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Comparative effectiveness of generic nifedipine versus Adalat long-acting nifedipine for hypertension treatment: A multi-institutional cohort study

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Abstract

This retrospective multi-institutional database analysis aimed to evaluate the blood-pressure-lowering efficacy and clinical outcomes of a generic versus brand-name nifedipine for hypertension management. A total of 12 693 patients who were prescribed a generic or brand-name nifedipine between January 1, 2011, and December 31, 2018, were identified from the Chang Gung Research Database of Chang Gung Memorial Hospitals, Taiwan. Among them, 2112 (21.4%) were prescribed generic nifedipine. After propensity score matching, both the generic and brand-name groups consisted of 2102 patients. At a mean follow-up of 3 years, the changes in office systolic (p for interaction = .791) and diastolic blood pressure (p for interaction = .689) did not differ significantly between the patients who received the generic and the brand-name nifedipine. There was no significant difference between the two study groups regarding the composite of all-cause mortality, acute myocardial infarction, stroke, coronary revascularization, or hospitalization for heart failure (hazard ratio 0.98, 95% confidence interval 0.85–1.13; $p = .774$). In conclusion, the generic nifedipine was comparable to its brand-name counterpart regarding office blood pressure reduction and the composite cardiovascular outcome for the treatment of patients with hypertension.

KEYWORDS
blood pressure, generic drug, nifedipine, outcome

1 | INTRODUCTION

Hypertension has long been considered a leading modifiable risk factor for cardiovascular disease.[1,2] The global burden of hypertension was 1.4 billion people in 2010, and the number may substantially exceed 1.6 billion by 2025.[3] In 2010, however, only approximately 14% of patients with hypertension had their systolic BP controlled below 140 mmHg.[3] The 2017 American College of Cardiology/American Heart Association Guidelines has lowered the diagnostic threshold for hypertension in adults to systolic BP ≥130 mmHg and/or diastolic BP ≥80 mmHg.[4] When this new definition was applied, the prevalence of hypertension in the US general population increased from 32.0% to 45.4%,[5] and

the increase was even greater in the Chinese general population, from 23.2% to 46.4%.[6]

Generic drugs, containing the same active chemical ingredients as brand-name products, provide an opportunity to offer similar treatments at a lower cost to patients and payers and thus have a huge impact on health policy and economics. Generic drugs have been increasingly used in daily practice worldwide and account for more than 80% of all prescriptions in the US.[7] To apply for regulatory approval, generic drug manufacturers are required to scientifically document pharmaceutical equivalence and bioequivalence with innovator drugs. However, a bioequivalence study typically requires only 24–36 healthy persons to qualify for "abbreviated" approval by the US Food and Drug Administration.[8] Since preclinical or clinical data to establish safety and efficacy are not mandatory for generic drug approval, whether pharmaceutical equivalence and bioequivalence with brand-name drugs could translate to equivalent clinical outcomes remains uncertain.

Long-acting nifedipine is one of the commonly prescribed dihydropyridine calcium-channel blockers (CCBs) for BP control. The osmotic-controlled release oral delivery system (OROS) uses osmotic pressure as the driving force to push the active drugs through the laser-drilled openings and thus ensures a more predictable pharmacokinetic profile.[9,10] In Taiwan, a postmarketing surveillance study has examined the efficacy of BP control and the tolerability of nifedipine OROS among hypertensive patients,[11] but clinical outcomes were not reported. The lack of long-term outcome data may raise concerns about the "clinical equivalence" of generic and brand-name drugs. In this study, we aimed to compare the BP-lowering effect and clinical outcomes of the generic and branded nifedipine OROS formulations for hypertension treatment.

2 | METHODS

2.1 | Data source

We used the Chang Gung Research Database (CGRD) to conduct this retrospective multi-institutional cohort study. The CGRD is derived from the electronic medical records of seven Chang Gung Memorial Hospitals (CGMH), including two medical centers, two regional hospitals, and three district hospitals, together covering 1.3 million patients, accounting for 6% of the population of Taiwan.[12,13] The CGRD contains standardized patient-level information since 2001, including disease category data, laboratory test results, imaging and procedural reports, prescription drugs, and the use of medical facilities. Disease diagnoses were coded using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes before 2016, and the ICD-9-CM and ICD-10-CM codes thereafter. To protect patient privacy and to ensure anonymity, the CGRD has encrypted all patients' personal identifiable information. Therefore, the requirement for informed consent was waived. This study was approved by the Institutional Review Board at Linkou Chang Gung Memorial Hospital, Taiwan (IRB No.201901524B0).

