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

Shu-Yuan Zhang1, Li-Yuan Tao2, Yun-Yun Yang1, Tao Kong1, Cun-Jin Wu1, Yang Wang3, Jing-Zhou Chen1, Lei Song1, Yi-Bo Wang1, Ru-Tai Hui1, Wei-Li Zhang1

1State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing 100037, China;
2Research Center of Clinical Epidemiology, Peking University Third Hospital, Beijing 100191, China;
3Medical Research & Biometrics Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing 100037, China.

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 difference in blood pressure 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 1.3 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 areas.

Shu-Yuan Zhang and Li-Yuan Tao contributed equally to this work.

Correspondence to: Prof. Wei-Li Zhang, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Peking Union Medical College & Chinese Academy of Medical Sciences, 167 Beilishi Rd., Xicheng District, Beijing 100037, China
E-Mail: zhangweili1747@yahoo.com

Access this article online

Quick Response Code: www.cmj.org

DOI: 10.1097/CM9.0000000000001360

Copyright © 2021 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2021;134(3)

Received: 17-10-2020 Edited by: Yin-Yan Jie and Xiu-Yuan Hao
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. 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.

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. 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.

Moreover, most studies were bioequivalence trials with small sample sizes and short follow-up periods. Because 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 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 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 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 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 5779 used generic antihypertensive drugs, as indicated by the information collected from doctor’s prescriptions.

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, 7935 patients having both baseline and follow-up data were included in this study; these patients, 2176 used brand-name drugs and 5779 used generic antihypertensive drugs.

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 nonadherence: a score of “≥1” indicated potential nonadherence 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 Supplementary Materials, http://links.lww.com/CM9/A453.
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 ($\Delta C$) between generic drugs and brand-name drugs divided by the difference in treatment effectiveness ($\Delta E$) 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 ($\Delta SBP$) 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 ($\Delta DBP$) 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 antihypertensives drugs, and baseline BP, no significant differences were observed in $\Delta SBP$ and $\Delta DBP$ 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 $\Delta SBP$ and $\Delta DBP$ 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 $\Delta SBP$ and $\Delta DBP$ were observed between the two groups [Supplementary Table S5, http://links.lww.com/CM9/A453].
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 (34.9) <0.001 875 (40.2) 1507 (34.6)  
≥3 medications 511 (23.5) 1214 (21.0) 0.001 511 (23.5) 955 (22.9) 0.001  

Values are presented as mean ± standard deviation, n (%) or median (interquartile range). *P values were calculated using Chi-square test for categorical variables, 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%.

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 |
|-----------|-----------------------------------|---------------------------------------------|
|           | Brand-name drugs                  | Generic drugs                               |
| Matched cohort (n = 6528) | -9.6 (−10.6, −8.6) | −7.4 (−8.1, −6.7) |
| By sex    |                                    |                                             |
| Men (n = 3236) | −10.4 (−11.8, −9.0) | −7.6 (−8.6, −6.6) |
| Women (n = 3292) | −8.7 (−10.1, −7.3) | −7.3 (−8.2, −6.3) |
| By age    |                                    |                                             |
| <60 years (n = 3258) | −10.6 (−12.1, −9.1) | −6.9 (−7.9, −6.0) |
| ≥60 years (n = 3270) | −8.6 (−9.9, −7.3) | −7.9 (−8.9, −6.9) |
| By CVD risk estimated from FRS |                                    |                                             |
| <10% (n = 3956) | −8.6 (−9.9, −7.4) | −5.9 (−6.8, −5.0) |
| 10%-19% (n = 1472) | −8.8 (−10.9, −6.7) | −8.1 (−9.3, −6.4) |
| ≥20% (n = 1100) | −14.4 (−16.8, −12.0) | −12.0 (−13.7, −10.3) |
| By No. of antihypertensive drugs |                                    |                                             |
| 1 medication (n = 2659) | −6.6 (−8.2, −5.1) | −1.6 (−2.5, −0.7) |
| 2 medications (n = 2560) | −10.3 (−11.8, −8.9) | −9.5 (−10.6, −8.4) |
| ≥3 medications (n = 1309) | −13.5 (−15.3, −11.6) | −17.4 (−19.3, −15.6) |
| By stage of BP at baseline† |                                    |                                             |
| Normal BP (n = 1954) | 5.6 (4.5, 6.8) | 8.3 (7.3, 9.3) |
| Stage 1 (n = 2360) | −7.9 (−9.0, −6.7) | −5.4 (−6.2, −4.5) |
| Stage 2 (n = 1447) | −20.2 (−22.0, −18.4) | −15.6 (−16.9, −14.4) |
| Stage 3 (n = 767) | −41.8 (−44.8, −38.8) | −34.7 (−36.9, −32.4) |

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.

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 $310 in the generic drug group and $59.8 in the brand-name drug group; thus, generic drugs treatment yielded an ICER of $315.4 per mmHg decrease in SBP compared with the brand-name drug treatment.

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].
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.x            | –                           | 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 = [Follow-up BP – 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. xThe 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 = ΔC/ΔE. CER: Cost-effectiveness ratio; ICER: Incremental cost-effectiveness ratio.
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.\[25\] 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 Qiangdao Huang Hui 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 Biototechnology 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.

