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ORIGINAL RESEARCH ARTICLE

Efficacy and Safety of a Fixed Combination of Irbesartan/Hydrochlorothiazide in Chinese Patients with Moderate to Severe Hypertension

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Abstract

Background and Objectives In a multi-center, single-arm, prospective study, we investigated the efficacy and safety of the fixed irbesartan/hydrochlorothiazide combination in Chinese patients with moderate to severe hypertension.

Methods Eligible patients were aged 18–75 years, with a blood pressure of 160–199 mmHg systolic or 100–119 mmHg diastolic during a 1-week wash-out phase off antihypertensive medication. The enrolled patients started antihypertensive treatment with irbesartan/hydrochlorothiazide 150 mg/12.5 mg once daily, with the possible addition of irbesartan 150 mg once daily and up-titration to irbesartan/hydrochlorothiazide 300 mg/25 mg once daily at 4 and 8 weeks of follow-up, respectively. The primary efficacy variable was the goal blood pressure-attaining rate at 12 weeks of follow-up (<140/90 mmHg, or <130/80 mmHg in patients with diabetes mellitus).

Results In the intention-to-treat analysis ($n = 501$) at 12 weeks of follow-up, the goal blood pressure-attaining rate was 57.3 %, and the mean change in blood pressure from baseline was 27.8 mmHg [95 % confidence interval (CI) 26.4–29.1 mmHg; $p < 0.001$] systolic and 13.5 mmHg (95 % CI 12.6–14.4 mmHg; $p < 0.001$) diastolic. Similar findings were observed in the per-protocol analysis ($n = 449$). The prevalence of microalbuminuria and left ventricular hypertrophy significantly ($p \leq 0.01$) decreased from 33.4 % (150/449) and 50.4 % (215/427) at baseline to 23.4 % (105/447) and 41.3 % (176/427) at the end of follow-up, respectively. Four patients (2.0 %) reported a serious adverse event.

Conclusion The fixed irbesartan/hydrochlorothiazide combination may control blood pressure to the target level in about 60 % of Chinese patients with moderate to severe hypertension, with an acceptable safety profile.

Clinical trial registration number (ClinicalTrials.gov): NCT00670566.

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1 Introduction

While the number of hypertensive patients is increasing in most countries because of longevity and unhealthy lifestyles, the control rate of hypertension remains low in many countries, such as China. According to the 2002 China National Nutrition and Health Survey, the prevalence of hypertension was 18.8 % among persons aged over 18 years, whereas the control rate of hypertension was only 6.2 % [1]. One of the major reasons for the low control rate is that the currently recommended antihypertensive drugs usually target one pathogenic pathway of hypertension and are sufficiently efficacious only in a fraction of hypertensive patients, even at high dosages [2, 3]. Combining two or more classes of antihypertensive drugs with complementary mechanisms might increase the blood pressure-lowering efficacy in specific patients and increase the number of patients who would have a significant response to antihypertensive therapy [2, 3]. Because a

fixed-dose combination in a single pill is probably an efficient approach to combination therapy, several single-pill combination drugs have been recently developed and are increasingly used in the management of hypertension in many countries, including China.

The combined use of an angiotensin receptor blocker and a thiazide diuretic is considered a preferred combination by most of the current guidelines [3–5]. This class of fixed-combination drugs has been extensively studied in Europe [6, 7] and North America [8–11]. However, there is still very limited clinical trial data in the Chinese population. The fixed irbesartan/hydrochlorothiazide combination became available in the Chinese market in 2004 [12, 13] and is currently the most commonly prescribed agent in its class in China. In this multi-center, single-arm, prospective study, we investigated the efficacy and safety of the fixed irbesartan/hydrochlorothiazide combination in Chinese patients with moderate to severe hypertension.

2 Methods

2.1 Study Design

The present study was designed as a multi-center, open-label, single-arm, prospective trial and was conducted from April 2008 to February 2009 in 18 hospitals across China. The study protocol was approved by the ethics committee of Ruijin Hospital, Shanghai Jiaotong University School of Medicine (Shanghai, China) and, as necessary, also by the ethics committees of the participating hospitals. All patients gave written informed consent.

The study consisted of a 1-week wash-out phase and a subsequent 12-week study treatment period. The 1-week wash-out phase included one screening visit at the beginning and one visit at the end for determination of eligibility. The 12-week study treatment period included four visits at 2, 4, 8, and 12 weeks of follow-up. At each of these clinic visits, blood pressure—as the major determining factor for inclusion in the study and the major efficacy variable of the study—was measured three times consecutively after at least 5 min of rest in the sitting position in the morning between 08:00 and 10:00 h, using a validated automated blood pressure monitor (HEM 7071; Omron Healthcare, Kyoto, Japan). These three blood pressure readings 30 to 60 s apart were averaged for clinical decisions and for the present analysis. When the arm circumference was larger than 32 cm, a larger cuff was used.