2.2 | Study population

A new user design was adopted to compare the generic nifedipine with the brand-name nifedipine. We first identified 23 921 patients who were diagnosed with hypertension and treated with the OROS formulations of generic (Nifedipine S.RFC, Chunghwa Yuming Healthcare Co., Taiwan) or brand-name nifedipine (Adalat OROS, Bayer) at a dose of 30 mg daily between January 1, 2011, and December 31, 2018, from the CGRD. We then excluded patients who were younger than 20 years old and had previously been prescribed any dihydropyridine CCBs (including the two study drugs). The date of the first prescription of the study drugs was defined as the index date, and the first 90 days after the index date was defined as the exposure time window. The use of the study drugs was ascertained by at least two outpatient prescriptions or one refilled prescription for treating chronic illness during the first 90-day window after the index date. We further excluded the patients who were concomitantly prescribed other dihydropyridine CCBs, switched between the generic and brand-name nifedipine, had died or developed cardiovascular events during the first 90 days after the index date, or had a follow-up period of less than 90 days, or whose baseline BP data were missing. Among the 12 693 patients who were eligible for further analysis, 2112 (16.6%) were prescribed generic nifedipine. **Figure 1** illustrates the details of patient inclusion and exclusion.

2.3 | Office BP

Information on office BP at follow-up clinic visits was extracted from the nursing records of the CGRD. At CGMH, BP measurement was performed by trained nurses with standardized techniques. Patients were required to rest for at least 5 minutes in a seated position before BP was measured. With the patient's arm resting on a desk, BP was measured with automated upper-arm cuff BP measurement devices (GE Dinamap Carescape V100, Florida, USA), which had been validated[14] and checked periodically for proper functioning.

2.4 | Clinical outcomes and follow-up

The primary outcome was major adverse cardiovascular events, which were defined as the composite of all-cause death, acute myocardial infarction (AMI), stroke, coronary revascularization (ie, percutaneous coronary intervention and coronary bypass graft surgery), and hospitalization for heart failure (HF). All of the abovementioned outcomes were detected using the inpatient claims data. AMI was identified with discharge diagnosis and ascertained with elevated cardiac troponin-I levels above the 99th percentile of upper reference limit. The diagnosis of stroke was further confirmed by brain imaging studies (computed tomography or magnetic resonance imaging). Coronary revascularization was identified by the Taiwan National Health Insurance reimbursement code. The diagnosis of HF required HF symptoms (eg, dyspnea) and elevated natriuretic peptide levels

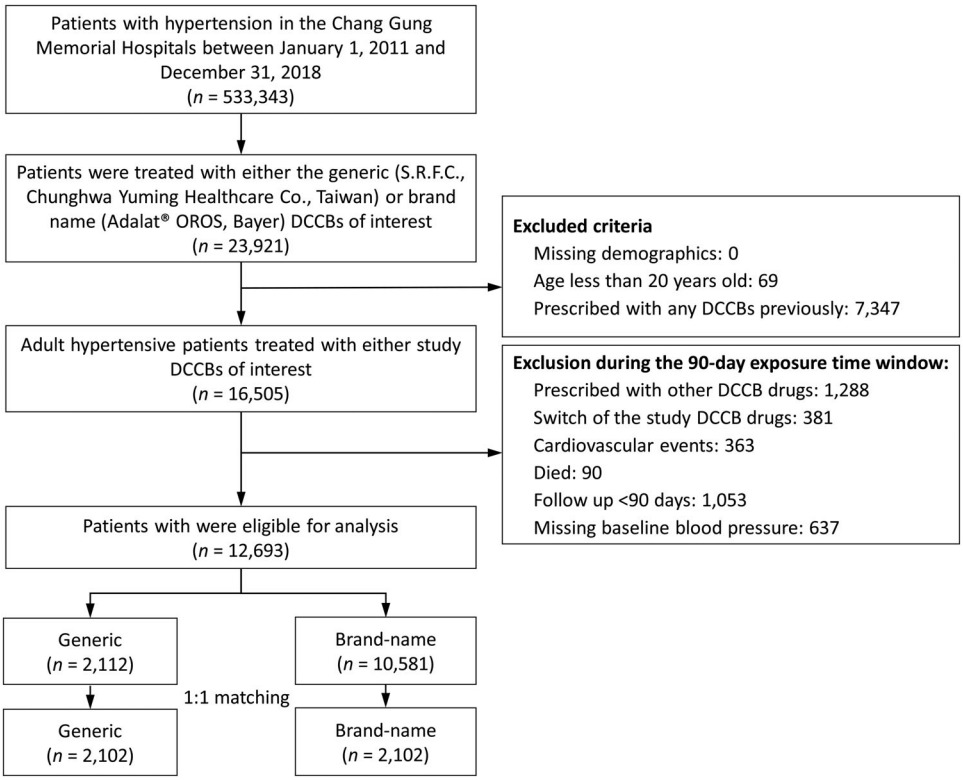

FIGURE 1 **Flowchart for patient inclusion and exclusion**. Abbreviations: DCCB, dihydropyridine calcium-channel blocker; OROS, osmotic-controlled release oral delivery system

(B-type natriuretic peptide > 100 pg/mL or N-terminal probrain natriuretic peptide > 300 pg/mL)[15] in addition to the inpatient diagnosis. All patients were followed from the index date until the occurrence of clinical outcomes, discontinuation of the initial study drug, any switch between the generic and brand-name nifedipine, the day of death, or the end of the database follow-up (September 30, 2019), whichever came first.

