Clinical Experience With Perindopril in African-American Hypertensive Patients: A Large United States Community Trial

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Background: The prevalence of hypertension is greater in African Americans, and management of this condition presents challenges for practicing physicians.

Methods: The effectiveness and safety of perindopril was evaluated in hypertensive African-American patients ($n = 1412$) and hypertensive white patients ($n = 7745$) who had participated in a large United States community trial. Patients received perindopril 4 mg once daily for 6 weeks. Based on physicians’ clinical judgment at week 6, the dose was either maintained or increased to 8 mg for an additional 6 weeks.

Results: Reduction of blood pressure (BP) was significant with perindopril monotherapy (4 to 8 mg once daily) in African Americans and whites ($P < .001$). The magnitude of BP reduction was significantly more in whites ($P < .001$). Up-titration of perindopril achieved additional BP reduction in both ethnic groups ($P < .001$). Control of BP (<140/90 mm Hg) in elderly (>65 years of age) and diabetic African-Americans subgroups was achieved in 32.1% and 31.6%, respectively. Perindopril was safe and well tolerated.


Key Words: Perindopril, African Americans, hypertension, up-titration.

In the United States, the incidence of hypertension is higher among African Americans compared with other ethnic groups. The prevalence of hypertension in adult African Americans is about 33% compared with the incidence of 25% in individuals of white ethnicity. Furthermore, African Americans are known to carry multiple cardiovascular risk factors associated with hypertension, resulting in higher rates of morbidity and mortality.

The management of hypertension in African Americans presents challenges for practicing physicians. Although angiotensin-converting enzyme inhibitors (ACEIs) are established as a major drug class in the treatment of hypertension, the perception in clinical practice is that ACEIs are less effective as monotherapy in African Americans because of low renin levels and a high degree of salt sensitivity. The efficacy and safety of perindopril, an ACEI, was investigated in a subgroup of African Americans from a large United States community trial.

Methods

Study Design

This was an open label, baseline-controlled study of 12 weeks’ duration. The objective of the study was to assess the effectiveness of perindopril monotherapy administered once a day on the sitting systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Study Population

Men and women who were ≥18 years of age were eligible to enroll in the community trial if they had a sitting SBP of 140 to 180 mm Hg or a sitting DBP of 95 to 114 mm Hg inclusive and at least one of the following: 1) newly diagnosed hypertension; 2) inability to tolerate other antihypertensive medications; or 3) lack of blood pressure (BP) control with any prior single antihypertensive medication.
Patients were excluded if they were pregnant or nursing, previously treated with perindopril, known to have contraindications based on allergic reactions, or known to have a history of acute myocardial infarction or clinically unstable condition in the past 3 months. In this study the patients were not sought by chart search, advertisement, or any other means of enhancing the study recruitment.

Before entering the studies, all patients signed informed consent forms approved by the institutional review boards. Subgroups of 1412 African-American patients and 7745 white patients who participated in the general practice-based clinical trial were included in this retrospective analysis.

**Study Conduct**

At study entry (visit 1), eligible patients were provided 4-mg perindopril tablets for 6 weeks from a participating local pharmacy. Patients were instructed not to take any antihypertensive medications other than perindopril and were also instructed to take the perindopril tablets at home at the same time every morning. However, the patients were allowed to take any other necessary drugs for cardiovascular indications other than hypertension. After 6 weeks on a 4-mg dose, patients returned to the clinic (visit 2). At this visit, after the BP measurement, the practicing physician decided whether further up-titration of perindopril was needed based on the clinical judgment of response. Patients deemed by the physician as responsive were maintained on 4-mg perindopril tablets for an additional 6 weeks (group I). In patients considered by the physicians to be less responsive, the dose of perindopril was increased to 8 mg/day for an additional 6 weeks (group II). Patients from both group I and group II then returned for the final visit at week 12 (visit 3).

**Study Procedures**

At visit 1, after sitting for 5 min, two BP readings, separated by 5 min, were taken and averaged for a mean baseline sitting SBP and DBP. Other variables collected at this visit include age, ethnicity, sex, duration of hypertension, cardiovascular disease history, previous antihypertensive therapy, and concurrent medications. At visit 2, in addition to BP measurement, the physician’s assessment of BP response to perindopril was obtained for titration decision. At visit 3, in addition to BP measurement, patients returned all remaining study drug.

**Efficacy Assessments**

In addition to BP changes from baseline to week 6 and week 12, BP control (<140/<90 mm Hg) was assessed at week 6 and week 12 in all patients.

**Safety**

All patients were questioned by study personnel regarding the occurrence of adverse events (AEs) at week 6 and week 12. Adverse events were coded using the COSTART dictionary, version 3.0. An AE was counted only once for each body system and preferred term.

