering. We compared a combination of 2 mg perindopril/0.625 mg indapamide with enalapril monotherapy on albumin excretion rate (AER) in patients with type 2 diabetes, albuminuria, and hypertension in a 12-month, randomized, double-blind, parallel-group international multicenter study. Four hundred eighty-one patients with type 2 diabetes and hypertension (systolic BP ≥140 mm Hg, <180 mm Hg, diastolic BP <110 mm Hg) were randomly assigned (age 59±9 years, 77% previously treated for hypertension). Results from 457 patients (intention-to-treat analysis) were available. After a 4-week placebo period, patients with albuminuria >20 and <500 μg/min were randomly assigned to a combination of 2 mg perindopril/0.625 mg indapamide or to 10 mg daily enalapril. After week 12, doses were adjusted on the basis of BP to a maximum of 8 mg perindopril/2.5 mg indapamide or 40 mg enalapril. The main outcome measures were overnight AER and supine BP. Both treatments reduced BP. Perindopril/indapamide treatment resulted in a statistically significant higher fall in both BP (−3.0 [95% CI −5.6, −0.4], $P=0.012$; systolic BP −1.5 [95% CI −3.0, −0.1] diastolic BP $P=0.019$) and AER −42% (95% CI −50%, −33%) versus −27% (95% CI −37%, −16%) with enalapril. The greater AER reduction remained significant after adjustment for mean BP. Adverse events were similar in the 2 groups. Thus, first-line treatment with low-dose combination perindopril/indapamide induces a greater decrease in albuminuria than enalapril, partially independent of BP reduction. A BP-independent effect of the combination may increase renal protection. **(*Hypertension*. 2003;41:1063-1071.)**

Key Words: albuminuria ■ microalbuminuria ■ hypertension, renal ■ diabetes mellitus ■ angiotensin-converting enzyme

Increased urinary albumin excretion is a major prognostic factor both for progressive diabetic renal disease[1,2] and increased cardiovascular morbidity and mortality rates in both type 1 and type 2 diabetes.[3–5] Albuminuria in type 2 diabetes is associated with cardiovascular risk factors such as raised blood pressure (BP), dyslipidemia, and endothelial activation.[4,6] Furthermore, regression of urinary albumin excretion is associated with a better renal and cardiovascular prognosis.[7,8]

Large multicenter trials have confirmed the benefits of "tighter" BP control in type 2 diabetes[9] and of the benefits of inhibitors of the renin-angiotensin system (RAS), particularly in patients with increased urinary albumin excretion.[10,11]

Treatment strategies vary and are often based on initial monotherapy with high doses of single agents. Tight BP control is, however, difficult to achieve in this group of patients, and combination therapy is usually required.[9] There is, however, at present very little data to guide the most appropriate combinations of therapy in patients with type 2 diabetes.

The combination of a diuretic and RAS inhibitor is potentially advantageous. First, the RAS inhibitor offsets the diuretic-induced increase in plasma renin activity, whereas the diuretic-induced salt loss potentiates the effect of the RAS inhibitor, an effect magnified by a reduced salt intake.[12] The use of this combination is particularly relevant in diabetes as

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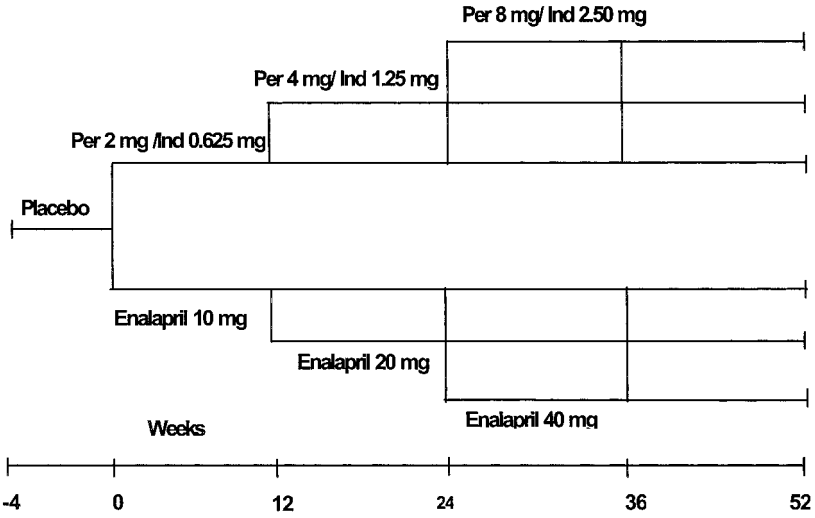

Figure 1. Study design. Per indicates perindopril; Ind, indapamide.

the result of the specific renoprotective effects of ACE inhibitors and the extra potential for sodium retention.[12]

The use of a low-dose combination of perindopril (a long-acting ACE inhibitor) and indapamide (a non–thiazide chlorosulfamoyl diuretic) as first-line treatment in hypertension gives greater BP normalization rates in comparison with angiotensin II antagonists[13] and a larger BP decrease than atenolol.[14]

In salt-sensitive Dahl rats loaded with sodium, a model with low plasma renin activity, the combination of perindopril/indapamide for 8 weeks lowered proteinuria and reduced glomerular lesions more than monotherapy with either agent despite little systemic antihypertensive effect, suggesting a BP-independent renoprotective effect.[15]

This study in patients with type 2 diabetes, hypertension, and albuminuria therefore compared the combination of low-dose perindopril/indapamide with monotherapy with enalapril—an ACE inhibitor of proven efficacy[8,16]—to determine the most effective treatment strategy in terms of albuminuria and BP lowering.

