Evaluation of blood pressure lowering effect by generic and brand-name antihypertensive drugs treatment: a multicenter prospective study in China

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Abstract

Background: Generic drugs are bioequivalent to their brand-name counterparts; however, concerns still exist regarding the effectiveness and safety of generic drugs because of small sample sizes and short follow-up time in most studies. The purpose of this study was to evaluate the long-term antihypertensive efficacy, cost-effectiveness and cardiovascular outcomes of generic drugs compared with brand-name drugs.

Methods: In a multicenter, community-based study including 7955 hypertensive patients who were prospectively followed up for an average of 2.5 years, we used the propensity-score-matching method to match the patients using brand-name drugs to those using generic drugs in a ratio of 1:2, 2176 patients using brand-name drugs and 4352 patients using generic drugs.

Results: There were no significant differences between generic drugs and brand-name drugs in blood pressure (BP)-lowering efficacy, BP control rate, and cardiovascular outcomes including coronary heart disease and stroke. The adjusted mean (95% confidence interval [CI]) of systolic BP (SBP)-lowering was –7.9 mmHg (95% CI, –9.9 to –5.9) in the brand-name drug group and –7.1 mmHg (95% CI, –9.1 to –5.1) in the generic drug group after adjusting for age, sex, body mass index, number of antihypertensive drugs and traditionally cardiovascular risk factors. Among patients aged <60 years, brand-name drugs had a higher BP control rate (47% *vs.* 41%; $P = 0.02$) and a greater effect in lowering SBP compared with generic drugs, with the between-group difference of 1.5 mmHg (95% CI, 0.2–2.8; $P = 0.03$). BP control rate was higher in male patients using brand-name drugs compared with those using generic drugs (46% *vs.* 40%; $P = 0.01$). Generic drugs treatment yielded an average annual incremental cost-effectiveness ratio of $315.4 per patient per mmHg decrease in SBP compared with brand-name drugs treatment.

Conclusions: Our data suggested that generic drugs are suitable and cost-effective in improving hypertension management and facilitating public health benefits, especially in low- and middle-income areas.

Keywords: Brand-name drugs; Cost-effectiveness; Cardiovascular diseases; Generic drugs; Hypertension

Introduction

Hypertension is a common medical condition and a leading cause of cardiovascular diseases (CVDs) and stroke worldwide. In China, the prevalence of hypertension has increased rapidly over the past few decades, with 244 to 300 million (23%–45%) Chinese adults having hypertension. However, hypertension remains inadequately controlled, and its treatment and control rates are less than 50% and 15%, respectively.[1-3] In particular, low- and middle-income people have a high economic burden of hypertension, which is an important risk factor for reduced life expectancy. Although China's healthcare reform has expanded the health insurance coverage dramatically, most patients still need to pay for outpatient clinic visits and bear the out-of-pocket medication costs.[4-6] The unaffordability of drugs is a major barrier to increased medication adherence among patients living in rural

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001360

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Chinese Medical Journal 2021;134(3)
Received: 17-10-2020 **Edited by:** Yin-Yan Jie and Xiu-Yuan Hao

areas.[7] Improved hypertension control would result in enormous health gains in China.

Use of generic drugs can help control drug costs. Generic drugs are chemically equivalent to their brand-name counterparts in terms of active ingredients but may differ in peripheral features and can legally be marketed by manufacturers after the brand-name drug's market exclusivity period ends.[8,9] Because of their bioequivalence and lower prices, generic drugs have been introduced in several countries to reduce health care costs and improve adherence to antihypertensive therapy.[10-13] For example, the insurance policy in Norway and the Clinical Guidelines Committee of the American College of Physicians recommend that doctors should prescribe generic medications, if possible, instead of the more expensive brand-name medications.[14,15] However, considerable concerns still exist among doctors and patients regarding the safety and effectiveness of generic drugs.

So far, several comprehensive meta-analyses have summarized the clinical characteristics of generic and brand-name drugs used for CVDs and indicated no evidence of the superiority of the latter over the former; however, it should be noted that between-study heterogeneities exist.[9,16-18] Moreover, most studies were bioequivalence trials with small sample sizes and short follow-up periods (ranging from 24 h to 6 months) that were powered to assess differences in pharmacokinetics but not differences in clinical outcomes. In addition, multiple complications and CVD risk factor profiles might affect the bioequivalence and long-term efficacy of generic drugs. Due to the limited available data, new evidence is needed to clarify whether generic antihypertensive drugs are equivalent to their brand-name counterparts in terms of clinical outcomes at a population level in a large cohort.

Therefore, in this study including 7955 hypertensive patients from 12 provinces in China who were prospectively followed up for 2.5 years, we aimed to (1) compare the magnitude of blood pressure (BP) lowering and control rate of hypertension between generic and brand-name drugs, (2) investigate whether generic drugs could offer similar cardiovascular benefits as brand-name drugs, and (3) evaluate the cost-effectiveness of the two drug types.

Methods

Ethical approval

The study was conducted in accordance with the Chinese Ethical Standards of Human Experimentation and the *Declaration of Helsinki* 1975 (revised in 2000). The study protocol was approved by the Ethics Committee of Fuwai Hospital and collaborating clinic centers. Written informed consent was obtained from all participants.

Study design and participants

This multicenter, community-based, prospective study was conducted at 18 clinic centers in 12 provinces in China [Supplementary Table S1, http://links.lww.com/CM9/A453]. In total, 2253 and 9674 patients were screened in 2009 and from January 2013 to November 2015, respectively; of them, 8696 patients with primary hypertension and complete clinical data were recruited. Hypertension is defined as systolic BP (SBP) of ≥140 mmHg and/or diastolic BP (DBP) of ≥90 mmHg, and/or current use of antihypertensive medications, and/or a history of hypertension. Patients with valvar heart disease, known secondary hypertension, or severe debilitating chronic illness (cancer or hepatic diseases) were excluded from the study.

