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Drug price, dosage and safety: Real-world evidence of oral hypoglycemic agents

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ABSTRACT

Objectives: Drug price reduction is one of the major policies to restrain pharmaceutical expenses worldwide. This study explores whether there is a relationship between drug price and clinical quality using real-world data.
Methods: Patients with newly-diagnosed type 2 diabetes receiving metformin or sulfonylureas during 2001 and 2010 were identified using the claim database of the Taiwan universal health insurance system. Propensity score matching was performed to obtain comparable subjects for analysis. Pharmaceutical products were categorized as brand-name agents (BD), highpriced generics (HP) or low-priced generics (LP). Indicators of clinical quality were defined as the dosage of cumulative oral hypoglycemic agents (OHA), exposure to other pharmacological classes of OHA, hospitalization or urgent visit for hypoglycemia or hyperglycemia, insulin utilization and diagnosis of diabetic complications within 1 year after diagnosis.
Results: A total of 40,152 study subjects were identified. A generalized linear mix model showed that HP and BD users received similar OHA dosages with comparable clinical outcomes. By contrast, LP users had similar outcomes to BD users but received a 39% greater OHA dosage. A marginally higher risk of poor glycemic control in LP users was also observed.
Conclusions: Drug price is related to indicators of clinical quality. Clinicians and health authorities should monitor the utilization, effectiveness and clinical safety indicators of generic drugs, especially those with remarkably low prices.

1. Introduction

Escalating pharmaceutical expenditure is a challenge for almost every developed country. In the past few decades, reduction of drug price and promotion of generic drug utilization have been major policies aimed at containing pharmaceutical spending [1,2]. Increasing the availability of low-cost generic medication may also improve patient adherence, contributing to favorable treatment outcomes and reduced medical expenses. Several organizations of healthcare professionals supported the use of generic drugs considering economic and clinical benefits, such as American Diabetes Association [3,4]. However, recent studies revealed that generic medications with low prices may be related to low quality. An international survey pointed out that drug products which failed at least one of the three designated quality tests (i.e., visual inspection of packaging and pills for correctness; minilab tests, including basic solubility and thin-layer chromatography to measure the concentration of active ingredients; Raman spectrometry test of the entire formula consisting of active ingredients, binding agents, dyes and other excipients) were priced 13.6–18.7% lower than non-failing drugs. Nevertheless, a large overlap between the price distribution of failing and non-failing products was observed, which indicated that the price signaling effect may be far from complete. The price dispersion seemed to be a reflection of market frictions along with imperfect information regarding drug quality [5]. In clinical practice, physicians, pharmacists and patients tend to be less confident in administering generic or low-priced drugs. The perception may be interfered with the maturity of the healthcare and pharmaceutical administration system in the country [6–9]. Since surveys showed that generic drugs are given less frequently to patients with medical training, advanced age, complex treatment or lower out-of-pocket costs [10,11], "discount price equates to 'discount'

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quality" of pharmaceutical agents appears to be a prevailing misconception among the general public [12–14].

Researchers have investigated clinical quality of generic pharmaceutical products to ensure patient safety and promote generic drug utilization. For example, a meta-analysis evaluated 74 randomized trials of cardiovascular medications to explore their treatment outcomes. The authors concluded that efficacy indicators and adverse events were comparable between patients receiving brand-name and generic products [15]. Clinical equivalence of generic antibiotics and their originators has also been established based on dataset of patients with mild or chronic infections [16,17]. Another study compared treatment outcomes between authorized generics (AGs, which were regarded as brand-name products in considering of identical formula) and independent generic medication (IGs). This study performed an indirect comparison between brand-name and generic drugs after controlling for perception bias since both drugs were generic. The results showed similar treatment outcomes between patients receiving IGs or AGs in terms of outpatient visits, urgent care visits, hospitalization and medication discontinuation [18]. However, the prices of products that contain the same active ingredients could vary remarkably among different manufacturers. Without a prudent investigation focusing on drug price, it is difficult to dispel the myth of the inferiority of generic pharmaceutical products.

Taiwan implemented a public universal healthcare system (i.e., National Health Insurance [NHI]) since 1995 [6,19]. The rising pharmaceutical cost is one of the major threats to this scheme. Drug cost accounts for approximately 25% of the total healthcare expenditure under Taiwan NHI, which is much higher than the average figures of the Organization for Economic Co-operation and Development (OECD) countries [20,21]. The Taiwan NHI Administration introduced a pricing strategy in year 1997 to contain drug expenditure and to minimize the gap between market prices and reimbursement prices of medications. As 2014, reimbursement prices were revised on Apr 2000, Apr 2001, Mar 2003, Sep 2005, Nov 2006, Oct 2009, Nov 2011 and May 2014 after nationwide surveys [21]. The majority of drug prices were adjusted downward after each survey, which led to complaints from pharmaceutical companies, healthcare professionals and patients due to drug-switching decisions [22]. However, the Taiwan NHI Administration decided to continue the policy until today since more than US $2 billion has been saved via this price reduction strategy [19]. Currently, there are many generic drugs with very low prices under the Taiwan NHI scheme. According to a study by Wang and colleagues, 47.5% of all prescribed oral drugs were priced at less than US $0.03 per unit [23]. From this point of view, the Taiwan NHI scheme is a good example for investigating the association between drug price, its utilization and clinical safety. Real-world evidence may contribute to the existing literature regarding drug price policy and may be of value to policymakers around the world.

