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ARTICLE

Generic substitution of amlodipine is not associated with increased risk of mortality or adverse cardiovascular events: An observational cohort study

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Abstract

This study aims to assess clinical outcomes following switching from originator to generic amlodipine. This population-based, matched, cohort study included users of originator amlodipine using claims data during 2018–2020 from a health system in Tianjin, China, in which usage of generic amlodipine was promoted by a drug procurement policy, the national volume-based procurement. Non-switchers refer to those remained on originator after the policy, while pure-switchers were those who switched to and continued using generic amlodipine, and back-switchers were those switched to generic amlodipine but then back to the originator. Propensity score matching generates comparable non-switchers and pure-switchers pairs, and non-switchers and back-switchers pairs. The primary outcome was major adverse cardiovascular events (MACEs), defined as all-cause mortality, stroke, and myocardial infarction during follow-up (April 1, 2019 to December 30, 2020). Secondary outcomes included heart failure, atrial fibrillation, and adherence to amlodipine. The hazard ratio (HR) for each clinical outcome was assessed through Cox proportional hazard regression. In total, 5943 non-switchers, 2949 pure-switchers, and 3061 back-switchers were included (mean age: 62.9 years; 55.5% men). For the matched pairs, pure-switchers ($N=2180$) presented no additional risks of clinical outcomes compared to non-switchers ($N=4360$) (e.g., MACEs: 2.86 vs. 2.95 events per 100 person-years; HR = 0.97 [95%CI: 0.70–1.33]). Back-switchers ($N=1998$) also presented no additional risk compared to non-switchers ($N=3996$) for most outcomes except for stroke (HR = 1.55 [95%CI: 1.03–2.34]). Pure-switchers and back-switchers all had better amlodipine adherence than non-switchers. Generic substitution of amlodipine is not associated with increased risk of cardiovascular events or all-cause mortality, but improves medicine adherence.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Generic substitution is widely proposed, but debates persist on its clinical efficacy and safety in real-world practice, particularly for antihypertensive medicines.

WHAT QUESTION DID THIS STUDY ADDRESS?

Is the risk of clinical outcomes different for patients who switched from originator to generic amlodipine (Switchers) compared with those who remained on the originator (non-switchers)?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Generic substitution of amlodipine is not associated with increased risk of mortality or adverse cardiovascular events by comparing the incidence of clinical outcomes between pure-switchers (those switched to and continued using generic amlodipine) and non-switchers, or between back-switchers (those switched to generic amlodipine but switched back to the originator) and non-switchers, while it improves adherence for switchers.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Generic substitution of amlodipine may be an effective and cost-saving way for hypertension management.

INTRODUCTION

Offering substantially lower prices than the branded originators, generic medicines are widely considered to support sustainable health development.[1] Many health systems mandatorily require evidence of bioequivalence of a generic medicine to its originator in entry approval, which, however, only justify the equivalent rate and extent of absorption instead of therapeutic efficacy.[2–6] Debates have been persisting on the clinical efficacy and safety of generic substitution,[7–9] with emerging real-world evidence on the comparative effectiveness in the field of oncology,[10–13] endocrine and metabolic diseases,[14–16] and mental disorders.[17–19] However, data are lacking for medicines that manage hypertension, the most common condition and a strong silent killer undermining population health.[20,21]

Indeed, practitioners are unclear whether generic substitution is more or less effective or safer in managing hypertension in real-world clinical practice. Previous randomized controlled trials (RCTs) comparing the efficacy of antihypertensive generics and originators were mostly based on healthy subjects with very limited sample sizes.[22–24] Our systematic search of the literature (Table S1) found only five cohort studies that compared the clinical benefits, in terms of blood pressure control, mortality, and incidence of adverse cardiovascular events, between antihypertensive originators and their corresponding generics.[4,15,25–27] Among these, three studies compared among new users or all users of originator and generic antihypertensive medicines.[15,25,26] Two studies compared continuous originator users and switchers to generics.[4,27] Conflicting findings are not uncommon. For example, Tian et al.[15] found a higher risk of negative events for new users of certain generic antihypertensive drugs than new originator users, but this trend was reversed for other antihypertensive drugs. Leclerc et al.,[27] reported an decreased risk of mortality for patients who switched to some type of generic angiotensin receptor blockers (ARBs) but no difference for the others. Such contradictions are also reported in other clinical fields such as mental disorders,[4,17–19] diabetes,[4,15] dyslipidemia.[14,28,29] Causes were attributed to the potential selection bias in defining the cohorts, as the preference for originator or generics may vary substantially among patients/physicians.[30,31]

In this retrospective cohort study we compared the incidence of clinical outcomes between continuous users of originator amlodipine, and users who switched from originator to generic amlodipine in Tianjin, China. We took advantage of China's National Volume-based Procurement (NVBP) policy to define study cohorts, which mandatorily required hospitals to increase procurement/usage volume of the target generic medicines.[32] We focus on amlodipine because it had the largest negotiated procurement volume and was the only Calcium Channel Blocker (CCB) included in the policy. Since switching is most likely driven by the exogenous policy, our design largely avoids the bias of patient selection and is able to provide more valid evidence for the comparative effectiveness of generic substitution.