2.5 | Covariates

The baseline covariates in this study included demographic data (age, sex, body mass index, history of smoking), comorbidities, the Charlson Comorbidity Index (CCI) score, the use of antihypertensive medications other than dihydropyridine CCBs, the use of other medications (ie, antiplatelet agents and oral hypoglycemic agents), vital signs (office systolic blood pressure [SBP], office diastolic blood pressure [DBP], and heart rate), and laboratory test results (ie, low-density lipoprotein cholesterol and serum creatinine). Other comorbidities were identified by any inpatient diagnosis or at least two outpatient diagnoses registered before the index date with the use of the ICD-9-CM and ICD-10-CM codes. Baseline medications were prescriptions during the 90-day window after the index date extracted from the medical records of CGRD. Laboratory data at the index date were also extracted from the outpatients' medical records of CGRD.

2.6 | Statistical analysis

We used the propensity score matching method to reduce confounding when comparing outcomes between generic and brand-name nifedipine. The propensity score, the predicted probability to be included in the generic nifedipine group, was derived from multivariable logistic regression using all the covariates listed in Table 1, except that the follow-up year was replaced by the index date. The continuous variables (eg, age) were not converted to categorical variables in the calculation of propensity score and the linearity between the continuous variables and the predicted probability was assumed. Patients in the generic nifedipine group and in the brand-name nifedipine group were matched at a 1:1 ratio. The matching was processed using a greedy, nearest-neighbor algorithm, with a caliper of 0.2 times the standard deviation of the logit of the propensity score, with random matching order and without replacement. The balance of baseline characteristics between the two groups was assessed using the absolute value of the standardized difference (STD), where a value of less than 0.1 was considered a negligible difference. Some records of body mass index, heart rate, and laboratory tests were missing (the available numbers of each covariate are listed in detail in Table 1). Therefore, the original data was singly imputed using the Expectation–Maximization algorithm and the matching was conducted on the imputed cohort.

The changes in the two groups' long-term office systolic and diastolic BP measurements from baseline over the course of follow-up

TABLE 1 Baseline characteristics of patients who were prescribed the generic and the brand-name nifedipine