2. Methods

This study performed a comparative effectiveness analysis by using a representative claims dataset from Taiwan NHI scheme. To identify an appropriate population to answer the study question, drug prices were obtained between the calendar years 2000 and 2010. Oral hypoglycemic agents (OHAs) were considered study candidates because the product prices can be clearly categorized. OHAs are essential in type 2 diabetes mellitus (T2DM) management especially within the first 3 ensuing years in newly-diagnosed patients [24,25]. In addition, real-world research or database analysis to explore the effectiveness, safety and policy impacts of OHAs are abundant to date, implying that claims datasets are decent research source for our study aims [6,26–29]. Therefore, OHAs were chosen to be the subjects of this study.

OHA products were classified into brand-name agents (BDs), high-priced generics (HPs) and low-priced generics (LPs). According to the price distribution and the author's consensus, HPs were defined as generic products priced above 50% of the original price of their brand-name counterparts. The remaining products were classified as LPs. The pricing trends (expressed as the proportion of the initial price of the brand-name agents) of BDs, HPs and LPs on the market during the calendar year 2000–2010 are presented in the Appendix (Supplementary Fig. 1). To facilitate readers' understanding, the drug ingredients described in this study are presented with their Anatomical, Therapeutic and Chemical (ATC) codes established by the World Health Organization [30].

2.1. Study subjects

Patients with newly diagnosed Type 2 diabetes mellitus (T2DM) between the calendar years 2000 and 2010 were identified in the Taiwan NHI claims database. These patients were defined as insured without a record of a diabetic-related diagnostic code (i.e., icd-9 code 250.xx, 362.0) in the preceding year. The day of first diagnosis of T2DM was defined as the index day of each patient. To minimize the heterogeneity of disease severity at diagnosis, patients exposed to any hypoglycemic agents (i.e., insulin [ATC code, A10A] or OHA [ATC code, A10B]) in the previous year, patients who received insulin, patients who were not regularly treated with an OHA (defined as a medication possession ratio [MPR] of less than 0.8) [25] or those exposed to more than one OHA product during the first 3 months after diagnosis were excluded. Patients who received an OHA prescription from more than one healthcare provider on the index day, who were treated with an ingredient that was rarely used (defined as case number less than 20 per year) or for which brand-name and generic versions were not simultaneously available in the same year were also excluded. The ingredient of the OHA product which patients received during the first 3 months after diagnosis is defined as the index OHA ingredient. After a baseline survey, eligible study patients received metformin (ATC code, A10BA02; abbreviated as the MT cohort) or sulfonylureas (i.e., glibenclamide [ATC code, A10BB01], glipizide [ATC code, A10BB07], gliclazide [ATC code, A10BB09] or glimepiride [ATC code, A10BB12]; abbreviated as the SU cohort) as their index OHA ingredients. The MT cohort consisted of only BD and HP users because the number of patients treated with LP was less than 20 annually. The SU cohort included BD, HP and LP users.

To increase the compatibility of patients, propensity score matching (PSM) was conducted in the MT cohort and SU cohort. We established 3 separate models of logistic regression separately to calculate the propensity scores (BD vs. HP of the MT cohort; BD vs. HP of the SU cohort; and BD vs. LP of the SU cohort). The reception of BDs, HPs or LPs was the dependent variable, and the factors associated with the product preference were considered independent variable candidates [6]. The backward selection technique was applied with a cut-off point of 0.10 to determine the inclusion of independent variables to minimize the bias of strong instruments and colliders [31]. The final models contained patient age, sex, Charlson's comorbidity index (CCI), calendar year of the index day, index OHA ingredient, delayed OHA prescription (defined as > 1 day between the index day and first OHA prescription), history of an emergency room (ER) visit /hospitalization or frequent utilization of outpatient service (defined as > 25 outpatient visits annually) in the previous year, urbanization level of the city in which the healthcare institute was located, prescriber specialty (i.e., endocrinologist or non-endocrinologist) and years of clinical experience. Past medical history was selectively included as covariates, including hypertension, stroke, ischemic heart diseases, coronary heart

diseases and malignancy. A 1:1 case-control matching stratified by the accreditation of the healthcare institute (i.e., medical centers or regional hospitals, community hospitals or clinics) was performed. During the matching process, greedy algorithms were adopted. All cases were initially matched to their "best" comparators (i.e., those with 8 digits matched on propensity score). For those that did not match, subjects were matched to their comparators using 7 digits of the propensity score, and sequentially to the lowest digit match of the propensity score (1 digit) [32]. The PSM case numbers within each matching step in the 3 comparison groups is presented in the Appendix (Supplementary Table 1).

2.2. Outcome measurement

Study subjects were followed for 12 months after the index day. BD users were regarded as the reference group in the analysis. The primary outcomes were the utilization and safety indicators of OHAs, which included (i) cumulative OHA dosage, (ii) exposure to OHA which belongs to the pharmacologic classes other than the index ingredient (defined by the fifth level of the ATC code [30]), and (iii) hospitalization or ER visit due to hypoglycemia or hyperglycemia. The secondary outcomes were signals of disease progression, namely, (i) exposure to insulin and (ii) diagnosis of any diabetic complications within the follow-up period. The cumulative OHA dosage was measured by the standardized dosage (i.e., defined daily dose, DDD) [30] and calculated on a monthly basis. To reduce the potential bias from disease severity at diagnosis, the analysis of the primary and secondary outcomes excluded records drawn within the first 3 months after diagnosis. With the exception of a descriptive graph illustrating the trends of the cumulative OHA dosage from the first month (m1) to the twelfth month (m12), outcomes are presented based on data collected from the fourth month (m4) to m12 after diagnosis.