If, at the screening visit, previously untreated patients had a blood pressure of 160–199 mmHg systolic or 100–119 mmHg diastolic, and if patients previously treated with antihypertensive monotherapy had a blood pressure of 140–179 mmHg systolic or 90–109 mmHg diastolic and had discontinued their previous antihypertensive monotherapy, they could enter the wash-out phase for determination of eligibility. After the wash-out run-in phase, eligible patients entered the 12-week study treatment period and started taking irbesartan/hydrochlorothiazide 150 mg/12.5 mg once daily. A tablet of irbesartan 150 mg and an additional tablet of irbesartan/hydrochlorothiazide 150 mg/12.5 mg could be added at 4 and 8 weeks of follow-up, respectively, for systolic/diastolic blood pressure to reach the target level of <140/90 mmHg, or <130/80 mmHg in patients with diabetes mellitus. The study medication could also be stopped in the presence of symptomatic hypotension or any other serious adverse events related to the study medication. The purpose of the clinic visit at 2 weeks of follow-up was to assure the safety of and patient compliance with antihypertensive therapy. It was decided that the study medication should not change at 2 weeks of follow-up, unless such a change was necessary. Patients were instructed to take the study medication between 08:00 and 10:00 h every morning except on the day of the clinic visit, when the medication was administered after blood pressure had been measured. Other antihypertensive agents or drugs with a potential blood pressure-lowering or blood pressure-increasing action were not to be used during the 12-week study treatment period. The study medication was supplied free of charge for the whole study period by Sanofi China (Shanghai, China).

2.2 Study Population

Eligible patients were men and women aged 18–75 years, with a blood pressure of 160–199 mmHg systolic or 100–119 mmHg diastolic at the clinic visit at the end of the 1-week wash-out phase. The exclusion criteria for the study were as follows: blood pressure ≥200 mmHg systolic or ≥120 mmHg diastolic; secondary hypertension; women who were pregnant, lactating, or of childbearing potential without proper contraception; cardiac diseases including cardiomyopathy, valvular heart disease, heart failure, or documented left ventricular ejection fraction reduction (<45 %); severe arrhythmias such as ventricular or supraventricular arrhythmia, pre-excitation syndrome, second-degree or third-degree atrioventricular block and sick sinus syndrome; and other significant, uncontrolled, or life-threatening conditions or diseases. We also excluded patients with a serum concentration of alanine or aspartate transaminase ≥2 times the upper normal limits; a serum creatinine concentration ≥176.8 μmol/l; creatinine clearance or an estimated glomerular filtration rate <30 ml/min per 1.73 m^2; albuminuria ≥2+ on a dipstick test; gout or serum uric acid ≥406 μmol/l in men or ≥348 μmol/l in women; a serum potassium concentration <3.5 mmol/l or ≥5.5 mmol/l; or uncontrolled diabetes mellitus, as

diagnosed by a plasma fasting glucose concentration >11.0 mmol/l or a plasma glycosylated hemoglobin concentration >8.5 %; and patients who were taking antidepressant medication or were allergic to the study medication.

The following diseases or conditions did not lead to exclusion: a history of stroke (excluding transient ischemic attack) at least 6 months prior to inclusion; the presence of coronary heart disease (a documented coronary atherosclerosis or stenosis); evidence of arrhythmia (on an electrocardiogram); dyslipidemia (a serum total cholesterol concentration ≥6.22 mmol/l, low-density lipoprotein cholesterol ≥4.14 mmol/l, or triglycerides ≥2.26 mmol/l, or use of statins); controlled diabetes mellitus (a fasting plasma glucose concentration from 7.1 to 11.0 mmol/l or on oral antidiabetic drugs or insulin); and chronic kidney disease (albuminuria or a serum creatinine concentration from 132.6 to 176.8 μmol/l in men and 123.8 to 176.8 μmol/l in women).

2.3 Efficacy and Safety Evaluations

The primary efficacy variable was the goal blood pressure-attaining rate at the end of the 12-week study. The goal blood pressure was defined as a systolic/diastolic blood pressure of <140/90 or <130/80 mmHg in the absence or presence of diabetes mellitus, respectively.