Methods

This study is described according to the CONSORT guidelines.[17]

Objective

The objective of the study was to compare low-dose 2 mg perindopril/0.625 mg indapamide versus enalapril for 52 weeks on urinary albumin excretion rate (AER) in patients with type 2 diabetes with hypertension and albuminuria.

Design

The study was designed as a 12-month, randomized, controlled, double-blind, 2–parallel group study conducted in 104 centers in 20 countries.

Patients

Patients between the ages of 40 and 75 years with type 2 diabetes,[18,19] hypertension defined as supine systolic BP (SBP) ≥140 mm Hg <180 mm Hg and supine diastolic BP (DBP) <110 mm Hg, and AER (≥20 μg/min <500 μg/min in at least 2 of 3 assays).

Patients with HbA1c ≥9% within the 3 months before the study, with presumed nondiabetic kidney disease, serum creatinine ≥140 μmol/L, known contraindications to ACE inhibitor therapy, or indapamide or other severe disease were excluded. Nonstudy antihypertensive drugs were not permitted.

Methods

The design is summarized in Figure 1. After an open 4-week prerandomization run-in period of receiving placebo once daily, patients were randomly assigned in a double-blind manner to once-a-day therapy with either 2 mg perindopril/0.625 mg indapamide or monotherapy with 10 mg enalapril.

Dose adjustment based on BP and/or BP response was permitted after week 12, with doubling of the dosage in 2 steps at 12-week intervals: W12, W24, or W36 in patients whose SBP remained ≥140 mm Hg and/or DBP ≥90 mm Hg. The adjustment was in double-blind steps: 4 mg perindopril/ 1.25 mg indapamide or 20 mg enalapril, then 8 mg perindopril/2.5 mg indapamide or 40 mg enalapril. The choice of antidiabetic treatment was left to the investigator.

After random assignment, the patients were seen on 7 occasions over the next 52 weeks.

AER was determined at each visit from a timed overnight urine collection,[20] and infection was excluded by dipstick. Three AER and urinary albumin/creatinine ratio[21] (ACR) evaluations were performed at baseline.[21]

BP was measured at rest after 10 minutes in the supine position and after 1 and 3 minutes in the standing position with a mercury sphygmomanometer in the morning at each visit at trough drug levels. The mean of 3 measurements in the supine position was taken.

HbA1c was determined by high-performance liquid chromatography. Cardiovascular adverse events were defined according to the International Classification of Disease (CD9–1975 revision, code 390–448, +7981, instantaneous death), and serious adverse events were predefined as those that were fatal or required prolonged hospitalization.

The primary outcome was the change in the AER (μg/min) after 1 year. Secondary outcome criteria were ACR, supine BP, and BP response defined as a reduction in SBP <140 mm Hg and DBP <90 mm Hg and/or reduction of SBP ≥20 mm Hg and/or reduction of DBP ≥10 mm Hg.

Ethics

The study was performed in accordance with the Declaration of Helsinki.[22] Ethics committee approval was obtained for each center, and written informed consent was obtained from all patients.

Statistical Analysis

Given the proven efficacy of ACE inhibitor therapy,[23] the sample size was calculated to allow assessment of the noninferiority of the

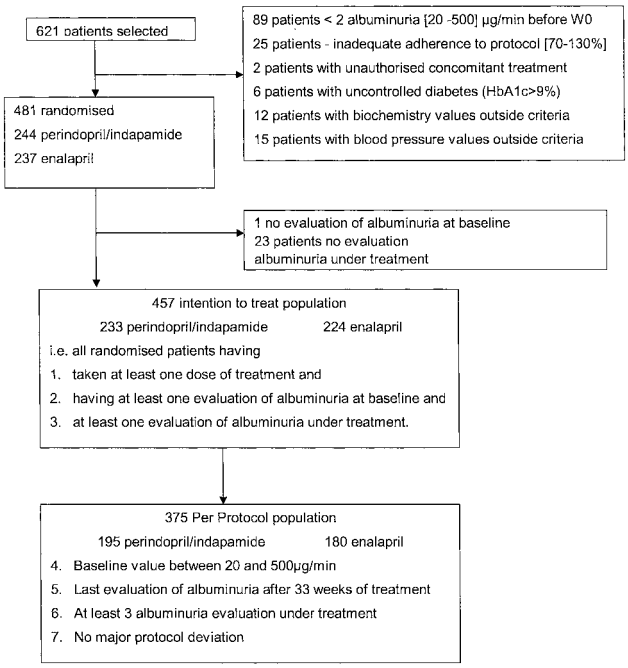

Figure 2. Flow chart of patient recruitment and inclusion in the PREMIER study. *Total >140, as one patient could have more than one exclusion criteria.