The study cohort was prospectively followed up for an average of 2.5 years (median, 2.2 years; range, 0.7–7.8 years), and 681 (7.8%) patients were lost due to immigration, and 60 (0.7%) patients using loop diuretics and mineralocorticoid receptor antagonists were excluded given that their BP-lowering efficacy and nature are different from thiazide-type diuretics. Thus, in total, 7955 patients having both baseline and follow-up data were included in this study; of these patients, 2176 used brand-name drugs and 5779 used generic antihypertensive drugs, as indicated by the information collected from doctor's prescriptions. Considering that treatment effects may be influenced by patient characteristics, we used the propensity score matching (PSM) method to match the patients using brand-name drugs to those using generic drugs in a ratio of 1:2, aiming to account for the potential imbalance in patient characteristics between the two groups. The patient cohort matched via the PSM method included 2176 patients using brand-name drugs and 4352 patients using generic drugs. Study flowchart is shown in Figure 1. The details of data collection are described in Supplementary Materials, http://links.lww.com/CM9/A453.

Follow-up and outcome assessment

This cohort was followed up annually by physicians until August 1, 2017, 6694 (84.1%) patients underwent face-to-face interviews during clinic visits, and 1261 (15.9%) patients were contacted via telephone. Regarding changes in the BP level, the last follow-up visit date was considered the censoring date. For patients undergoing face-to-face interviews, the follow-up BP was measured by physicians, whereas for those contacted via telephone, self-reported BP levels were recorded. Data on anthropometric measurements, smoking and drinking status, antihypertensive medications, and outcome events were updated using structured questionnaires during a follow-up survey. Antihypertensive medication adherence was assessed using a derived version of the Brief Medication Questionnaire, which included seven items for assessing potential non-adherence;[19] a score of "≥1" indicated potential non-adherence to current medications, and a score of "0" indicated medication adherence.

The study endpoint was a composite of CVDs, including acute myocardial infarction, hospitalization for unstable angina or acute decompensated heart failure, coronary revascularization, and stroke (ischemic or hemorrhagic), which were ascertained by local physicians mainly through self-reports and medical record reviews. Definitions of the endpoints are shown in Supplemental Materials, http://links.lww.com/CM9/A453.

