Postmarketing Surveillance Study of Benazepril in Chinese Patients with Hypertension: An Open-Label, Experimental, Epidemiologic Study

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ABSTRACT

Background: Benazepril hydrochloride is an angiotensin-converting enzyme inhibitor. Previous clinical trials show that antihypertensive treatment with benazepril provides effective blood pressure (BP) control and is generally well tolerated by patients with hypertension. However, the long-term antihypertensive effects and tolerability of benazepril remain to be established in Chinese patients with hypertension.

Objective: The aim of this study was to investigate the long-term efficacy and tolerability of benazepril in Chinese patients with essential hypertension.

Methods: This 36-month, community-based, open-label, postmarketing surveillance study was conducted in the Nanshi District (Shanghai, China). Chinese patients with essential hypertension were to receive 1 or more benazepril tablets PO QD in the morning for 36 months. Data for BP and pulse pressure (PP) were collected at baseline (month 0) and throughout the surveillance period. The rate of patients achieving BP targets (systolic BP [SBP]/diastolic BP [DBP], <140/<90 mm Hg) was determined, as was the rate of decrease in BP. Subanalyses by sex and age group also were conducted.

Results: A total of 1831 patients (1090 men, 741 women; mean [SD] age, 55.8 [10.1] years [range, 35–88 years]) entered the study. After the 36-month treatment period, 75.7% of patients receiving benazepril as prescribed (1289 patients) had achieved the SBP target, 87.4% achieved the DBP target, and 71.5% achieved both targets. After 36 months of treatment, the mean (SD) decreases in SBP, DBP, and PP were 15.1 (0.4) mm Hg, 11.0 (0.3) mm Hg, and 4.2 (0.4) mm Hg, respectively, among compliers. In general, the rate of BP decrease slowed

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over time. No serious adverse drug reactions (ADRs) were detected during the 36-month follow-up period. All ADRs except cough (19.9%) occurred at a relatively low incidence rate (<3.0%). The cumulative incidence of benazepril-related cough was statistically significantly higher in women than in men (23.6% vs 18.8%, respectively; $P = 0.007$). Of the 1831 patients studied, 1360 patients (74.3%) persisted in taking benazepril and were considered optimally compliant at 36-month follow-up.

Conclusion: In this study of Chinese patients with hypertension, benazepril was associated with prolonged, stable efficacy in lowering BP and a relatively low incidence of ADRs. (*Curr Ther Res Clin Exp.* 2004;65:000–000) Copyright © 2004 Excerpta Medica, Inc.

Key words: adverse effects, angiotensin-converting enzyme inhibitors, cough, hypertension, product surveillance, postmarketing.

INTRODUCTION

Antihypertensive treatment (AHT) greatly reduces the risk for cardiovascular disease and associated morbidity and mortality.^{1–4} Drug efficacy and safety are keys to effective prevention and cure of hypertension. Randomized clinical trials (RCTs) are considered the “gold standard” for assessing the efficacy and safety of drugs. However, RCTs are conducted in accordance with strict patient selection criteria, and most are of short duration, involve a small number of patients, and are rarely community based. Thus, the generalizability of the conclusions of RCTs is limited. Also, RCTs may not always answer the questions asked by practicing clinicians.⁵ Thus, epidemiologic studies are needed to answer unresolved questions and to complement the information from RCTs. The purpose of postmarketing surveillance is to obtain information on the actual use of drugs and their long-term effects in the general patient population.

Angiotensin-converting enzyme (ACE) inhibitors are safe and effective in lowering blood pressure (BP) and are particularly effective in reducing morbidity and mortality in heart failure and in retarding the progression of renal disease in patients with type 1 diabetes mellitus, especially in the presence of proteinuria.⁶ Both the 1999 World Health Organization–International Society of Hypertension (WHO–ISH) Guidelines for the Management of Hypertension⁶ and The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI)⁷ recommend using ACE inhibitors as first-line AHT. Benazepril hydrochloride* is an ACE inhibitor with active carboxyl moieties.⁸

The long-term antihypertensive effects and tolerability of benazepril remain to be established in Chinese patients with hypertension. Therefore, the pur-

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pose of this study was to assess the long-term efficacy and tolerability of benazepril in these patients.

PATIENTS AND METHODS

Study Design

This 36-month, community-based, open-label, postmarketing surveillance study was conducted in the Nanshi district (Shanghai, China). It was designed and organized by the Department of Epidemiology and Biostatistics, School of Public Health, Peking University Health Science Center. It was one of the key tasks of the Community-Based Comprehensive Prevention and Control of Hypertension (CCPACH) project of the China National Ninth Five-Year-Plan Funding Program (1997–2001). Approval of the study protocol was obtained from the institutional review board at Peking University Health Science Center.

