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ORIGINAL ARTICLE

Cross-sectional survey of biosimilar insulin utilization in Asia: The Joint Asia Diabetes Evaluation Program

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ABSTRACT

Aims/Introduction: Biosimilar insulin can reduce treatment costs, although the extent of its use is largely unknown. We examined biosimilar insulin use and its associations with the quality of glycemic control using the Joint Asia Diabetes Evaluation register.

Materials and Methods: We carried out a cross-sectional analysis in 81,531 patients with type 1 and type 2 diabetes enrolled into the Joint Asia Diabetes Evaluation Program from 2007 to 2014. All insulin related terms are extracted from the Joint Asia Diabetes Evaluation portal, and compared clinical profiles between biosimilar and originator insulin users. Multivariate analysis was performed to assess the association of biosimilar insulin compared with originator insulin with dosage, glycated hemoglobin and hypoglycemia events.

Results: Amongst 81,531 patients, 20.5% (n = 16,738) were insulin-treated. In four countries with high use of biosimilar insulin, 4.7% (n = 719) of insulin users (n = 10,197) were treated with biosimilar insulin (India n = 507, 70.3%; the Philippines n = 90, 12.5%; China n = 62, 8.6%; Vietnam n = 60, 8.3%). Biosimilar insulin users were younger and had higher body mass index, glycated hemoglobin, insulin dosage and more frequent hypoglycemia than originator insulin users. These associations were non-significant after adjustment for confounders. Only age, college education, diabetes education, lipid control, physical activity and history of cardiovascular complications were independently associated with these quality measures.

Conclusions: Biosimilar insulin use is not uncommon in Asia. Data exclusion due to incomplete capturing of brand names suggests possibly higher use. The multiple determinants of the quality of glycemic control call for establishment of prospective cohorts and diabetes registers to monitor the safety and efficacy of different brands of biosimilar insulin and their impacts on clinical outcomes.

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INTRODUCTION

In 2011, $465 billion was spent on diabetes and its complications, worldwide[1]. In diabetes management, antidiabetic agents and diabetes supplies constitute approximately 12% of the direct medical cost. Expenditure on insulin accounted for at least 1.5-fold that of all other antihyperglycemic agents combined. In the past decade, the estimated spending for insulin per patient has tripled from $231.48 in 2002 to $736.09 in 2013 (data from the USA)[2]. In Asia, more than 100 million people have been diagnosed with diabetes, with the sharpest increase in the young-to-middle-aged group[3]. With pancreatic β-cell insufficiency being a hallmark of type 2 diabetes, many of these patients will eventually require insulin to maintain glycemic control[4].

Along with the patent expiry of originator insulin, biosimilar insulins are being increasingly developed with the potential to reduce healthcare costs. Biosimilar insulins are designed to be highly similar to the originator (or reference) insulin product prescribed to a patient[5]. Generic versions of small-molecule drugs are produced by chemical synthesis with uniform, stable and predictable structures. By contrast, protein-based products, often referred as biologics, such as insulin, are produced in living organisms. These proteins are structurally complex and require specific conditions to ensure stability[6]. Hence, small differences in the drug design and formulation could cause unpredictable changes in pharmacokinetic or pharmacodynamics properties[7]. Quality control during the design and manufacturing processes[8] of structurally complex protein compounds is critically important. This was illustrated in the epoetin incident, where a confluence of factors related to production, handling and route of administration of epoetin led to the increased incidence of Eprex-associated pure red-cell-aplasia up to a year after exposure to the product[9–11].

The specific terminology and federal regulatory pathways for insulin use differ between countries and regions. In several regions including the European Union, these follow-on insulin products are regulated by similar approval processes applied to other biosimilar products. In the USA, they are developed under a different regulatory pathway[12]. In these high-income areas, the principles of showing biosimilarity to an approved reference product are strongly upheld. Recently, the European Medicines Agency has approved the use of LY2963016 insulin glargine (Abasaglar®; Eli Lilly Nederland B/V, Utrecht, the Netherlands, and Boehringer Ingelheim, Ridgefield, CT, USA)[13]; MK-1293 insulin glargine (Lusduna®; Merck, Kenilworth, NJ, USA)[14]; and biosimilars of Lantus® (Sanofi, Paris, France) insulin glargine. In 2015, the United States Food and Drug Administration granted final approval of Basaglar® (Eli Lilly). There are now new data with other biosimilar insulin products, such as biosimilar insulin lispro (SAR342434). This product has been studied in two phase 1 trials (NCT02273258[15] and NCT02603510[16]) and two phase 3 trials (SORELLA 1: EudraCT2013-002945-12[17], NCT00273180[18] and SORELLA 2: EudraCT 2014-002844-41, NCT02294474[19]). Mylan and Biocon are co-developing a biosimilar insulin glargine (Basalog), which is being studied in phase 3 clinical trials in people with type 1 and type 2 diabetes. In November 2016, the European Medicines Agency accepted Mylan's marketing authorization application for review[20].