METHODS

The reporting followed the guideline of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). The Tolerability and Ethics Committee of the School of Pharmaceutical Science and Technology in Tianjin University waived the requirement of ethics approval for the current study as this was a retrospective observational study using anonymous claims data.

Patient selection and study design

We obtain claims data from the Urban Employee Basic Medical Insurance (UEBMI) scheme in Tianjin, China, during 2018–2020. With a per-capita disposable income of CNY 39,506, 140.0% of the national average level,[33,34] this health system accommodates 5.75 million beneficiaries in 2018, of which 1.5 million were recorded diagnoses of hypertension. The Chinese government implemented the NVBP policy at the end of 2018.[32,35] The policy promoted the use of 23 generics, including amlodipine, where the bid-winning generics must be qualified with proven bioequivalence to their originators.[32] In Tianjin, the policy initiated at April 1, 2019, when the UEBMI mandatorily required increasing the use of bid-winning generics to 60–70%. Consequently, nearly half originator users switched to bid-winning generic amlodipine after April 1, 2019 in Tianjin (Figure S1).

We draw a random sample of 30% beneficiaries from Tianjin's UEBMI based on the anonymous IDs uniquely assigned to each beneficiary in Tianjin's UEBMI. We include a baseline period of 12 months prior to the index date, that is, the first amlodipine prescription after April 1, 2019 (Figure 1). We define an originator amlodipine user as a beneficiary who had at least two separate outpatient records of hypertension diagnoses and at least two outpatient records of originator amlodipine prescriptions in the baseline period. We exclude users who discontinued amlodipine, defined as no amlodipine prescription 60 days before the index date. For chronic conditions, this approach was widely used in the literature to define the discontinuation of a medicine.[36,37] We also exclude beneficiaries who discontinued enrolling the UEBMI, and users of non-bid-winning generic amlodipine which did not show evidence of bioequivalence and were not promoted by the policy (Figure S2).

To define the cohorts, we adopt an inclusion period of 6 months (April 1, to September 30, 2019). We then separate switchers and non-switchers among all originator amlodipine users. We define a patient to be a non-switcher if he/she continued using the originator amlodipine, and a switcher if he/she switched to generic amlodipine in the inclusion period. We exclude patients whose "switching" to generic amlodipine happened after the inclusion period because we believe that "switching" during the inclusion period is most likely affected by the exogenous policy. Among switchers, we further separate pure-switchers if the patients continued using generic amlodipine afterward; and back-switchers if the patients switched back and forth between originator and generic amlodipine during the follow-up period (Figure 1, Figure S2).

We apply identical inclusion and exclusion criteria for the three cohorts. Each cohort was followed from the index date to censoring (the end of 2020, UEBMI disenrollment, died) or 3 months after amlodipine discontinuation, using the same 60-day criteria.

Outcomes

We ascertain outcomes from April 1, 2019 to December 30, 2020. The primary outcome is any incidence of major adverse cardiovascular events (MACEs), defined as all-cause mortality, stroke, and myocardial infarction (MI). Causes were identified by the ICD-10 (Table S2). We ascertain two types of secondary outcomes: other cardiovascular events, and the prescription, adherence, and discontinuation of amlodipine. Other cardiovascular events include heart failure and atrial fibrillation, which are also highlighted in Chinese guidelines for hypertension management.[21] We appraise amlodipine prescription by reporting daily dosage per patient, and the length of

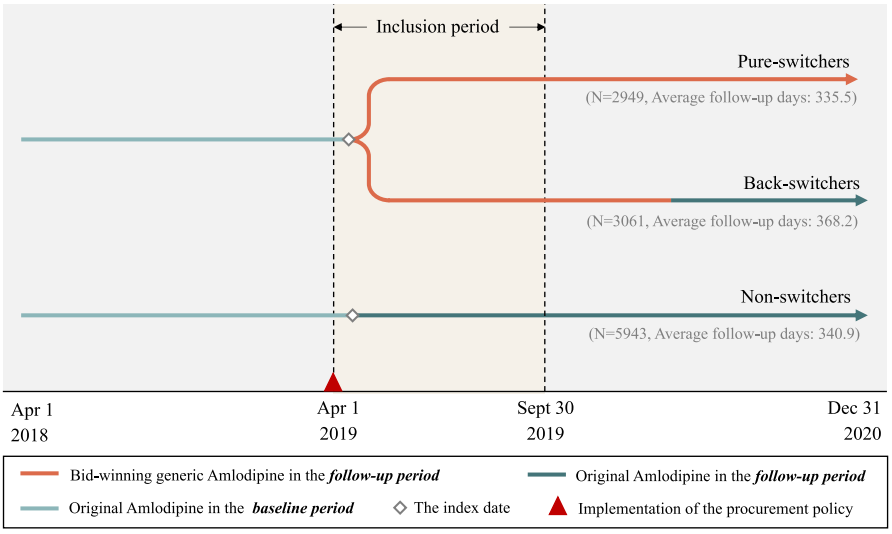

FIGURE 1 Study design. All back-switchers had ≥1 switching between original and bid-winning generic amlodipine after the index date, but to simplify the illustration, only the first switching (generic to original) after the index date was displayed in Figure 1.

days per prescription. We ascertain amlodipine adherence by measuring the proportion of days covered (PDC) which was calculated as the number of days covered by amlodipine prescriptions divided by the follow-up days, using 0.8 as the cut-off point to define adequate adherence.[38,39]

Covariates

We adjust four types of baseline characteristics. For demographic characteristics, we include age and sex. For comorbidities, we include diabetes, dyslipidemia, peripheral arterial disease, chronic kidney disease, and charlson comorbidity index (CCI). We also count the baseline clinical outcomes and uptake of procedures of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). For baseline medication, we include patients' use of other antihypertensive medicines, including angiotensin-converting enzyme inhibitor (ACEI), ARB, diuretics, α-blocker, β-blocker, and their fixed-dose combinations. Finally, we include patients' baseline healthcare utilization characteristics, including admission, number of outpatient encounters, and associated costs.

