

# Low rate of resistant hypertension in Chinese patients with hypertension: an analysis of the HOT-CHINA study

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**Objective:** The rate of resistant hypertension in China is unknown. This is an analysis of resistant hypertension based on Hypertension Optimal Treatment Study in China.

**Methods:** The study was conducted in 148 cities in mainland China from April 2001 to February 2002, which included 54 590 hypertensive patients ( $\geq 18$  years of age), and used a five-step treatment programme. Patients not achieving blood pressure (BP) target ( $< 140/90$  mmHg) within 2 weeks received preplanned additional drugs. Resistant hypertension was defined in the participants with uncontrolled hypertension after 2 weeks of treatment on Step 5.

**Results:** The rate of resistant hypertension was 1.9%. Patients with resistant hypertension were characterized by following features: higher male percentage (65.6 vs. 60.2%); younger age ( $59.51 \pm 13.02$  vs.  $61.76 \pm 12.27$  years); higher BMI ( $24.8 \pm 3.5$  vs.  $24.0 \pm 3.4$  kg/m<sup>2</sup>); longer disease course; higher fasting blood glucose ( $6.60 \pm 2.69$  vs.  $5.99 \pm 2.12$  mmol/l); higher total cholesterol ( $5.67 \pm 1.63$  vs.  $5.32 \pm 1.24$  mmol/l); higher triglycerides ( $2.15 \pm 1.32$  vs.  $1.96 \pm 1.09$  mmol/l); and higher percentage of grade 3 hypertension (71.1 vs. 27.2%) (all  $P < 0.001$ ). Patients with resistant hypertension also had a higher rate of metabolic syndrome (45.9 vs. 35.4%), diabetes mellitus (25.5 vs. 14.7%) and history of myocardial infarction (4.7 vs. 3.3%) or stroke (17.0 vs. 11.6%) ( $P < 0.001$ ). Multivariate analyses revealed an association of resistant hypertension with younger age, higher BP, BMI, longer disease course, higher fasting blood glucose and total cholesterol ( $P < 0.05$ ).

**Conclusion:** Resistant hypertension in Chinese patients is associated with overweight/obesity, higher BP and metabolic syndrome. The rate of resistant hypertension in China, however, is much lower than previously reported. Another intriguing characteristic is the association of resistant hypertension with younger age.

**Keywords:** cardiovascular risk, China, resistant hypertension

**Abbreviations:** ABPM, ambulatory BP monitoring; ACEI, angiotensin-converting enzyme inhibitor; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack; ARB, angiotensin receptor blocker; BP, blood pressure; Ccr, creatinine clearance rate; CI, confidence

interval; FBG, fasting blood glucose; HOT, Hypertension Optimal Treatment; IDF, International Diabetes Federation; MI, myocardial infarction; OR, odds ratio; SD, standard deviation; TC, total cholesterol

## INTRODUCTION

Resistant hypertension is defined as uncontrolled hypertension (SBP  $\geq 140$  mmHg and/or a DBP  $\geq 90$  mmHg) despite treatment with at least three antihypertensive agents of different classes (one of which is a diuretic) at best tolerated doses, or a condition that requires at least four antihypertensive drug classes regardless of BP [1]. The American Heart Association (AHA) estimated that resistant hypertension could develop in 20–30% of hypertensive patients [1]. Using data from the National Health and Nutrition Examination Survey from 2003 to 2008, Persell [2] reported that 8.9% of adults with hypertension in the USA met the criteria for resistant hypertension, representing 12.8% of all hypertensive adults treated with drug therapy. A study from Spain reported 14.8% resistant hypertension in patients with hypertension [3]. A recent retrospective study by Hanselin *et al.* [4] in a large USA sample estimated the percentage at 2.6% using the criterion based on concurrent use of at least four antihypertensive agents. This number is smaller than that in previous epidemiological studies. Another retrospective cohort study of 205 750 patients with incident hypertension, enrolled in two integrated health plans, revealed that 1.9% developed resistant hypertension within a median of 1.5 years from initial treatment [5].