	Before matching				After matching		
Variables	**Available number**	**Generic (no. = 2112)**	**Brand-name (no. = 10 581)**	**STD**	**Generic (no. = 2102)**	**Brand-name (no. = 2102)**	**STD**
Age, years	12 693	63.7 ± 15.1	62.8 ± 14.4	0.07	63.8 ± 15.1	63.9 ± 14.5	<0.01
Male	12 693	1,106 (52.4)	5865 (55.4)	−0.06	1,102 (52.4)	1106 (52.6)	<0.01
Body mass index, kg/m^2	9588	26.3 ± 4.5	26.7 ± 4.6	−0.07	26.4 ± 4.1	26.3 ± 4.2	0.01
Smoker	12 693	372 (17.6)	1723 (16.3)	0.04	368 (17.5)	396 (18.8)	−0.03
Cardiovascular disease							
Coronary artery disease	12 693	350 (16.6)	2267 (21.4)	−0.12	350 (16.7)	334 (15.9)	0.02
Peripheral artery disease	12 693	128 (6.1)	551 (5.2)	0.04	128 (6.1)	132 (6.3)	−0.01
Acute coronary syndrome	12 693	45 (2.1)	289 (2.7)	−0.04	45 (2.1)	45 (2.1)	<0.01
Stroke	12 693	163 (7.7)	927 (8.8)	−0.04	163 (7.8)	163 (7.8)	<0.01
Any cardiovascular disease	12 693	566 (26.8)	3282 (31.0)	−0.09	566 (26.9)	549 (26.1)	0.02
Comorbidity							
Diabetes mellitus	12 693	803 (38.0)	3766 (35.6)	0.05	794 (37.8)	815 (38.8)	−0.02
Chronic kidney disease	12 693	863 (40.9)	3535 (33.4)	0.15	853 (40.6)	906 (43.1)	−0.05
Atrial fibrillation	12 693	105 (5.0)	467 (4.4)	0.03	105 (5.0)	108 (5.1)	−0.01
Malignancy	12 693	548 (25.9)	2,290 (21.6)	0.10	544 (25.9)	545 (25.9)	<0.01
Prior heart failure	12 693	83 (3.9)	351 (3.3)	0.03	81 (3.9)	84 (4.0)	−0.01
Liver cirrhosis	12 693	76 (3.6)	296 (2.8)	0.05	75 (3.6)	85 (4.0)	−0.02
Chronic obstructive pulmonary disease	12 693	183 (8.7)	875 (8.3)	0.01	182 (8.7)	178 (8.5)	0.01
Charlson's Comorbidity Index score	12 693	2.8 ± 2.6	2.4 ± 2.4	0.16	2.8 ± 2.6	2.9 ± 2.8	−0.05
Anti-hypertensive medications							
ACE inhibitors/ARBs	12 693	1068 (50.6)	5400 (51.0)	−0.01	1064 (50.6)	1093 (52.0)	−0.03
Beta-blockers	12 693	953 (45.1)	4819 (45.5)	−0.01	946 (45.0)	945 (45.0)	<0.01
Diuretics	12 693	508 (24.1)	2294 (21.7)	0.06	504 (24.0)	519 (24.7)	−0.02
Alpha blockers	12 693	30 (1.4)	277 (2.6)	−0.09	30 (1.4)	46 (2.2)	−0.06
Nitrates	12 693	107 (5.1)	621 (5.9)	−0.04	106 (5.0)	107 (5.1)	<0.01
Vasodilators	12 693	403 (19.1)	1905 (18.0)	0.03	400 (19.0)	408 (19.4)	−0.01
Number of anti-hypertensive agents	12 693	1.45 ± 1.16	1.45 ± 1.13	<0.01	1.45 ± 1.16	1.48 ± 1.11	0.03
Other medications							
Antiplatelet agents	12 693	586 (27.7)	3470 (32.8)	−0.11	585 (27.8)	589 (28.0)	<0.01
Metformin	12 693	348 (16.5)	1923 (18.2)	−0.04	347 (16.5)	350 (16.7)	<0.01
GLP-1 receptor agonists	12 693	13 (0.6)	26 (0.2)	0.06	11 (0.5)	14 (0.7)	−0.02
SGLT2 inhibitors	12 693	17 (0.8)	61 (0.6)	0.03	17 (0.8)	16 (0.8)	0.01
Other oral hypoglycemic agents	12 693	421 (19.9)	2126 (20.1)	<0.01	420 (20.0)	437 (20.8)	−0.02
Insulin	12 693	207 (9.8)	754 (7.1)	0.10	204 (9.7)	226 (10.8)	−0.03
Statins	12 693	580 (27.5)	3277 (31.0)	−0.08	579 (27.5)	572 (27.2)	0.01
Fibrates or gemfibrozil	12 693	59 (2.8)	398 (3.8)	−0.05	59 (2.8)	64 (3.0)	−0.01
Vital signs at baseline							
Systolic blood pressure, mm Hg	12 693	155.3 ± 26.1	157.4 ± 24.8	−0.08	155.4 ± 26.1	155.1 ± 24.9	0.01
Diastolic blood pressure, mm Hg	12 693	84.8 ± 17.0	85.8 ± 16.0	−0.06	84.7 ± 16.4	84.6 ± 16.0	0.01
Heart rate, beats/min	12 613	80.5 ± 15.5	79.9 ± 14.9	0.04	80.5 ± 15.4	80.6 ± 15.2	−0.01

(Continues)

TABLE 1 (Continued)

Variables	Before matching				After matching		
	Available number	Generic (no. = 2112)	Brand-name (no. = 10 581)	STD	Generic (no. = 2102)	Brand-name (no. = 2102)	STD
Laboratory data at baseline							
LDL-C, mg/dL	9744	74.2 ± 58.7	73.9 ± 59.3	0.01	74.2 ± 50.5	73.7 ± 48.2	0.01
HDL-C, mg/dL	9182	45.9 ± 14.3	46.6 ± 13.2	−0.05	46.3 ± 12.0	46.2 ± 11.4	0.01
Non-HDL-C, mg/dL	7485	137.3 ± 41.6	138.3 ± 40.3	−0.02	137.5 ± 35.1	136.5 ± 34.9	0.03
Total cholesterol, mg/dL	9969	183.2 ± 43.6	185.2 ± 41.9	−0.05	184.0 ± 37.8	182.6 ± 37.1	0.04
Triglyceride, mg/dL	9794	154.8 ± 104.2	152.1 ± 99.1	0.03	154.2 ± 89.5	150.3 ± 83.7	0.04
HbA1C, %	7959	6.7 ± 1.5	6.8 ± 1.5	−0.02	6.62 ± 1.23	6.61 ± 1.20	0.01
Fasting glucose, mg/dL	8234	118.8 ± 42.8	118.8 ± 42.6	<0.01	118.9 ± 35.1	119.1 ± 37.6	<0.01
Creatinine, mg/dL	12 006	2.3 ± 2.9	1.9 ± 2.5	0.14	2.2 ± 2.8	2.4 ± 3.0	−0.07
eGFR, mL/min/1.73m^2	12 006	60.4 ± 36.3	65.4 ± 34.6	−0.14	61.2 ± 35.5	59.2 ± 35.8	0.06
Uric acid, mg/dL	8413	6.7 ± 1.9	6.7 ± 1.9	−0.01	6.6 ± 1.6	6.6 ± 1.7	−0.01
ALT, U/L	10 711	27.8 ± 22.1	27.6 ± 20.9	0.01	27.8 ± 20.5	28.1 ± 21.0	−0.02
AST, U/L	7038	30.4 ± 19.6	29.8 ± 18.1	0.03	29.5 ± 16.0	29.8 ± 16.4	−0.02
Follow-up, years	12 693	3.0 ± 2.3	3.8 ± 2.3	−0.38	3.0 ± 2.3	3.2 ± 2.1	−0.11

Data were presented as frequency (percentage) or mean ± standard deviation.