**Statistical Analysis**

All statistical tests were two-tailed, and all analyses were considered statistically significant if the two-sided \( P \) value was < .050. Baseline demographic and clinical characteristics, as well as efficacy variables, were compared between the ethnic groups using the Student \( t \) or \( \chi^2 \) tests for continuous and categorical variables, respectively. For change in BP from week 6 to week 12 when increasing in dose from 4 mg to 8 mg, a paired \( t \) test was used to test the null hypothesis that the mean change in BP from week 6 to week 12 = 0. McNemar’s test was performed within each ethnic group to test whether a shift in BP control rate occurred from week 6 to week 12 in group II patients when increasing in dose from 4 mg to 8 mg.

**Results**

**Patient Disposition**

**African Americans** Of the 1412 patients included in the efficacy analysis, 1069 patients completed the study. Among the remaining 343 patients, 339 did not complete the study for the following reasons: AE (\( n = 129 \)), withdrew consent (\( n = 11 \)), protocol violation (\( n = 25 \)), lost to follow-up (\( n = 88 \)), investigator decision (\( n = 19 \)), sponsor discretion (\( n = 1 \)), other (\( n = 35 \)), and unknown (\( n = 31 \)). Completion status was not available for four patients.

**White Patients** Of the 7745 patients included in the efficacy analysis, 6183 patients completed the study. In the remaining 1562 patients, 1542 patients did not complete the study for the following reasons: AE (\( n = 695 \)), withdrew consent (\( n = 48 \)), protocol violation (\( n = 108 \)), lost to follow-up (\( n = 275 \)), investigator decision (\( n = 106 \)), sponsor discretion (\( n = 4 \)), other (\( n = 140 \)), and unknown (\( n = 166 \)). Completion status was not available for 20 patients.

**Baseline Characteristics**

**Demographic Characteristics** The mean age of African Americans was significantly lower than that of whites (52.3 v 56.8 years, \( P < .001 \)). The majority of the patients were <65 years of age and were female among African Americans (80.9% and 56.0%, respectively) compared with whites (69.1% and 49.6%, respectively). These differences were statistically significant (\( P < .001 \)).

**Clinical Characteristics** Mean duration of hypertension was significantly longer in African Americans compared with whites (3.9 v 3.3 years, \( P < .001 \)). Baseline mean SBP was similar in both ethnic groups: 156.3 mm Hg in African Americans and 157.0 mm Hg in whites; however, the baseline mean DBP was significantly higher in African Americans compared with whites (96.5 mm Hg v 94.1 mm Hg, \( P < .001 \)). The percentage of patients with
diabetes was significantly more in African Americans (10.3%) than in whites (7.6%).

Effect on BP

The effect of perindopril on sitting BP in African Americans and whites is shown in Table 1. A significant reduction in BP from baseline to week 6 and week 12 was obtained with perindopril (4 to 8 mg once daily) in both ethnic groups ($P < .001$). Furthermore, in both ethnic groups, a clinically significant BP reduction with perindopril was observed in newly diagnosed hypertensive individuals, in patients with a history of hypertension, in both genders, in elderly patients ($\geq 65$ years of age), and in patients with diabetes. Similar to all patients, the magnitude of BP reduction to perindopril was slightly but consistently more in whites compared with African Americans in all subgroups ($P < .05$).

Mean reduction in SBP and DBP from baseline to week 6 and week 12 was $-10.7/ -7.1$ mm Hg and $-14.4/-9.1$ mm Hg in African Americans, and was $-15.3/-8.9$ mm Hg and $-18.2/-10.6$ mm Hg in whites.

Dose Titration

Of the patients entering the study, 52.7% of African Americans ($n = 744$) and 60.9% of whites ($n = 4715$) remained on their starting dose of perindopril (4.0 mg) at week 6 (group I). In the remaining African-American ($47.3\%$, $n = 668$) and white patients ($39.1\%$, $n = 3030$), the dose was increased to 8.0 mg at week 6 (group II).

Group I The majority of reduction in BP from baseline was achieved at week 6 on the 4-mg dose in both ethnic groups. Mean reduction from baseline in BP at weeks 6 and 12 in African Americans was $16.0/10.9$ mm Hg and $17.8/11.6$ mm Hg, respectively, and in whites the reduction was $20.0/11.4$ mm Hg and $20.2/11.7$ mm Hg, respectively. This BP reduction from baseline was significant in both ethnic groups ($P < .001$).

Group II Unlike group I, the BP reduction from baseline on 4 mg dose at week 6 was significantly less than the reduction observed at week 12 in both ethnic groups ($P < .001$). The mean BP reduction in African Americans and whites at week 6 was $4.7/3.0$ mm Hg and $8.0/5.0$ mm Hg, respectively. With up-titration to 8 mg dose, the total reduction from baseline to week 12 was $11.3/6.8$ mm Hg in African Americans and $15.4/9.2$ mm Hg in whites. In both ethnic groups, group II patients had significantly higher baseline BP than group I in both ethnic groups ($P < .001$).