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The current study is based on the results from Hypertension Optimal Treatment Study in China (HOT-CHINA) study, an extension of Hypertension Optimal Treatment (HOT) study that attempted to observe the antihypertensive effects control rates for blood pressure side effects and compliance by adopting the five-step treatment protocol of the HOT study in Chinese hypertensive patients. The HOT-CHINA study adopted a classical five-step regimen [6–9] and was carried out in a period from April 2001 to February 2002, in 148 cities in mainland China. All participants were at least 18 years of age at the enrolment, and were monitored for 10 weeks. The study revealed that a combination of antihypertensive drugs based on the long-acting calcium antagonist has stronger effects and higher control rates for blood pressure as well as lower side effects and better compliance in Chinese hypertensive patients [10]. Here, we present the results of a posthoc analysis of resistant hypertension in the HOT-CHINA study.

## PATIENTS AND METHODS

### Study design

The HOT-CHINA study was an observational study conducted during a period from April 2001 to February 2002 in 148 cities of mainland China [10]. All participants were adult patients (at least 18 years of age) with hypertension (SBP  $\geq 140$  mmHg and/or DBP  $\geq 90$  mmHg). All participants had a wash-out period for at least 4 weeks prior to the enrolment, and participated voluntarily. Individuals with secondary hypertension, new-onset heart disease, cerebrovascular disease (within the past 3 months) or a history of allergy to calcium antagonists were excluded. Pregnant and lactating women were also excluded.

The HOT-CHINA study was approved by the Ethics Committees of all participating hospitals. All patients signed written informed consent at the time of the enrolment.

### Therapeutic regimens

The HOT-CHINA study was conducted using a five-step treatment programme, as described in the HOT study [6], with minor modification. After a wash-out period of at least 4 weeks, participants started to receive extended-release felodipine (5 mg daily; Step 1). Patients who did not achieve the BP target ( $< 140/90$  mmHg) within 2 weeks of treatment advanced to the next steps in increment, as described below:

Step 2: felodipine (5 mg) and an angiotensin-converting enzyme inhibitor (ACEI) at low dose or the beta-blocker metoprolol (25 mg twice daily);

Step 3: felodipine (10 mg) and an ACEI at low dose or the beta-blocker metoprolol (25 mg twice daily);

Step 4: felodipine (10 mg) and an ACEI of high dose or the beta-blocker metoprolol (50 mg twice daily);

Step 5: felodipine (10 mg) and an ACEI at high dose or/and metoprolol (50 mg twice daily) and hydrochlorothiazide (up to 25 mg daily).

### Diagnostic criteria

#### Resistant hypertension

Resistant hypertension was defined as uncontrolled hypertension (SBP  $\geq 140$  mmHg and/or a DBP  $\geq 90$  mmHg)

despite treatment with at least three antihypertensive agents of different classes (one being a diuretic) at best tolerated doses, namely in the participants with uncontrolled hypertension after 2 weeks of treatment on Step 5 in the HOT-CHINA study. BP was measured for three times (at 1-min interval after being seated for 5 min) using a mercury manometer, and averaged at each office visit. The appearance of the first Korotkoff sound was taken as the SBP, and the pressure at which the Korotkoff sounds disappeared as the DBP. At the screening and final visits, a full physical examination was carried out, and a blood sample was taken for risk factor and safety evaluation.

#### Metabolic syndrome

Metabolic syndrome was assessed using the 2005 International Diabetes Federation (IDF) global definition [11], and based on central obesity, defined using ethnicity-specific values for waist circumference (Chinese: men  $\geq 90$  cm, women  $\geq 80$  cm), along with any two of the following: elevated triglycerides ( $\geq 150$  mg/dl or 1.7 mmol/l) or the use of a lipid-lowering drug; reduced high-density lipoprotein (HDL)-cholesterol ( $< 40$  mg/dl or 1.03 mmol/l in men;  $< 50$  mg/dl or 1.29 mmol/l in women) or specific treatment for this lipid abnormality; hypertension (SBP  $\geq 130$  mmHg or DBP  $\geq 85$  mmHg) or the use of an antihypertensive; elevated fasting plasma glucose ( $\geq 100$  mg/dl or 5.6 mmol/l) or previously established diagnosis of type-2 diabetes.

#### Statistical analysis

Data are presented as percentages for qualitative variables, and as means  $\pm$  standard deviations (SD) for quantitative variables. Difference in the subgroup analysis was assessed with the chi-squared test for qualitative data and the independent-samples *t*-test for quantitative data. An enter method of logistic regression analysis was used to determine potential association between resistant hypertension and suspected clinical variables. The variables in the multiple logistic regression analysis included all independent variables with a *P* value of less than 0.05. Statistical analyses were performed using SPSS v12.0 software (SPSS Inc., Chicago, Illinois, USA).