Secondary efficacy variables included changes from baseline in systolic and diastolic blood pressure at 4, 8, and 12 weeks of follow-up, and in the echocardiographically measured left ventricular mass and urinary albumin excretion as measured on a first morning void urine sample at 12 weeks of follow-up. We defined left ventricular hypertrophy as a left ventricular mass index of at least 112 g/m^2 in men and 105 g/m^2 in women, and microalbuminuria as a urinary albumin-to-creatinine ratio of at least 2.5 mg/mmol in men and 3.5 mg/mmol in women.

All adverse events were documented for information on symptoms, severity, relation to the study medication, intervention, and outcome. Routine biochemical tests of blood and urine were performed for clinical laboratory safety evaluations. Any clinically significant changes in physical examinations or laboratory findings were recorded as adverse events.

2.4 Statistical Analysis

We performed intention-to-treat and per-protocol analyses in all patients who entered the study treatment period and in the patients who completed the 12-week study on study drugs, respectively. The safety analysis was performed in all patients who had ever started the study treatment. Continuous and categorical variables were analyzed using the Student's t test and χ^2 test, respectively. Normality of distributions was evaluated by the Shapiro–Wilk statistic. Analysis of changes from baseline in blood pressure and other continuous efficacy or safety variables was performed by the paired t test if they were normally distributed and by the Wilcoxon signed rank test if they were not normally distributed. We performed multiple logistic regression to study factors associated with the use of high-dose antihypertensive medication. We performed subgroup analyses according to sex (men vs. women), age (≥55 years vs. <55 years), body mass index (≥25 kg/m^2 vs. <25 kg/m^2), and the presence and absence of isolated systolic hypertension (systolic blood pressure ≥160 mmHg and diastolic blood pressure <90 mmHg), diabetes mellitus, and chronic kidney disease.

3 Results

3.1 Patient Characteristics

Of the 632 screened patients, 501 were enrolled in the study and started treatment with irbesartan/hydrochlorothiazide 150 mg/12.5 mg once daily. During the 12-week study treatment period, 52 patients (10.4 %) were withdrawn because they withdrew their consent ($n = 18$, 3.6 %), did not follow the study protocol ($n = 5$, 1.0 %), because of adverse events ($n = 13$, 2.5 %), or other reasons ($n = 16$, 3.2 %). In total, 449 patients completed the 12-week study follow-up.

Table 1 shows the baseline characteristics of the 501 patients by sex [264 (52.7 %) were women]. Compared with the women, the men were slightly younger (−1.8 years; $p = 0.03$), had lower systolic blood pressure (−1.9 mmHg; $p = 0.05$), had higher diastolic blood pressure (+3.0 mmHg; $p < 0.0001$) and hence narrower pulse pressure (−4.9 mmHg; $p < 0.0001$), and included more users of antihypertensive drugs ($p = 0.02$) and antidiabetic drugs ($p = 0.03$). However, the men and women were similar in most baseline characteristics such as the body mass index; pulse rate; presence of diabetes mellitus, dyslipidemia, or chronic kidney disease; previous history of stroke; and previous use of specific classes of antihypertensive drugs ($p > 0.05$).

In the intention-to-treat analysis ($n = 501$), during the study treatment period, the dosage of the study medication remained at 150 mg/12.5 mg of irbesartan/hydrochlorothiazide per day in 313 patients (62.5 %) and increased to 300 mg/12.5 mg and to 300 mg/25 mg of irbesartan/hydrochlorothiazide per day in 111 patients (22.2 %) and 77 patients (15.3 %), respectively. In the per-protocol analysis ($n = 449$), the corresponding numbers of patients were 272 (60.6 %), 105 (23.4 %), and 72 (16.0 %), respectively.

Table 1 Baseline characteristics of the patients included in the intention-to-treat analysis

