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Long-Term Efficacy and Tolerability of a Fixed-Dose Combination of Antihypertensive Agents

An Open-Label Surveillance Study in China

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Abstract

Background: A fixed-dose combination (FDC) of four compounds, hydrochlorothiazide 12.5 mg, triamterene 12.5 mg, dihydralazine 12.5 mg and reserpine 0.1 mg (HTDR), is widely used as an antihypertensive treatment in China. Although HTDR has been used in China for more than 30 years, there have been few comprehensive evaluations of this treatment.

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

Methods: This was a 36-month, community-based, open-label surveillance study, conducted in the Huangpu District (Shanghai, China). The study was based in local primary healthcare settings. Subjects were recruited if they had essential hypertension, were aged ≥35 years at the time of enrolment, were expected to remain in the area for 3 years, and were able to provide informed consent. Patients who had secondary hypertension, myocardial infarction or stroke within 6 months of screening, impaired renal or hepatic function, history of cardiomyopathy or chronic heart failure, or were pregnant or lactating were excluded. HTDR was administered as one or two tablets per day in the morning. If necessary, additional hydrochlorothiazide was added. Blood pressure (BP) was measured at baseline and throughout the 36-month surveillance period every 3 months. Biochemical indicators (e.g. fasting blood glucose, plasma lipid parameters, plasma sodium and potassium, plasma uric acid and serum creatinine) were also measured, and adverse events were noted. BP reductions and the rate at which patients achieved BP targets (systolic BP [SBP] <140 mmHg and diastolic BP [DBP] <90 mmHg) throughout the period were determined. Subgroup analyses by sex and age were also conducted.

Results: A total of 1529 patients (550 male, 979 female; mean age 65.7 years) entered the study. After the 36-month treatment period, 93.1% of patients had achieved the SBP target, 97.9% had achieved the DBP target, and 92.1% had achieved both. The mean decreases in SBP and DBP were 15.3 mmHg and 9.9 mmHg, respectively. Overall, 127 adverse events in 119 patients (7.8%) occurred during the follow-up period, most of which were mild to moderate. Plasma lipid profiles were improved after 24 months of treatment. In addition, a significant increase in plasma potassium and a significant reduction in plasma uric acid were seen.

Conclusion: HTDR was found to have good long-term efficacy and tolerability in Chinese patients with essential hypertension.

Introduction

Evidence from several clinical studies suggests that the majority of hypertensive patients require more than one antihypertensive medication to reach an acceptable blood pressure (BP) goal[1-4] and most treatment guidelines for hypertension now advocate the use of a combination of two or more drugs in fixed doses to achieve better BP control.[5,6] The advantages of fixed-dose combinations (FDCs) include greater BP-lowering effects, lower doses of component drugs, a lower incidence of clinical and metabolic adverse effects, a longer duration of action, decreased costs and improved patient compliance.[7-9] Many effective and well tolerated FDCs are now available, and their use is increasingly favoured by primary-care physicians and hypertensive patients.

In China the most widely used FDC for hypertension is a compound with four components: hydrochlorothiazide 12.5 mg, triamterene 12.5 mg, dihydralazine 12.5 mg and reserpine 0.1 mg (HTDR). This compound is known in China as 'Compound Hypotensive Tablets No. 0' but is here referred to by its acronym, HTDR. The Ministry of Health of China ratified clinical application of this compound in 1977. Compared with other commonly used double or triple FDCs, each component of this FDC has a relatively low dose and therefore less potential for adverse affects.[10] Currently, HTDR is the most widely used quadruple FDC for hypertension in China with more than 15 million Chinese hypertensive patients (>10% of market share) taking this compound.[11-13] However, although HTDR has been used for more than 30 years, its long-term effectiveness and tolerability have not been systematically studied. The widespread use of this combination without evidence of its effects has now become a public health concern. Thus, the aim of this surveillance study was to evaluate the long-term efficacy and tolerability of HTDR in Chinese patients with essential hypertension.

Methods

Study Design

This community-based, open-label surveillance study was conducted in the Huangpu District in Shanghai, China over a period of 36 months. It was designed and organized by the School of Public Health, Peking University, as one of the key tasks of the Community-Based Prevention and Control of Cardiocerebrovascular Disease (CPCC) Project of the China National Tenth Five-Year-Plan Funding Program (2002–7). The protocol was approved by the ethics review boards of the Peking University Health Science Center and all participating subjects gave written informed consent.