Statistical analysis

We report the means (SDs) and frequencies/proportions of patients' baseline characteristics for the three cohorts, adopting Chi-square tests and t-tests to compare across cohorts. We perform propensity score matching (PSM) to generate pure-switchers and non-switchers pairs, and back-switchers and non-switchers pairs, respectively. For each set of matching, we include all baseline covariates in a logistic regression to estimate the propensity score and then perform 2:1 nearest matching without replacement. The propensity score was defined as the probability of switching from originator to generic amlodipine, conditioning on the covariates.

Based on the matched pairs, we analyze clinical outcomes at the time of the occurrence of the first event. For each clinical outcome, we report the Kaplan–Meier survival curves and perform the log-rank tests to compare pure-switchers and non-switchers, and back-switchers and non-switchers, respectively. We then perform Cox proportional hazard regression to estimate the risk for the incidence of clinical outcomes and the risk of discontinuation, between the two types of switchers to non-switchers. We employ logistic regression to estimate the effect of switching on medicine adherence. Statistics analysis was conducted using STATA 15.0 (StataCorp LP, College Station, TX, USA). The significance level was set as two-sided $\alpha < 0.05$.

Sensitivity analysis

To test how amlodipine adherence and discontinuation may affect the results, we perform two subgroup analyses stratifying the cohorts by quartiles of PDC value or time to discontinuation. We also perform four types of sensitivity analyses to check whether our findings are sensitive to the analytical approach. First, the data show that 80% of the "switching" happened within 180 days after April 1, 2019, the implementation of the policy (Figure S3). In practice, we adopt an inclusion period of 6 months, and we believe that switching to generic amlodipine would more likely be affected by such an exogenous policy, if "switching" happened closer to the implementation date. To test whether such a choice would affect the findings, we additionally perform the analyses using 1, 2, 3, and 9 months to define the inclusion period, as well as including all patients without an inclusion period. Second, to test whether tailoring the sample by PSM would affect the results, we performed the same analyses in unmatched cohorts. Third, we exclude patients who report any baseline cardiovascular event or procedure, including stroke, MI, heart failure, atrial fibrillation, CABG, or PCI, to check with the main analysis. Fourth, considering the relatively short time of exposure, we only include patients who have 12 months and above of exposure in the follow-up period to check the robustness.

RESULTS

Sample and follow-up

We include 20,509 originator amlodipine users from the baseline period. We then excluded 5777 users who discontinued originator amlodipine before the index date, 1829 users of non-bid-winning generics, 61 users who dis-enrolled insurance, and 799 users who switched to generic amlodipine after the inclusion period. We finally arrived at 11,953 originator amlodipine users: 5943 non-switchers, 2949 pure-switchers, and 3061 back-switchers (Figure S2). After PSM, 4360 of the non-switchers were matched to 2180 pure-switchers, while 3996 non-switchers were matched to 1998 back-switchers (Details of PSM: Tables S3, S4, Figure S4).

The cohorts of non-switchers, pure-switchers, and back-switchers were followed up for 340.9, 335.5, and 368.2 days, respectively (Table S5). The leading reasons of censoring were discontinuation of amlodipine (73.4%), followed by end of study (23.6%), UEBMI dis-enrollment (1.5%), and death (1.4%). Reasons for censoring do not differ between non-switchers and pure-switchers or back-switchers, except that discontinuation of amlodipine were

slightly lower in back-switchers ($p < 0.001$). PSM does not change these patterns (Table S6).

Patient characteristics

The mean age of the three cohorts was 62.9 (SD 12.9) years. 55.5% were males. With a mean CCI of 2.2 (SD 1.9), 36.9%, 67.9%, and 16.1% of the patients had records of diabetes, dyslipidemia, and chronic kidney diseases, respectively. The cohorts also recorded a variety of baseline outcomes of stroke (4.2%), heart failure (3.4%), atrial fibrillation (2.4%), and MI or procedure of revascularization (7.7%). Rates of annual admission were 31.0% among these patients, who were also treated by a variety of other types of antihypertensive medicines at the baseline (Table 1).

Before matching, both types of switchers were older than non-switchers (63.1/64.4 vs. 61.9). They also had slightly higher CCI (2.3/2.4 vs. 2.1), higher incidence of cardio-cerebrovascular events, and higher admission and medical costs at the baseline. The PSM largely balanced these characteristics, reporting no statistical difference after matching (Tables S7, S8).