Characteristic	Men (n = 237)	Women (n = 264)	p value
Age (years; mean ± SD)	54.1 ± 9.8	55.9 ± 8.6	0.03
Body mass index (kg/m^2; mean ± SD)	25.8 ± 3.1	25.7 ± 3.5	0.77
Systolic blood pressure (mmHg; mean ± SD)	161.5 ± 11.3	163.4 ± 10.0	0.05
Diastolic blood pressure (mmHg; mean ± SD)	99.5 ± 8.6	96.5 ± 8.4	0.0001
Pulse rate (beats/min; mean ± SD)	74.7 ± 9.7	74.1 ± 10.1	0.46
Previous or concomitant disease [n (%)]			
Stroke[a]	3 (1.2)	1 (0.4)	0.27
Coronary heart disease[b]	5 (2.1)	14 (5.3)	0.06
Arrhythmia[c]	12 (5.1)	9 (3.4)	0.36
Dyslipidemia[d]	4 (1.7)	9 (3.4)	0.23
Diabetes mellitus[e]	35 (14.8)	50 (18.9)	0.21
Chronic kidney disease[f]	77 (32.5)	98 (37.1)	0.28
Previous treatment [n (%)][g]			
Antihypertensive treatment	117 (49.4)	158 (59.9)	0.02
Calcium channel blockers	52 (21.9)	70 (26.5)	0.23
Angiotensin-converting enzyme inhibitors	29 (12.2)	32 (12.1)	0.97
Angiotensin receptor blockers	27 (11.4)	25 (9.5)	0.48
β-Blockers	5 (2.1)	11 (4.2)	0.19
Diuretics	5 (3.0)	9 (3.4)	0.38
Other antihypertensive drugs	12 (5.1)	27 (10.2)	0.03
Aspirin	4 (1.7)	3 (1.1)	0.60
Statins	1 (0.4)	1 (0.4)	0.94
Antidiabetic drugs	4 (1.7)	14 (5.3)	0.03

[a] Excluding transient ischaemic attack

[b] Defined as a documented coronary atherosclerosis or stenosis

[c] Arrhythmia evidenced by an electrocardiogram

[d] Defined as a serum concentration of at least 6.22 mmol/l total cholesterol, 4.14 mmol/l low-density lipoprotein cholesterol, or 2.26 mmol/l triglycerides, or as the use of statins

[e] Defined as a fasting plasma glucose concentration from 7.1 to 11.0 mmol/l, or as the use of antidiabetic drugs or insulin

[f] Defined as albuminuria or a serum creatinine concentration from 132.6 to 176.8 μmol/l in men and from 123.8 to 176.8 μmol/l in women

[g] Use of drugs during the 2 weeks prior to the screening visit

3.2 Antihypertensive Efficacy

In the intention-to-treat analysis, the irbesartan/hydrochlorothiazide combination therapy reduced systolic/diastolic blood pressure from 162.5/97.9 mmHg at baseline to 138.7/86.4, 135.6/84.3, 134.2/83.9, and 134.7/84.4 mmHg at 2, 4, 8, and 12 weeks of follow-up, respectively (Fig. 1).

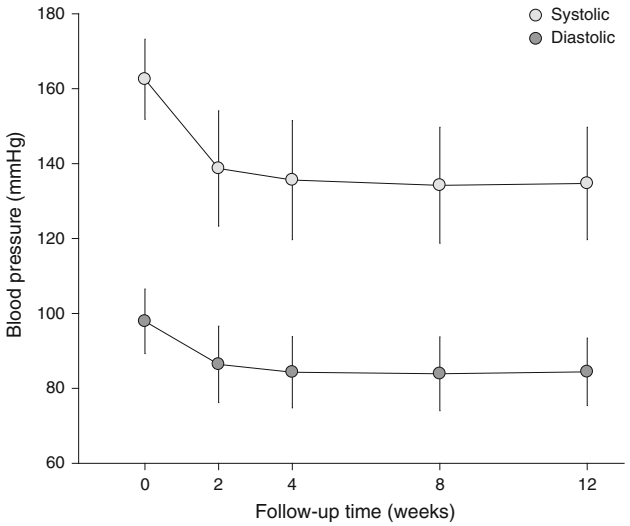

Fig. 1 Systolic and diastolic blood pressure at baseline and during follow-up in the intention-to-treat analysis. The *vertical lines* denote the standard deviations of the mean systolic and diastolic blood pressure values

The mean changes from baseline in systolic/diastolic blood pressure were −23.8/−11.6 mmHg, −26.8/−13.6 mmHg, −28.2/−14.0 mmHg, and −27.8/−13.5 mmHg at 2, 4, 8, and 12 weeks of follow-up, respectively (Fig. 2).

At 12 weeks of follow-up, the percentage of patients who attained the goal systolic/diastolic blood pressure (<140/90 mmHg, or <130/80 mmHg in patients with diabetes mellitus) was 57.3 % (Table 2). The goal blood pressure-attaining rates in patients treated with irbesartan/hydrochlorothiazide 150 mg/12.5 mg per day (n = 313), 300 mg/12.5 mg per day (n = 111), and 300 mg/25 mg per day (n = 77) were 68.1, 53.2, and 19.5 %, respectively. If the goal systolic/diastolic blood pressure was defined as 140/90 mmHg in diabetic as well as nondiabetic patients, the goal blood pressure-attaining rates were 66.1 % in all subjects and 77.0, 62.2, and 27.3 % in patients treated with irbesartan/hydrochlorothiazide 150 mg/12.5 mg (n = 313), 300 mg/12.5 mg per day (n = 111), and 300 mg/25 mg per day (n = 77), respectively (Table 2; Fig. 3).