2.3. Statistical analysis

All statistical analysis were performed using SAS software version 9.4 (SAS, Cary, NC, USA). Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as frequency and percentage. The Kruskal-Wallis test was applied for comparisons of continuous variables, and Pearson's chi-square test was used for examining categorical ones. Considering that the data were collected from multiple healthcare providers and the error term might not be normally distributed, a generalized linear mixed model (GLMM; i.e., GLIMMIX procedure in SAS software) was applied for multivariate analysis [33]. While analyzing the cumulative drug dosage, the gamma distribution and log link were used considering the data were notably skewed to the right. For the remaining outcomes, the binary distribution and logit link were used. The confounders included in the GLMM were age, sex, CCI, healthcare utilization in the previous year, the index OHA ingredient, specialty and clinical experience of the prescribers and accreditation level of the healthcare institute. Study subjects from the MT cohort and the SU cohort were analyzed together in the multivariate model while the index OHA ingredients were considered a confounding factor. In light of the issue of multiplicity, the study applied the Bonferroni adjustment. A P value < 0.01 was adopted as the significance level.

To make our results more practical, analysis of the cumulative OHA dosage was performed as a table of parameter estimates (i.e., Supplementary Table 3). The mathematical difference of compared groups could be calculated as follows:

$$\mathrm{E}[y|x,\ z_1, z_2, \ldots, z_n] = \exp\left(\alpha + \beta * x + \gamma * z_1 + \ldots + \omega * z_n\right) = \hat{y}(1)$$

*In Eq. (1), x represents the variable of study interest (i.e., BD, HP or LP) and z represents all other variables included in the GLMM.

The mathematic difference of compared groups could be calculated via the following equation:

$$\begin{aligned}&\mathrm{E}[y\,|z_1, z_2, \ldots, z_n,\ x = 1] - \mathrm{E}[y\,|z_1, z_2, \ldots, z_n,\ x = 0]\\ &= \exp\left(\alpha + \beta + \gamma * z_1 + \ldots + \omega * z_n\right)\\ &- \exp\ (\alpha + \gamma * z_1 + \ldots + \omega * z_n)\end{aligned} \quad (2)$$

*In Eq. (2), $x = 0$ represents brand-name users (as reference), and $x = 1$ represents high-priced (among BD vs. HP comparison) or low-priced generic users (among BD vs. LP comparison).

2.4. Sensitivity analysis

Considering that drug adherence of new onset DM patients may be varied, sensitivity analysis was performed for PSM subjects with regular visits and good drug adherence. Patients with regular visits were defined as ≥ 1 record of outpatient/ER visit or hospitalization every 3 months. Patients with good adherence were defined as those with MPR of OHA above 0.8 during the study period. This strategy is advantageous for confirming the relationship between the index drugs and their treatment effects. The definition of the outcomes, covariates and methods of statistical analysis were identical to those mentioned above.

3. Results

3.1. Subject selection

The study subject selection process is illustrated in the Appendix (Supplementary Fig. 2). A total of 909,874 adult patients were diagnosed with new-onset T2DM during the study period; 268,185 patients (29.5%) were regarded as receiving stable OHA treatment. After excluding patients who received OHA prescriptions from multiple providers at the index day and who were treated with more than one OHA product during the initial 3 months, 94,989 subjects were identified. More than 99% of the study patients had completed the 1-year follow-up. The SU cohort was composed of 15,864 BD users, 17,449 HP users and 17,258 LP users. The MT cohort contained 6,838 BD users and 28,769 HP users. The PSM procedure determined 40,152 subjects in 3 comparison groups for analysis: BD vs. HP users in the SU cohort, with 8,615 patients in each group; BD vs. HP users in the MT cohort, with 6,825 patients in each group; and BD vs. LP users in the SU cohort, with 4,636 patients in each group. The proportion of matched subjects in each arm of the cohort was similar, with a range from 26.9% to 54.3%, except for the MT cohort (i.e., 99.8% and 23.7%) of which the case numbers of the two comparators were remarkably different. The percentages were fairly acceptable referring to other well-performed comparative effectiveness analyses using PSM [29,34]. The distribution of the propensity score among cases after matching was similar according to the Kernel densities illustration (Appendix, Supplementary Fig. 3).

3.2. Characteristics of subjects

Table 1 presents the basic characteristics of the study subjects in the three matched cohorts. The properties of the pre-matched subjects are provided in the Appendix (Supplementary Table 2) for reference. Approximately half of the study subjects were middle-aged. In general, a range from 64.5% (BD users in the MT cohort in the BD vs. HP comparison) to 71.5% (BD users in the SU cohort in the BD vs. LP comparison) of the patients had a CCI score of 0. Approximately one-third of subjects had hypertension. Regarding the prescription properties, 24.0% (BD users in the SU cohort in the BD vs. HP comparison) to 34.5% (HP users in the MT cohort in the

Table 1
Basic characteristics of the study population after propensity score matching.