Main outcomes

Figures 2, S5, and S6 show the Kaplan-Meir survival curves for each clinical outcome and compare them between matched pairs of pure-switchers and non-switchers, and back-switchers and non-switchers. The cumulative incidence curves overlap for most of the comparisons, with each log-rank test reporting statistical insignificance. However, the incidence of stroke seems to be higher among the back-switchers compared to the non-switchers (Log-rank test: $Chi^2 = 4.91$, $p = 0.029$).

Among the matched pairs (Figure 3), 2.6% pure-switchers experienced MACEs during the follow-up period (2.86 events per 100 patients-years), where 1.2% died, 1.5%, 0.1%, 2.2%, and 1.5% were recorded incidence of stroke, MI, heart failure and atrial fibrillation, respectively. Similarly, 3.3% back-switchers experienced MACEs during the follow-up period (3.32 events per 100 patients-years), where 1.0% died, 2.2%, 0.5%, 2.1%, and 1.6% recorded incidences of stroke, MI, heart failure, and atrial fibrillation, respectively.

Figure 3 also reports the hazard ratios (HRs) comparing between switchers and non-switchers for the risk for incidence of each outcome, adjusting for all baseline covariates. The analyses are also stratified by pure-switchers versus non-switchers, and back-switchers versus non-switchers. All comparisons report small-sized hazard ratios, with no statistically significant difference identified between pure-switchers and non-switchers for each outcome. When comparing between back-switchers and non-switchers, the hazard ratios are no different from 1 for most outcomes as well, despite 55% higher risk was found for stroke in back-switchers than non-switchers (adjusted HR: 1.55 [95%CI: 1.03–2.34]).

Medication prescription and adherence

Table 2 describes the prescription, adherence, and discontinuation of amlodipine for the three cohorts after matching. Results for the unmatched cohorts are similar (Table S9). For the matched pairs, back-switchers reported the highest value of amlodipine daily dosage (7.44 mg/day), followed by pure-switchers (6.57 mg/day), and non-switchers (6.02 mg/day). The length of days per amlodipine prescription was 30.9 and 27.8 days for pure-switchers and back-switchers, respectively, which were also higher than the average of 24.1 days for non-switchers.

Amlodipine adherence, measured as PDC, and discontinuation show a similar pattern, where switchers reported better adherence (PDC = 0.55 for pure-switchers and 0.59 for back-switchers) than non-switchers (PDC = 0.52). Notably, back-switchers report the lowest possibility of amlodipine discontinuation than the other two cohorts (adjusted HR: 0.85 [95%CI: 0.80–0.91] comparing back-switchers with non-switchers, 1.01 [95%CI: 0.96–1.07] comparing pure-switchers with non-switchers).

Sensitivity analyses

The subgroup analyses by quartiles of PDC and time to amlodipine discontinuation are reported in Table S10 and Figure S7. No difference in hazards is found when comparing pure-switchers to non-switchers for each outcome in either subgroup. Back-switchers reported largely indifferent hazards for most outcomes, despite stroke. Notably, back-switchers who had higher PDC values (Quartile 3 [PDC: 0.53–0.73] and 4 [PDC > 0.73]), and who had a longer time to amlodipine discontinuation (Quartile 4, >520 days) reported a substantially higher risk of stroke as compared to non-switchers.

The four groups of sensitivity analyses report that neither the choice of inclusion period, the methods of matching, including/excluding patients who had baseline cardiovascular events or procedures, nor the time of follow-up, affect the findings in the main analyses (Table S11).

TABLE 1 Baseline characteristics of switchers and non-switchers, before propensity score matching.