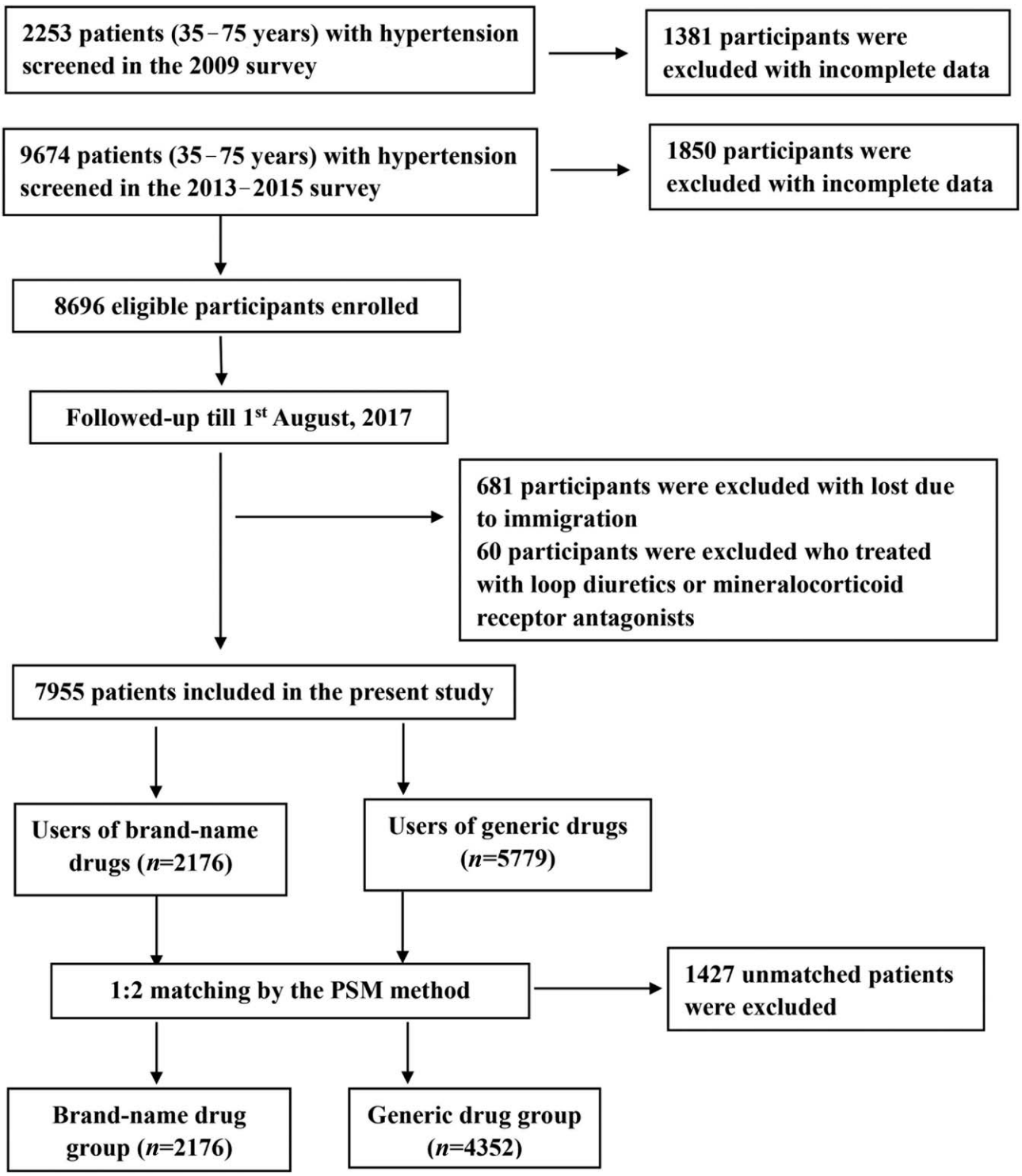

Figure 1: Flowchart of the present study. PSM: Propensity-score matching.

Cost-effectiveness estimation

We assessed economic burden of hypertension in terms of direct costs including drug costs and hypertension-related hospitalization fees. The drug costs were estimated according to the lowest retail price designated by the National Development and Reform Commission of the People's Republic of China [Supplementary Table S2, http://links.lww.com/CM9/A453]. The cost of hospitalization was assessed on the basis of per capita medical expenses for inpatients according to the national data from China Public Health Statistical Yearbook.[20] All costs were converted to US dollars using the average exchange rate at the time of data collection in 2017 ($1 = 6.33RMB).

The cost-effectiveness of generic drugs and brand-name drugs was presented as the average and incremental costs in $US per mmHg reduction in BP. Treatment effectiveness was calculated as follows: Effectiveness (E) = |Follow-up BP–Baseline BP|. The cost-effectiveness ratio (CER) was calculated as the ratio of annual average costs per patient (C) divided by effectiveness (E) in the generic drug and brand-name drug treatment groups: $CER = C/E$. The incremental cost-effectiveness ratio (ICER) was calculated as the difference in annual average costs (ΔC) between generic drugs and brand-name drugs divided by the difference in treatment effectiveness (ΔE) of the two groups: $ICER = \Delta C/\Delta E$ = (brand-name drugs costs – generic drugs costs)/(brand-name drugs effectiveness – generic drugs effectiveness).

Statistical analysis

In this study, categorical variables were presented as numbers (percentages) and compared between groups using the Chi-square test. Continuous variables were presented as mean ± standard deviation and compared using the Student's t test. Serum triglyceride levels were presented as median (interquartile range) due to their skewed distribution and compared using the non-parametric Mann-Whitney U test. The comparisons of BP-lowering efficacy and cardiovascular outcomes between generic and brand-name drugs were based on drugs used at baseline.

The PSM method was used to match hypertensive patients using brand-name drugs with those using generic drugs in a ratio of 1:2. For each patient, a propensity score was estimated using a logistic regression model, in which the use of generic or brand-name drugs was considered as the dependent variable and potential confounders including age, sex, BP, as well as number and class of antihypertensive drugs at baseline were controlled as covariates. PSM was performed using MatchIt (version 3.0.2) in R (version 3.6.1; R Foundation, Vienna, Austria). Balance in the baseline covariates between the two groups after matching was examined using standardized differences, and an absolute standardized difference of <0.1 implied an adequate match.

A generalized linear regression model was used for between-group comparisons of SBP and DBP during the follow-up, with adjustment for age, sex, body mass index, BP, medical history, smoking and drinking status, lipids profile, annual household income, and number of antihypertensive medications used at baseline. A logistic regression model was used for between-group comparison of the BP control rate after adjusting for the aforementioned covariates. Here the BP control rate was defined as the percentage of patients achieving an SBP of <140 mmHg and DBP of <90 mmHg at study endpoint. The cox proportional hazards regression model was used to examine the relationship of generic and brand-name drugs with cardiovascular outcomes after adjusting for age, sex, and the aforementioned covariates. Person-years of follow-up were calculated from the date of recruitment to the date of CHD, stroke, death, or the end of follow-up (August 2017), whichever came first.

A two-tailed P value of ≤0.05 was considered to be significant. Analyses were performed using SPSS (version 20.0; IBM Corp., Armonk, NY, USA).

Results

Clinical characteristics of patients

The clinical characteristics of patients in the original and matched cohorts are shown in Table 1. The baseline covariates between the two groups in the matched cohort were adequately matched as shown by small standardized differences in age, sex, BP, and antihypertensive drugs class at baseline. Compared with patients using brand-name drugs, patients using generic drugs had a higher alcohol intake, more severe dyslipidemia, a lower comorbidity burden of CHD, and a lower household income (<$13,000 per year). The percentage of patients using beta-blockers was lower in the generic drug group compared with the brand-name drug group at baseline and during the follow-up period.

Effect of generic and brand-name drugs on BP

There were no significant differences in the ability of generic drugs and brand-name drugs to lower BP ($P = 0.08$). The change in SBP (ΔSBP) during the follow-up period was –7.9 mmHg (95% confidence interval [CI], –9.9 to –5.9) in the brand-name drug group and –7.1 mmHg (95% CI, –9.1 to –5.1) in the generic drug group in the matched cohort after adjusting for potential risk factors including age, sex, body mass index, baseline BP, smoking and alcohol status, medical history, annual household income, lipids profile, and number of antihypertensive medications [Table 2]. The change in DBP (ΔDBP) was similar between the generic drug group and the brand-name drug group [Supplementary Table S3, http://links.lww.com/CM9/A453]. In the stratified analysis by age, sex, Framingham risk score, number of antihypertensive drugs, and baseline BP, no significant differences were observed in ΔSBP and ΔDBP between the two groups. Of note, among patients aged <60 years, brand-name drugs had a greater SBP-lowering effect compared with generic drugs during the follow-up period, and the between-group difference was 1.5 mmHg (95% CI, 0.2–2.8; $P = 0.03$). The multiplicative interaction was determined using the likelihood ratio test, and the P value of the interaction was <0.001 by age.