Study Population

Subjects were recruited from local primary healthcare clinics in the Huangpu District. Subjects were patients with essential hypertension, aged ≥35 years at the time of enrolment, expected to remain in the area for 3 years, and able to

provide informed consent. Initial baseline BP was measured in the morning three times using standardized sphygmomanometers and the mean values calculated. Hypertension was defined as mean diastolic BP (DBP) ≥90 mmHg or mean systolic BP (SBP) ≥140 mmHg, or current use of antihypertensive medication. Exclusion criteria included: secondary hypertension; myocardial infarction or stroke within 6 months of screening; impaired renal or hepatic function; history of cardiomyopathy or chronic heart failure; or being pregnant or lactating.

Treatment

HTDR was administered to all participants with the objective of achieving control of BP (<140/90 mmHg). The initial daily dosage was one HTDR tablet. Another tablet was added if the target BP level had not been reached within 2 months. For those who still did not reach the BP target level at two tablets a day, additional hydrochlorothiazide was commenced. If BP was still not controlled with hydrochlorothiazide after 2 months, patients could be started on other therapeutic regimens, at which point they were excluded from the study. During the 36-month follow-up period, all patients were expected to discontinue all antihypertensive medications except HTDR and hydrochlorothiazide.

All patients were also counselled regarding non-pharmacological methods of BP control, including limiting salt intake, increasing fresh fruit and vegetable intake, weight loss (where appropriate), and the importance of aerobic exercise.

Follow-Up and Data Collection

The study was conducted in the local primary healthcare setting in the communities. The general physicians who participated in this study were well trained and qualified and had considerable research experience.

Routine follow-up visits were scheduled once a month during the first 6 months, then every 3 months thereafter, with additional visits if necessary. At each visit, BP and heart rate were measured for all patients in the same way as at baseline, as described in the Study Population section. Patients were advised to take their regular non-hypertensive medications as usual.

Investigators recorded the severity, time of occurrence, duration and prognosis of adverse events (AEs). AEs were defined as any untoward medical occurrences in a participant that may, or may not, have been caused by HTDR treatment. AEs were classified as mild, moderate or severe in accordance with US FDA practice. Mild AEs were those of a minor irritant type requiring no medication or medical evaluation. Moderate AEs were those interfering with daily activities, but which usually improved with simple therapeutic measures. Severe AEs were events that interrupted the participant's normal daily activities and generally required systemic treatment, or may have resulted in death, hospitalization or significant disability.

Fasting blood samples were collected at study entry and 24 months thereafter to determine concentrations of plasma sodium and potassium, serum creatinine, plasma uric acid, fasting blood glucose and plasma lipid profiles.

Statistical Analysis

Baseline demographic characteristics are shown as means (and standard deviations) for continuous variables and as numbers (and percentages) for categorical measures. BP parameters after 36 months were calculated for all patients and for different sex and age subgroups (≤60 years, 61–70 years, >70 years). Results in patients who withdrew prematurely were also calculated.

All of the analyses were carried out using Statistical Analysis System software, version 8.2 (SAS Institute, Cary, NC, USA). Only either t- or chi-squared (χ^2) tests are reported. All p-values are two sided. p-Values less than 0.05 were considered statistically significant.

Results

Baseline Characteristics

In total 1529 subjects met the inclusion criteria and agreed to take part in the study. Baseline characteristics of the 1529 patients are shown in table I by sex. There were significant differences between men and women in all variables (i.e. age,

Table I. Patients' characteristics at study entry

Characteristic	Males (n = 550)	Females (n = 979)
Demographic [mean ± SD]		
Age (y)[a]	67.8 ± 9.4	64.5 ± 9.6
Clinical [mean ± SD]		
Body weight (kg)[a]	66.9 ± 10.0	63.6 ± 10.2
Height (cm)[a]	166.0 ± 8.1	161.4 ± 7.4
BMI (kg/m^2)	24.2 ± 3.0	24.4 ± 3.5
Heart rate (beats/min)	74.0 ± 5.7	73.6 ± 5.6
SBP (mmHg)[a]	147.8 ± 9.6	145.3 ± 9.5
DBP (mmHg)[a]	88.8 ± 7.7	87.8 ± 7.5
Medical history [n (%)]		
Stroke[a]	29 (5.3)	26 (2.7)
Coronary heart disease[a]	52 (9.5)	49 (5.0)

a $p < 0.05$ between sexes.