combination of perindopril/indapamide versus enalapril. This was determined by using an $\alpha=2.5\%$,[24] with an assumed limit of noninferiority at the final visit being a clinically significant difference in AER (>35% of the value in the enalapril group).[25] The sample size was calculated to be 200 patients per group.[26] AER and ACR were logarithmically transformed and are presented as the geometric means with their 95% confidence intervals.

All analyses were adjusted for the country of treatment with the baseline value as a covariate. Changes from baseline (randomization) to week 52 in AER, ACR, and BP were analyzed with a linear model for ANCOVA.

If noninferiority was demonstrated superiority, comparisons were performed using the Student *t* test for independent samples.[24]

Analyses were performed on 3 populations.[27] The intention-to-treat population, a per-protocol analysis, and finally, to assess tolerability, a safety set analysis. Analyses on the intention-to-treat population are presented unless otherwise stated. SAS software (version 6.07) was used.

Results

Patient Enrollment and Baseline Characteristics

Potential patients (n=621) were identified between March 1997 and January 2000. One hundred forty withdrew during the 4-week run-in period, resulting in 481 (77%) randomly assigned patients. Thus, 457 (95% of those randomly assigned) were considered as the intention-to-treat population; 375 patients (82% of the intention-to-treat population) fulfilled the criteria for the per-protocol population (Figure 2).

There were no significant differences between the intention-to-treat, per-protocol, and safety population in age, gender, ethnicity, or duration of type 2 diabetes.

The characteristics of the patients are summarized in Table 1. There were no significant differences in baseline characteristics between treatment groups. Baseline AER values were nonsignificantly different in the perindopril/indapamide group as compared with the enalapril group, as was the ACR. All analysis was performed after adjustment on baseline

TABLE 1. Baseline Characteristics of Patients

Demographic and Clinical Characteristics	Perindopril/Indapamide (n=233)	Enalapril (n=224)
Age, y [range]	58.2 (8.6) [30.0–78.0]	59.6 (8.7) [36.0–75.0]
Male, n (%)	132 (57)	148 (66)
BMI, kg/m^2	30 (3)	30 (4)
Weight, kg	83 (12.4)	82 (13)
Height, cm	168 (9.4)	168 (9)
Ethnicity, n (%) White/black/Asian/other	218/8/2/5 (94/3/1/2)	198/12/2/12 (88/5/1/5)
HbA1c, %	7.2 (1.2)	7.3 (1.2)
AER, µg/min* [IQR]	75.3 [36.4–153.4]	89.1 [39.5–192.5]
ACR, mg/mmol* [IQR]	7.9 [3.4–18.1]	9.2 [4.5–17.5]
SBP, mm Hg	158.0 (11.5)	158.8 (12.1)
DBP, mm Hg	93.3 (8.7)	93.3 (8.7)
Diabetes history		
Duration, y	7.5 (6.6)	8.0 (6.9)
Requiring insulin, n (%)	68 (29)	83 (37)
Hypertension history		
Duration, y	6.8 (7.9)	7.0 (7.3)
Previous treatment, n (%)	178 (76)	174 (78)
Diuretic, n (%)	31 (12)	31 (12)
RAS Inhibitor, n (%)	96 (41)	111 (50)

IQR indicates interquartile range. Data are expressed as mean (SD) except where otherwise indicated.

*Geometric mean.

value to ensure the comparison balance. There were fewer men randomly assigned to perindopril/indapamide therapy, but there were no gender differences in AER at baseline: 83 μg/min men (64 to 108) compared with 87 μg/min women (64 to 118) (geometric mean, 95% CI, μg/min). Similar proportions in both treatment groups required dose adjustments; 90 patients (39%) remained on 2 mg perindopril/0.625 mg indapamide, 71(30%) on 4 mg perindopril/1.25 mg indapamide, 72 (31%) on 8 mg perindopril/2.5 mg indapamide, as compared with 78 (35%) on 10 mg enalapril, 72 (32%) on 20 mg enalapril, and 74 (33%) on 40 mg enalapril. Most of the first dose adjustments occurred at week 12 (77%).

Effect on Blood Pressure and Urinary Albumin Excretion

Blood Pressure

Both treatments reduced BP. Over the duration of the study, BP (systolic/diastolic) was reduced by, on average, −14.8/8.8 (±15.8/±9.3 SD) mm Hg in the group assigned to perindopril/indapamide and −12.3/7.3 (±15.5/±9.0 SD) mm Hg in the group assigned to enalapril. Perindopril/indapamide treatment resulted in a statistically higher fall in BP (−3.0 [95% CI −5.6, − 0.4] $P=0.012$ for SBP; −1.5 [95% CI −3.0, −0.1] for DBP $P=0.019$) (Table 2).