Patients

We recruited Chinese patients with essential hypertension from among the long-term residents (ie, those who were unlikely to move out of the area in the following 3 years) of the Nanshi District of Shanghai using the following inclusion criteria: age ≥ 35 years; a history of essential hypertension or systolic BP (SBP) ≥ 140 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg on 2 different days ≥ 2 weeks apart at baseline (month 0); and a willingness to participate in a 36-month study. Patients were excluded if they had unstable angina within 3 months before the study, were receiving adrenocortical hormone, or had a known sensitivity to benazepril. Women who were pregnant or breast-feeding were also excluded. Patients provided written informed consent prior to entering the study.

Baseline Investigation

At baseline, recruited patients were administered an interview questionnaire, the purpose of which was to provide the following information: (1) demographic data, including age, sex, educational level, and occupation; (2) medical history; and (3) lifestyle factors, including history of smoking and alcohol consumption. A fasting blood sample was collected by the trained physicians at a local community clinic from each participant to determine concentrations of high-density lipoprotein cholesterol, total cholesterol, triglycerides, serum creatinine concentration, and fasting serum glucose. The concentration of low-density lipoprotein cholesterol was determined according to the Friedewald formula.⁹ SBP/DBP and pulse pressure (PP) were measured.

Methods

Treatment

Because of ethical considerations, no washout period was included in the study design. One benazepril tablet was given QD in the morning. The initial dosage

was 5 mg/d for patients whose SBP/DBP was 140–<160/90–<100 mm Hg, whereas patients whose SBP/DBP remained $\geq 160/\geq 100$ mm Hg despite previous combination therapy were started on 10 mg/d. The initial dosage was maintained if BP was controlled (target SBP/DBP: <140/<90 mm Hg) or DBP was lowered ≥ 10 mm Hg, or in patients with isolated systolic hypertension, SBP was controlled (target, <140 mm Hg) or was lowered ≥ 20 mm Hg. The protocol was determined before JNC VI and WHO–ISH guidelines were issued, so our targets differed slightly from the guidelines. The dosage was increased in 5-mg/d increments at 2-week intervals if BP was not controlled or lowered to meet the criteria until the maximum dosage of 20 mg/d was reached. Combination therapy with hydrochlorothiazide (12.5–25.0 mg/d) was started if benazepril monotherapy failed to meet the above criteria. If BP was not controlled with combination therapy, patients could be started on other therapeutic regimens, at which point they were excluded from the study. During the 36-month follow-up period, patients were to discontinue all AHT medications except benazepril and hydrochlorothiazide.

Patients were asked to attend a specified community clinic monthly, where BP and PP were measured between 9:00 AM and 11:00 AM (after dosing), by the same trained clinicians, in the same patient's arm each time, using a standard mercury sphygmomanometer, with the patient in a sitting position after ≥ 5 minutes of rest. Korotkoff's phases I and V were used to determine SBP and DBP, respectively. During each visit, BP was measured 3 times, and the mean of the 3 measurements was calculated.

Compliance

Patients were also requested to report whether they had taken the medication as prescribed in the past month, and if not, how many days they had not complied with the treatment regimen and why. Because of the community health education included in the CCPACH project and the simple treatment regimen (QD in the morning), we believed that self-reporting was a reliable method for assessing compliance. Optimal compliance was defined as taking medication as prescribed for $\geq 90\%$ of the follow-up period.

Efficacy Assessments

We calculated the rate of achieving the BP targets; calculated the decrease in mean BP after 36 months of treatment; compared the mean BP at the first visit in patients who discontinued treatment within the first 3 months, 3 to 6 months, and 6 to 9 months with those who adhered to the treatment regimen for >9 months; and used a mixed linear model technique¹⁰ to fit the individual changes in BP in the 36-month follow-up. The BP records, measured at baseline and every 3 months thereafter up to 36 months, were used to model the BP growth curves. If follow-up records showed that a patient had not taken benazepril as prescribed since his or her last visit, the corresponding BP measurement was excluded.

Tolerability Assessment

Spontaneous reporting of adverse events (AEs) was used to determine tolerability. Specially trained physicians then assessed the AEs according to the Karch and Lasagna classification.¹¹ We regarded patients with definite, probable, or possible benazepril-related AEs as having adverse drug reactions (ADRs).

Statistical Analysis

The Gabriel test (1-way analysis of variance [ANOVA]) was used for pairwise comparisons in multiple means comparisons with equal variances. The crude incidence of each ADR was calculated as the number of patients with the ADR at any time during the study divided by the total number of patients. In addition, we calculated the incidence of cough using the life table method. The log-rank test was used to test the difference in the incidence of cough between men and women.