Abbreviations: ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; ARBs, angiotensin receptor blockers; AST, aspartate transaminase; eGFR, estimated Glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1C, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; SGLT2, sodium-glucose co-transporter 2; STD, standardized difference.

were compared using a linear mixed model. Two random effects were set in the linear mixed model: the intercept (the baseline value) and the slope (the effect of time). Cox proportional hazards model was used to compare the risks of fatal time-to-event outcomes (ie, all-cause death and the composite outcome) between the generic and brand-name nifedipine groups. The Fine and Gray subdistribution hazards model was used to account for the competing risk of death in the comparison of the two groups' risks of nonfatal time-to-event outcomes (ie, MI, stroke, HF, or coronary revascularization). The study group was the only explanatory variable in the survival models. The within-pair clustering of outcomes after matching was accounted for by using a robust standard error.[16]

Furthermore, we performed subgroup analysis on the primary composite outcome stratifying by several prespecified variables at baseline, including age (< 65 and ≥65 years), sex, body mass index (< 27 and ≥27 kg/m^2 [the World Health Organization definition of obesity for Asian populations]),[17] SBP (< 140, 140–160, and ≥160 mmHg), DBP (< 90, 90–100, and ≥100 mmHg), history of any cardiovascular disease, diabetes, estimated glomerular filtration rate (eGFR; < 30, 30–60, and ≥60 mL/min/1.73 m^2), CCI score (< 3 and ≥3), alanine aminotransferase (ALT; < 35 U/L [1× upper limit of normal] and ≥35 U/L), and use of statins. A two-sided *p*-value < .05 was considered to be statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Patient characteristics

A total of 12 693 patients were eligible for this study. Among them, there were 2112 incident users of the generic nifedipine and 10 581 were incident users of the brand-name nifedipine. The patient characteristics are shown in Table 1. Before propensity score matching, the mean ages were 63.7 ± 15.1 and 62.8 ± 14.4 years (STD = 0.07) and male patients constituted 52.4% and 55.4% (STD = 0.06) of the generic group and the brand-name group, respectively. Atherosclerotic cardiovascular disease was common in both groups (26.8% vs 31.0%; STD = 0.09), with coronary artery disease more prevalent in the brand-name group (16.6% vs 21.4%; STD = 0.12). The generic group had a markedly higher CCI score (2.8 ± 2.6 vs 2.4 ± 2.4; STD = 0.16) due to their higher prevalence of chronic kidney disease (40.9% vs 33.4%; STD = 0.15) and malignancy (25.9% vs 21.6%; STD = 0.1). Concomitant use of other antihypertensive drugs was common and the numbers in the two groups were comparable (1.45 vs 1.45, STD < 0.01). Approximately half of the patients received angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, 45% received beta-blockers, and 22% received diuretics. There was no significant difference in baseline systolic (155.3 vs 157.4 mmHg; STD = 0.08) and diastolic BP (84.8 vs 85.8 mmHg; STD = 0.06) and heart rates (80.5 vs 79.9 beats per minute; STD = 0.04) between the two groups.