In the per-protocol analysis, similar findings were observed with regard to blood pressure changes from baseline and the percentages of patients who achieved the goal blood pressure (Table 2; Fig. 3).

3.3 Determinants of Antihypertensive Efficacy

In multiple logistic regression analysis of the intention-to-treat study sample, we identified male sex [odds ratio (OR) 1.73, 95 % confidence interval (CI) 1.16–2.56; p = 0.007] and baseline systolic blood pressure (+10 mmHg; OR

1.59, 95 % CI 1.31–1.92; $p < 0.0001$) and diastolic blood pressure (+5 mmHg; OR 1.17, 95 % CI 1.04–1.32; $p = 0.007$) as significant factors associated with the use of high dosage of irbesartan/hydrochlorothiazide. In further intention-to-treat analysis, we studied the blood pressure changes from baseline and the percentage of patients who achieved the goal blood pressure at the end of follow-up, while accounting for various baseline characteristics (Table 3). The goal blood pressure (<140/90 mmHg)-attaining rate was significantly lower in overweight and obese patients than in normal-weight subjects (59.6 vs. 75.1 %; $p \leq 0.0003$) and significantly lower in patients with chronic kidney disease than in those with normal renal function (53.1 vs. 73.0 %; $p \leq 0.0003$).

3.4 Left Ventricular Hypertrophy and Microalbuminuria

In the per-protocol analysis, the irbesartan/hydrochlorothiazide combination therapy significantly reduced the prevalence of albuminuria ($n = 449$) by 30 % (95 % CI 12–46; $p = 0.004$) from 33.4 % at baseline to 23.4 % at the end of follow-up, and significantly reduced the prevalence of left ventricular hypertrophy ($n = 427$) by 19 % (95 % CI 4–32; $p = 0.01$) from 50.4 % to 41.3 % over the same period.

3.5 Safety

Of the 501 patients who started treatment with the irbesartan/hydrochlorothiazide combination, 163 (32.5 %) reported at least one adverse event. Table 4 shows adverse events with an incidence >1 % and those typically relevant to the use of irbesartan/hydrochlorothiazide combination therapy. Hyperuricemia was the most frequent ($n = 23$, 4.6 %) of the 77 adverse events (15.4 %) that were related to the study medication. A total of 4 serious adverse events (0.8 %) in 4 patients were reported, including 1 hemorrhagic stroke, 1 hypertensive emergency, 1 hypertensive urgency, and 1 spinal disc herniation. None of these serious adverse events led to death.

4 Discussion

Our study showed that fixed irbesartan/hydrochlorothiazide combination therapy administered in a dosage range of 150 mg/12.5 mg to 300 mg/25 mg once daily may control systolic/diastolic blood pressure to a level below 140/90 mmHg in approximately two thirds of Chinese patients with moderate to severe hypertension. Increasing the dose of irbesartan/hydrochlorothiazide in 40 % of patients might substantially increase the goal blood