We used the mixed linear model technique¹⁰ to fit the individual BP change pattern. The curvilinear polynomial model was used to approximate the non-linear changes in SBP and DBP. Orthogonal polynomials^{12–14} were used to solve multicollinearity. To calculate the BP level of the j th patient at the i th time point (Y_{ij}), we used the following equation:

$$Y_{ij} = \pi_{0j} + \pi_{1j}(\text{Time}_l)_{ij} + \pi_{2j}(\text{Time}_q)_{ij} + r_{ij},$$

where Time_l and Time_q , respectively, represent the linear and quadratic parts of the time variable after orthogonal conversion. The intercept, π_{0j} , was the expected BP when $\text{Time}_l = 0$. However, $\text{Time}_l = 0$ now represents the time period halfway through the study (ie, 18 months after starting benazepril treatment). The slope, π_{1j} , was not only the rate of change when $\text{Time}_l = 0$ but also the mean rate of growth or mean velocity during the data-collection period. The quadratic coefficient, π_{2j} , captured the curvature in each growth trajectory, and $2\pi_{2j}$ represented the acceleration. Based on the change characteristics of PP, we fitted a piecewise growth model,¹⁵ an individual quadratic growth model from 0 to 9 months (π_{0j} , π_{1j} , π_{2j}), and a linear growth model from 9 to 36 months (π_{3j}). Variations in the individual parameters of intercept, slope, and acceleration were modeled as a function of age (centered around the mean of 55.8 years) and sex (1 = female, 0 = male). We used the SAS software Proc Mixed procedure^{16–21} (SAS Institute Inc., Cary, North Carolina) to fit these models. $P \leq 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 1831 patients (1090 men, 741 women; mean [SD] age, 55.8 [10.1] years [range, 35–88 years]) participated in the study. Baseline characteristics of all patients, by sex, are shown in **Table I**. Of these, 172 patients (9.4%) had newly diagnosed essential hypertension. Six hundred forty-nine patients (35.4%) had never received AHT. Eight hundred seven patients (44.1%) had been receiving other AHT at study entry. Of these, 375 (46.5%) were receiving therapy with

Table I. Baseline demographic and clinical characteristics of study patients (N = 1831).

Characteristic	Men (n = 1090)	Women (n = 741)
Age, y		
Mean (SD)	55.8 (10.5)	55.7 (9.5)
Range	35–88	35–84
Body weight, mean (SD), kg*	71.3 (9.3)	61.7 (9.0)
Height, mean (SD), cm*	170.7 (5.3)	158.8 (5.1)
BMI, mean (SD), kg/m ²	24.5 (2.8)	24.5 (3.4)
Biochemical assay, mean (SD)		
LDL-C, mmol/L [†]	3.31 (1.02)	3.43 (1.01)
HDL-C, mmol/L*	1.35 (0.34)	1.53 (0.41)
TC, mmol/L*	5.25 (0.98)	5.45 (1.02)
TG, mmol/L*	1.80 (1.32)	1.61 (0.81)
FSG, mmol/L	5.50 (1.35)	5.55 (1.45)
SCC, μ mol/L*	138.0 (25.8)	119.2 (20.8)
Smoking status, no. (%)*		
Current smoker	432 (39.6)	11 (1.5)
Former smoker	136 (12.5)	4 (0.5)
Current white spirit drinker, no. (%)*	115 (10.6)	2 (0.3)
Educational status, no. (%)*		
≤Elementary school	46 (4.2)	96 (13.0)
High school	467 (42.8)	380 (51.3)
≥Junior college	577 (52.9)	265 (35.8)
Employed, no. (%)*	737 (67.6)	441 (59.5)
Medical history, no. (%)		
Coronary heart disease	69 (6.3)	48 (6.5)
Diabetes	34 (3.1)	32 (4.3)
Stroke	29 (2.7)	16 (2.2)

BMI = body mass index; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; FSG = fasting serum glucose; SCC = serum creatinine concentration.

* $P < 0.001$ between sexes.

[†] $P = 0.016$ between sexes.

Chinese fixed-dose combination drugs, 228 (28.3%) calcium antagonists, 128 (15.9%) ACE inhibitors, 84 (10.4%) beta-blockers, and 30 (3.7%) diuretics. Seven hundred thirty-four treated patients (91.0%) were receiving monotherapy. At baseline, BP was adequately controlled (SBP/DBP <140/<90 mm Hg) in only 217 of the 1831 treated patients (11.9%). In treated patients, the mean [SD] SBP was 149.0 [15.1] mm Hg; the mean [SD] DBP 93.4 [8.4] mm Hg; and the mean [SD] PP, 55.6 [13.5] mm Hg at baseline (**Table II**).

Benazepril Monotherapy and Combination Therapy

During the 36-month follow-up, 1610 patients (87.9%) received benazepril monotherapy, whereas 221 patients (12.1%) received short-term combination

Table II. Blood pressure (BP)* before and during 36 months of benazepril treatment in study patients (N = 1831).