Control of BP

Control of BP ($\leq 140/\leq 90$ mm Hg) increased over time during the 12-week treatment period in both ethnic groups. The BP control achieved at weeks 6 and 12 was $29.6\%$ and $38.9\%$ in African Americans and was $39.2\%$ and $50.2\%$ in whites.
In group II, a significantly greater percentage of BP control was achieved with up-titration ($P = .001$). At weeks 6 and 12, the percentage of BP control achieved was 5.3% and 23.5% in African Americans and 7.1% and 35.7% in whites, respectively.

Among elderly and diabetic patients, BP control was achieved at week 12 in 32.1% and 31.6% African Americans and 42.0% and 44.3% whites, respectively.

**Safety Assessment**

The AE profile was similar in both ethnic groups. Cough was the most frequent AE (African Americans, 6.1%; whites, 8.4%). The incidence of angioedema was 0.8% in African Americans and 0.3% in whites. The percentage of patients discontinued because of AEs was 9.5% in African Americans and 10.7% in whites.

**Discussion**

In this general practice-based, community clinical trial, the effectiveness of perindopril in the management of hypertension in African-American patients was assessed. A significant and clinically relevant BP reduction from baseline was achieved with perindopril monotherapy in both ethnic groups, although the magnitude of reduction was slightly but significantly greater in hypertensive individuals of white ethnicity. This observation of lesser response in African-American patients compared with white patients with perindopril monotherapy is consistent with all ACEIs.

Previously it was reported that ACEIs as single-drug therapy are less effective than other classes of antihypertensive drugs in African Americans with hypertension. Recently, the The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed that diuretic-based therapy is associated with a larger decrease in BP than an ACEI-based treatment and this BP difference was particularly pronounced in African Americans. Although no active comparators were included in the present study, perindopril monotherapy was shown to be effective in reducing BP in African-American patients. Furthermore, in this study using a titration approach, an increase in the dose of perindopril from 4 mg to 8 mg was shown to achieve a significantly greater reduction in SBP and DBP among African-American patients with inadequate response at the low dose (group II). Our findings are consistent with previous observations reported by Saunders et al. and Drayer and Weber, who found a substantial improvement in BP response in African Americans with upward titration of the dose of captopril. Similar AE profiles at doses of 4 mg and 8 mg demonstrate that perindopril does not compromise safety while being effective at high doses.

It is known that plasma renin activity is significantly lower in African-American compared with white individuals, and that the responsiveness of renin–angiotensin system in general is diminished in African Americans. The lesser response to ACEIs in African Americans compared with whites could be attributed to this diminished enzyme activity. Despite the pathophysiologic and socioeconomic differences in hypertension in African-American versus white individuals, effective BP control could be achieved in African Americans with ACEIs by using appropriate dosages. Recently it has been shown that ACEIs that act both in the plasma and at the tissue level may have better effectiveness and could be considered as first-line therapy in African Americans. Perindopril is known to have significant ACE inhibitory activity in both plasma and tissues.

In this study, BP control ($<140/90$ mm Hg) was achieved with perindopril monotherapy in 38.9% of African-American patients at week 12. Despite an increase in the dose of perindopril from 4 mg to 8 mg at week 6, the majority of the African-American patients (68%) with higher baseline BP in group II did not achieve BP control, suggesting that perindopril combination therapy might be beneficial in such a resistant patient population. Although socioeconomic factors and lifestyle may be significant barriers to BP control in African Americans, guidelines from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommend the addition of a diuretic to achieve BP control.

The coexistence of hypertension and diabetes is known to increase the risk of cardiovascular events. Recent guidelines for management of high BP in African Americans recommended a lower BP target of 130/80 mm Hg for African Americans with hypertension and concomitant diabetes. In our study, perindopril monotherapy with up-titration achieved target BP goal (130/80 mm Hg) in only 2.0% of African-American diabetic hypertensive patients, suggesting that perindopril combination therapy may be required in these high-risk patients. Recent JNC 7 guidelines recommend a combination of two or more agents to achieve the target goal of $<130/80$ mm Hg in patients with diabetic hypertension.

African-American patients tolerated perindopril well in the dose range of 4 to 8 mg, with a low withdrawal rate due to AEs (9.5%). The incidence of angioedema observed in this study (0.8%) is consistent with the recently reported ALLHAT results in African Americans (0.7%).

In conclusion, this study demonstrated that perindopril monotherapy is a viable initial therapeutic option for managing hypertension in African-American patients. Combination therapy may be beneficial for controlling BP in the high-risk diabetic patient population.

**References**