	Brand-name (BD) vs. high-priced generic (HP) users										Brand-name (BD) vs. low-priced generic (LP) users				
	SU cohort after PSM (n = 17,230)					MT cohort after PSM (n = 13,650)					SU cohort after PSM (n = 9,272)				
	BD		HP		P value	BD		HP		P value	BD		LP		P value
Patient properties															
Male, n (%)	4,749	(55.1%)	4,801	(55.7%)	0.4254	3,371	(49.4%)	3,490	(51.1%)	0.0416	2,605	(56.2%)	2,606	(56.2%)	0.9833
Age					0.2182										
20- 44	1,277	(14.8%)	1,308	(15.2%)		1,411	(20.7%)	1,424	(20.9%)	0.5288	682	(14.7%)	692	(14.9%)	0.3935
45- 64	4,805	(55.8%)	4,877	(56.6%)		3,584	(52.5%)	3,629	(53.2%)		2,546	(54.9%)	2,596	(56.0%)	
≥ 65	2,533	(29.4%)	2,430	(28.2%)		1,830	(26.8%)	1,772	(26.0%)		1,408	(30.4%)	1,348	(29.1%)	
Charlson's score (CCI)					0.0944										
0	6,093	(70.7%)	6,101	(70.8%)		4,400	(64.5%)	4,439	(65.0%)	0.4286	3,313	(71.5%)	3,284	(70.8%)	0.4010
1- 2	2,285	(26.5%)	2,231	(25.9%)		2,201	(32.2%)	2,187	(32.0%)		1,213	(26.2%)	1,222	(26.4%)	
≥ 3	237	(2.8%)	283	(3.3%)		224	(3.3%)	199	(2.9%)		110	(2.4%)	130	(2.8%)	
Comorbidities															
Hypertension	2,724	(31.6%)	2,581	(30.0%)	0.0183	2,327	(34.1%)	2,266	(33.2%)	0.2692	1,390	(30.0%)	1,371	(29.6%)	0.6661
Stroke	165	(1.9%)	167	(1.9%)	0.9117	142	(2.1%)	129	(1.9%)	0.4251	81	(1.7%)	85	(1.8%)	0.7541
Ischemic heart diseases	789	(9.2%)	794	(9.2%)	0.8951	710	(10.4%)	704	(10.3%)	0.8662	417	(9.0%)	437	(9.4%)	0.4726
Coronary heart diseases	381	(4.4%)	371	(4.3%)	0.7092	299	(4.4%)	262	(3.8%)	0.1107	197	(4.2%)	207	(4.5%)	0.6109
Malignancy	178	(2.1%)	193	(2.2%)	0.4311	205	(3.0%)	174	(2.5%)	0.1063	86	(1.9%)	108	(2.3%)	0.1104
Healthcare utilization in previous year															
ER visit or hospitalization	1,561	(18.1%)	1,593	(18.5%)	0.5284	1,519	(22.3%)	1,536	(22.5%)	0.7270	847	(18.3%)	951	(20.5%)	0.0063
Outpatient visit time > 25	2,974	(34.5%)	2,841	(33.0%)	0.0321	2,531	(37.1%)	2,462	(36.1%)	0.2201	1,555	(33.5%)	1,519	(32.8%)	0.4271
Prescription properties															
Delayed OHA prescription	2,071	(24.0%)	2,101	(24.4%)	0.5937	2,369	(34.7%)	2,352	(34.5%)	0.7597	1,274	(27.5%)	1,229	(26.5%)	0.2925
Index OHA ingredient (ATC code)					<0.0001					.					0.0681
Metformin (A10BA02)	.		.			6,825	(100.0%)	6,825	(100.0%)		.	.	.	.	
Glibenclamide (A10BB01)	3,472	(40.3%)	3,793	(44.0%)		.		.			2,705	(58.3%)	2,719	(58.6%)	
Glipizide (A10BB07)	2,093	(24.3%)	2,060	(23.9%)		.		.			238	(5.1%)	185	(4.0%)	
Gliclazide (A10BB09)	670	(7.8%)	582	(6.8%)		.		.			1,691	(36.5%)	1,730	(37.3%)	
Glimepiride (A10BB12)	2,380	(27.6%)	2,180	(25.3%)		.		.			2	(0.0%)	2	(0.0%)	
Properties of prescribers															
Acceleration level of healthcare institute					1.000					1.000					1.000
Medical centers or regional hospitals	3,023	(35.1%)	3,023	(35.1%)		4,266	(62.5%)	4,266	(62.5%)		1,827	(39.4%)	1,827	(39.4%)	
Community hospitals or clinics	5,592	(64.9%)	5,592	(64.9%)		2,559	(37.5%)	2,559	(37.5%)		2,809	(60.6%)	2,809	(60.6%)	
Endocrinologist	304	(3.5%)	412	(4.8%)	<0.0001	688	(10.1%)	649	(9.5%)	0.2614	236	(5.1%)	383	(8.3%)	<0.0001
Clinical experience					0.0130					0.0012					0.0008
< 5 years	2,940	(34.1%)	2,793	(32.4%)		1,680	(24.6%)	1,505	(22.1%)		1,583	(34.1%)	1,414	(30.5%)	
5-14 years	4,785	(55.5%)	4,839	(56.2%)		4,086	(59.9%)	4,183	(61.3%)		2,521	(54.4%)	2,672	(57.6%)	
≥ 15 years	890	(10.3%)	983	(11.4%)		1,059	(15.5%)	1,137	(16.7%)		532	(11.5%)	550	(11.9%)	

BD vs. HP comparison) of patients received an OHA prescription at the day of diagnosis. The majority of patients who received SU were managed at community hospitals or clinics, yet more patients treated by MT were managed at medical centers or regional hospitals. Considering the specialty of prescribers, only 3.5% (BD users in the SU cohort in the BD vs. HP comparison) to 10.1% (BD users in MT cohort in the BD vs. HP comparison) of the patients were managed by endocrinologists; and more than 65% of subjects were treated by prescribers with more than 5 years of clinical practice experience.