Month	Received Benazepril as Prescribed, No. (%)	Achieved BP Target, No. (%)	SBP		DBP		PP, Mean (SD), mm Hg
			Achieved SBP Target, No. (%)	Mean (SD), mm Hg	Achieved DBP Target, No. (%)	Mean (SD), mm Hg	
0	—	217 (11.9)	455 (24.8)	149.0 (15.1)	522 (28.5)	93.4 (8.4)	55.6 (13.5)
6	1577 (86.1)	728 (46.2)	873 (55.4)	139.4 (12.9)	997 (63.2)	87.3 (7.4)	52.1 (10.4)
12	1426 (77.9)	797 (55.9)	945 (66.3)	136.6 (11.4)	1025 (71.9)	85.7 (7.7)	50.9 (9.6)
18	1375 (75.1)	753 (54.8)	878 (63.9)	137.2 (11.4)	1002 (72.9)	86.0 (6.9)	51.2 (9.5)
24	1235 (67.4)	812 (65.7)	887 (71.8)	135.4 (10.0)	1011 (81.9)	84.2 (6.8)	51.1 (8.6)
30	1334 (72.9)	898 (67.3)	956 (71.7)	135.0 (10.7)	1113 (83.4)	83.5 (6.9)	51.5 (9.0)
36	1289 (70.4)	921 (71.5)	976 (75.7)	133.8 (9.9)	1126 (87.4)	82.5 (6.5)	51.4 (8.5)

SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure.

*Target SBP/DBP = <140/<90 mm Hg.

therapy with hydrochlorothiazide. The median of the proportion of combination therapy duration to their follow-up duration was 8.0%. A total of 1643 patients (89.7%) were treated with a median benazepril dosage of ≤ 15 mg/d for the entire follow-up period.

Withdrawal and Treatment Noncompliance

During the study, 471 patients (25.7%) discontinued benazepril therapy (**Table III**) (intolerable ADR, 183 patients [38.9%]; refused treatment, 156 patients [33.1%]; and changed medication, 82 patients [17.4%]). The median time to discontinuation was 6 months, with 222 (47.1%) of the withdrawals occurring within the first 6 months and 370 (78.5%) within the first 12 months. The proportions of women (219 patients [46.5%] vs 522 patients [38.4%]; $\chi^2 = 9.561$; $P = 0.002$), those aged ≥ 65 years (140 patients [29.7%] vs 229 patients [16.8%]; $\chi^2 = 36.099$; $P < 0.001$), those who had completed junior high school or less (161 patients [34.2%] vs 234 patients [17.2%]; $\chi^2 = 59.594$; $P < 0.001$), and those who were unemployed (257 patients [54.6%] vs 396 patients [29.1%]; $\chi^2 = 98.734$; $P < 0.001$) were higher in the patients who withdrew by halfway through the study ($n = 471$) than in the persistent patients ($n = 1360$), respectively.

Of the 1831 patients in the study, 429 patients (23.4%) (787 patient-days) had reported intermittently failing to take the study medication as prescribed. The most common reasons for not taking medication as prescribed were forgetfulness (311 patient-days [39.5%]), ADRs (159 patient-days [20.2%]), staying out (ie, being away from home [where the medication was] for a period of time) (140 patient-days [17.8%]), normal BP measurements (102 patient-days [13.0%]), and other illnesses (35 patient-days [4.4%]). A total of 1359 patients (99.9%) were optimally compliant with the treatment regimen.

Efficacy

Rate of Achieving Target Blood Pressure

As indicated in Table II, the proportion of patients taking benazepril as prescribed decreased as the follow-up period progressed, except for a small fluc-

Table III. Reasons for discontinuing benazepril therapy ($n = 471$).

Reason	No. (%) of Patients
Intolerable adverse drug reaction	183 (38.9)
Noncompliance	
Refused treatment	156 (33.1)
Changed medication	82 (17.4)
Discontinued treatment for 2 months	13 (2.8)
Lack of efficacy	19 (4.0)
Inappropriate inclusion in study	11 (2.3)
Acute coronary event or stroke	4 (0.8)
Death unrelated to treatment	3 (0.6)

tuation between 24 and 30 months, with the greatest decline occurring within the first 12 months (from 86.1% at 6 months to 77.9% at 12 months). After 36 months of treatment, 976 (75.7%) of the 1289 patients taking benazepril as prescribed had achieved the target SBP, 1126 (87.4%) achieved the DBP target, and 921 (71.5%) achieved the total BP target. When analyzed by sex and age (**Table IV**), the rates of achieving targets in women were similar to those in men. Patients aged ≥ 65 years had lower rates of achieving the target SBP and total BP and higher rates of achieving the DBP target.