Characteristic	Non-switchers (*N* = 5943)	Switchers			Total (*N* = 11,953)
		Pure-switchers (*N* = 2949)	Back-switchers (*N* = 3061)	All switchers (*N* = 6010)	
Age, mean (SD), yr	61.9 (12.8)	63.1 (13.1)***	64.4 (12.6)***	63.8 (12.8)***	62.9 (12.9)
Sex					
Male	3250 (54.7)	1726 (58.5)**	1656 (54.1)	3382 (56.3)**	6632 (55.5)
Medical history					
Charlson comorbidity index, mean (SD)	2.1 (1.9)	2.3 (2.0)***	2.4 (2.0)***	2.4 (2.0)***	2.2 (1.9)
Coronary artery bypass grafting	29 (0.5)	29 (1.0)**	15 (0.5)	44 (0.7)**	73 (0.6)
Percutaneous coronary intervention	377 (6.3)	224 (7.6)*	272 (8.9)***	496 (8.3)*	873 (7.3)
Diabetes	2168 (36.5)	1122 (38.0)	1125 (36.8)	2247 (37.4)	4415 (36.9)
Dyslipidemia	4007 (67.4)	1960 (66.5)	2144 (70.0)*	4104 (68.3)	8111 (67.9)
Peripheral arterial disease	238 (4.0)	133 (4.5)	169 (5.5)*	302 (5.0)	540 (4.5)
Chronic kidney disease	936 (15.7)	468 (15.9)	521 (17.0)	989 (16.5)	1925 (16.1)
Baseline outcomes					
Stroke	192 (3.2)	156 (5.3)***	154 (5.0)**	310 (5.2)***	502 (4.2)
Myocardial infarction	6 (0.1)	22 (0.7)***	18 (0.6)**	40 (0.7)***	46 (0.4)
Heart failure	181 (3.0)	113 (3.8)	107 (3.5)	220 (3.7)	401 (3.4)
Atrial fibrillation	112 (1.9)	76 (2.6)*	97 (3.2)***	173 (2.9)*	285 (2.4)
Concomitant drugs					
ACEI	613 (10.3)	350 (11.0)*	352 (11.5)	702 (11.7)*	1315 (11.0)
ARB	2861 (48.1)	1516 (51.4)**	1574 (51.4)**	3090 (51.4)***	5951 (49.8)
Diuretics	299 (5.0)	200 (6.8) **	117 (5.8)	377 (6.3)**	676 (5.7)
β-blocker	2594 (43.6)	1225 (41.5)	1318 (43.1)	2543 (42.3)	5137 (43.0)
α-blocker	57 (1.0)	44 (1.5)*	38 (1.2)	82 (1.4)*	139 (1.2)
αβ-blocker	118 (2.0)	74 (2.5)	53 (1.7)	127 (2.1)	245 (2.0)
CCB/ACEI	20 (0.3)	16 (0.5)	19 (0.6)	35 (0.6)*	55 (0.5)
CCB/ARB	65 (1.1)	48 (1.6)*	39 (1.3)	87 (1.4)	152 (1.3)
ACEI/Diuretic	5 (0.1)	3 (0.1)	4 (0.1)	7 (0.1)	12 (0.1)
ARB/Diuretic	1438 (24.2)	775 (26.3)*	690 (22.5)	1465 (24.4)	2903 (24.3)
Healthcare utilization					
All-cause admissions[a]	1447 (24.3)	1127 (38.2)	1131 (36.9)	2258 (37.6)	3705 (31.0)
Hypertension-related admissions[a]	55 (0.9)	29 (1.0)	32 (1.0)	61 (1.0)	116 (1.0)

TABLE 1 (Continued)

Characteristic	Non-switchers (*N* = 5943)	Switchers			Total (*N* = 11,953)
		Pure-switchers (*N* = 2949)	Back-switchers (*N* = 3061)	All switchers (*N* = 6010)	
No. of all-cause outpatient visits per patient, mean (SD)	38.6 (36.2)	38.4 (32.7)	40.0 (33.3)	39.2 (33.0)	38.9 (34.6)
No. of hypertension-related outpatient visits per patient, mean (SD)	15.0 (14.7)	16.0 (16.5)**	15.9 (13.0)**	16.0 (14.8)***	15.5 (14.8)
Direct medical cost					
All-cause cost per patient, median (IQR), ¥	6961 (4814–14,994)	7741 (5008–21,097)***	8032 (5253–20,772)***	7855 (5121–20,816)***	7340 (4958–18,251)
Hypertension-related cost per patient, median (IQR), ¥	2698 (1719–3964)	2935 (1809–4734)***	2954 (1940–4685)***	2944 (1887–4696)***	2835 (1805–4277)

Note: Values are numbers (percentages) unless otherwise indicated.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; IQR, interquartile range; no., number; SD, standard deviation; yr, year.

[a]The admission rate was calculated by dividing the number of hospitalizations by the total number of patients.

* Indicates $p < 0.05$. **Indicates $p < 0.01$. ***Indicates $p < 0.001$ when compared with non-switchers. p values were computed by Student's t-tests for mean comparisons, by median test for median comparison, and by Chi-square tests for categorical variables.

DISCUSSION

Main findings

In this retrospective cohort study, we assess the incidence of cardiovascular events and all-cause mortality following switching from originator to generic amlodipine, after the implementation of an exogenous policy aiming to promote generic substitution in China. We separate two groups of analyses that compare continuous originator users (non-switchers) with pure-switchers to generics who continued using generic amlodipine, and back-switchers who switched back and forth between originator and generic amlodipine. During about 1 year's follow-up, we found no difference in the incidence of clinical outcomes across the cohorts, though the risk of stroke seems to be slightly higher among back-switchers than the non-switchers. Compared to the non-switchers, both pure-switchers and back-switchers report higher daily dose and better medication adherence to amlodipine.

Interpretations

The negative clinical impact of generic substitution in 'real-life' hypertension management remains largely unknown. Given ethical or regulatory considerations, prior RCTs that evaluated the efficacy of generic antihypertensive medicines were based on healthy populations, with very limited sample size (<100) and several weeks' follow-up.[22–24] Most previous cohort studies adopted the head-to-head design, with new or all users divided into the originator cohort and the generic cohort for comparison. Only two cohort studies compared continuous originator users and switchers to generic antihypertensive medicine.[4,27] However, these studies may encounter substantial selection bias because some patients or physicians might be more/less prone to originators/generics if given the choice freely.[30,31] Our study provides unique evidence because the NVBP mandatorily requires a substantially increasing volume of generic amlodipine, the only CCB in the policy. Since switching to generic amlodipine is more likely driven by the policy, our design largely avoids potential selection bias and provides more valid evidence to test the clinical equivalence of large-scale generic substitution in real-world practice.