3.3. Descriptive results of the cumulative dosage and other outcomes

The trends of monthly cumulative dosage of OHA among the 3 comparison groups are presented in Fig. 1. The curves are fairly linear, which agrees with the fact that 60.3% to 65.4% of PSM subjects had MPR above 0.8 within study period (Appendix, Supplementary Table 3). Large standard deviations of the cumulative dosage were also observed, revealing an existing variability of drug dosage (Appendix, Supplementary Table 4). Among the BD vs. HP comparisons, users in the SU and MT cohorts had similar dosage curves over 12 months. The cumulative dosages of BD and HP users in the SU cohort at m12 were 241.7 and 246.3 DDDs, respectively; for BD and HP users in the MT cohort, the dosages were 147.2 and 140.3 DDDs, respectively (i.e., absolute difference: <5%). However, in the BD and LP matched groups, LP users received a higher cumulative OHA dosage from the beginning of the treatment and the difference increased over time. At m12, LP users and BD users received 317.9 DDDs and 207.1 DDDs of cumulative OHA, respectively (i.e., absolute difference: 53.5%).

Table 2 presents the results of bivariate analysis of the primary and secondary outcomes. After excluding data from the initial 3 months of the study to minimize the effect of disease severity at diagnosis, we found variations in the cumulative OHA dosage among BD, HP and LP users which were consistent with those shown in Fig. 1. While comparing BD and HP users in the SU cohort and MT cohort, patients received a similar cumulative dosage of OHAs (168.6 vs. 171.5 DDDs and 100.1 vs. 97.3 DDDs; absolute difference: 1.7–2.8%). When comparing BD and LP users, there was a remarkably higher dosage among LP users than BD users (216.6 vs. 147.5 DDDs; absolute difference: 46.8%). Regarding the remaining outcome measurements, 19.0% (BD users in the MT cohort in the BD vs. HP comparison) to 26.1% (BD users in the SU cohort in the BD vs. HP comparison) of the study subjects were exposed to other pharmacologic classes of OHA, and less than 3% received insulin. The rates of hospitalization or ER visits due to hypoglycemia or hyperglycemia were generally low (i.e., <0.5%). The percentage of diabetic complication diagnosis was 10.9% (BD users in the MT cohort in the BD vs. HP comparison) to 12.8% (BD users in the SU cohort in the BD vs. LP comparison). The differences of outcome measurements between the BD and HP matched groups were not significant except for the cumulative dosage. LP users tended have an increased risk of poor glycemic control compared to BD users, though the incidences were both low.

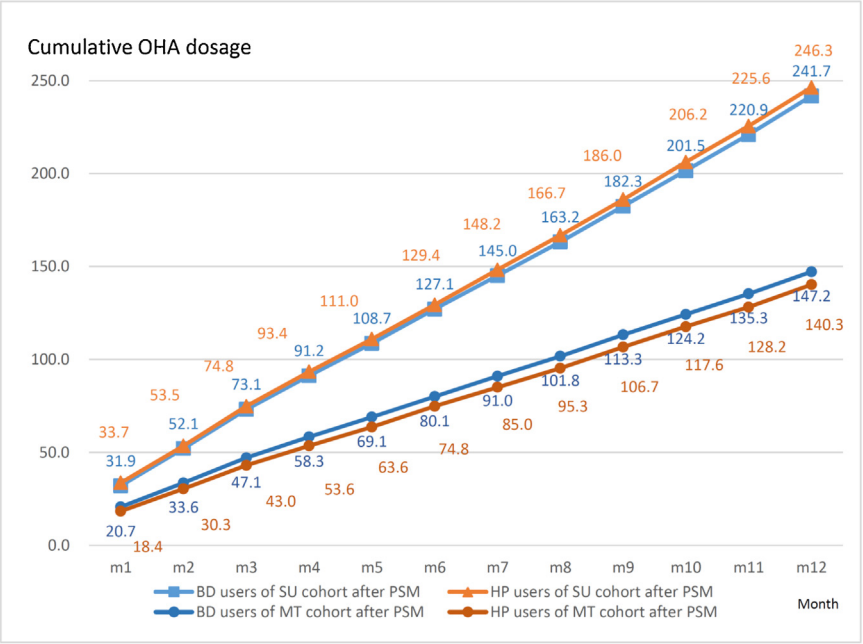
3.4. Results of GLMM analysis

The results of the multivariate analysis performed by GLMM are shown in Table 3. After controlling for potential confounders, no significant differences between HP and BD matched users were found in the primary outcomes or secondary outcomes. By contrast, LP users received a significantly higher cumulative OHA dosage. The estimated parameter of drug product variable (i.e., BD or LP) was 0.3294 ± 0.0176, which means that the cumulative dosage from m4 to m12 for LP users was 1.39 (95% CI, 1.34–1.44) times