Change in Mean Blood Pressure

After 36 months of treatment, the mean (SD) decreases in SBP, DBP, and PP were 15.1 (0.4) mm Hg, 11.0 (0.3) mm Hg, and 4.2 (0.4) mm Hg, respectively, in those who complied with treatment. As indicated in Table II, mean SBP and DBP decreased over time, except for a small fluctuation between 12 and 18 months, with the greatest decreases occurring within the first 12 months of treatment. As indicated in Table IV, mean SBP and PP increased with age; conversely, mean DBP decreased with age. The mean (SD) PP in patients aged 35 to 49 years remained stable during the 36-month follow-up (0 month, 49.9 [10.4] mm Hg; 36 months, 49.5 [6.8] mm Hg); however, the mean PP decreased in patients aged ≥ 65 years.

Mean Blood Pressure of Patients Withdrawn Prematurely

Not all mean SBP and PP measurements were similar among the 4 groups (patients who discontinued treatment within the first 3 months, 3 to 6 months, or 6 to 9 months, and those who adhered to treatment >9 months) (SBP: $F = 3.338$, $P = 0.019$; PP: $F = 4.547$, $P = 0.004$), but all mean DBP measurements were similar among the 4 groups ($F = 1.448$). The results of pairwise comparisons showed that the mean [SD] SBP in patients discontinuing treatment within the first 3 months (153.3 [17.6] mm Hg) was higher than that of patients adhering to treatment >9 months (148.5 [15.0] mm Hg) ($P = 0.010$). The mean [SD] PP of patients discontinuing treatment within the first 3 months (59.1 [14.1] mm Hg) ($P = 0.018$) and patients discontinuing treatment at 3 to 6 months (58.0 [14.1] mm Hg) ($P = 0.025$) were higher than those adhering to treatment >9 months (55.1 [13.4] mm Hg).

Growth Curve Modeling

A maximum of 23,803 BP records (ie, 13 records/patient) was possible. Because of loss to follow-up, attrition, and the earlier mentioned exclusion criteria, 18,684 records were actually included in the mixed linear model analysis. The fitted individual growth models of SBP, DBP, and PP are shown in **Table V**, and the fitted growth curves by sex and age are shown in the **figure**. Individual patients' BPs decreased over time; the mean acceleration of BP decrease was positive and significant (SBP and DBP, both $P < 0.001$; PP, $P = 0.017$). Thus, on average, patients' BPs declined at a decreasing rate over time. The terms u_{0j} , u_{1j} , u_{2j} , and u_{3j} denoted the estimates for the variances in individual growth param-

Table IV. Blood pressure (BP) before (0 month) and after 36 months of benazepril treatment in study patients (N = 1831), by sex and age.

	Sex		Age Group, y		
	Men (n = 1090)	Women (n = 741)	35–39 (n = 551)	50–64 (n = 911)	≥65 (n = 369)
Achieved target, no. (%) [*]					
SBP					
0 Month	267 (24.5)	188 (25.4)	170 (30.9)	233 (25.6)	52 (14.1)
36 Months	569/789 (72.1)	407/500 (81.4)	341/428 (79.7)	496/651 (76.2)	139/210 (66.2)
DBP					
0 Month	276 (25.3)	246 (33.2)	100 (18.1)	248 (27.2)	174 (47.2)
36 Months	679/789 (86.1)	447/500 (89.4)	359/428 (83.9)	573/651 (88.0)	194/210 (92.4)
Total BP					
0 Month	112 (10.3)	105 (14.2)	52 (9.4)	126 (13.8)	39 (10.6)
36 Months	538/789 (68.2)	383/500 (76.6)	317/428 (74.1)	466/651 (71.6)	138/210 (65.7)
BP, mean (SD) ^{†‡}					
SBP					
0 Month	148.9 (15.0)	149.0 (15.2)	144.9 (13.0)	148.7 (14.8)	155.6 (16.5)
36 Months	134.7 (9.8)	132.5 (9.8)	132.6 (9.0)	133.8 (9.1)	136.4 (13.0)
DBP					
0 Month	94.3 (8.6)	92.1 (7.9)	95.1 (7.8)	93.7 (8.2)	90.1 (8.8)
36 Months	82.7 (6.9)	82.1 (5.9)	83.2 (6.8)	82.6 (5.9)	80.7 (7.3)
PP					
0 Month	54.6 (13.2)	56.9 (13.9)	49.9 (10.4)	55.0 (12.3)	65.4 (15.0)
36 Months	52.0 (8.7)	50.4 (8.2)	49.5 (6.8)	51.2 (7.7)	55.7 (11.9)

SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure.

^{*}Target SBP/DBP = <140/<90 mm Hg.[†]All, $P < 0.001$ between sexes, except SBP at 0 month and DBP at 36 months (both, $P = \text{NS}$).[‡]All, $P < 0.001$ between age groups.