BMI = body mass index; **DBP** = diastolic blood pressure; **SBP** = systolic blood pressure.

body weight, height, blood pressure and history of stroke and coronary heart disease) except body mass index and heart rate. Of all the participants, 96.5% were initially taking antihypertensive therapy, but only 21.3% of these patients had their BP under control. Of those who were taking therapy at baseline, 85.3% (n = 1257) were taking antihypertensive monotherapy or an FDC alone, while the remainder were taking two or more separately prescribed antihypertensive agents. The most commonly used agents were FDCs (n = 627; 33.8%), calcium channel antagonists (n = 368; 19.9%), ACE inhibitors (n = 259; 14.0%), diuretics (n = 227; 12.2%) and β-adrenergic antagonists (n = 79; 4.3%).

Treatment and Withdrawal

During the 36-month follow-up, 1421 patients (92.9%) took HTDR exclusively. The other 108 patients (7.1%) took HTDR in combination with additional hydrochlorothiazide, with about 50% of these patients taking the additional treatment for one-third of the follow-up period. In those who took HTDR alone, the majority (1410; 99.3%) took only one tablet a day.

During the study, 376 patients (24.6%) discontinued therapy. The reasons for discontinuation are described in table II. The median time to discontinuation was 7 months, with 172 (45.7%) of the withdrawals occurring within the first 6 months and 281 (74.7%) within the first 12 months. A comparison of the baseline characteristics of patients who withdrew prematurely and patients who remained in the study showed that the sex distribution was similar, i.e. 145 males (38.6%) versus 405 males (35.1%; p = 0.224), respectively. Patients who withdrew were older than patients who remained in the study (mean ± SD age 66.9 ± 10.1 years vs 65.3 ± 9.5 years; p = 0.007) and baseline BP levels were similar between these two groups (mean ± SD SBP 146.8 ± 9.5 vs 146.0 ± 9.6 mmHg, p = 0.146, respectively; mean ± SD DBP 88.5 ± 7.5 vs 88.0 ± 7.6 mmHg, p = 0.361, respectively).

Efficacy

Rate of Achieving Target Blood Pressure (BP)

As indicated in table III, after 36 months of treatment, 1051 (93.1%) of the 1129 patients who remained in the study had achieved only target SBP, 1105 (97.9%) had achieved only target DBP, and 1040 (92.1%) had achieved both targets. When analysed by sex and age (table IV), achievement of target BPs was similar, except for DBP differences by age (96.4% for patients aged ≤60 years, 97.5% for patients aged 61–70 years, and 99.7% for patients aged >70 years; p = 0.008).

Change in Mean BP

After 36 months of treatment, the mean ± SD decrease in SBP in patients who remained in the study was 15.3 ± 11.1 mmHg and the mean ± SD decrease in DBP was 9.9 ± 8.5 mmHg. Subgroup

Table II. Reasons for discontinuing therapy (n = 376)

Reason	No. (%)
Met the exclusion criteria	
moved away from the community	156 (41.5)
hepatic, renal or cardiovascular hospitalization	17 (4.5)
Non-compliance	
changed medication	86 (22.9)
refused treatment	42 (11.2)
Adverse events	53 (14.1)
Acute coronary event or stroke	12 (3.2)
Lack of efficacy	10 (2.7)