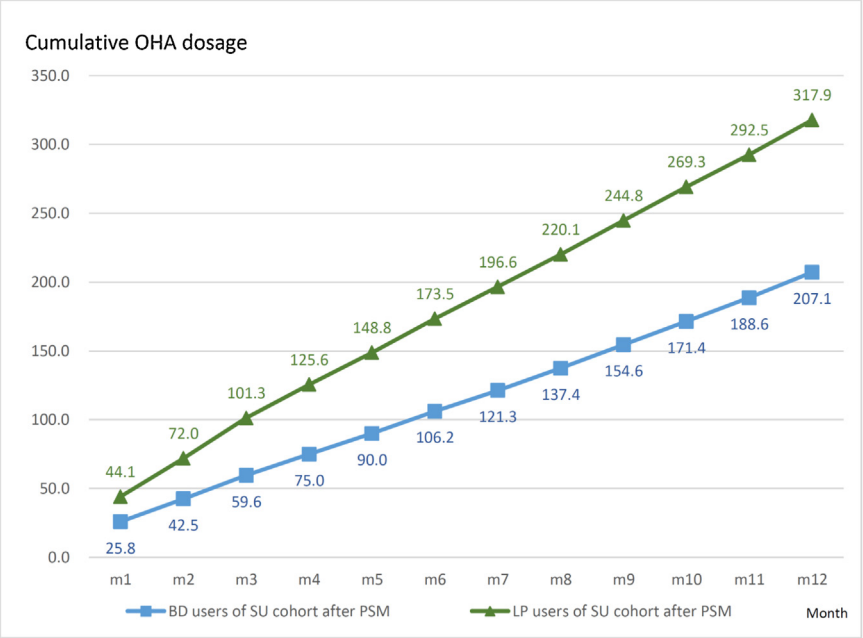
Table 2
Results of bivariate analysis.

	Brand-name (BD) vs. high-priced generic (HP) users						Brand-name (BD) vs. low-priced generic (LP) users					
	SU cohort after PSM (n = 17,230)			MT cohort after PSM (n = 13,650)			SU cohort after PSM (n = 9,272)					
	BD (n = 8615)	HP (n = 8615)	P value	BD (n = 6825)	HP (n = 6825)	P value	BD (n = 4636)		LP (n = 4636)		P value	
Primary outcomes												
Cumulative dosage of OHA*	168.6 ± 145.3 (70.0, 240.0)	171.5 ± 150.7 (68.3, 240.0)	0.5022	100.1 ± 91.0 (42.0, 137.0)	97.3 ± 95.6 (35.0, 133.0)	<0.0001	147.5 ± 125.7 (66.0, 195.8)		216.6 ± 210.7 (74.7, 298.7)		<0.0001	
Exposure to other pharmacologic classes of OHA (%)	2,249	(26.1%)	2,228	(25.9%)	0.7153	1,295	(19.0%)	1,386	(20.3%)	0.4699	1,496	(32.3%)	1,527	(32.9%)	0.1250
Hospitalization or ER visit due to hypoglycemia or hyperglycemia (%)	24	(0.3%)	40	(0.5%)	0.0595	10	(0.1%)	6	(0.1%)	0.3170	11	(0.2%)	23	(0.5%)	0.0392
Secondary outcomes												
Exposure to insulin (%)	249	(2.9%)	260	(3.0%)	0.6206	114	(1.7%)	121	(1.8%)	0.6451	133	(2.9%)	135	(2.9%)	0.9013
Diagnosis of diabetic complications (%)	1,037	(12.0%)	1,046	(12.1%)	0.8334	744	(10.9%)	805	(11.8%)	0.0997	593	(12.8%)	531	(11.5%)	0.0485

* Presented as mean ± SD (the first quartile, the third quartile).



(a) Brand-name agents (BD) vs. high-priced generic (HP) users



(b) Brand-name agents (BD) vs. low-priced generic (LP) users

Fig. 1. Cumulative OHA dosage of (1a) brand-name agents vs. high-priced generic users, and (1b) brand-name agents vs. low-priced generics users.
(1a) Brand-name agents (BD) vs. high-priced generic (HP) users.
(1b) Brand-name agents (BD) vs. low-priced generic (LP) users.

of that for BD users. Applying all of the estimated parameters calculated by GLMM for the cumulative OHA dosage (Appendix, Supplementary Table 5), a typical LP subject (i.e., a man aged 45–64 years with a CCI score = 0, outpatient visit $\leq$ 25 times and no ER visit or hospitalization record in the previous year of T2DM diagnosis, receiving glibenclamide from a non-endocrinologist with 5–14 years of practicing experience at clinics located in high to median developed cities) in the year 2008 received 62.9 more DDDs compared with BD users from m4 to m12. The hazard ratio of being hospitalized or visiting ER due to hypoglycemia or hyperglycemia was 2.281 (95% confidence interval, 1.078–4.827), though it did not reach the statistical significance after Bonferroni correction. No significant difference was found in other outcome variables.

Table 3
Results of multivariate analysis (reference: brand-name agent users).