Mean BP (MBP) was lowered significantly more in the group by perindopril/indapamide treatment than by enalapril treatment (−10.8±10.3 mm Hg perindopril/indapamide versus −9.0±10.1 mm Hg enalapril).

At the final visit, 159 of 233 (68%) patients in the perindopril/indapamide group were responders versus 135 of 224 (60%) in the enalapril group.

Urinary Albumin Excretion

Both treatments significantly lowered AER, perindopril/indapamide by a mean of −42% (95% CI −50% to 33%) and enalapril by a mean of −27% (95% CI −37% to 16%). Overall perindopril/indapamide remained more effective than enalapril in reduction in albuminuria after adjustment for baseline AER and country of origin (estimated treatment effect, −24%; [95% CI −38% to 8%], $P=0.002$, perindopril/indapamide versus enalapril). AER was reduced by on average 31.6 μg/min by perindopril/indapamide and 24.4 μg/min by enalapril (Table 2). Similar results were obtained after additional adjustments for gender, body mass index, and previous treatment of hypertension. Figure 3 illustrates that changes in AER were maintained throughout the period of follow-up.

The greater antiproteinuric effect in the perindopril/indapamide group remained after adjustment for MBP lowering, with an estimated treatment effect: −22% [95% CI −36% to 6%, $P=0.005$] and after adjustment for systolic BP of −22% [95% CI −36% to 6%, $P=0.002$]. Furthermore, for each quartile of MBP change, the residual AER was consistently lower in the perindopril/indapamide group (Figure 4). There was a 29% reduction in AER in those treated with perindopril/indapamide even in the quartile of patients with the lowest fall in MBP (<3.3 mm Hg), whereas in the group treated with enalapril, in which there was no reduction in BP, there was no reduction in AER.

The effect was present from low doses of perindopril/indapamide, with a 30% reduction in AER in 90 of 233 patients who remained for the duration of the study on 2 mg perindopril/0.625 mg indapamide first dose versus 25% for the 78 of 244 who remained on 10 mg enalapril. Furthermore, the greater effect on urinary albumin lowering remained after adjustment for dose modifications (−21% [95% CI −43% to 14%], $P=0.02$).

Perindopril/indapamide treatment also lowered ACR by a mean of 21% (95% CI 5% to 35%, $P=0.007$) more than enalapril. Similar results were obtained after additional adjustments for gender, body mass index, and previous treatment of hypertension and different effect on BP. The results were similar in the per-protocol analyses.

In the subgroup of patients with stricter definition of microalbuminuria between 20 and 200 μg/min at inclusion, from a baseline of 62.0 and 62.2 μg/min (geometric mean) in the perindopril/indapamide and enalapril groups, respectively, a reduction of 37% with perindopril/indapamide and 25% in AER with enalapril was observed.

Duration of Follow-up, Tolerability, and Adherence to Treatment

The mean duration of follow up was 328 (±99) days in those assigned to perindopril/indapamide and 321 (±106) in those assigned to enalapril; 80% of those randomly assigned completed the study. The main reasons for early withdrawal were adverse events (19 of 244 perindopril/indapamide; 21 of 237 enalapril), nonmedical reasons (12 of 244 perindopril/indapamide; 10 of 237 enalapril), major protocol deviations (6 of 244 perindopril/indapamide; 4 of 237 enalapril), and lack of efficacy (13 of 244 [5.2%] perindopril/indapamide; 25 of 237 [11%] enalapril, $P=0.03$). One patient was lost to follow-up. The global adherence to therapy was 97% (±8) in the perindopril/indapamide group and 99% (±5) in the enalapril group.

Tolerability was comparable between therapies. The proportions of adverse events related to drug treatment were 47 events in 34 patients (13.9%) for perindopril/indapamide and 48 events in 35 patients (14.8%) for enalapril. The most frequent were cough (perindopril/indapamide, 3.7%; enalapril, 2.1%) and dizziness (perindopril/indapamide, 1.2%; enalapril, 2.1%). Analysis of serious cardiovascular adverse events showed an incidence of 2.5% (6 of 244) in the perindopril/indapamide group versus 6.3% (15 of 237) in the enalapril group (relative risk=2.65 [95% CI 1.03, 6.83], log-rank test, $P=0.036$) (Figure 5).