Table III. Changes in blood pressure (BP) during treatment

Time (mo)	Patients who remained in the study [no. (%)]	Patients who achieved SBP and DBP targets [no. (%)]	Patients who achieved SBP target only [no. (%)]	SBP [mm Hg (mean ± SD)]	Patients who achieved DBP target only [no. (%)]	DBP [mm Hg (mean ± SD)]
Baseline	1529 (100.0)	314 (20.5)	335 (21.9)	146.2 ± 9.6	916 (59.9)	88.2 ± 7.6
6	1481 (96.9)	892 (60.2)	926 (62.5)	137.4 ± 9.7	1244 (84.0)	83.4 ± 6.3
12	1309 (85.6)	1021 (78.0)	1039 (79.4)	132.9 ± 8.5	1213 (92.7)	80.4 ± 6.1
18	1242 (81.2)	986 (79.4)	1002 (80.7)	133.4 ± 7.7	1143 (92.0)	80.1 ± 6.0
24	1213 (79.3)	1036 (85.4)	1054 (86.9)	131.5 ± 7.9	1156 (95.3)	78.9 ± 6.3
30	1154 (75.5)	942 (81.6)	962 (83.4)	133.2 ± 7.1	1083 (93.8)	80.1 ± 5.7
36	1129 (73.8)	1040 (92.1)	1051 (93.1)	130.9 ± 6.9	1105 (97.9)	78.2 ± 5.8

DBP = diastolic BP; **SBP** = systolic BP.

analysis showed that the mean DBP reduction in men was higher than in women ($p = 0.009$). As indicated in table III, mean SBP and DBP tended to decrease over time with the greatest decrease occurring within the first 12 months of treatment. As shown in table IV, at 36 months, mean DBP had decreased with age and SBP was lower in women than in men.

BP of Patients Who Discontinued Treatment

Table V shows the final BP levels for patients who discontinued treatment (n = 376). 318 (84.6%) of these patients achieved target BP reductions in both SBP and DBP, while 324 (86.2%) achieved only target SBP, and 348 (92.6%) achieved only target DBP. From baseline to withdrawal, the mean ± SD change in SBP was 13.6 ± 11.7 mmHg and the mean ± SD change in DBP was 8.5 ± 9.2 mmHg. Patients who withdrew from the study were divided into four groups, i.e. patients who discontinued treatment: within the first 3 months, from 3–6 months, from 6–9 months, and after 9 months. Baseline SBP and DBP measurements were similar among the four groups, but the final SBP and DBP measurements differed (SBP: $F = 2.950$, $p = 0.033$; DBP: $F = 7.290$, $p < 0.001$), as did the proportion of patients who achieved target BP (SBP: $\chi^2 = 12.045$, $p = 0.007$; DBP: $\chi^2 = 13.709$, $p = 0.003$; total BP: $\chi^2 = 14.410$, $p = 0.002$).

Adverse Events

Overall, 127 AEs in 119 participants (7.8%) were reported. Of the 127 adverse events, 38 (29.9%) were mild, 66 (52.0%) were moderate and 23 (18.1%) were severe. Seventy-three percent of the AEs occurred within 6 months. The most common AEs were dizziness (26.0%), death (18.1%), abdominal discomfort (11.8%), palpitation (11.8%), sleepiness (9.4%), chest distress (4.7%), headache (4.7%), fatigue (3.9%) and nausea (3.1%). The 23 severe AEs occurring in the study were all deaths unrelated to treatment. Fifty-three patients discontinued from the study because of AEs, including death (n = 23), dizziness (n = 9), abdominal discomfort (n = 8), fatigue (n = 4), palpitations (n = 2), arthralgia (n = 2), depression status (n = 2), diarrhoea (n = 1), chest distress (n = 1) and bradycardia (n = 1). The symptoms of AEs in the other 66 patients who continued in the study were successfully mitigated with treatment where necessary.

Biochemical Analyses

Changes in biochemical parameters over 24 months' treatment are shown in table VI. Total cholesterol, low-density lipoprotein cholesterol, alanine aminotransferase, uric acid and creatinine all decreased, while the remaining parameters, i.e. high-density lipoprotein cholesterol, triglycerides, glucose, sodium and potassium, increased. Some of the differences were statistically significant, although clinically unimportant.