Table V. The fitted individual growth models of systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) in study patients (N = 1831) by linear mixed model technique.¹⁰

$$\begin{aligned}
 \text{SBP}_{ij} &= \pi_{0j} + \pi_{1j}(\text{Time}_l)_{ij} + \pi_{2j}(\text{Time}_q)_{ij} + r_{ij} \\
 \pi_{0j} &= 138.39 + 0.2696(\text{Age} - 55.8) - 1.8148\text{Female} + u_{0j} \\
 \pi_{1j} &= -0.7721 - 0.01629(\text{Age} - 55.8) + u_{1j} \\
 \pi_{2j} &= 0.07076 + u_{2j} \\
 \\
 \text{DBP}_{ij} &= \pi_{0j} + \pi_{1j}(\text{Time}_l)_{ij} + \pi_{2j}(\text{Time}_q)_{ij} + r_{ij} \\
 \pi_{0j} &= 86.2240 - 0.06068(\text{Age} - 55.8) - 1.4713\text{Female} + u_{0j} \\
 \pi_{1j} &= -0.6699 - 0.003986(\text{Age} - 55.8) + 0.08594\text{Female} + u_{1j} \\
 \pi_{2j} &= 0.04107 - 0.00125(\text{Age} - 55.8) + u_{2j} \\
 \\
 \text{PP}_{ij} &= \pi_{0j} + \pi_{1j}(\text{Time}_{l1})_{ij} + \pi_{2j}(\text{Time}_{l1})_{ij}^2 + \pi_{3j}(\text{Time}_{l2})_{ij} + r_{ij} \\
 \pi_{0j} &= 52.5883 + 0.3955(\text{Age} - 55.8) + u_{0j} \\
 \pi_{1j} &= -0.8770 - 0.06175(\text{Age} - 55.8) - 0.9501\text{Female} + u_{1j} \\
 \pi_{2j} &= 0.2544 + 0.02704(\text{Age} - 55.8) + 0.4209\text{Female} \\
 \pi_{3j} &= -0.01542(\text{Age} - 55.8) + u_{3j}
 \end{aligned}$$

i = time point; j = patient no.; π_{0j} = the intercept (expected BP when $\text{Time}_l = 0$); π_{1j} = the slope (the rate of change when $\text{Time}_l = 0$ and the mean rate of growth or mean velocity during the data-collection period); Time_l = linear part of the time variable after orthogonal conversion; π_{2j} = the quadratic coefficient (captured the curvature in each growth trajectory); Time_q = quadratic part of the time variable after orthogonal conversion; r = random error; Time_{l1} = the linear part of the time variable from 0 to 9 months; Time_{l2} = the linear part of the time variable from 9 to 36 months; π_{3j} = the slope from 9 to 36 months; u_{0j} , u_{1j} , u_{2j} , and u_{3j} = the estimates for the variances in individual growth parameters; these estimates reflect the nature of the deviations of the individual growth trajectories from the mean curves.

eters and reflected the nature of the deviations of the individual growth trajectories from the mean curves. These random effects were statistically significant (all, $P < 0.001$), except for u_{2j} in the growth model of PP.

The correlations among the random effects reflected the relationship between individual BP changes and initial BP. Weak negative correlations were found between π_{0j} and π_{1j} ($r = -0.1707$; $P < 0.001$) and between π_{0j} and π_{2j} ($r = -0.1708$; $P < 0.010$) in the SBP fitted model (ie, in patients who had higher initial SBP, SBP decreased at a significantly faster rate). Similar negative and weak correlations were also detected between π_{0j} and π_{2j} ($r = -0.2899$; $P < 0.001$) in the DBP fitted model and between π_{0j} and π_{3j} ($r = -0.3877$; $P < 0.001$) and between π_{1j} and π_{3j} ($r = -0.2654$; $P < 0.020$) in the PP fitted model.

Sex and age related significantly to the parameters of individual BP trajectories. Women had lower SBP and DBP than men (all, $P < 0.001$). No sex-related difference was detected in PP or in the rate of SBP decrease. A lower rate of DBP decrease was seen in women than in men ($P < 0.003$). SBP and the rate of SBP decrease increased with age (both, $P < 0.001$). In contrast to SBP, DBP and the rate of DBP decrease decreased with age ($P < 0.001$, $P < 0.006$). PP and the rate of PP decrease increased with age (both, $P < 0.001$).

(continued)

Figure. The fitted growth curves for systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) before (0 month) and during 36 months of benazepril treatment, by sex (A).

Figure. (continued) The fitted growth curves for systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) before (0 month) and during 36 months of benazepril treatment, by age (B).

Tolerability

A total of 428 patients (23.4%) experienced ≥ 1 benazepril-related ADR, and a total of 501 ADRs were reported. **Table VI** indicates the overall reported incidence of ADRs. The most frequently reported ADRs were cough (364 patients [19.9%]), dizziness (49 patients [2.7%]), throat tickle (35 patients [1.9%]), and headache (10 patients [0.5%]).