Several complementary analyses were conducted in this study. First, considering potential bias due to self-reported BP data, we conducted a sensitivity analysis after excluding these patients (15.9%) via telephone interview during the follow-up period. No significant differences in ΔSBP and ΔDBP were observed between the generic drug group and the brand-name drug group [Supplementary Table S4, http://links.lww.com/CM9/A453]. Second, given that some patients (9.7%) had cross-over in the use of generic and brand-name drugs during the follow-up period, we excluded these patients from the sensitivity analysis. No significant differences in ΔSBP and ΔDBP were observed between the two groups [Supplementary Table S5, http://links.lww.com/CM9/A453].

Table 1: Clinical characteristics of patients using generic drugs and brand-name drugs in the original cohort and the propensity-score-matched cohort.

Characteristics	Original cohort			Matched cohort (1:2 ratio)		
	Brand-name drug ($n = 2176$)	Generic drug ($n = 5779$)	P^*	Brand-name drug ($n = 2176$)	Generic drug ($n = 4352$)	Std Diff†
Age, years	59.2 ± 11.5	59.8 ± 10.7	0.030	59.2 ± 11.5	59.5 ± 10.7	0.03
Men, *n* (%)	1135 (52.2)	2464 (42.6)	<0.001	1135 (52.2)	2101 (48.3)	0.08
Body mass index (kg/m^2)	25.4 ± 3.3	25.5 ± 3.3	0.130	25.4 ± 3.3	25.5 ± 3.2	0.04
Baseline BP (mmHg)						
Systolic BP	147 ± 21.5	153 ± 22.1	<0.001	147 ± 21.5	149 ± 21.1	0.10
Diastolic BP	87 ± 14.0	89 ± 12.9	<0.001	87 ± 14.0	88 ± 12.6	0.08
Fasting serum glucose (mmol/L)	6.3 ± 2.5	6.3 ± 1.8	0.940	6.3 ± 2.5	6.3 ± 1.8	0.01
Lipids profiles (mmol/L)						
Total cholesterol	5.0 ± 1.2	5.5 ± 1.1	<0.001	5.0 ± 1.2	5.4 ± 1.1	0.37
Triglycerides	1.5 (1.0–2.1)	1.7 (1.1–2.3)	<0.001	1.5 (1.0–2.1)	1.7 (1.0–2.3)	0.01
HDL-C	1.2 ± 0.4	1.3 ± 0.4	<0.001	1.2 ± 0.4	1.3 ± 0.4	0.26
LDL-C	3.1 ± 1.0	3.4 ± 0.9	<0.001	3.1 ± 1.0	3.4 ± 0.9	0.28
Current smoking, *n* (%)	537 (25.3)	1603 (28.0)	0.020	537 (25.3)	1234 (28.7)	0.08
Current drinking, *n* (%)	359 (16.8)	1566 (27.4)	<0.001	359 (16.8)	1197 (27.9)	0.27
Medical history, *n* (%)						
Diabetes mellitus	439 (22.0)	967 (19.4)	0.010	439 (22.0)	726 (19.1)	0.07
Coronary heart disease	567 (27.3)	1173 (21.0)	<0.001	567 (27.3)	858 (20.4)	0.16
Stroke	279 (13.1)	848 (14.8)	0.060	279 (13.1)	603 (13.9)	0.03
Annual household income, *n* (%)						
<$8000 (<¥50,000)	262 (12.0)	1919 (33.2)	<0.001	262 (12.0)	1553 (35.7)	0.93
$8000–13000 (¥50,000- ¥80,000)	1009 (46.4)	3425 (59.3)		1009 (46.4)	2450 (56.3)	
≥$13,000 (≥¥80,000)	905 (41.6)	435 (7.5)		905 (41.6)	349 (8.0)	
Framingham risk score‡, *n* (%)						
<10%	1375 (63.2)	3474 (60.1)	0.040	1375 (63.2)	2581 (59.3)	0.08
10%–19%	451 (20.7)	1277 (22.1)		451 (20.7)	1021 (23.5)	
≥20%	350 (16.1)	1028 (17.8)		350 (16.1)	750 (17.2)	
Class of antihypertensive drugs at baseline, *n* (%)						
Calcium channel blocker	1301 (59.8)	3629 (62.8)	0.010	1301 (59.8)	2687 (61.7)	0.04
Angiotensin receptor blocker	861 (39.6)	2255 (39.0)	0.660	861 (39.6)	1741 (40.0)	0.01
Angiotensin converting enzyme inhibitor	613 (28.2)	1201 (20.8)	<0.001	613 (28.2)	1083 (24.9)	0.07
Beta-blocker	1013 (46.6)	1546 (26.8)	<0.001	1013 (46.6)	1515 (34.8)	0.24
Thiazide-type diuretics	360 (16.5)	1356 (23.5)	<0.001	360 (16.5)	724 (16.6)	0.002
Number of antihypertensive drugs at baseline, *n* (%)						
1 medication	789 (36.3)	2677 (46.3)	<0.001	789 (36.3)	1870 (43.0)	0.13
2 medications	888 (40.8)	2103 (36.4)		888 (40.8)	1672 (38.4)	
≥3 medications	499 (22.9)	999 (17.3)		499 (22.9)	810 (18.6)	
Class of antihypertensive drugs at follow-up, *n* (%)						
Calcium channel blocker	1303 (59.9)	3781 (65.4)	<0.001	1303 (59.9)	2826 (64.9)	0.100
Angiotensin receptor blocker	929 (42.7)	2428 (42.0)	0.590	929 (42.7)	1857 (42.7)	0.001
Angiotensin converting enzyme inhibitor	591 (27.2)	1174 (20.3)	<0.001	591 (27.2)	1052 (24.2)	0.070
Beta-blocker	1022 (47.0)	1527 (26.4)	<0.001	1022 (47.0)	1456 (33.5)	0.280
Thiazide-type diuretics	342 (15.7)	1524 (26.4)	<0.001	342 (15.7)	903 (20.7)	0.130
Number of antihypertensive medications at follow-up, *n* (%)						
1 medication	790 (36.3)	2607 (45.1)	<0.001	790 (36.3)	1850 (42.5)	0.140
2 medications	875 (40.2)	1958 (33.9)		875 (40.2)	1507 (34.6)	
≥3 medications	511 (23.5)	1214 (21.0)		511 (23.5)	995 (22.9)	