The biochemical changes are shown in Table 3. There was a statistically significant mean change in HbA1c in both groups [mean±SD; perindopril/indapamide, 7.2% (±1.4) to 7.7% (±1.8); enalapril, 7.2% (±1.4) to 7.4% (±1.7)]. In patients randomly assigned with higher levels of HbA1c (>8%), no significant change was observed (mean±SD; perindopril/indapamide, −0.0%±1.8, n=68, enalapril, −0.3%±1.4, n=77). The same proportion of patients in each group required a change in their antidiabetic treatment during the year of follow-up (perindopril/indapamide, 13%; enalapril, 11%), no patient became newly insulin-dependent. There were small changes in creatinine clearance (Cockcroft for-

TABLE 2. Change in Albuminuria, Blood Pressure, and Response Rate

Intention to Treat Analysis	Perindopril/Indapamide (n=233)	Enalapril (n=224)
Albumin excretion rate, μg/min		
Baseline geometric mean [IQR]	75.3 [36.4–153.4]	89.1 [39.5–192.5]
Final geometric mean [IQR]	43.7 [18.1–92.8]	64.7 [27.2–155.7]
% AER reduction [95% CI]	−42% [−50%–−33%]	−27% [−37%–−16%]
Estimated treatment effect Per/Ind/Ena [95% CI]	0.76 [0.62–0.92]	
Gain between Per/Ind and Ena [95%CI] (1-estimated treatment effect)	0.24 [0.08–0.38]	
P noninferiority*	<0.001	
P superiority†	0.002	
Albumin/creatinine ratio, mg/mol		
Baseline geometric mean [IQR]	7.9 [3.4–18.1]	9.2 [4.5–17.5]
Final geometric mean [IQR]	4.8 [1.9–9.9]	6.7 [2.8–15.2]
% reduction albumin/creatinine ratio [95%CI]	−40% [−48%–−31%]	−27% [−37%–−16%]
Estimated treatment effect Per/Ind /Ena [95%CI]	0.79 [0.65–0.95]	
Gain between Per/Ind and Ena [95%CI] (1-estimated treatment effect)	0.21 [0.05–0.35]	
P noninferiority*	<0.001	
P superiority†	0.007	
Diastolic blood pressure, mm Hg		
Baseline mean (SD)	93.3 (8.7)	93.3 (8.7)
Final	84.5 (9.2)	86.0 (9.8)
Change mean (SD)	−8.8 (9.3)	−7.3 (9.0)
Diff Per/Ind–Ena [95% CI]	−1.54 [−2.99–−0.08]	
P equivalence‡	0.265	
P superiority§	0.019	
Systolic blood pressure, mm Hg		
Baseline mean (SD)	158.0 (11.5)	158.8 (12.1)
Final	143.2 (16.5)	146.5 (17.0)
Change mean (SD)	−14.8 (15.8)	−12.3 (15.5)
Diff Per/Ind–Ena [95% CI]	−3.01 [−5.62–−0.41]	
P equivalence‡	0.229	
P superiority§	0.012	
Responders		
Percentage of patients	68.2	60.3

*Noninferiority test: 1-tailed Student *t* test for independent samples (α=2.5%) after adjustment on W0 and country factor studied on the log-transformed values of albuminuria with a limit of noninferiority of 0.30 and antilogged transformed to give clinical results (1.35 antilogged limit).

†Superiority test: 1-tailed Student *t* test for independent samples (α=2.5%) after adjustment on W0 and country factor studied on the log-transformed values of albuminuria with a superiority tested to 0 and antilogged transformed to give clinical results (superiority tested to 1).

‡Equivalence test with limits of equivalence of [−2–2] for DBP and [−4–4] for SBP; two 1-tailed Student *t* test for independent samples (α=2.5%) after adjustment on W0 and country factor.

§Superiority test to 0 mm Hg: 1-tailed Student *t* test for independent samples (α=2.5%) after adjustment on W0 and country factor.

mula), with no treatment difference (−4.8±9.7 mL/min perindopril/indapamide; −4.1±11.4 mL/min enalapril).

Eight patients (3.3%) had hyperkalemia (>5.5 mmol/L) in the perindopril/indapamide group versus 13 (5.5%) in the enalapril group. Six patients (2.5%) had kalemia <3.4 mmol/L in the perindopril/indapamide group and 4 (1.7%) had kalemia <3.4 mmol/L in the enalapril group.

Discussion

This trial in patients with type 2 diabetes, hypertension, and albuminuria demonstrates the benefits of first-line therapy with a combination of a low dose of 2 mg perindopril, half the conventional starting dose, and 0.625 mg indapamide, one-quarter the conventional starting dose, in the reduction of both BP and AER.