## RESULTS

### Percentage of resistant hypertension in the HOT-CHINA study

A total of 54 590 patients met the criteria for inclusion in the study. The intention-to-treat (ITT) population consisted of 53 040 patients (60.3% men, 39.7% women) with a mean age of  $61.7 \pm 12.3$  years (45% at 65 years or older). The BMI of the ITT population was  $24.6 \pm 3.0$  kg/m<sup>2</sup>. The baseline BP was  $164.8 \pm 15.8/98.3 \pm 10.1$  mmHg. Isolated systolic hypertension accounted for 9.4% of the sample. The per-protocol population consisted of 48 291 patients. Among these, 932 patients (611 men and 321 women; 1.9% of the per-protocol population) met the criteria for resistant hypertension, with a mean age of  $59.51 \pm 13.02$  years, and a mean BMI of  $24.76 \pm 3.54$  kg/m<sup>2</sup>. The baseline BP in patients with resistant hypertension was  $180.72 \pm 19.11/107.07 \pm 12.45$  mmHg, with 71.1% having

**TABLE 1. Clinical characteristics of patients with resistant hypertension**

Parameter	Non-RH	RH	P
Age (years)	61.76 ± 12.27	59.51 ± 13.02	<0.001
≥65 years (%)	45.3	38.3	<0.001
Sex (% male)	60.2	65.6	<0.001
BMI (kg/m <sup>2</sup> )	24.01 ± 3.40	24.76 ± 3.54	<0.001
Baseline SBP (mmHg)	163.77 ± 16.03	180.72 ± 19.11	<0.001
Baseline DBP (mmHg)	97.82 ± 10.08	107.07 ± 12.45	<0.001
Grade 1 hypertension (%)	23.0	1.8	
Grade 2 hypertension (%)	49.8	27.0	<0.001
Grade 3 hypertension (%)	27.2	71.1	
MS (%)	35.4	45.9	<0.001
Diabetes (%)	14.7	25.5	<0.001
MI (%)	3.3	4.7	<0.001
Stroke (%)	11.6	17.0	<0.001
Course of disease <1 year (%)	13.4	6.1	<0.001
Course of disease ≥1, <5 years (%)	27.5	20.5	
Course of disease ≥5, <10 years (%)	32.2	35.5	
Course of disease ≥10 years (%)	26.9	38.0	
Baseline serum creatinine (μmol/l)	94.87 ± 25.60	102.56 ± 28.63	<0.001
Ccr (ml/min)	69.66 ± 28.54	69.87 ± 32.71	0.657
Baseline FBG (mmol/l)	5.99 ± 2.12	6.60 ± 2.69	<0.001
Baseline TC (mmol/l)	5.32 ± 1.24	5.67 ± 1.63	<0.001
TG (mmol/l)	1.96 ± 1.09	2.15 ± 1.32	<0.001

Ccr, creatinine clearance rate, using Cockcroft-Gault formula; FBG, fasting blood glucose; MS, metabolic syndrome; MI, myocardial infarction; RH, resistant hypertension; TC, total cholesterol; TG, triglyceride level.

grade 3 hypertension (≥180/110 mmHg). Disease duration was at least 10 years in 354 (38.0%) of the patients with resistant hypertension. Around 45.9% of the patients with resistant hypertension had metabolic syndrome, and 25.5% had type-2 diabetes. A history of previous cardiovascular disease was present in 21.7%, with a history of myocardial infarction in 4.7% and of stroke in 17.0% of patients with resistant hypertension (Table 1).