Values are presented as mean ± standard deviation, *n* (%) or median (interquartile range). *P values were calculated using Chi-square test for categorical variables, the *t* test for continuous variables, or the Mann-Whitney *U* test for triglycerides. †Balance in covariates after matching via the propensity-score-matching method was assessed using standardized difference, with a value of >0.1 representing a meaningful imbalance. ‡The Framingham risk score was calculated according to the conventional risk factors including age, sex, hypertension, diabetes, hypercholesterolemia, and smoking. The low cardiovascular risk corresponded to a score of <10%, medium risk to a score of 10% to 19%, and high risk to a score of ≥20%.[29] BP: Blood pressure; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; Std Diff: Standardized difference; $1 = 6.33 RMB (exchange rate in year 2017).

Table 2: Analysis of SBP-lowering efficacy between generic drug and brand-name drug groups in the matched cohort.

Variables	Mean (95% CI) of SBP-lowering,* mmHg		Adjusted mean (95% CI) of SBP-lowering,† mmHg		Adjusted between-group difference (95% CI) of SBP-lowering,† mmHg	*P* value†
	Brand-name drugs	Generic drugs	Brand-name drugs	Generic drugs		
Matched cohort ($n=6528$)	−9.6 (−10.6, −8.6)	−7.4 (−8.1, −6.7)	−7.9 (−9.9, −5.9)	−7.1 (−9.1, −5.1)	0.9 (−0.1, 1.8)	0.08
By sex						
Men ($n=3236$)	−10.4 (−11.8, −9.0)	−7.6 (−8.6, −6.6)	−8.5 (−11.8, −5.1)	−7.2 (−10.4, −3.9)	1.3 (−0.2, 2.8)	0.09
Women ($n=3292$)	−8.7 (−10.1, −7.3)	−7.3 (−8.2, −6.3)	−12.0 (−15.1, −8.8)	−11.2 (−14.3, −8.0)	0.8 (−0.7, 2.3)	0.29
By age						
<60 years ($n=3258$)	−10.6 (−12.1, −9.1)	−6.9 (−7.9, −6.0)	−7.6 (−10.5, −4.7)	−6.1 (−8.9, −3.3)	1.5 (0.2, 2.8)	0.03
≥60 years ($n=3270$)	−8.6 (−9.9, −7.3)	−7.9 (−8.9, −6.9)	−8.1 (−11.0, −5.2)	−7.8 (−10.6, −4.9)	0.3 (−1.1, 1.7)	0.68
By CVD risk estimated from FRS						
<10% ($n=3956$)	−8.6 (−9.9, −7.4)	−5.9 (−6.8, −5.0)	−6.8 (−9.3, −4.4)	−6.4 (−8.8, −4.0)	0.4 (−0.7, 1.6)	0.47
10%-19% ($n=1472$)	−8.8 (−10.9, −6.7)	−8.1 (−9.5, −6.6)	−4.4 (−9.1, −0.3)	−2.6 (−7.1, 2.0)	1.8 (−0.3, 3.9)	0.09
≥20% ($n=1100$)	−14.4 (−16.8, −12.0)	−12.0 (−13.7, −10.3)	−14.3 (−20.7, −7.8)	−13.3 (−19.8, −6.8)	0.9 (−1.7, 3.6)	0.49
By No. of antihypertensive drugs						
1 medication ($n=2659$)	−6.6 (−8.2, −5.1)	−1.6 (−2.5, −0.7)	−3.4 (−6.7, −0.1)	−2.3 (−5.5, 1.0)	1.1 (−0.3, 2.5)	0.14
2 medications ($n=2560$)	−10.3 (−11.8, −8.9)	−9.5 (−10.6, −8.4)	−9.3 (−12.7, −6.0)	−8.0 (−11.3, −4.7)	1.4 (−0.3, 3.0)	0.10
≥3 medications ($n=1309$)	−13.5 (−19.3, −15.6)	−17.4 (−19.3, −15.6)	−11.9 (−16.1, −7.7)	−11.9 (−16.1, −7.8)	0.01 (−2.2, 2.2)	0.99
By stage of BP at baseline‡						
Normal BP ($n=1954$)	5.6 (4.5, 6.8)	8.3 (7.3, 9.3)	10.7 (7.4, 14.1)	10.6 (7.3, 13.9)	−0.2 (−1.7, 1.3)	0.81
Stage 1 ($n=2360$)	−7.9 (−9.0, −6.7)	−5.4 (−6.2, −4.5)	5.1 (−8.3, −2.0)	−5.3 (−8.4, −2.2)	−0.2 (−1.7, 1.4)	0.83
Stage 2 ($n=1447$)	−20.2 (−22.0, −18.4)	−15.6 (−16.9, −14.4)	−21.7 (−27.1, −16.2)	−19.5 (−24.9, −14.0)	2.2 (−0.1, 4.6)	0.06
Stage 3 ($n=767$)	−41.8 (−44.8, −38.8)	−34.7 (−36.9, −32.4)	−37.0 (−44.0, −33.0)	−35.2 (−41.8, −28.5)	1.9 (−2.0, 5.8)	0.36