	High-priced generic (HP) users			Low-priced generic (LP) users		
	Estimator (Continuous variable) or Odds ratio (Categorical variable)	95% CI	P value	Estimator (Continuous variable) or Odds ratio (Categorical variable)	95% CI	P value
Primary outcomes						
Cumulative dosage of OHA*	0.00859 ± 0.00903	−0.0091 – 0.0263	0.2820	0.3294 ± 0.0176	0.2949 – 0.3639	<0.0001
Exposure to other pharmacologic classes of OHA	1.038	0.983 - 1.095	0.1764	0.939	0.853 - 1.034	0.1993
Hospitalization or ER visit due to hypoglycemia or hyperglycemia	1.372	0.872 – 2.157	0.1709	2.281	1.078 - 4.827	0.0310
Secondary outcomes						
Exposure to insulin	1.084	0.935 - 1.256	0.2866	1.016	0.794 - 1.300	0.9003
Diagnosis of diabetic complications	1.045	0.974 - 1.121	0.2223	0.889	0.782 - 1.010	0.0707

*Presented as mean ± SD.
Note. The confounders included in the multivariate model were age, sex, CCI, healthcare utilization in previous year, main ingredient of oral hypoglycemic agent (OHA), specialty and experience of prescribers, and accreditation level of the healthcare institute.

3.5. Results of sensitivity analysis

As presented in Supplementary Table 3, 57.0% (BD users in the MT cohort) to 66.9% (BD users in the SU cohort) of patients had a MPR ≥ 0.8 during the study period. After PSM, the rates of MPR ≥ 0.8 with regular follow up were between 60.3% and 65.4%. A total of 18,525 PSM subjects and 5,845 PSM subjects were proceed to sensitivity analysis for comparison of BD vs. HP and BD vs. LP, respectively.

The results of the sensitivity analysis are presented in the Appendix (Supplementary Table 6) and are similar to the primary analysis. Among PSM subjects with MPR ≥ 0.8 and regular follow up, LP users received a 1.45 times (95% CI, 1.40–1.50) higher cumulative dosage of OHA than BD users. The other primary and secondary outcomes were not significantly different between BD vs. LP users or BD vs. HP users.

4. Discussion

This study explored the association among drug prices, their utilization and patient-level outcomes using real-world data. The results demonstrate that generic drugs with prices close to those of brand-name agents satisfied clinical needs of newly diagnosed T2DM patients, which were characterized by the accumulated OHA dosage and whether other diabetic medication was required. Analysis of safety and effectiveness proxies in the first year of treatment were favorable as well. However, generic drugs priced notably lower than the originators required a higher dosage to achieve comparable clinical outcomes. After controlling for potential confounders, patients treated by low-priced generics received a 39% greater accumulated OHA dosage than brand-name users. A higher risk of poor glycemic control was also observed, though the actual incidence was low and the P value did not hit the lowest limit of statistical significance. These results are worthy of attention from countries that attempt to contain pharmaceutical expenditure by pursuing low drug prices.

4.1. Drug price reduction, a low unit price and their impacts

Ensuring reasonable prices and a sustained supply of essential medicine are crucial to healthcare systems and global welfare [35]. Experts are calling for policy solutions for price negotiation to decrease the cost of drugs and increase the availability of low-priced medication [36–38]. Taiwan, similar to other developed countries, has a pricing mechanism to adjust drug prices regularly. The NHI Administration conducts a drug price survey every 1 or 2 years and adjusts (mostly decreases) the reimbursement price accordingly. However, there was no regulation concerning the basic (i.e., lowest) unit price until 2016. According to a survey performed in 2007, the NHI scheme of Taiwan has been abundant by drugs with very low prices [23]. Recent studies pointed out the problem of low-priced pharmaceutical agents. For example, medications with lower marketed prices in the United States were believed to be less profitable, and would be at higher risks of a fluctuating supply [39]. Cutting corners in ways that compromise production quality was also suspected, but direct evidence is absent to date. In our opinion, the very low prices of drug products might have forced pharmaceutical firms to reduce the quality (e.g., the amount of active ingredients) of their products to maintain profits, which might be one of the major reason for the higher dose requirement in our patients who received LPs. Nevertheless, this inference is difficult to determine based on real-world data.

From another point of view, lowering drug prices may lead to an alteration of prescribing pattern. Previous studies have explored the effects of drug price reduction and their clinical consequences. A Danish survey found a significant correlation between the price of ciprofloxacin, its consumption and the rate of drug-resistant organisms. While the median price per DDD of ciprofloxacin was decreased by 53% after introducing generic products, its utilization surged from 0.13/1,000 to 0.33/1,000 inhabitant-days. Meanwhile, the frequency of ciprofloxacin-resistant organisms increased by 200% [40]. Another study evaluated the effects of direct drug price control by the government of Colombia. The results showed that real pharmaceutical expenditures almost doubled after policy enactment, mainly due to an increase in units sold. Inappropriate and unnecessary drug utilization was suspected, but it could not be explored in the data source used [41]. Korean experts also noted that an increasing number of drugs and expanding daily dosage were the side effects of the price reduction policy. Compared to providing prescription recommendations, direct price control would be an inferior strategy to constrain pharmaceutical expenditure [42]. However, these studies did not incorporate patient-related outcomes and clinical interpretation [18]. Our study, instead, applied a real-world patient-based analysis and evaluated the clinical outcomes of medications at different prices. The results demonstrated that patients treated with low-priced generic drugs may have comparable clinical outcomes to those treated by brand-name agents, but higher dosage was required.