**Characteristics of patients with resistant hypertension**

In comparison with the remaining individuals, the patients with resistant hypertension were characterized by overrepresentation by men (65.6 vs. 60.2%), younger age (59.51 ± 13.02 vs. 61.76 ± 12.27 years), higher BMI (24.76 ± 3.54 vs. 24.01 ± 3.40 kg/m<sup>2</sup>), higher serum creatinine (102.56 ± 28.63 vs. 94.87 ± 25.60 μmol/l), higher fasting glucose (6.60 ± 2.69 vs. 5.99 ± 2.12 mmol/l), higher total cholesterol (5.67 ± 1.63 vs. 5.32 ± 1.24 mmol/l) and higher triglyceride (2.15 ± 1.32 vs. 1.96 ± 1.09 mmol/l)

(all *P* < 0.001). Grade-3 hypertension occurred much more often in patients with resistant hypertension (71.1 vs. 27.2% in those without; *P* < 0.001). Metabolic syndrome (45.9 vs. 35.4%), diabetes mellitus (25.5 vs. 14.7%) and previous myocardial infarction (4.7 vs. 3.3%) or stroke (17.0 vs. 11.6%) was also more common in patients with resistant hypertension (*P* < 0.001 vs. individuals without resistant hypertension). Creatinine clearance rate did not differ between the two groups.

A multiple logistic regression revealed association of resistant hypertension with the following factors: younger age, higher BP, higher BMI, longer duration of hypertension, higher fasting blood glucose and cholesterol (all *P* < 0.05) (Table 2).

**DISCUSSION**

The current study revealed only 1.9% resistant hypertension in Chinese individuals with hypertension, in contrast to a much higher estimated rate of 20–30% by the AHA [1]. Such

**TABLE 2. Multiple logistic regression analysis of clinical variables showing differences between resistant hypertension and nonresistant hypertension groups**

Parameter	OR	95% CI	P
Age (years)	0.98	0.97–0.98	<0.001
Sex (% male)	0.86	0.72–1.03	0.093
BMI (kg/m <sup>2</sup> )	1.02	1.00–1.05	0.043
Grade 1 hypertension			
Grade 2 hypertension	7.90	3.69–16.92	<0.001
Grade 3 hypertension	39.05	18.46–82.58	<0.001
Course of disease <1 year			
Course of disease ≥1, <5 years	1.75	1.19–2.60	0.005
Course of disease ≥5, <10 years	2.73	1.88–3.97	<0.001
Course of disease ≥10 years	2.91	1.97–4.29	<0.001
Baseline FBG (mmol/l)	1.04	1.01–1.07	0.019
Baseline TC (mmol/l)	1.14	1.07–1.21	<0.001

CI, confidence interval; FBG, fasting blood glucose; OR, odds ratio; RH, resistant hypertension; TC, total cholesterol.

a dramatic difference could reflect several key issues, as explained below.

First, previous studies typically enrolled hypertensive patients at high cardiovascular risk. For example, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial enrolled older patients (55 years or older) with at least one other cardiovascular risk factor: 36% of the participants had diabetes, and the mean BMI was 30 kg/m<sup>2</sup> [12]. In the Spain study [5], BMI was 30.4 ± 4.7 kg/m<sup>2</sup> (vs. 24.6 ± 3.0 kg/m<sup>2</sup> in the current study), and obesity (BMI ≥ 30 kg/m<sup>2</sup>) was present in 49.5% of the participants. In the current study, patients with new-onset heart disease or cerebrovascular disease (within the past 3 months) were excluded. Also, type-2 diabetes was only 25.5% even in individuals with resistant hypertension.

Second, Chinese patients with hypertension are characterized by high sodium and low potassium intake, and a high incidence of stroke [13,14]. Combination treatment based on dihydropyridine calcium antagonist along with an ACEI or angiotensin receptor blocker (ARB), a β blocker, or a thiazide diuretic, is recommended for all patients [15]. The HOT-CHINA treatment programme was in line with this approach, and expected to strengthen BP control and decrease the apparent rate of resistant hypertension. Also, target BP was achieved at a much higher rate in the current study (79.2 and 87.0% at 10 weeks in the ITT and per-protocol population, respectively) than in the HOT study at 3 months (77% for DBP <90 mmHg) [10]. Specific for the ALLHAT study, 35% of the participants in the chlorthalidone, amlodipine and lisinopril treatment arm were black, who tend to be less sensitive to ACEIs [16–18]. In the study by Persell [2], only 85.6% of individuals with resistant hypertension used a diuretic. In the study by Hanselin *et al.* [4], the prescription of antihypertensive drugs in patients with resistant hypertension was clearly suboptimal: evidence-based and recommended agents, such as chlorthalidone and aldosterone antagonists, were underused, and a total of 15.6% of patients were treated with an ACEI along with an ARB.