Values are presented as mean (95% CI). *Mean (95% CI) of SBP-lowering was calculated using the Student *t* test. †Adjusted mean (95% CI) of SBP-lowering, adjusted between-group difference (95% CI) of SBP-lowering, and *P* value were calculated using generalized linear model after adjusting for age, sex (except in sex-stratified analysis), body mass index, BP (except in BP stage-stratified analysis), current smoking and alcohol status, medical history, annual household income, lipids profile, and number of antihypertensive medications at baseline (except in antihypertensive medication-stratified analysis). ‡The normal BP was defined as BP <140/90 mmHg, stage 1 as SBP 140–159 mmHg and/or DBP 90–99 mmHg, stage 2 as SBP 160–179 mmHg and/or DBP 100–109 mmHg, and stage 3 as SBP ≥180 mmHg, and/or DBP ≥110 mmHg. SBP: Systolic blood pressure; CI: Confidence interval; FRS: Framingham risk score.

Finally, considering that the PSM model might lead to a decrease in statistical power because of the smaller sample size, we repeatedly evaluated the BP-lowering effect of generic and brand-name antihypertensive drugs in the original cohort. The results were comparable with those of the matched cohort [Supplementary Tables S6 and S7, http://links.lww.com/CM9/A453].

Effect of generic and brand-name drugs on the BP control rate

The BP control rates were similar between the generic drug group (42%) and the brand-name drug group (46%) after adjusting for the aforementioned risk factors. Among patients aged <60 years, patients using brand-name drugs had a higher BP control rate compared with those using generic drugs (47% *vs.* 41%, $P=0.02$) [Figure 2A]. The sex-specific analysis showed that BP control rate was higher in male patients using brand-name drugs compared with male patients using generic drugs (46% *vs.* 40%, $P=0.01$) [Figure 2B]. The number of antihypertensive drugs used and the Framingham risk score had no effect on the relationship between antihypertensive drugs and BP control rate [Figure 2C and 2D]. In addition, among patients with CVD and diabetes with a recommended target BP of <130/80 mmHg, the BP control rates were similar between the generic drug group and the brand-name drug group ($P>0.05$). We also evaluated the BP control rate between the two drug groups in the original cohort, and the results were consistent with the matched cohort [Supplementary Figure S1, http://links.lww.com/CM9/A453].

Effect of generic and brand-name drugs on the outcome events at follow-up

The study endpoint was a composite of cardiovascular events including CHD and stroke. After a mean follow-up period of 2.5 years, in total, 320 cardiovascular events (including 158 CHD and 162 stroke events) were documented. Because some patients developed both CHD and stroke during the follow-up period, in these cases, we only considered the follow-up time to the date of the first endpoint (CHD or stroke) in the overall analysis of total CVDs to avoid double counting. After adjusting for the aforementioned potential risk factors, there was no significant association between incident stroke/CHD events and generic drug use or brand-name drug use (all $P>0.05$) [Supplementary Table S8, http://links.lww.com/CM9/A453].

Cost-effectiveness of generic and brand-name drugs for lowering BP

As shown in Table 3, the average annual cost per patient in the generic drug group was significantly lower compared with the annual average cost per patient in the brand-name drug group ($220.4 *vs.* $472.7, respectively). Using generic drugs had an average incremental cost-saving of $252.3 per patient annually, whereas SBP-lowering effect was similar between the two groups (7.1 ± 1.0 *vs.* 7.9 ± 1.0 mmHg, respectively). The CER (average annual cost of reducing SBP by 1 mmHg at follow-up) was 31.0 in the generic drug group and 59.8 in the brand-name drug group; thus, generic drugs treatment yielded an ICER of $315.4 for per mmHg decrease in SBP compared with the brand-name drug treatment.