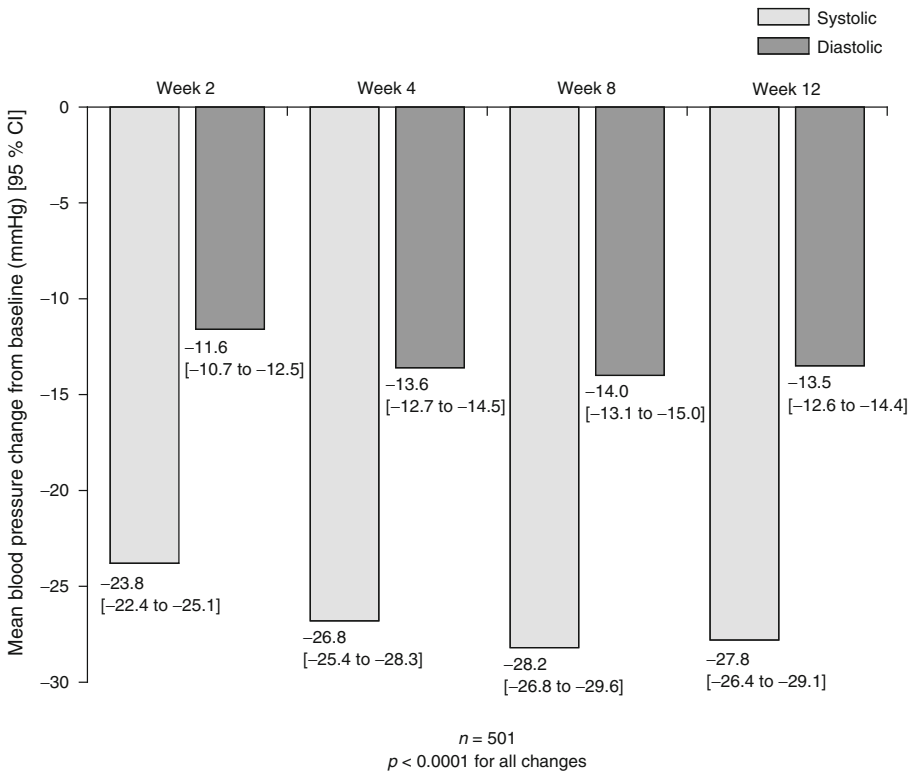

Fig. 2 Mean changes from baseline in systolic and diastolic blood pressure in the intention-to-treat analysis

Table 2 Percentages of patients who attained the goal blood pressure

Rate of attainment of goal blood pressure	Follow-up time (weeks)			
	2	4	8	12
Intention-to-treat analysis ($n = 501$)				
Goal blood pressure <140/90 mmHg, or <130/80 mmHg in diabetic patients (%)	39.7	55.7	59.7	57.3
Goal blood pressure <140/90 mmHg (%)	45.7	62.5	66.3	66.1
Per-protocol analysis ($n = 449$)				
Goal blood pressure <140/90 mmHg, or <130/80 mmHg in diabetic patients (%)	42.8	60.5	65.3	62.6
Goal blood pressure <140/90 mmHg (%)	49.2	67.9	72.5	72.2

pressure-attaining rate from 48.1 to 66.1 % of all enrolled patients. Even if the goal blood pressure was defined as a systolic/diastolic pressure of <130/80 mmHg in patients with diabetes, the rate of control of hypertension was still nearly 60 %.

Our finding is in line with the results of the INCLUSIVE (Irbesartan/Hydrochlorothiazide Blood Pressure Reductions in Diverse Patient Populations) trial, which was conducted as a multi-center, prospective, open-label, single-arm study in an American population [9]. The INCLUSIVE trial consisted of four periods: 4–5 weeks of placebo, 2 weeks of hydrochlorothiazide 12.5 mg/day, and 8 weeks each of irbesartan/hydrochlorothiazide 150 mg/12.5 mg and 300 mg/25 mg per day, respectively. In the intention-to-treat analysis, the blood pressure-lowering efficacy was evaluated in 736 patients for the total 18-week study treatment period from commencement of hydrochlorothiazide to the end of the trial. The mean changes from baseline in systolic/diastolic blood pressure were 15.1/7.2 and 21.5/10.4 mmHg at 10 and 18 weeks of follow-up, respectively. The corresponding rates of attainment of goal blood pressure (<140/90, or <130/80 mmHg in patients with diabetes) were 48 and 69 %, respectively. The slightly higher rate of attainment of goal blood pressure in the INCLUSIVE trial than in our study (69 vs. 57.3 %) may be attributable to the forced titration of combination therapy in a large majority of the enrolled patients and the inclusion of patients with mild hypertension in the INCLUSIVE trial [9].

Our observation in subgroup analysis is also in keeping with the results of various subgroup analyses of the INCLUSIVE trial [14]. In the INCLUSIVE trial, the rate of attainment of goal blood pressure was similar across different ethnicities (70 % in Caucasians, 66 % in African Americans, and 65 % in Hispanics) [15], similar in older and younger patients (72 % in patients aged ≥65 years and 68 % in those aged <65 years) [16], and similar in patients with and without isolated systolic hypertension (systolic blood pressure control in 74 vs. 81.6 %) [17], but slightly lower in men than in women (60 vs. 76 %) [18], slightly