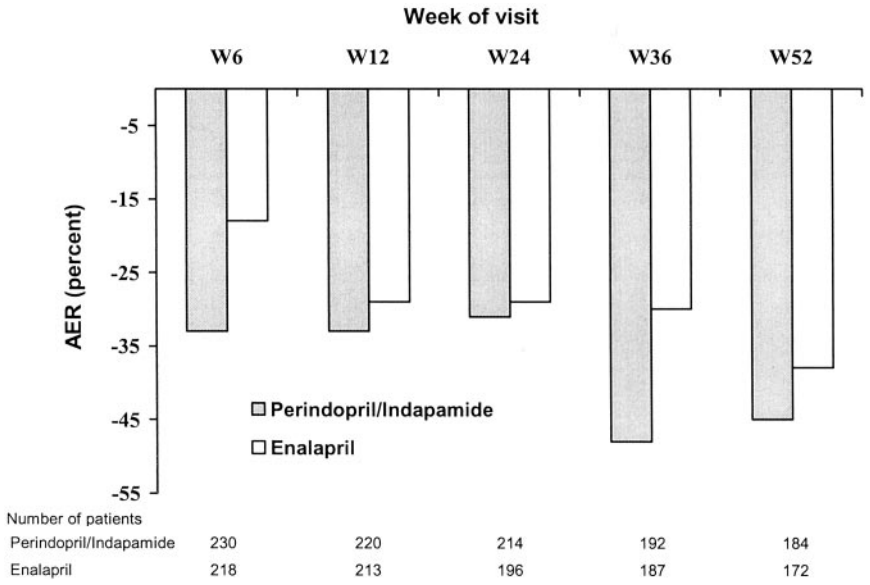

Figure 3. Decrease in percent AER at each visit by treatment group.

The combination therapy was superior in these respects to monotherapy with enalapril an agent of proven benefit in terms of renal and cardiovascular protection started at a conventional dose of 10 mg; 10 to 20 mg of enalapril and 4 to 8 mg perindopril are all first-line therapy providing similar BP decrease.[28]

Given current BP targets, ≈80% of patients with type 2 diabetes will have hypertension,[29] whereas the estimated prevalence of albuminuria in type 2 diabetes is ≈30%.[30] Thus, this study addresses a common clinical problem.

Increased urinary albumin excretion is associated with worsened renal and cardiovascular outcomes, and BP-lowering therapies that produce the largest reductions in albuminuria give the greatest renal and cardiovascular protection.[8,10] In the Micro–Hope substudy of the Heart Outcomes Prevention Evaluation Study (HOPE),[11] treatment with an ACE inhibitor in 3577 patients with type 2 diabetes lowered the risk of a combined end point of myocardial infarction, stroke, or cardiovascular disease death by 25% and total mortality rate by 24% as compared with placebo/conventional antihypertensive drugs.

Cost-benefit analyses suggest that therapies that reduce AER by ≥10% save money.[31] Therefore, the mean estimated treatment effect of a 24% greater reduction in AER in those treated with perindopril/indapamide as compared with enalapril would have significant benefits in terms of cost savings.

The 42% reduction in AER demonstrated in this study with perindopril/indapamide therapy is greater than that previously reported in ACE inhibitor studies. Ravid et al[32] described a 15% reduction in AER in 1 year with enalapril treatment in type 2 diabetes, whereas Hallab et al[33] described a 36% reduction in AER using enalapril over a period of 1 year in type 1 diabetes.

In a trial of irbesartan in 590 patients with type 2 diabetes and microalbuminuria, there was a dose-dependent reduction in AER of between 24% and 38% at 1 year, and this was associated with up to a 70% risk reduction in the risk of progression to overt albuminuria.[10]

In the Candesartan And Lisinopril Microalbuminuria (CALM) study,[34] which compared an ACE inhibitor with an angiotensin II antagonist in patients with type 2 diabetes, hypertension, and microalbuminuria, there was a 24% reduction in the ACR ratio with the use of a high dose of an

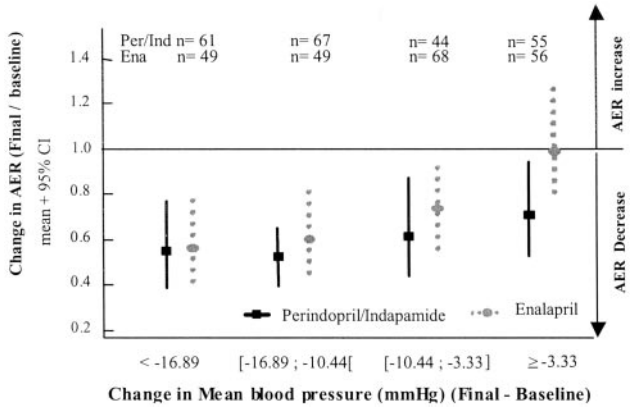

Figure 4. Change in AER (μg/min by MBP quartile changes).

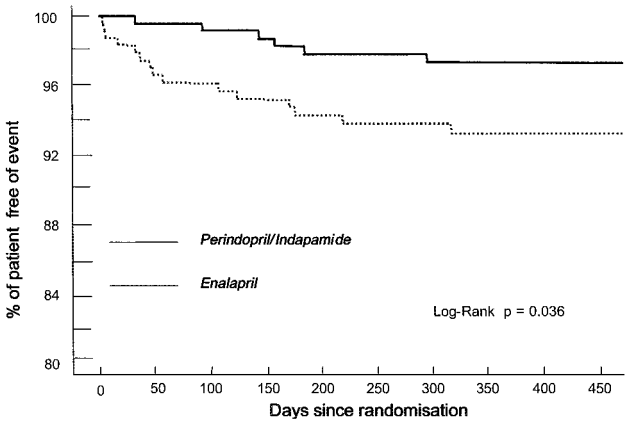

Figure 5. Occurrence of serious cardiovascular adverse events in PREMIER. Definition following ICD9-1975 revision (code 390-448, +7981, instantaneous death).