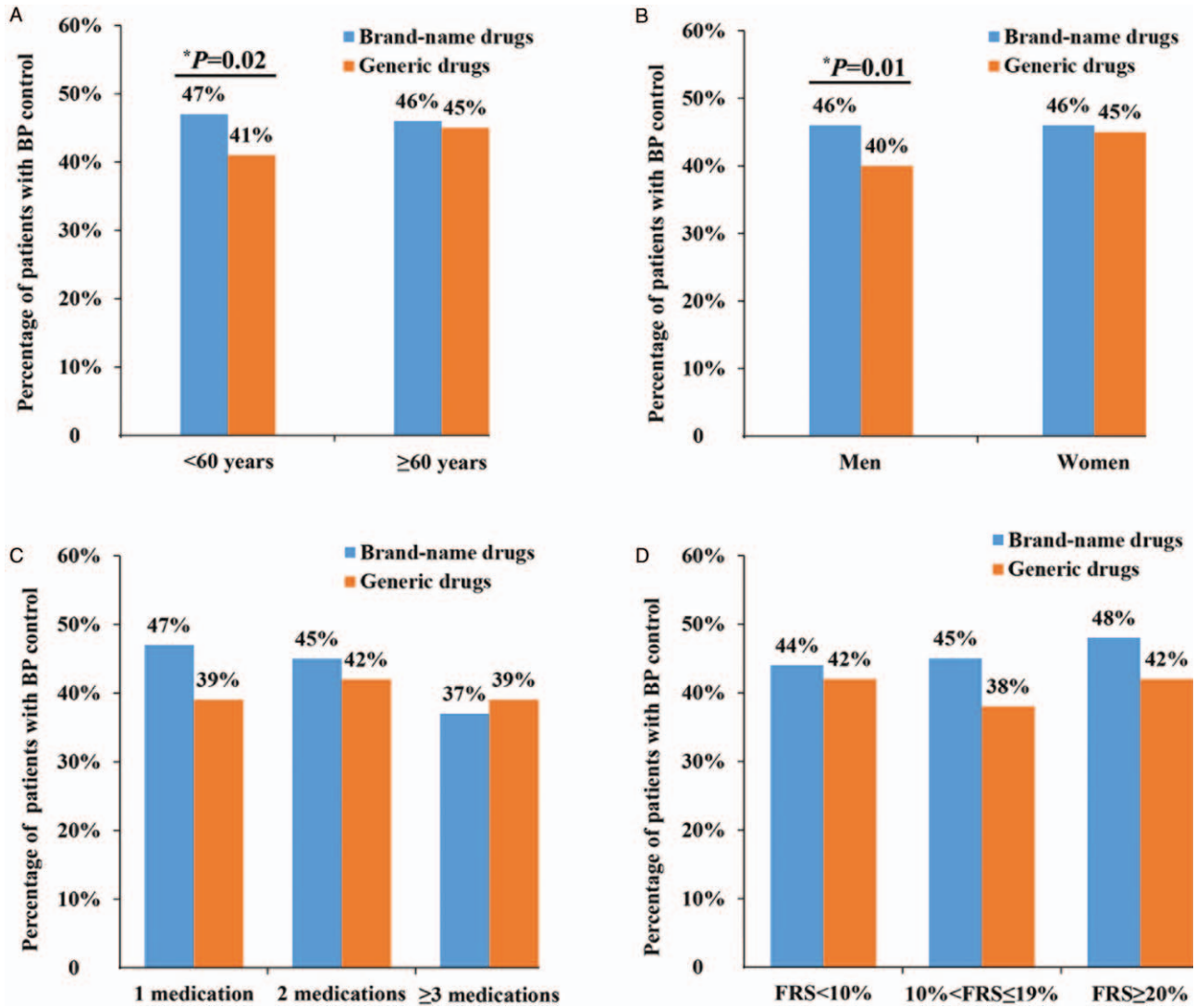

Figure 2: Percentage of BP control in the generic and brand-name drug groups at follow-up in the matched cohort. BP control was defined as BP <140/90 mmHg. Comparisons of BP control rate between generic drugs and brand-name drugs in subgroups stratified by age and sex (A), by number of antihypertensive medications (B), and by Framingham risk score (C), respectively. *P* value was calculated using the logistic regression model after adjusting for age, sex (except in sex-stratified analysis), body mass index, BP, smoking and alcohol status, medical history, annual household income, lipid profiles, and number of antihypertensive medications at baseline (except in antihypertensive medication-stratified analysis). $^{*}P < 0.05$, generic drug group *vs.* brand-name drug group. BP: Blood pressure; FRS: Framingham risk score.

Table 3: Cost-effectiveness analysis of lowering blood pressure in the matched cohort during the follow-up.

	Brand-name drugs ($n = 2176$)	Generic drugs ($n = 4352$)
Costs per patient, $		
Antihypertensive drugs costs	822.6	420.8
Total costs*	1020.0	600.8
Annual average costs	472.7	220.4
Treatment effectiveness,† mmHg	7.9 ± 1.0	7.1 ± 1.0
CER‡	59.8	31.0
ICER§	–	315.4

Values are presented as mean or mean ± standard deviation. *The total cost included antihypertensive drug costs and hypertension-related hospitalization expenditures. †Treatment effectiveness (*E*) was the systolic blood pressure-lowering that adjusted for the aforementioned covariates in footnote of Table 2. The equation is $E = |\text{Follow-up BP} - \text{Baseline BP}|$. ‡The CER was calculated as the ratio of annual average costs per patient (*C*) divided by treatment effectiveness (*E*) in the generic drug and brand-name drug groups: $CER = C/E$. §The ICER was calculated as the difference in annual average costs (ΔC) between generic drugs and brand-name drugs divided by the difference in treatment effectiveness (ΔE) of the two groups: $ICER = \Delta C/\Delta E$. CER: Cost-effectiveness ratio; ICER: Incremental cost-effectiveness ratio.

Discussion

In this multicenter, large-scale cohort study, we evaluated the BP-lowering effect and cost-effectiveness of generic and brand-name antihypertensive drugs. During the 2.5-year follow-up period, there were no significant differences in BP lowering, BP control rate, or occurrence of incident CVDs between the generic drug group and the brand-name drug group. The cost-effectiveness analysis showed that generic drug treatment was cost-saving, with an average incremental annual cost-saving of $252.3 per patient. Among male patients or patients aged <60 years, we observed that brand-name drugs had a greater effectiveness on BP lowering and BP control rate compared with generic drugs. Given their bioequivalence and lower prices, generic drugs are suitable and effective for the control of hypertension.