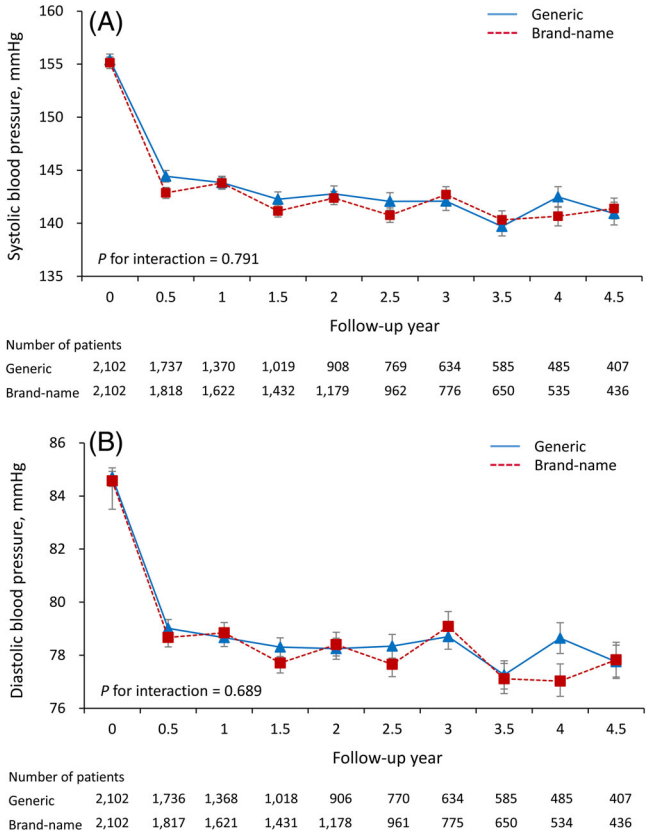

FIGURE 2 Changes in the office systolic (A) and diastolic (B) blood pressure measurements at the long-term follow-up visits

In addition, the generic group was more frequently prescribed insulin (9.8% vs 7.1%; STD = 0.1), and the brand-name group was more frequently prescribed antiplatelet agents (27.7% vs 32.8%, STD = 0.11) due to a higher prevalence of CAD. No significant difference between the two groups was observed in terms of the use of other antidiabetic drugs, statins or other lipid-lowering agents, vital signs, or laboratory data, except that eGFR was markedly lower in the generic group (60.4 ± 36.3 vs 65.4 ± 34.6 mL/min/1.73 m^2; STD = 0.14) due to a higher prevalence of chronic kidney disease. The follow-up period was 3.0 ± 2.3 years in the generic group and 3.8 ± 2.3 years in the brand-name group (STD = 0.38). After propensity score matching, all covariates were balanced between the two groups (Table 1).

3.2 | Office BP

As shown in **Figure 2**, there was no significant difference between the generic and the brand-name nifedipine regarding the changes in office BP measurements throughout clinical follow-up (*p* for interaction = .791 for SBP and .689 for DBP). At a mean follow-up of 3 years, the mean SBP was 140.9 mmHg in the generic group and 141.4 mmHg in the brand-name group (*p* = .748), and the mean DBP was 85.3 mmHg in the generic group and 85.0 mmHg in the brand-name group (*p* = .939). The mean reduction in SBP from baseline was 12.5 mmHg in the generic group and 14.8 mmHg in the brand-name group (*p* = .281); the mean reduction in DBP from baseline was 7.5 mmHg in the generic group and 7.1 mmHg in the brand-name group (*p* = .734). The mean number of additional antihypertensive drugs administered per patient was comparable at the end of follow-up (1.33 vs 1.33; *p* = .938). The percentages of patients who achieved the conventional target BP of < 140/90 mmHg were 45.2% and 48.4% in the generic and the brand-name groups, respectively (*p* = .349), while the numbers decreased to 23.6% and 27.7%, respectively, when the intensive target BP of < 130/80 mmHg was applied (*p* = .169).

3.3 | Clinical outcomes

Table 2 shows the results of the primary outcome and its components after propensity score matching. At a mean follow-up of 3 years, the primary outcome occurred in 15.6% of the generic group and in 17.1% of the brand-name group (hazard ratio [HR] 0.98; 95% confidence interval [CI] 0.85–1.13). The cumulative event rates for the primary outcome are shown in **Figure 3**. There was no significant difference between the two groups with respect to all-cause death (6.9% vs 6.2%; HR 1.22; 95% CI 0.97–1.54), MI (1.9% vs 2.3%; subdistribution HR [SHR] 0.87; 95% CI 0.58–1.32), stroke (4.4% vs 4.8%; SHR 0.97; 95% CI 0.73–1.28), HF hospitalization (4.5% vs 5.9%; SHR 0.81; 95%

TABLE 2 Clinical outcomes of the patients prescribed with the generic and the brand-name nifedipine in the propensity-score-matched cohort

Outcome	Generic (no. = 2102)	Brand-name (no. = 2102)	HR/SHR (95% CI) for Generic	*p*
Coronary intervention	67 (3.2)	75 (3.6)	0.96 (0.69–1.33)	.785
Acute myocardial infarction	40 (1.9)	49 (2.3)	0.87 (0.58–1.32)	.523
Stroke	92 (4.4)	101 (4.8)	0.97 (0.73–1.28)	.828
All-cause death	146 (6.9)	130 (6.2)	1.22 (0.97–1.54)	.090
Heart failure hospitalization	94 (4.5)	124 (5.9)	0.81 (0.62–1.05)	.112
Composite cardiovascular outcome*	328 (15.6)	360 (17.1)	0.98 (0.85–1.13)	.774

Data were presented as frequency (percentage).
*Anyone having a coronary intervention, acute myocardial infarction, stroke, all-cause death, or heart failure hospitalization.
Abbreviations: CI, confidence interval; HR, hazard ratio; SHR, subdistribution hazard ratio.