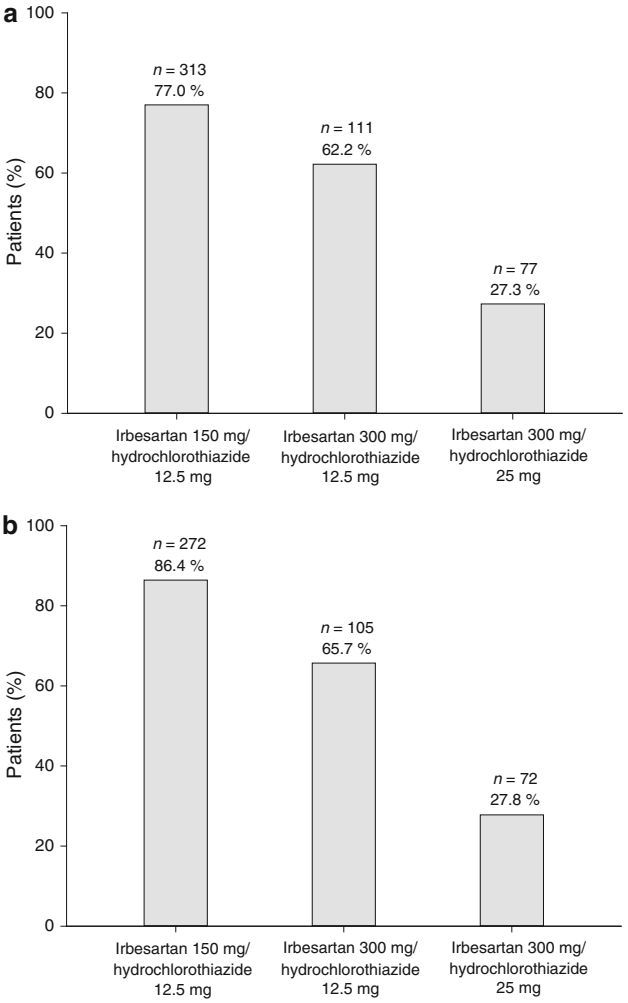

Fig. 3 Percentage of patients who achieved the goal blood pressure (<140/90 mmHg) at various dosages: **a** intention-to-treat analysis; **b** per-protocol analysis

lower in overweight and obese patients than in normal-weight patients (66.7 vs. 82.5 %) [19], and (taking into account the lower goal blood pressure thresholds in patients with diabetes), slightly lower in diabetic patients than in nondiabetic patients (40.1 vs. 81.7 %) [19, 20].

Our findings should also be compared with the results of a previous Chinese study, which studied the efficacy and safety of the fixed irbesartan/hydrochlorothiazide 150 mg/12.5 mg combination in 926 patients with mild to moderate hypertension (diastolic blood pressure 90–109 mmHg and systolic blood pressure <180 mmHg) [13]. In the per-protocol analysis ($n = 920$) of that 8-week, multi-center, single-arm, prospective study, 637 patients (69 %), 211 patients (22.9 %), and 72 patients (7.8 %) used irbesartan/hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg, and 300 mg/25 mg per day, respectively. The irbesartan/hydrochlorothiazide combination therapy reduced systolic/diastolic blood pressure by 22/16 mmHg from 149/95 mmHg at

Table 3 Subgroup analysis on the blood pressure-lowering efficacy in the intention-to-treat analysis

Parameter	*n*	Change in blood pressure				Rate of attainment of goal blood pressure			
		Systolic		Diastolic		<140/90 mmHg		<130/80 mmHg (in diabetic patients)	
		mmHg; mean ± SD	*p* value	mmHg; mean ± SD	*p* value	Patients (%)	*p* value	Patients (%)	*p* value
Sex									
Male	237	−26.6 ± 15.1	0.07	−13.7 ± 10.9	0.59	63.7	0.29	54.0	0.16
Female	264	−28.8 ± 15.8		−13.3 ± 10.1		68.2		60.2	
Age									
<55 years	246	−28.3 ± 15.4	0.75	−15.9 ± 9.6	<0.0001	68.3	0.30	59.8	0.27
≥55 years	255	−27.3 ± 15.6		−11.2 ± 10.8		63.9		54.9	
Body mass index									
<25 kg/m^2	209	−29.4 ± 15.0	0.10	−14.1 ± 10.5	0.30	75.1	0.0003	64.1	0.009
≥25 kg/m^2	292	−26.6 ± 15.7		−13.0 ± 10.5		59.6		52.4	
Isolated systolic hypertension[a]									
No	414	−28.0 ± 15.7	0.97	−15.8 ± 9.5	<0.0001	66.4	0.71	58.0	0.5
Yes	87	−26.9 ± 14.7		−2.65 ± 8.0		64.4		54.0	
Diabetes mellitus[b]									
No	416	−27.0 ± 15.3	0.007	−13.7 ± 10.5	0.30	65.1	0.33	65.1	<0.0001
Yes	85	−31.3 ± 15.8		−12.4 ± 10.2		70.6		18.8	
Left ventricular hypertrophy[c]									
No	233	−27.2 ± 14.6	0.34	−13.4 ± 10.3	0.87	66.5	0.71	57.9	0.72
Yes	245	−28.4 ± 16.4		−13.6 ± 11.0		64.9		56.3	
Chronic kidney disease[d]									
No	326	−28.7 ± 14.1	0.07	−13.6 ± 10.3	0.77	73.0	<0.0001	62.6	0.001
Yes	175	−26.0 ± 17.7		−13.3 ± 10.9		53.1		47.4	