To date, concerns still exist among patients and physicians in that generic drugs may be clinically inferior to brand-name drugs.[21] The view of editorialists on this issue also remain inconsistent. Among editorials published between 2000 and 2008, 6 of 14 (43%) expressed a negative view about the interchangeability of generic drugs and 8 of 14 (57%) encouraged substitution of generic drugs.[9] One explanation is that commentaries may be more likely to highlight physicians' concerns based on anecdotal experience and non-clinical trials.

Although many bioequivalence trials have reported consistency between generic antihypertensive drugs compared with brand-name antihypertensive drugs, most studies are constrained by small sample sizes (<50 cases) and relatively short follow-up period (the shortest was 24 h, and the longest was 6 months), which led to insufficient statistical power to assess clinical events.[18,22-26] Therefore, instead of comparing one generic drug with its corresponding brand-name drug, we investigated the clinical effectiveness of these two drug types by enlarging the sample size and improving the overall power in this cohort.

Our data show that compared with brand-name drugs, generic drugs can effectively reduce BP and CVD risk at follow up. Considering that multiple complications and risk factor profiles of patients might affect the long-term efficacy and clinical outcomes of antihypertensive drugs, we conducted a further analysis stratified by the Framingham risk score. We found that generic drugs had a comparable effectiveness for lowering BP compared with brand-name drugs among high-risk patients. Among patients with diabetes and CVD with a recommended BP of <130/80 mmHg, the BP control rate was also similar between the two drug groups.

Hypertension is a leading risk factor for CVD. A recent global impact assessment showed that increasing coverage of antihypertensive medications to 70% alone would delay 39.4 million deaths worldwide over 25 years, and treatment of even 50% of patients would greatly reduce cardiovascular mortality.[27] In China, 27.9% of adults (approximately 270 million; ≥18 years of age) have hypertension, but <50% of patients receive treatment and <16% of those have adequate BP control.[28] Specifically, BP control rate is no more than 6% in low- and middle-income areas.[1,2] Poor compliance is largely associated with drug cost. The unaffordability of brand-name drugs is a major barrier to increased medication adherence among patients, especially patients living in rural areas.[2,7]

In our study, the economic analysis indicates that generic drug treatment is highly cost-effective. The data show that patients using generic antihypertensive drugs have equivalent treatment outcomes but pay much lower costs (approximately half) compared with patients using brand-name drugs. These results may reassure physicians and primary healthcare providers to preferentially use generic drugs instead of expensive brand-name drugs to lower BP. In particular, in low- and middle-income areas, significant savings can be achieved through more cost-effective prescription of generic drugs, which may greatly improve BP control and provide public health benefits.

The first major strength of this study is that we used data from a large-scale, community-based cohort that included hypertensive patients at 18 clinic centers in 12 provinces in China. During a 2.5-year follow-up period, we compared the effectiveness of CVDs prevention between generic and brand-name drugs. Second, we minimized possible bias using a uniform protocol to train all physicians and nurses; we also used the same Omron electronic devices to measure BP. Third, considering that treatment effects may be affected by patient characteristics due to the observational study design, we estimated propensity scores and matched patients using brand-name drugs to those using generic drugs, aiming to account for the potential imbalance in patient characteristics between the two groups.

One important limitation should be acknowledged. There was no dosing information of antihypertensive drugs used in each patient, and moreover, the BP-lowering effect among antihypertensive agents within a given class may vary greatly. Therefore, although we controlled age, sex, BP, and number and class of antihypertensive drugs at baseline as covariates to construct the PSM model, the results of our study may be subject to bias. Another important limitation is that our study cannot exclude the potential confounding effect due to differences in drugs used during the follow-up period, even all belonging to generic or brand-name drugs.

Several other limitations of this study should also be mentioned. First, despite our efforts to minimize selection bias through restrictions and PSM analysis, some factors were not measured, such as salt intake and lifestyle changes. Second, one criticism of the PSM method is the small sample size, which may have a decreased statistical power. Therefore, we reevaluated the BP-lowering effect of generic drugs and brand-name drugs in the original cohort, and the effect on BP control was similar between the two groups. Third, we did not assess adverse effects between generic and brand-name drugs due to lack of data such as hypotension, hypokalemia, and renal dysfunction. In addition, we did not collect information regarding the duration of hypertension, so we could not evaluate whether it affects BP control between the two drug types.

Further studies are needed to clarify these issues. Finally, we calculated the cost of antihypertensive agents and hypertension-related hospitalization, but lack of expenditure on other pharmaceutical treatments for CVD and renal disease may have affected the cost-effectiveness estimation.

In summary, a reliable supply of quality-assured and affordable generic drugs will increase the coverage of hypertension treatment, improve BP control rate, and facilitate public health benefits, especially in low- and middle- income areas.

Acknowledgements

The authors would like to acknowledge the physicians and staffs at the collaborating hospitals for data collection and management. And also like to appreciate all participants for their contribution and generous support from Qingdao Huang Hai Pharmaceutical Co., Ltd., Shandong province, China, for supplying the antihypertensive drugs. The authors thank Liwen editor, Edanz Group China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.

Funding

The study was supported by grants from the China National Center for Biotechnology Development fund (Nos. 2018YFC1312400, 2018YFC1312405), the National Science and Technology Pillar Program during the Twelfth Five-year Plan Period (No. 2011BAI11B04), and the Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (No. 2016-I2M-1-006).

Conflicts of interest

None.

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How to cite this article: Zhang SY, Tao LY, Yang YY, Kong T, Wu CJ, Wang Y, Chen JZ, Song L, Wang YB, Hui RT, Zhang WL. Evaluation of blood pressure lowering effect by generic and brand-name antihypertensive drugs treatment: a multicenter prospective study in China. Chin Med J 2021;134:292–301. doi: 10.1097/CM9.0000000000001360