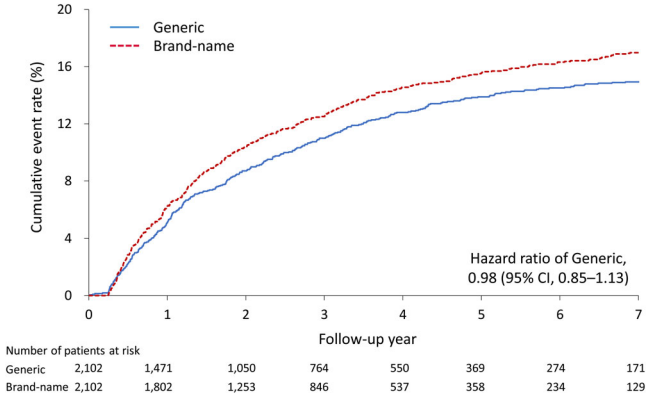

FIGURE 3 **Cumulative event rates of the primary composite outcome for patients who were prescribed the generic and the brand-name nifedipine in the propensity-score-matched cohort**

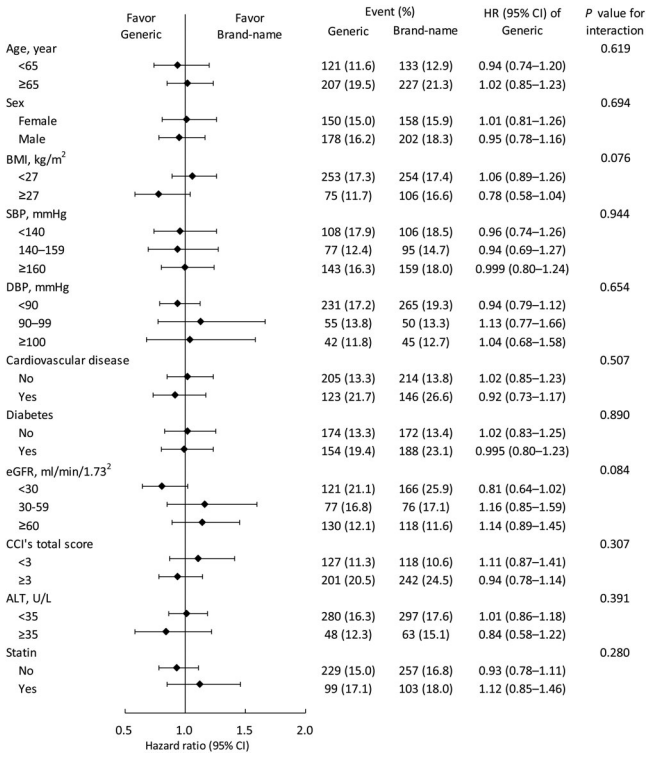

FIGURE 4 **Subgroup analyses of the primary composite outcome in the propensity-score-matched cohort**. Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; CCI, the Charlson Comorbidity Index; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, hazard ratio; SBP, systolic blood pressure

CI 0.62–1.05), or coronary revascularization (3.2% vs 3.6%; SHR 0.96; 95% CI 0.69–1.33). **Figure 4** illustrates the results of subgroup analysis for the primary composite outcome. Consistent with the main analysis, the generic and brand-name nifedipine had comparable effects on the primary outcome across all subgroups stratified by the baseline characteristics.

4 | DISCUSSION

This multi-institutional cohort study compared BP-lowering efficacy and clinical outcomes of hypertensive patients who were treated with the OROS formulations of either generic or brand-name nifedipine. The generic nifedipine was comparable to its brand-name counterpart regarding the reduction in SBP and DBP from baseline, BP control rates, and the composite outcome of all-cause death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for HF.

In this study, comparable BP reduction and control rates associated with the generic and the brand-name nifedipine suggest "therapeutical equivalence" between these two drugs. This finding is consistent with the results of prior meta-analyses of RCTs comparing generic and brand-name drugs in the treatment of hypertension or other cardiovascular diseases.[18,19] In the meta-analysis conducted by Kesselheim and associates, nine subclasses of cardiovascular medications were analyzed and no evidence of brand-name drug superiority was observed in a wide spectrum of cardiovascular diseases as compared with their generic counterparts. However, more than half of the editorials analyzed in their systematic review argued against generic interchangeability.[18] Similarly, the meta-analysis performed by Manzoli and associates revealed no significant differences between the generic and brand-name drugs regarding the combined estimate of efficacy or possible serious adverse events.[19] However, more than half of the trials included in these meta-analyses are bioequivalence studies, which were conducted in predominantly young and healthy persons with small samples sizes and short duration of follow-up, limiting their generalizability to the real-world management of hypertension or other cardiovascular diseases. Furthermore, the clinical efficacy examined in these comparative studies were usually surrogate markers or soft endpoints and may not be translated to long-term clinical outcomes. In a more recent meta-analysis, Leclerc and associates revealed that 60% of studies on generic vs. brand-name cardiovascular drugs revealed no difference between drug types regarding clinical measures or all-cause hospital visits, while 26% concluded the brand-name drug to be more effective or safe, 13% were inconclusive, and only 1% showed that generics did better.[20] In this study, generic drugs were associated with a moderate increase in the crude risk ratio (RR) for all-cause hospital visits (RR 1.14; 95% CI 1.06–1.23) but a comparable risk for cardiovascular hospital visits (RR 1.05; 95% CI 0.98–1.14). However, the enrolled studies were too heterogeneous to draw firm conclusions from the results and a comparison of "hard" endpoints was not available in this study.