Varying adherence could also affect the observed rate of resistant hypertension. The study by de la Sierra *et al.* [3] did not implement a uniform treatment programme and was unable to determine the compliance. The HOT-CHINA Study was a short-term analysis of the effect of antihypertensive agents and implemented a strict programme for both the treatment and follow-up.

Consistent with previous studies [1,19], obesity, diabetes and high baseline BP are characteristics of patients with resistant hypertension in the current study. Earlier studies [1,2,10,20,21] showed that resistant hypertension is more common in the elderly. Elderly individuals tend to have higher baseline BP, higher arterial stiffness, lower efficacy to antihypertensive medications and higher incidence of organ damage and comorbidities. In addition, the elderly tend to have excess salt intake, higher weight, higher alcohol consumption, higher nicotine use, poorer treatment compliance, higher rate of pseudohypertension and more frequent NSAID use. It is more difficult to control BP in older patients than in younger ones [22,23], and hence, resistant hypertension is more common in the elderly [2,21].

The current study, however, found that resistant hypertension was less common in the elderly. This finding is counterintuitive, and may reflect the different lifestyle in elderly vs. young Chinese, for example, high alcohol and nicotine intake, high work pressure, neglect of health despite knowledge in young Chinese people. A study in the general population of five areas of China revealed that both 3-month and 1-year drinking rates increased with age, reached a peak at 41–50 years old in men and 36–40 years old in women and then declined [24]. Le *et al.* [25] also found that age was negatively associated with the probability of consuming alcohol. Another study reported that 48.9% of men and 3.2% of women were current smokers in 2003. Smoking was most frequent among men aged 35–64 years (55–61%) and among women 65 years of age or older [26]. Considering the low hypertension awareness in China, maybe age is more credible.

Our study is an intervention trial of antihypertensive treatment probably excludes a significant number of patients who, having resistant hypertension or being treated with three or more drugs, are not suitable for being engaged in such trial, which needs a complete withdrawal for at least 4 weeks. The follow-up was short. Maybe it did not reflect what happens in everyday practice. In the HOT-CHINA study, the target for BP control was less than 140/90 mmHg for all patients. The guidelines recommend less than 130/80 mmHg for those with diabetes or chronic renal disease, and this practice could increase the apparent resistant hypertension. In this study, resistant hypertension was based on office measurements of BP, and not ambulatory BP monitoring (ABPM). White-coat hypertension or isolated office RH, reported to as high as 37.5% in a previous study [3], may be present in the HOT-CHINA study. The 'true' rate of resistant hypertension therefore requires additional study. Also, urinary albumin, an early indicator of renal damage, was not examined in the HOT-CHINA study. Last but not least, our results were extracted from data collected 10 years earlier. The data need to be updated to establish the current situation of resistant hypertension.

Finally, inadequate treatment of hypertension appears to be more common than true resistance. More clinical research is needed to determine the optimal therapeutic strategies for hypertensive patients as well as those with resistant hypertension.

## ACKNOWLEDGEMENTS

### Conflicts of interest

The authors have not reported any conflicts of interest.

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## Reviewers' Summary Evaluations

### Reviewer 1

**Strengths:** This is the first paper examining prevalence and clinical correlates of resistant hypertension in an Asian population. The sample is very large.

**Weaknesses:** Prevalence of resistant hypertension is examined after a short trial of antihypertensive treatment (2 weeks of the last treatment change). Not all patients received appropriate doses of all the drugs used. Most of the clinical correlates of resistant hypertension found here are similar to those previously reported.

### Reviewer 2

Major efforts are currently directed to control blood pressure blood pressure in hypertensive patients using hygienic measures and pharmacological treatment. The data pre-

sented in this paper involve observations made in a very large number of Chinese patients with blood pressure values remaining  $\geq 140/90$  mmHg despite the taking of  $\geq 3$  drugs acting by different mechanisms, including a diuretic. An unexpected low rate of resistant hypertension was found. This could be partly explained by the fact that doctors in charge of the patients had to follow a predefined 5-step treatment program to reach the target blood pressure. There was therefore little room for clinical inertia. Unfortunately blood pressure was measured in this study only in a clinical setting. It might therefore well be that a large fraction of patients were considered as hypertensive at inclusion in the study albeit they had normal out-of-office blood pressures. This points to the need of 24-h ambulatory blood pressure monitoring or self-measurement of blood pressure at home for establishing the diagnosis of true-resistant hypertension.