Eighty-eight ADRs (64.2%) other than cough initially occurred within the first 4 weeks, and 109 (79.6%) occurred within the first 3 months. However, for

Table VI. Patients who experienced ≥ 1 treatment-related adverse drug reaction* (ADR) during benazepril treatment (N = 1831).

Body System/ADR	No. (%) of Patients
Lung and nasopharynx	
Cough	364 (19.9)
Throat tickle	35 (1.9)
Sore throat	2 (0.1)
Throat burning sensation	1 (0.1)
Neurologic and psychiatric	
Dizziness	49 (2.7)
Headache	10 (0.5)
Drowsiness	3 (0.2)
Insomnia	3 (0.2)
Dry mouth	2 (0.1)
Decreased libido	1 (0.1)
Hunger sensation	1 (0.1)
Taste perversion	1 (0.1)
Gastrointestinal	
Nausea	5 (0.3)
Diarrhea	4 (0.2)
Increased stool frequency	2 (0.1)
Upper abdominal discomfort	1 (0.1)
Cardiovascular	
Bradycardia	1 (0.1)
Lower limb edema	1 (0.1)
Palpitation	1 (0.1)
Skin	
Pruritis	2 (0.1)
Rash	1 (0.1)
Other	
Increased diaphoresis	4 (0.2)
Chest discomfort	3 (0.2)
Asthenia	2 (0.1)
Dribbling urination	1 (0.1)
Hemoptysis	1 (0.1)

*A total of 501 ADRs were experienced by 428 patients (23.4%).

cough, 90 (24.7%) cases initially occurred within the first 4 weeks and 198 cases (54.4%) occurred within the first 3 months. One case of cough (0.3%) developed after 29 months of benazepril therapy. Excluding data for patients withdrawn from the study, 72 cases of ADRs (92.3%) other than cough lasted (continuously or intermittently) <3 months, with the longest lasting <6 months. In contrast, 54 cases of cough (31.9%) lasted >6 months, with the longest lasting 2.5 years.

By sex, 196 (18.0%) men and 168 (22.7%) women experienced benazepril-related cough. Patients experiencing cough ranged in age from 35 to 80 years. By sex, the incidences of cough in the first 3 months of treatment, calculated using the life table method, were 103 women (14.0%) and 95 men (8.8%). The 36-month cumulative incidence was 168 women (23.6%) and 196 men (18.8%). Women reported cough significantly more often than men ($\chi^2 = 7.2522$; $P < 0.007$).

DISCUSSION

Results of RCTs appear to show that each reduction of 10 to 14 mm Hg in SBP and 5 to 6 mm Hg in DBP results in approximately two fifths less incidence of stroke, one sixth less incidence of coronary heart disease, and one third less incidence of major cardiovascular events overall.⁶ Thus, we could predict the long-term benefit for our patients who have persisted with benazepril for 3 years and showed a mean reduction of ~15 mm Hg in SBP and ~10 mm Hg in DBP. Several clinical trials²²⁻²⁴ using monotherapy showed similar decreases in BP. According to the WHO-ISH hypertension guidelines,⁶ when drugs from the main classes of AHT were used as monotherapy at the recommended doses, they produced similar BP reductions.

The change in BP between pretreatment and posttreatment is an important index for assessing the efficacy of AHT. Simply calculating the difference in mean BP between 2 time points does not reflect the course of the BP decrease. If the mean is computed for each time period, followed by a repeated-measures ANOVA, this method would be used to analyze mean BP rather than directly testing questions about how a particular individual's BP changed over time. In addition, the issue of missing data in longitudinal research is frequently encountered. In repeated-measures ANOVA, cases with missing values must be dropped from the analysis, which, in turn, may result in biased parameter estimates and lowering of the power of the study. However, a variety of improvements have been made in the analysis of longitudinal data. One such method, the mixed linear model,¹⁰ can easily accommodate missing data, as long as the amount of missing data is not too great and the missing data occur in a somewhat random fashion. At the same time, we can examine both the mean growth parameters and the amount of individual variation around them.

In our study, we modeled the growth curve of BP. During the 36 months of treatment, benazepril showed prolonged and stable efficacy in lowering BP. The BP of hypertensive patients who had a higher initial BP decreased continuously despite a decreasing rate over time. In hypertensive patients with relatively

lower initial BP, the BP decreased somewhat and then stabilized. Because the relationship between cardiovascular risk and BP is continuous and without a lower threshold, it is necessary to treat hypertension persistently to reach and maintain an appropriate target BP.