TABLE 3. Tolerability of Perindopril/Indapamide and Enalapril

	Perindopril/Indapamide (n=244)			Enalapril (n=237)		
Variable	Baseline	Final Value	Change	Baseline	Final Value	Change
Potassium, mmol/L	4.4 (0.4)	4.3 (0.4)	−0.1(0.4)*	4.4 (0.4)	4.5 (0.4)	+0.1(0.4)*
Sodium, mmol/L	139.6 (2.6)	138.7 (2.6)	−0.8(3.1)*	140.0 (2.4)	139.4 (2.6)	−0.7(2.4)*
Creatine Clearance, mL/min (Cockcroft formula)	95.1 (26.6)	91.1 (26.4)	−4.8(9.7)*	90.4 (26.3)	86.1 (27.3)	−4.1(11.4)*
Uric acid, μmol/L	344.7 (76.9)	378.2 (89.9)	+34.4(67.7)*	339.9 (81.1)	350.4 (88.5)	+10.5(64.9)*
Glucose, mmol/L	9.2 (3.2)	9.5 (3.4)	+0.4(3.7)	9.3 (3.3)	9.1 (3.1)	−0.2(3.4)
HBA1c, %	7.2 (1.4)	7.7 (1.8)	+0.6(1.6)*	7.2 (1.4)	7.4 (1.7)	+0.2(1.4)*
Total cholesterol, mmol/L	5.3 (1.1)	5.5 (1.1)	+0.1(0.9)	5.3 (1.1)	5.2 (1.0)	−0.1(0.9)
HDL cholesterol, mmol/L	1.2 (0.3)	1.1 (0.3)	−0.0(0.2)*	1.2 (0.3)	1.2 (0.3)	−0.0(0.2)
LDL cholesterol, mmol/L	3.3 (0.9)	3.4 (0.9)	+0.1(0.7)	3.3 (0.9)	3.3 (0.9)	+0.0(0.7)
Triglycerides, mmol/L	2.0 (1.6)	2.4 (3.1)	+0.4(2.1)*	2.0 (1.7)	1.8 (1.0)	−0.2(1.7)
ALAT, IU/l	21.4 (11.7)	21.8 (12.5)	+0.2(11.4)	20.9 (14.3)	19.8 (10.0)	−0.7(9.8)
ASAT, IU/l	15.7 (6.9)	16.2 (9.1)	+0.5(7.9)	15.8 (8.1)	15.0 (5.7)	−0.7(5.8)

Data are mean (SD).
*$P<0.05$.

angiotensin II antagonist and a 39% reduction with the use of the ACE inhibitor, which compares with a 40% reduction in ACR in this study with perindopril/indapamide.

It is widely recognized that combination therapy is required to achieve current BP treatment targets. In the irbesartan study in patients with type 2 diabetes and microalbuminuria, ≈44% of the patients required additional antihypertensive drugs.[10]

Perindopril/indapamide therapy was associated with greater lowering of systolic and diastolic BP as compared with enalapril, and this is usually associated with a greater fall in AER.[35] We do not have any data on salt intake; however, the beneficial effect of the combination in BP lowering is likely to be related at least in part to a diuretic-induced salt loss, which potentiates the effect of RAS inhibition. The BP-lowering effect of both perindopril/indapamide and enalapril is undoubtedly crucial in lowering the AER. Nevertheless, the beneficial effects of the perindopril/indapamide combination on AER persisted after adjustment for mean or systolic BP reduction. Furthermore, there was an antiproteinuric effect at the lowest doses of perindopril and indapamide and an ≈30% reduction in AER even when the fall in MAP was <3.3 mm Hg. This raises the suggestion of a renoprotective mechanism independent of systemic BP lowering with this combination. Indapamide, in addition to its diuretic and vasodilating effects, may act as a free radical scavenger,[36,37] whereas RAS inhibitors including perindopril may also have BP-independent renoprotective effects.[38] The mechanism of any BP-independent effect, however, has not been addressed by this study.

In epidemiological studies, pulse pressure also has been associated with microalbuminuria and may be a marker of greater cardiovascular risk.[39] We found a greater reduction in AER with perindopril/indapamide as compared with enalapril despite the fact there was no significant reduction in pulse pressure, although we cannot in this study exclude that lowering pulse pressure would be beneficial.

There has been some discussion recently as to whether enalapril is more efficacious used twice daily. We cannot exclude that differences occurred in nighttime BP and that this may account in part for the benefits seen. However, changes in nighttime BP are unlikely to be a major confounder of the results because the efficacy of the once-daily enalapril regimen has been clearly demonstrated in diabetic kidney disease.[25,40] Second, a clinically and statistically significant decrease in BP measured at trough was observed in this study. As a reflection of the efficacy of both treatment strategies in terms of BP lowering, approximately one third of patients were adequately controlled on the lowest doses of both therapies. Equal proportions in each group required dose adjustments, with only approximately one third of patients requiring the highest doses.