In Asia, the biosimilar regulatory landscape is more diverse, ranging from highly regulated markets, such as Japan, to countries with emerging guidelines (e.g., Singapore, Malaysia, Thailand etc.), and those without specific guidelines (e.g., Vietnam)[21]. In Asia, many companies, such as Cipla, Dr Reddy's Laboratories, Biocon, Wockhardt, Celltrion and Scinopharm, have shown capabilities and competitiveness in developing and commercializing biosimilars for the Asia market. The anticipated release of the United States Food and Drug Administration guidelines should guide Asian biosimilar firms to conform to more standard requirements of showing a high degree of similarity to the original biologic[22].

Patient access is the main driving force behind the manufacture of follow-on biologics. Some countries address these rising demands without enforcing the rigorous demonstration of a high degree of similarity to the originator molecule. As a result, some non-comparable follow-on biologics have entered the market without meeting the comparability criteria with the originator molecules[22]. In Asia, biosimilar insulin, such as Basalog® (Biocon, Bangalore, India), Glaritus® (Wockardt, Mumbai, India) and Basalin® (Gan & Lee, Beijing, China), are registered and prescribed in countries such as China, India, Pakistan, Peru, Thailand and Mexico, where biosimilar regulations are relatively lax[23].

The Joint Asia Diabetes Evaluation (JADE) Program is a quality improvement program developed by the Asia Diabetes Foundation. It utilizes a web-based portal to enable practitioners to establish a diabetes register for quality improvement while contributing data to a regional register[24,25]. The JADE Program was launched in 2007, and the Monthly Index of Medical Specialities database was added to the portal in 2012 to improve drug data collection. By June 2014, 281 clinics from 11 countries/areas in Asia had enrolled over 80,000 patients. In this large multinational, cross-sectional cohort, we examined the use of biosimilar insulin and its association with the quality of glycemic control in Asia.

METHODS

Study design

This was a cross-sectional study carried out in 11 countries/areas across Asia with patient enrolment into the JADE Program. Patient data were extracted from their first comprehensive assessment carried out by their healthcare providers on enrollment into the JADE Program. The rationale, design, implementation and adoption of the JADE Program have been published[24].

The portal incorporates templates to guide data collection that included demographics, types and duration of diabetes, history of cardiovascular diseases, presence or absence of microvascular complications including retinopathy and sensory neuropathy, self-reported hypoglycemia, self-reported adherence

to self-care activities, and current medications. Hypoglycemia was defined as typical self-reported symptoms occurring at least once monthly over the past 3 months. As much as possible, the brand or generic name of medications was captured, either through selection from the drug list provided by Monthly Index of Medical Specialities or as free text. Blood and urine samples were also collected for measurement of glycemic indices, lipid profile, renal function and albuminuria. To sustain this quality improvement program, laboratory testing and resource-intensive processes (e.g., retinal photography) were left to the discretion of each center. Patients did not receive incentives, while participating centers received JADE access, training and a small stipend to cover data entry costs. All participating patients gave written informed consent for use of their anonymized data for research and publication purpose. The program was approved by the Joint Chinese University Hong Kong – New Territories East Cluster Clinical Research Ethics Committee and ethics board of each participating institution. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Study participants, clinic settings and healthcare systems in each country