[a] Defined as a systolic blood pressure of at least 160 mmHg and a diastolic blood pressure less than 90 mmHg

[b] Defined as a fasting plasma glucose concentration from 7.1 to 11.0 mmol/l, or as the use of antidiabetic drugs or insulin

[c] Defined as a left ventricular mass index of at least 112 g/m^2 in men and 105 g/m^2 in women

[d] Defined as albuminuria or a serum creatinine concentration from 132.6 to 176.8 μmol/l in men and from 123.8 to 176.8 μmol/l in women

baseline to 127/79 mmHg at 8 weeks of follow-up. In that previous study, which included patients with mild hypertension, 6.7 % of patients reported adverse events [13].

Our study should be interpreted within the context of its limitations. The evaluation of blood pressure-lowering efficacy relied mainly on blood pressure measurement in the clinic. We did not perform ambulatory blood pressure monitoring nor other hemodynamic investigations. Another major limitation of our study was its noncomparative design. Without a proper control group, placebo effects, observer bias, and regression to the mean may influence the evaluation of blood pressure-lowering efficacy. However, observations in noncomparative studies, such as the amplitude of changes in blood pressure from baseline and the rate of attainment of goal blood pressure, are similar to those in routine clinical practice. Despite the noncomparative design of our study, our findings are also in keeping with observations in the irbesartan/hydrochlorothiazide combination arms of controlled studies [21–26]. In those studies, the fixed irbesartan/hydrochlorothiazide combination alone normalized blood pressure in 51.4 and 50.2 % of patients with hypertension previously uncontrolled by monotherapy who were receiving clinic blood pressure monitoring (<140/90 mmHg) or home blood pressure monitoring (<135/85 mmHg), respectively [7, 21], and also in 53.4 % of patients with moderate hypertension [10] and in 34.6 % of patients with severe hypertension [11, 22]. In addition, those studies also confirmed that the blood pressure-lowering efficacy of the fixed irbesartan/hydrochlorothiazide combination was largely independent of sex [21], age [21, 23, 24], and methods of blood pressure measurement [6–8]; slightly less prominent in obese or diabetic patients [23–25]; and more prominent in patients with a higher initial blood pressure [23, 26].

In line with the results of previous studies [27, 28], the safety data from our study demonstrated that the irbesartan/hydrochlorothiazide combination was well tolerated even at the high dose, and was associated with few and mild

Table 4 Adverse events in the safety dataset ($n = 501$)

Adverse event[a]	Patients [n (%)]	Events possibly related to the study medication [n (%)]
Dizziness	41 (8.2)	11 (2.2)
Hyperuricemia	25 (5.0)	23 (4.6)
Headache	7 (1.4)	4 (0.8)
Upper respiratory tract infection	6 (1.2)	0
Severe hypertension	5 (1.0)	4 (0.8)
Palpitation	5 (1.0)	3 (0.6)
Fatigue	5 (1.0)	2 (0.4)
Elevation of alanine or aspartate transaminase	4 (0.8)	3 (0.6)
Hypokalemia	3 (0.6)	2 (0.4)
Hyperkalemia	1 (0.2)	1 (0.2)
Gout	1 (0.2)	1 (0.2)
Total	163 (32.5)	77 (15.4)

[a] The adverse events reported in this table are those with an incidence >1 % and those relevant to the use of irbesartan/hydrochlorothiazide combination therapy

adverse events. Hyperuricemia was the most frequently recorded adverse event. Nonetheless, gout was reported in only one patient.

5 Conclusion

The fixed irbesartan/hydrochlorothiazide combination may control blood pressure to the target level in about 60 % of Chinese patients with moderate or severe hypertension, with an acceptable safety profile. These blood pressure changes are clinically important in the protection of target organs and in the prevention of cardiovascular events, as evidenced by the significant changes in the prevalence of left ventricular hypertrophy and albuminuria observed in our short-term follow-up study.

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