This finding implies that clinical quality of low-priced medication may have been decreased to some extent.

4.2. Favorable generic products with reasonable price

By contrast, we found that generic medications priced closer to their originator provided satisfying clinical outcomes at equal dosages. This finding is in agreement with other studies performed in our country. A hospital-based research noticed that the treatment outcomes of DM patients receiving metformin, for which low-priced products have not been generally applied, were stable after switching from brand-name to generic agents [43]. Considering the financial benefits, generic drugs are reasonable alternatives to brand-name medications. Generic substitution contributes to a lower drug cost and public healthcare expenditure in most healthcare systems. Doctors are strongly encouraged to prescribe cheaper available versions of a drug, especially in European and Scandinavian countries [44–48]. Nevertheless, healthcare providers and patients are less confident in generic medications due to their low prices, regardless of the continuing effort of renovating pharmaceutical regulation by governments (e.g., Pharmaceutical Inspection Co-operation Scheme [PIC/S]) or updated positive clinical evidence [5,13,42]. According to the results of our study, generic products with higher reimbursement prices provided favorable outcomes that were comparable to their originators at equal dosages. These results suggest that health authorities and the general population be more confident in applying generic medication at a reasonable price, yet they may pay attention to pharmaceutical products with a very low price. We believe that reasonable prices for medication are essential for pharmaceutical firms to ensure the clinical quality of their products as well as patient safety.

4.3. Limitations

Several limitations should be mentioned while applying the study results to clinicians and policy makers. First, this was a clinical observational study using an existing claims dataset. We did not conduct a direct examination of the medication (e.g., measurement of active ingredients and excipients) [5] or evaluate the drug efficacy by laboratory data (e.g., glycated hemoglobin). However, the outcome measures in this study were practical in clinical settings, which are adherent to recent trends in research requirement and population needs [49]. Additionally, confounders may exist when applying the claims dataset for drug effectiveness research. It is possible that patients received BDs, HPs or LPs in association with their basic characteristics, disease status or properties of healthcare providers. To overcome the disadvantage, PSM procedures were conducted to select comparable subjects for analysis. The percentage of matched subjects to the entire cohort varied between 23.7% and 99.8%, which may be related to the fact that patients receiving BDs, HPs or LPs were disparate and there were unequal numbers of BD and HP users among the MT cohort. The innate property of the data made low attrition rates with adequate matching unattainable. To preserve a favorable intrinsic validity, we proceeded with a proper PSM and formulated comparable subjects. The PSM procedure is decent according to a current guideline [50]. After the matching process, the patient profiles demonstrated that most of the characteristics did not differ significantly. Furthermore, data from the first 3 months after the initial diagnosis were excluded considering that they may be related to disease severity rather than drug efficacy. Sensitivity analysis was performed to decrease the influence of drug adherence. In light of the study design, the generalizability of our findings may be limited to patients receiving a stable drug treatment rather than those who require intermittent pharmacotherapy or a frequent change in medication.

Second, the definitions of high- and low-priced generic products in this study were determined based on the authors' consensus and were calculated according to list prices. Confidential pharmaceutical price discounts may exist but are usually inaccessible for evaluation, which may obscure the relationship between price and quality [51]. Considering that this study categorized generic products into two groups with a cut-off point of 50% of the original price of the innovator product, we believed the impacts of classified price discounts on the clinical indicators would be minor. However, this cut-off point may not be a vigorous suggestion for general pricing policy. Third, we applied Bonferroni correction considering the issue of multiplicity. The Bonferroni method has been regarded to be fundamental to adjust for multiple comparisons. However, some experts have noted that it may result in overly conservative conclusions and required discreet interpretation [52,53]. Finally, we could not further investigate the underlying reasons for the dosage differences. To the best of our knowledge, there is a lack of research exploring the reason for various drug dosages according to the product price. Clinical needs of a higher dosage of low-priced generics have been mentioned, but formal studies have yet to be performed. In our opinion, lower drug potency is suspected to be the major impetus of higher dosage among LP users in this study. However, other driving factors cannot be ruled out, such as patient requirements, healthcare institute policies, and physician preference. The relationship between drug price and outcome measures shall be interpreted carefully.

5. Conclusion

This study revealed that drug price is related to indicators of clinical quality and safety. Among newly diagnosed T2DM patients, those treated with low-priced generic OHAs may have comparable outcomes to brand-name users but require a 39% greater accumulated dosage. By contrast, patients treated by generic OHAs which priced close to their originators had similar clinical outcomes with equal dosages. Since drug price reduction and promoting generic adoption are the main policies to restrain pharmaceutical expenses worldwide, health authorities shall monitor the utilization and clinical outcomes of medication, especially those with remarkably low prices. A reasonable drug pricing strategy is recommended for policy makers regarding patient safety.

Conflict of Interest Statement: The authors certified that there was no involvement in any organization with a direct financial interest in the subject matter in the paper.

CRediT authorship contribution statement

Yu-Shiuan Lin: Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Min-Ting Lin:** Methodology. **Shou-Hsia Cheng:** Project administration, Supervision, Funding acquisition, Methodology, Validation, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.healthpol.2019.08.005.

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