References
1. Yang G, Wang Y, Zeng Y, Gao GF, Liang X, Zhou M, et al. Rapid health transition in China, 1990-2010: findings from the global burden of disease study 2010. Lancet 2013;381:1987-2015. doi: 10.1016/S0140-6736(13)6097-1.
2. Lu J, Lu Y, Wang X, Lindeman GC, Wu C, Cheng X, et al. Prevalence, awareness, treatment, and control of hypertension in China: data from 1.7 million adults in a population-based screening study (China PEACE million persons project). Lancet 2017;390:2549-2558. doi: 10.1016/S0140-6736(17)32478-9.
3. Wang Z, Chen Z, Zhang L, Wang X, Hao G, Zhang Z, et al. China hypertension survey investigators. Status of hypertension in China: results from the China hypertension survey, 2012-2015. Circulation 2018;137:2344-2356. doi: 10.1161/CIRCULATIONAHA.117.032380.
4. Gu D, He J, Coxson PG, Rasmussen PW, Huang C, Thannaaveerat A, et al. The cost-effectiveness of low-cost essential antihypertensive medicines for hypertension control in China: a modelling study. PLoS Med 2015;12:e1001860. doi: 10.1001/medecine.166.3.332.
5. Corrao G, Soranna D, La Vecchia C, Catapano A, Agabiti-Rosei E, Gensini G, et al. Medication persistence and the use of generic and brand-name blood pressure-lowering agents. J Hypertens 2014;32:1146-1153. doi: 10.1097/01.HJH.0000000000001130.
6. Dalen DM, Furu K, Locatelli M, Strom S. Generic substitution: micro evidence from register data in Norway. Eur J Health Econ 2007;11:49-59. doi: 10.1007/s10198-006-0226-w.
7. Choudhry NK, Denberg TD, Qaseem A. Clinical Guidelines Committee of American College of Physicians. Improving adherence to therapy and clinical outcomes while containing costs: opportunities from the greater use of generic medications: best practice advice from the clinical guidelines committee of the American College of Physicians. Ann Intern Med 2016;164:41-49. doi: 10.7326/M14-2427.
8. Svarstad BL, Chewning BA, Sleath BL, Claesson C. The brief medication questionnaire: a tool for screening patient adherence and barriers to adherence. Patient Educ Couns 1999;37:113-124. doi: 10.1016/S0738-3991(98)00107-4.
9. The Ministry of Health of the People’s Republic of China, 2018. China’s Public Health Statistical Yearbook 2018. Beijing, China: The Peking Union Medical College Press.
10. Leclerc J, Blass C, Rochette I, Hamel D, Guenette L, Poirier P. Impact of the commercialization of three generic angiotensin II receptor blockers on adverse events in Quebec, Canada: a population-based time series analysis. Circ Cardiovasc Qual Outcomes 2017;10: e003891. doi: 10.1161/CIRCOUTCOMES.117.003891.
11. Liu Y, Lu C, Chen Q, Wang W, Li SJ, et al. Pharmacokinetics and bioequivalence evaluation of two losartan potassium 50-mg tablets: a single-dose, randomized-sequence, open-label, two-way crossover study in healthy Chinese volunteers. Clin Ther 2010;32:1387-1395. doi: 10.1016/j.clinthera.2010.06.018.
12. Li KY, Liang JP, Hu BQ, Qu Y, Luo CH, Jiang Y, et al. The relative bioavailability and bioequivalence of two tablet formulations of carvedilol 25-mg: a single-dose, randomized-sequence, open-label, two-way crossover study in healthy Chinese male volunteers. Drug Res (Stuttg) 2013;63:747-78. doi: 10.1055/s-0032-1331768.

www.cmj.org
25. Liu Y, Jia J, Liu G, Li S, Lu C, Yu C. Pharmacokinetics and bioequivalence evaluation of two formulations of 10-mg amlodipine besylate: an open-label, single-dose, randomized, two-way crossover study in healthy Chinese male volunteers. Clin Ther 2009;31:777–783. doi: 10.1016/j.clinthera.2009.04.013.

26. Liu YM, Pu HH, Liu GY, Jia JY, Weng LP, Xu RJ, et al. Pharmacokinetics and bioequivalence evaluation of two different atorvastatin calcium 10-mg tablets: a single-dose, randomized-sequence, open-label, two-period crossover study in healthy fasted Chinese adult males. Clin Ther 2010;32:1396–1407. doi: 10.1016/j.clinthera.2010.07.004.

27. Kontis V, Cobb LK, Mathers CD, Frieden TR, Ezzati M, Danaei G. Three public health interventions could save 94 million lives in 25 years. Circulation 2019;140:715–725. doi: 10.1161/CIRCULATIONAHA.118.038160.

28. Zhao D, Liu J, Wang M, Zhang X, Zhou M. Epidemiology of cardiovascular disease in China: current features and implications. Nat Rev Cardiol 2019;16:203–212. doi: 10.1038/s41569-018-0119-4.

29. D’Agostino RS, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743–753. doi: 10.1161/CIRCULATIONAHA.107.699579.

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