Despite concerns on bioequivalence, previous literature raised two major explanations to how generic substitution may affect clinical effectiveness. On the one hand, some argue that patients tend not to believe in generic medicines, and the psychological suspicions may negatively affect the treatment efficacy or tolerability, which

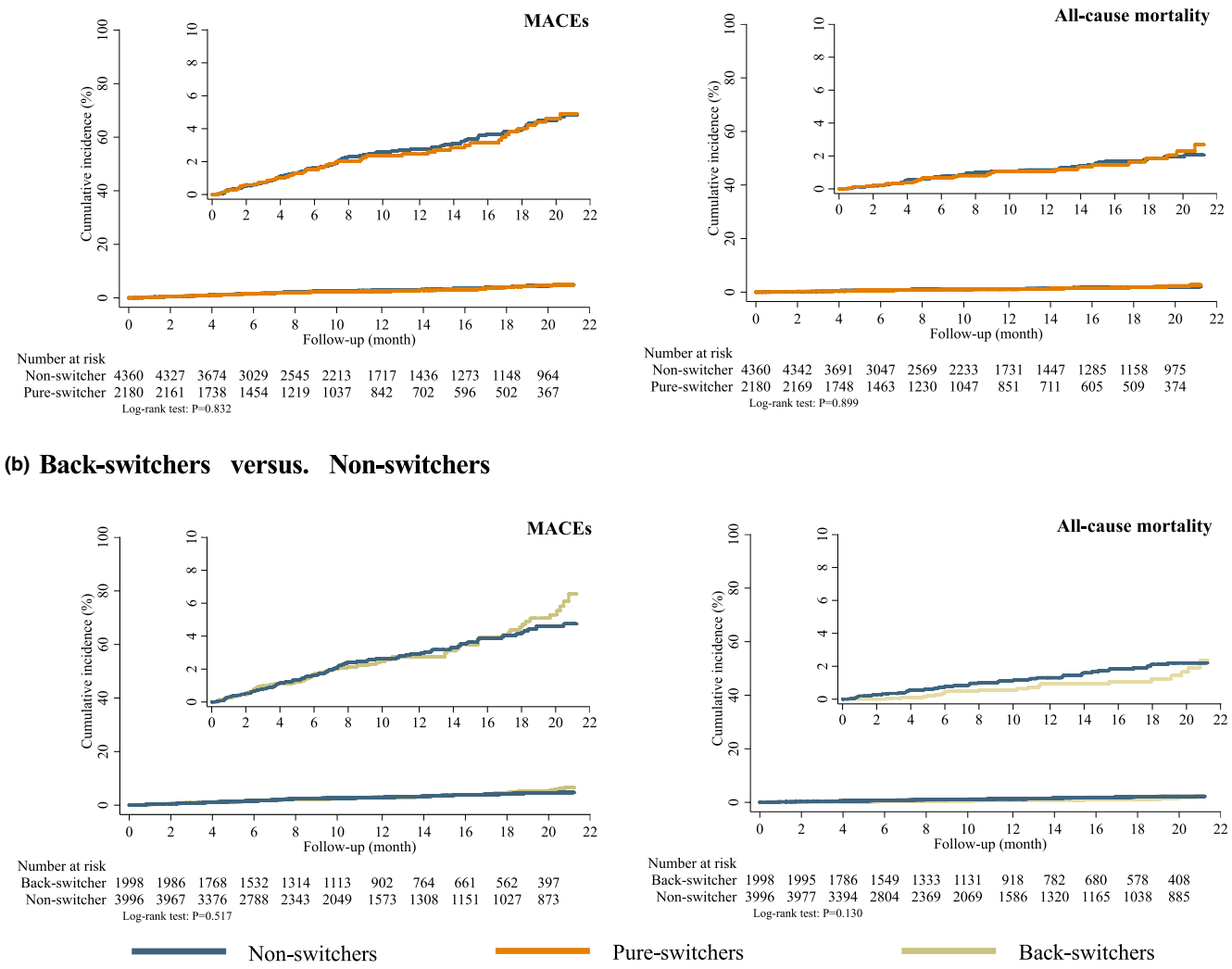

FIGURE 2 Comparison of cumulative incidence of MACEs and mortality between (a) pure-switchers and (b) non-switchers, and back-switchers and non-switchers, after propensity score matching. MACEs, major adverse cardiovascular events.

eventually leads to a higher occurrence of adverse events, that is, the nocebo effects.[40,41] While on the other hand, evidence is emerging that better adherence and consequent improvement in clinical outcomes may be observed in generic users because of the less expensive prices.[42,43] Our data provide a better understanding of these conflicting mechanisms by separating pure-switchers and back-switchers, which is the first attempt in the comparative effectiveness literature.

Pure-switchers are less likely to be affected by the nocebo effects than back-switchers because the initial switching to generics is largely affected by the exogenous policy, and they do not switch back to the originator later on. We observe better medication adherence and a similar possibility of amlodipine discontinuation comparing pure-switchers to non-switchers, which supports the second mechanism that better adherence may be associated with generic substitution. However, this does not support the existence of nocebo effects. Because should patients not believe in generics, they would be more likely to discontinue treatment and less likely to adhere to such prescription.[40] To control the confounding of medication use, we further stratified our analyses by quartiles of PDC and time to discontinuation. The consistent findings of no difference in the incidence of clinical outcomes between pure-switchers and non-switchers therefore suggest satisfied clinical equivalence of generic amlodipine in our case.