In patients with higher initial BP levels, BP tended to decrease at a somewhat faster rate, thereby resulting in a greater reduction. This is consistent with the WHO-ISH hypertension guidelines,⁶ with a decrease amplitude typically of ~4% to 8% for both SBP and DBP after adjusting for the placebo effect. The change rate in BP presented a difference by sex and age, which could be attributed partly to the differences by sex and age in absolute BP. As some cross-sectional and longitudinal studies²⁵⁻²⁷ have shown, we also found that elderly patients generally had higher SBP and lower DBP, resulting in higher PP. Although mean BP reductions were greater in patients with higher initial BPs, the rates of achieving total target were lower in elderly patients. In addition, SBP was more difficult to control than DBP because most of the elderly patients showed increased SBP and decreased DBP.

Both the WHO-ISH⁶ and JNC VI⁷ guidelines recommend that all individuals with uncomplicated hypertension should, at minimum, achieve a target SBP/DBP <140/<90 mm Hg; even lower BP targets have been proposed^{6,7} for patients with proteinuria or diabetes mellitus. It is important to lower both SBP and DBP to the targets to achieve adequate protection from cardiovascular disease. To reach appropriate BP targets, most individuals will likely require combination AHT rather than monotherapy. The Hypertension in African Americans Working Group of the International Society on Hypertension in Blacks²⁸ recommends that patients with an SBP $\geq$ 15 mm Hg above their target or a DBP $\geq$ 10 mm Hg above their target be treated with combination AHT. In other words, when a patient is unable to achieve the appropriate BP targets with low-dose monotherapy, it is generally preferable to add a low dose of a second drug rather than increasing the dose of the first drug. This approach may produce fewer AEs than increasing the dose of a single agent and may yield additional BP reductions of ~8 to 11 mm Hg in SBP and ~4 to 6 mm Hg in DBP compared with the highest recommended dose of monotherapy.²⁸

No serious ADRs (eg, angioedema) were observed. In this study, cough was the most common ADR, which is consistent with the AE profile of ACE inhibitors. This bothersome AE occurred more frequently in women than in men and was an important reason for withdrawal and noncompliance with benazepril therapy.

Discontinuation and noncompliance remain significant obstacles to effective AHT.^{29,30} Discontinuing therapy can lead to inadequate control of hypertension, which in turn increases the risk for stroke, myocardial infarction, and other cardiovascular events. The main factors affecting compliance with AHT include inadequate knowledge of the risks for hypertension and of the favorable consequences of well-controlled BP, the side-effect profile of the drug, the complexity of the treatment regimen, irregular lifestyle, and cost.^{30,31} In this study,

satisfactory persistence and compliance might have resulted from the following 3 factors: (1) benazepril was taken QD in the morning; (2) the CCPACH project included community health education, thereby heightening patients' awareness of the deleterious effects of hypertension; and (3) monthly follow-up enhanced the physician-patient relationship and improved patient compliance. Female, elderly (aged ≥ 65 years), less educated, and unemployed patients were more likely to discontinue treatment halfway through the follow-up period than other patients in the present study.

Conlin et al³² found that the greatest decrease in persistence with the treatment regimen occurred during the first year of therapy, after which a consistent 4% decrease in persistence occurred for every additional 6 months of follow-up. This decrease occurred with all classes of AHT. Benson et al³³ found that the median time to discontinuation was 3 months regardless of drug class. Our findings were consistent with the results of those studies, so we believe that patients usually need time to adapt to the new therapeutic regimen, and that once a patient has become accommodated to the treatment, it is possible to achieve long-term treatment goals.

The logistic difficulties in designing and performing satisfactory postmarketing surveillance studies applied to our study.³⁴ These limitations included a high dropout rate and the lack of both a parallel control group and a washout period. In addition, our study began in 1997, prior to publication of the JNC VI⁷ and WHO-ISH⁶ guidelines. Therefore, some of our information was not current. We defined lowering SBP by ≥ 20 mm Hg and DBP ≥ 10 mm Hg as 1 of the targets, and allowed patients reaching those targets to remain on their existing drug regimen. These were different from the latter recommendation in some guidelines that patients should, at minimum, achieve a target SBP/DBP $<140/90$ mm Hg. This method directly limited the rate of achieving targets in the present study. However, 1 superior aspect of postmarketing surveillance studies over strict premarketing RCTs is not the study design but the more general and representative study participants and the more complex drug-administration environments seen in the former studies.

The 36-month treatment period in the present study was chosen because AHT is a long-term and continuous process. According to a MEDLINE search (key term, benazepril; years searched: 1974–2003), this study was one of the longest-duration postmarketing surveillance studies of benazepril.^{35–41} The large sample size made it possible to include various types of patients and to observe different responses to the same drug. The large sample size and long duration of follow-up made this study particularly useful.

CONCLUSION

In this study of Chinese patients with hypertension, benazepril showed prolonged, stable efficacy in lowering BP and a relatively low incidence of ADRs.

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