Treatment with the combination of perindopril/indapamide was associated with some metabolic changes, notably a small change in HbA1c predominantly seen in those with tight glycemic control at inclusion, there being no deterioration in those with a HbA1c >8% at baseline. There was no difference in the need to modify diabetic therapy between the groups during the study, suggesting the effect was clinically modest. Similarly, changes in the lipid profile were small.

These metabolic effects are commonly seen with diuretic therapy and may be ameliorated by the combination with ACE inhibitor therapy.[41]

The decrease in creatinine clearance seen in both groups is in keeping with that seen with most antihypertensive therapy and particularly with RAS inhibitors.

A lower incidence of serious cardiovascular events was observed in the perindopril/indapamide group. It is difficult to be certain of the significance of this finding because it was not a designed end point of this study; therefore, it will need to be confirmed in an appropriately designed study.

Perspectives

Recent guidelines indicate the importance of aggressive BP lowering in patients with diabetes for both renal and cardio-

vascular prognosis.[42] Achievement of these tight BP targets is difficult, especially in those with albuminuria. The most effective clinical strategies need to be determined. This study demonstrates the efficacy of a low-dose combination of perindopril/indapamide in both BP and AER reduction and suggests that combination therapy should be offered early in the treatment schedule of this important condition.

Appendix

The following persons participated in the PREMIER study: Steering committee: C.E. Mogensen (International coordinator), G.C. Viberti (Chairman), S. Halimi (Cochairman), P.W. de Leeuw (Netherlands coordinator), G. Erdogan (Turkey coordinator), A. Hamani (Morocco coordinator), S. Halimi (France coordinator), B. Hess (Switzerland coordinator), G. Jermendy (Hungary coordinator), A. Luger (Austria coordinator), R. Mechmeche (Tunisia coordinator), J. Nolan (Ireland coordinator), A. Ribeiro (Brazil coordinator), E. Ritz (Germany coordinator), L. Ruilope (Spain coordinator), J. Rull (Mexico coordinator), R. Sanchez (Argentina coordinator), P. Sareli (South Africa coordinator), A. Scheen (Belgium coordinator), J. Sirotiakova (Slovakia coordinator), J. Taton (Poland coordinator), G.C Viberti (United Kingdom coordinator), J. Widimsky (Czech Republic coordinator). Principal Investigators: Argentina (10): R. Sanchez; Austria (5): A. Luger; Belgium (4): L. De Paepe, R. De Wasch; Brazil (10): A. Ribeiro; Czech Republic (40): R. Cifkova, I. Poapska, H. Rosolova, J. Rybka, J. Toman, A. Klimovicova; France (87): S. Arlot, J.-R. Attali, J. Bringer, C. Broussole, C. Brunetiere, G. Cathelineau, B. Charbonnel, G. Charpentier, B. Colle, D. De Brouker, J.-P. Donnet, Y. Derennes Limbour, J.M. Drouin, B. Estour, T. Gabreau, D. Houlbert, A. Lagier, S. Halimi, M. Levy, Y. Lorcy, Y. Reznik, R. Marechaud, L. Meyer, E. Mollet, A. Penfornis, C. Oliver, X. Ducottet, J.-C. Paffoy, M. Pinget, M. Daumont, J.-P. Riou, M. Rodier, J. Roy, B. Schmitt, G. Seng, J.-P. Tauber, P. Vague, C. Kichenin, F. Archambeaud; Germany (88): H. Alawi, A. Kapelle, U. Kleinecke-Pohl, S. Krok, O. Muller, R. Scherenberg, H. Steinhauer, H. Christian Weber, J. Wiese, H. Ziegenhorn; Hungary (43): Z. Kerenyi, G. Winkler, J. Patkay, E. Juhasz, T. Hidvegi, F. Tarnok; Ireland (8): J. Nolan; Mexico (12): J. Rull, L. Alcocer; Morocco (6): A. Hamani; Netherlands (11): W. Feis, L. Harm Oosterhuis, W. Alsem; Poland (19): B. Krupa-Wojciechowska, Z. Szybinski, M. Tendera, B. Werusz-Wysocka, M. Grzywa, D. Zytkiewicz-Jaruga, E. Bandurska-Stankiew, J. Imiela; Slovakia (5): J. Sirotiakova; South Africa (19): P. Sareli, F. Maritz, D. Weich, H. Oosthuizen; Spain (71): L. Ruilope, J. Abellan, C. Calvo-Gomez, B. Gil Extremera, J. Nieto, A. Otero; Switzerland (3): G. Colque-Comot, P. Diem, G. Spinas; Tunisia (1): R. Mechmeche; Turkey (18): G. Erdogan, O. Gedik, T. Yilmaz; United Kingdom (21): D. Barnes, S. Jones, G.C. Viberti, J. Walker.

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