Discussion

We have presented the results of a follow-up investigation of 1529 patients treated for hypertension with HTDR, a compound that consists of hydrochlorothiazide, triamterene, dihydralazine

Table IV. Changes in blood pressure (BP) before and after 36 months' treatment in study patients, by sex and age

Variable	Sex		Age group (y)		
	male (n = 550)	female (n = 979)	≤60 (n = 439)	61–70 (n = 561)	>70 (n = 529)
Patients who achieved BP target [no. (%)]					
SBP only					
baseline	105 (19.1)	230 (23.5)	101 (23.0)	114 (20.3)	120 (22.7)
36 mo	361/395 (91.4)	690/734 (94.0)	307/333 (92.2)	403/435 (92.6)	341/361 (94.5)
DBP only					
baseline	313 (56.9)	603 (61.6)	235 (53.5)	336 (59.9)	345 (65.2)
36 mo[a]	388/395 (98.2)	717/734 (97.7)	321/333 (96.4)	424/435 (97.5)	360/361 (99.7)
SBP and DBP					
baseline	96 (17.5)	218 (22.3)	91 (20.7)	107 (19.1)	116 (21.9)
36 mo	359/395 (90.9)	681/734 (92.8)	301/333 (90.4)	398/435 (91.5)	341/361 (94.5)
BP [mmHg, mean ± SD]					
SBP					
baseline[b]	147.8 ± 9.6	145.3 ± 9.5	145.5 ± 8.9	146.4 ± 9.5	146.5 ± 10.2
36 mo[b]	131.9 ± 7.2	130.4 ± 6.7	130.8 ± 6.6	131.3 ± 6.9	130.6 ± 7.3
difference	16.0 ± 10.9	14.9 ± 11.2	14.5 ± 10.0	15.4 ± 10.9	15.8 ± 12.2
DBP					
baseline[a,b]	88.8 ± 7.7	87.8 ± 7.5	89.3 ± 7.5	88.3 ± 7.2	87.1 ± 7.9
36 mo[a]	78.4 ± 6.1	78.2 ± 5.6	79.2 ± 5.3	78.1 ± 5.6	77.5 ± 6.3
difference[b]	10.8 ± 8.7	9.4 ± 8.3	10.0 ± 8.3	10.2 ± 8.2	9.5 ± 8.9

a $p < 0.05$ among age groups.

b $p < 0.05$ between sexes.

DBP = diastolic BP; **SBP** = systolic BP.

and reserpine. The results have shown that, after treatment for 36 months, mean SBP decreased by 15.3 mmHg, mean DBP decreased by 9.9 mmHg, and the proportion of patients whose BP was under control was 92.1%.

The observed mean BP reductions in the study were substantial. The 15.3/9.9 mmHg SBP/DBP reductions are consistent with results for thiazide combinations reported in a meta-analysis.[14] The reductions occurred in all age groups and both sexes. Previous studies have shown that a prolonged 10–14 mmHg lower level of usual SBP or 5–6 mmHg lower level of DBP is associated with about a 40% lower risk of stroke, a 17% lower risk of coronary heart disease, and a 33% lower risk of all cardiovascular events.[15] The SBP and DBP levels of the study patients steadily decreased over time, with the greatest decline occurring within the first 12 months. After 36 months' treatment, older patients had lower SBP and DBP levels and higher BP control rates, but the differences among age groups showed no statistical significance.

A total of 127 AEs occurred in 119 participants (7.8%). Reported adverse events that exceeded 3% incidence were dizziness, death, abdominal discomfort, palpitation, sleepiness, chest distress, headache, fatigue and nausea. All adverse events other than 23 deaths were of mild to moderate severity. None of the deaths could be attributed to the HTDR treatment. Hypokalaemia and hyperuricaemia are the most specific adverse events of hydrochlorothiazide,[16,17] but the biochemical analyses showed an apparent increase in plasma potassium and an apparent reduction in plasma uric acid, although these changes were not clinically significant. Previous studies have shown that hydrochlorothiazide in high doses (25 mg/day) may cause unfavourable changes in carbohydrate metabolism and in the plasma lipid profile.[18-20] These changes may limit the response to antihypertensive therapy.[21] However, in our study,