In the present study, the rates of composite clinical outcomes were comparable between the generic and the brand-name nifedipine at a mean follow-up of 3 years. Although there was a tendency toward a higher risk of death in the generic group, this finding could be play of chance, since the absolute risk difference was small (0.7%) and the BP-lowering efficacy and the risks of other cardiovascular events were comparable between the two groups. In our prior study using the National Health Insurance Research Database (NHIRD) of Taiwan, the risk of major adverse cardiovascular events, a composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary

revascularization, and heart failure hospitalization, had not differed significantly between the two drugs at a mean follow-up of 4.1 years.[21] The NHIRD study did not observe significant difference in the risk of all-cause death (7.2% vs 7.1%; $p = .597$). However, the NHIRD does not contain BP records, laboratory test results, or clinically relevant demographic data, such as body mass index and smoking history, that may have an impact on cardiovascular outcomes. Complementary to our prior work, the present study took into account baseline BP, lipid profiles, and blood glucose levels as well as other important demographic factors to mitigate potential confounders in the propensity score method. More importantly, the comparable BP reduction between generic and brand-name drugs supports our conclusion that the generic nifedipine was comparable to its brand-name counterpart for the prevention of cardiovascular events. It has recently been shown that machine learning methods can potentially have better ability than traditional statistics models to detect predictors of adverse events associated with cardiovascular medications.[22] Although our two database analyses may provide real-world evidence for "clinical equivalence" between the generic and the brand-name nifedipine, further studies using machine learning may help investigate differences between generic and brand-name medications in the future.

BP control rates remained suboptimal in our study cohort. Less than half of the study patients achieved the traditional target of < 140/90 mmHg at the end of follow-up. When the 2017 American College of Cardiology/American Heart Association BP guidelines were applied, only approximately a quarter of them achieved the more stringent BP target (below 130/80 mmHg).[23] The reasons for inadequate BP control are multifactorial. In a developed health care setting, therapeutic inertia and medication adherence have been considered major impediments to achieving BP goals.[24,25] Although we were not able to identify the reasons behind poor BP control in our cohort, the reluctance of physicians or patients to intensify their antihypertensive regimens may be attributable to a high comorbid burden, the numbers of antihypertensive and other concomitant medications, and closeness to the target BP of 140/90 mmHg at follow-up.[26–28] Nevertheless, the BP-lowering efficacy of the generic and the brand-name nifedipine was similar and was above that of a standard dose of a single antihypertensive drug (10/5 mmHg) due to a relatively high BP level at baseline.

5 | STUDY LIMITATIONS

The strength of this study is its long-term follow-up for office BP measurements and clinical outcomes, as well as the large sample size for specific comparison between a generic antihypertensive drug and its brand-name counterparts to avoid heterogeneity among included studies in systematic reviews and meta-analyses. However, there are several inherent limitations in this study. The nonrandomized study design may be subject to selection bias since the choice of the generic or the brand-name nifedipine was at physicians' discretion, which may have been affected by their perception of generic drugs. Although we matched the baseline characteristics of the two study groups rigorously, unmeasured variables could still confound the analytical results. Despite the standardized protocol for BP measurement, patients may not always take a 5-minute sitting rest in a busy hospital setting, and three consecutive BP readings may not be taken for averaging all the measurements. Apart from the potential technical errors, office BP is known to be subject to a random error influencing casual BP readings and a systematic error associated with the "white coat effect.[29]" How these factors may have affected the comparative BP results is unknown. The clinical outcomes were simply extracted from the CGRD and were not validated independently. For a patient who had a clinical event but had not received management at CGMH, the event rates could have been underestimated. The study results were derived from a single research database containing information from only 6% of the population in Taiwan and may not be representative of hypertension management in Taiwan. We did not analyze common side effects associated with CCBs or other antihypertensive treatments, such as edema, constipation, or hypotension, since physicians may not always register these side effects in their daily practice. Although the study results supported therapeutic and clinical equivalence between the generic and the brand-name nifedipine OROS, the results are hypothesis-generating and could not be generalized to other formulations of nifedipine or different antihypertensive drugs.

6 | CONCLUSIONS

In this multi-institutional cohort study, the generic nifedipine was comparable to its brand-name counterpart regarding BP-lowering efficacy and clinical outcomes at long-term follow-up.

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CONFLICT OF INTEREST

None.

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