Between November 2007 and July 2014, 281 clinics in 11 countries/areas in Asia enrolled 81,531 patients into the JADE Program from diverse settings including community and hospital clinics in private and public systems, under both generalist and specialist care. We did not capture the details of each clinic, but the specifics of healthcare systems of the participating countries are summarized in Table 1. As examples, Hong Kong has a heavily subsidized, single-payer public healthcare system, and China has a national, public healthcare system requiring co-payment. Vietnam and Thailand have public healthcare systems that are more resource-limited than Hong Kong. Korea and Taiwan have national public insurance systems with reimbursement and co-payment schemes from multiple care providers. Singapore has a public healthcare system with a complex savings scheme. In all these countries, private systems also exist with different insurance schemes. The majority of JADE patients from these countries were managed in public or subsidized healthcare systems, although coverage for laboratory tests and medications was not universal. In contrast, the majority of JADE patients from the Philippines and India were seen in private clinics where payments were predominantly out-of-pocket.

Drug identification

We identified nearly 250,000 medication records prescribed to 56,000 patients, and of these, 14,000 drug items were classified as insulin. After extracting all insulin drugs recorded within the JADE portal, two authors (LG and AL) reviewed the list of insulin drugs independently to re-classify them into biosimilar or originator insulin. Recombinant human insulin or insulin analogs were classified as biosimilar if the insulin was produced by agencies other than companies that developed the innovator pharmaceuticals. Insulin with the generic name only and without clear indication on whether the insulin was manufactured by an innovator or a non-innovator company was excluded from the analysis. Patients treated with insulin with names written in foreign characters or languages that could not be decoded by the portal were also excluded from the analysis. We also reviewed the pattern of insulin regimen used if they were recorded within the portal (pre-mixed, basal only, basal-plus and basal-bolus), and the total daily dose (units/kg) prescribed to patients treated with insulin.

Statistical analysis

All analysis was carried out using the R version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria)[26]. All data were expressed as mean ± standard deviation, median (interquartile range), percentages and point estimates with 95% confidence intervals (CI). Between-group comparisons were made using the χ^2-test, Student's *t*-test and Wilcoxon rank-sum test as appropriate. We first quantified the number of

Table 1 | Different healthcare payment systems in countries involved in the Joint Asia Diabetes Evaluation Program

Country	Public or private healthcare clinics	Generalist or specialist care	Community or hospital-based clinics
China	Mainly public with less resourced subsidy	Specialist	Hospital
Hong Kong	Mainly public with single care provider (Hospital Authority) with only nominal charge and some private	Both	Both
India	Mainly private with out of pocket payment	Both	Both
Korea	Mainly private with reimbursement by national insurance scheme	Specialist	Hospital
Philippines	Mainly private with out of pocket payment	Both	Both
Vietnam	Mainly public with less resourced subsidy	Both	Hospital
Taiwan	Mainly private with reimbursement by national insurance scheme	Specialist	Hospital
Thailand	Mainly public with nominal charge and some private	Specialist	Hospital
Singapore	Mainly private with support from medical saving scheme and national insurance scheme but minimal subsidy for drugs and lab tests which often require out of pocket payment	Specialist	Hospital

biosimilar insulin users in the JADE Program and the region where use was most prevalent. We then compared clinical profiles between biosimilar insulin and originator insulin users in the high-use area. We used a backward stepwise elimination to model our outcomes of interest and variables collected in the JADE Register. We carried out a univariate regression on each variable and the outcomes of interest (glycated hemoglobin [HbA1c], insulin dosage and frequency of hypoglycemia). India was the top user of biosimilar insulin (>50%), and was used as the reference country in the assessment of the association of different countries with outcomes of interest (HbA1c, insulin dosage and hypoglycemia). Variables with a *P*-value of <0.05 were selected into a final multivariate regression analysis to model the relationship between our outcomes of interest and use of biosimilar insulin after adjusting for significant variables in our univariate analysis. The regression analysis was linear for HbA1c and insulin dosage, and logistic regression for the binary outcome of hypoglycemia. The insulin dose was log-transformed due to skewed distribution. The log transformation of the regression is:

$$\log(y) = a + bx,$$

$$y = \exp(a) * \exp(b)^x.$$

This is a model based on the geometric mean with 'exp(b)' related to y and x.