Compared to non-switchers, back-switchers of amlodipine reported equivalent risks of MACEs, despite that a 55% higher hazard ratio were observed for the incidence of stroke. Back-switchers were older, who had higher Charlson comorbidity index, and higher baseline MACEs prevalence than non-switchers. The PSM largely

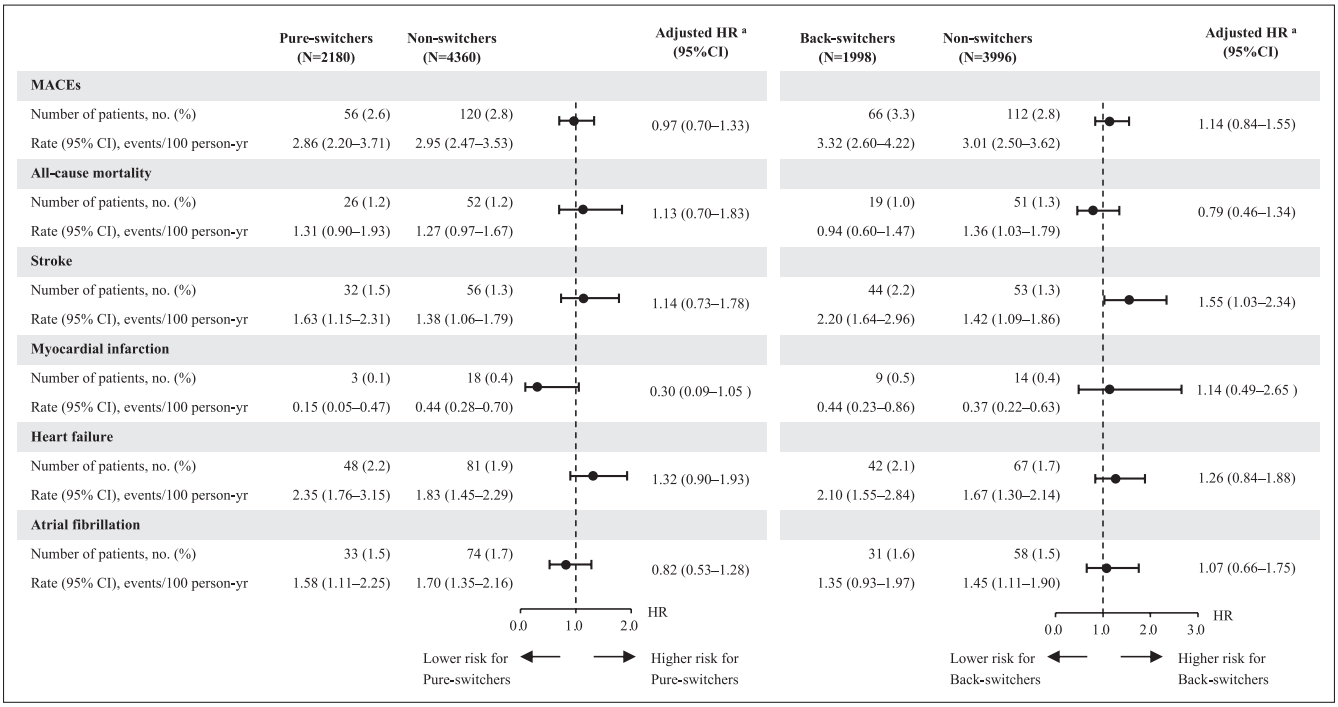

FIGURE 3 Association between switching and cardiovascular outcomes and mortality, after propensity score matching. *The hazard ratios were adjusted for all baseline covariates. CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; No., number; Yr, year.

balanced these observable confounders, and our sensitivity analyses excluding cases with baseline MACEs reported similar findings also. One possible explanation is that back-switchers were themselves more liable to stroke, but these factors were not fully documented in the records. Notably, we find that back-switchers relied more on amlodipine than non-switchers, with back-switchers reporting significantly higher daily dosage, better adherence, and lower likelihood to discontinue amlodipine compared to non-switchers. This evidence does not support the nocebo effects either. Amlodipine is the most commonly used CCB and the only CCB included in the policy. The Chinese guidelines for hypertension management recommends priority use of CCB for patients who have cerebrovascular diseases, including minor causes that are liable to stroke.[21] Back-switcher had the highest baseline prevalence of atrial fibrillation, dyslipidemia, and chronic kidney disease, which were all risk factors for stroke.[44–46] However, the claims data may not record all risk factors such as the blood pressure,[47] for which physicians should have more information and judgment. In the subgroup analyses, we report a rising extra risk of stroke among back-switchers as compliance to amlodipine increases (Table S10, Figure S5). The increasing risk of stroke among back-switchers may thus reflect additional selection bias out of control, since patients liable to stroke may be more likely to rely on amlodipine. Future studies are warranted to better understand the differences between pure-switchers and back-switchers in generic substitution practice.

Strengths and limitations

We conduct the first cohort study that compares risks of cardiovascular events and mortality between originator and generic antihypertensive medicines in Asia. By separating pure-switchers and back-switchers, we provide insights into the possible mechanisms that may affect the real-world clinical effectiveness of generic substitution.