Table V. Changes in blood pressure (BP) in subjects who discontinued treatment

Variable	Time of discontinuation (mo)				Total
	≤3 (n = 64)	3–6 (n = 115)	6–9 (n = 73)	>9 (n = 124)	(n = 376)
Patients who achieved BP target [no. (%)]					
SBP only[a]	47 (73.4)	101 (87.8)	68 (93.2)	108 (87.1)	324 (86.2)
DBP only[a]	54 (84.4)	103 (89.6)	72 (98.6)	119 (96.0)	348 (92.6)
SBP and DBP[a]	45 (70.3)	98 (85.2)	68 (93.2)	107 (86.3)	318 (84.6)
BP [mmHg, mean ± SD]					
SBP					
baseline	147.7 ± 8.6	145.3 ± 10.0	147.3 ± 9.3	147.5 ± 9.6	146.8 ± 9.5
last[a]	136.2 ± 13.0	133.3 ± 9.0	131.8 ± 6.3	132.4 ± 7.9	133.2 ± 9.2
difference[a]	11.1 ± 13.1	12.0 ± 10.6	15.4 ± 11.2	15.3 ± 12.0	13.6 ± 11.7
DBP					
baseline	89.4 ± 7.7	88.8 ± 6.7	88.3 ± 7.6	87.8 ± 8.1	88.5 ± 7.5
last[a]	82.6 ± 7.7	81.0 ± 6.0	78.6 ± 5.1	78.8 ± 5.6	80.1 ± 6.2
difference	6.9 ± 10.5	7.9 ± 9.0	9.6 ± 8.0	9.3 ± 9.1	8.5 ± 9.2

a $p < 0.05$ among the four groups.

DBP = diastolic BP; **SBP** = systolic BP.

biochemical analyses showed that plasma lipid profiles improved slightly, and fasting glucose did not change. Use of a combination of drugs in low doses may partially explain the different results observed in our study.[22] In addition, because we did not restrict the use of cardiovascular drugs (such as statins) other than other antihypertensive agents, the true effect of HTDR may have been confounded.

Although there has been some concern that reserpine, one of the compounds included in HTDR, may cause depression,[23] only two cases of depression were observed in our study. However, we did not use a mood scale (such as the Center for Epidemiologic Studies Depression Scale) to actively observe depression; it was reported only as an adverse event by the physicians and mild depression status may have gone unnoticed.

There are some potential limitations to this study. Firstly, as participants in the study were recruited from only one community and were not randomly selected, the generalizability of our findings may be limited. Secondly, the study had a relatively high dropout rate of 24.6%. Withdrawers were

Table VI. Changes in biochemical parameters before and after 24 months' treatment (n = 1165)

Parameter	Before treatment[a]	After treatment[a]	Intraindividual difference (mean)	95% CI
Total cholesterol (mmol/L)	5.26 ± 0.92	5.14 ± 0.91	−0.13[b]	−0.19, −0.07
LDL-cholesterol (mmol/L)	3.53 ± 0.76	2.85 ± 0.78	−0.68[b]	−0.73, −0.63
HDL-cholesterol (mmol/L)	1.36 ± 0.29	1.48 ± 0.45	0.12[b]	0.09, 0.15
Triglycerides (mmol/L)	1.72 ± 0.89	1.84 ± 0.82	0.12[b]	0.07, 0.18
Fasting glucose (mmol/L)	5.54 ± 1.43	5.56 ± 1.22	0.02	−0.05, 0.10
ALT (mmol/L)	20.77 ± 8.43	19.89 ± 13.43	−0.87[b]	−1.73, 0.01
Uric acid (mmol/L)	0.34 ± 0.09	0.31 ± 0.09	−0.03[b]	−0.03, −0.02
Creatinine (μmol/L)	79.51 ± 27.13	77.95 ± 16.31	−1.57	−3.31, 0.18
Sodium (mmol/L)	140.08 ± 2.96	140.94 ± 2.95	0.86[b]	0.63, 1.10
Potassium (mmol/L)	3.85 ± 1.09	4.09 ± 0.36	0.24[b]	0.18, 0.30

a Data are mean ± SD.

b $p < 0.05$ for after vs before treatment.

ALT = alanine aminotransferase; **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein.

older than patients who remained in the study, which may have biased the results. Thirdly, as all patients in this study were also advised about non-pharmaceutical interventions, the pure effect of HTDR may have been confounded. Fourthly, there was no initial washout period for the study, although this is not a major concern given the long follow-up period of this study. Finally, this was an observational surveillance study and did not include a parallel control group.

Conclusion

Although this study had limitations, it is the first study with a sufficiently large sample to evaluate a widely used Chinese antihypertensive compound. As it is a surveillance study, the study provides a profile of the typical antihypertensive effects of HTDR. The major conclusion of this study is that HTDR is well tolerated and offers prolonged, stable efficacy in lowering BP.

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