Our study has several important limitations. First, although we believe that the exogenous policy facilitates generating better comparable cohorts, both groups of switchers are older and less healthy than the non-switchers at the baseline. The PSM may largely balance the cohorts, however, the extra higher risk of stroke in back-switchers still suggests uncontrolled selection bias. Second, the cohorts recorded about 70% of amlodipine discontinuation and PDC values ranging 0.52–0.59 during nearly 1 year's follow-up. Compliances are generally low, thus our study might not be powerful enough to detect the clinical benefits. However, these data corroborate findings from other real-world studies.[48,49] The subgroup analyses stratifying patients by PDC and time to discontinuation report consistent findings, also suggesting that medication

TABLE 2 Comparison of the prescription, adherence, and discontinuation of amlodipine between pure-switchers and non-switchers, and back-switchers and non-switchers, after propensity score matching.

Amlodipine treatment	Pure-switchers vs. Non-switchers			Back-switchers vs. Non-switchers		
	Pure-switchers (*N* = 2180)	Non-switchers (*N* = 4360)	*p* value	Back-switchers (*N* = 1998)	Non-switchers (*N* = 3996)	*p* value
Average daily dosage, mean (SD), mg/day	6.57 (5.53)	6.02 (5.34)	<0.001	7.44 (18.17)	6.06 (5.47)	<0.001
Length of days per prescription, mean (SD), day	30.9 (9.3)	24.1 (7.3)	<0.001	27.8 (7.5)	23.9 (7.3)	<0.001
Adherence						
PDC, mean (SD)	0.55 (0.25)	0.52 (0.24)	<0.001	0.59 (0.22)	0.52 (0.24)	<0.001
PDC, median (IQR)	0.55 (0.35–0.74)	0.50 (0.32–0.70)	<0.001	0.59 (0.41–0.77)	0.50 (0.32–0.70)	<0.001
PDC distribution, no. (%)						
(0, 0.2]	97 (4.4)	399 (9.2)		46 (2.3)	359 (9.0)	
(0.2, 0.4]	602 (27.6)	1117 (25.6)		417 (20.9)	1000 (25.0)	
(0.4, 0.6]	544 (25.0)	1265 (29.0)		579 (29.0)	1162 (29.1)	
(0.6, 0.8]	511 (23.4)	950 (21.8)		547 (27.4)	887 (22.2)	
(0.8, 1.0]	426 (19.5)	629 (14.4)		409 (20.5)	588 (14.7)	
Adjusted OR (95%CI) of being adherent[a,b]	1.44 (1.25–1.65)	1 [Reference]	<0.001	1.47 (1.27–1.69)	1 [Reference]	<0.001
Discontinuation						
Patients who discontinued amlodipine, no. (%)	1669 (76.6)	3254 (74.6)	0.089	1413 (70.7)	2984 (74.7)	0.001
Time to discontinuation[c], mean (SD), day	262.4 (220.9)	275.2 (116.1)	0.029	305.6 (219.9)	275.6 (224.8)	<0.001
Time to discontinuation[c], median (IQR), day	199 (57–455)	224 (70–497)	0.038	258 (104–542)	228 (70–486)	<0.001
Adjusted HR (95%CI)[a]	1.06 (0.99–1.12)	1 [Reference]	0.056	0.85 (0.80–0.91)	1 [Reference]	<0.001

Note: Continuous data are presented as the mean (standard deviation) or as the median (interquartile range), and categorical data are presented as *n* (%). *p*-values were computed by Student's *t*-tests for mean comparisons, by median test for median comparison, and by Chi-square tests for categorical variables.

Abbreviations: CI, confidence interval; HR, hazard ratio; IQR, interquartile range; no., number; OR, odds ratio; PDC, proportion of days covered; SD, standard deviation.

[a]The odds ratio and hazard ratio were adjusted for all baseline covariates.

[b]Being adherent indicates PDC > 0.8.

[c]Time to discontinuation refers to the number of days between the index date and the data that the last fill before discontinuation had ran out, and was truncated to the end of the follow-up period for patients who did not discontinue amlodipine.

compliance may not bias the results. Third, we do not ascertain cardiovascular mortality because the claims data does not provide data for causes of death. We evaluate all-cause mortality instead and specify a comprehensive list of adverse cardiovascular events. Fourth, we only evaluate one CCB in the market and just follow about 1 year. Nevertheless, many clinical trials evaluating the efficacy of antihypertensive drugs have also employed relatively short follow-up durations, ranging from a few weeks to about 1 year.[22–24,50–52] We have also conducted sensitivity analysis by only including patients with a follow-up duration longer than 1 year to validate the robustness of the study findings, however, caution on follow-up duration is still needed when interpreting the findings.

CONCLUSIONS

Generic substitution for originator amlodipine does not appear to affect clinical outcomes. Better medication adherence among switchers to generics suggests that generic substitution of amlodipine seems acceptable. Future research is warranted regarding the increasing risk of stroke among back-switchers, long-term effects of generic substitution, and comparative pharmacoeconomic analysis.

AUTHOR CONTRIBUTIONS

B.Y.Z., J.W., and X.L.F. wrote the manuscript; J.W. and X.L.F. designed the research; B.Y.Z. and C.Z.L. performed the research; B.Y.Z. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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