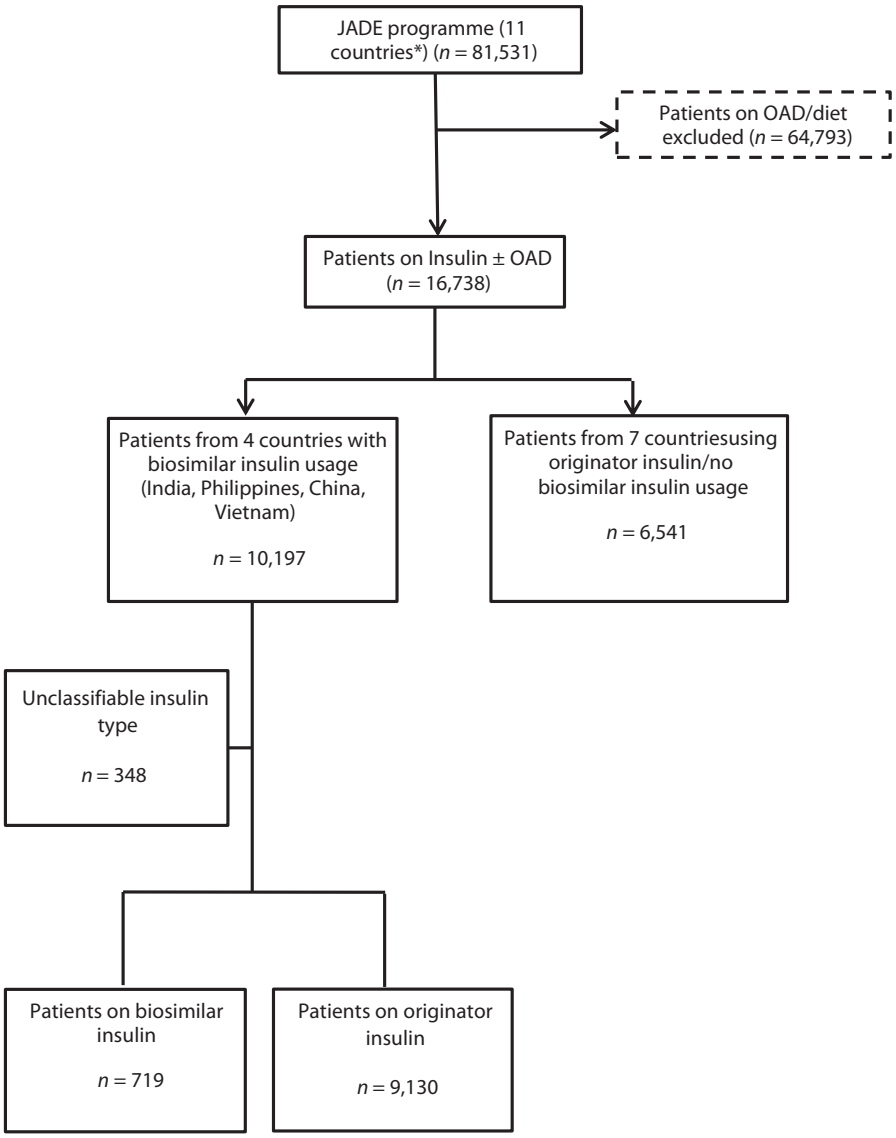

Figure 1 | The Joint Asia Diabetes Evaluation (JADE) Program study population of patients on biosimilar versus originator insulin. OAD, oral antidiabetic drug.

RESULTS

Figure 1 shows the selection of patients treated with biosimilar or originator insulin in the JADE Program. By July 2014, 81,531 patients were enrolled in the JADE Program, of whom, 16,738 were treated with insulin. Biosimilar insulin was used in four of 11 countries, including India, the Philippines, China and Vietnam. Amongst insulin users in these countries (n = 10,197), biosimilar insulin was prescribed to 719 (7.1%) patients and originator insulin to 9130 (89.5%). The remaining 348 (3.4%) of patients were excluded from the analysis due to the uncertain or unclassifiable nature of the insulin. Of these, six were entered as foreign symbols that were not in keeping with any of the local languages in the countries. Another 342 were entered as generic insulin names that could not be classified as originator or biosimilar products. Biosimilar insulin users were mainly in India (n = 507, 70.3%), the Philippines (n = 90, 12.5%), China (n = 62, 8.6%) and Vietnam (n = 60, 8.3%). Amongst the biosimilar insulin-treated patients (n = 719), 58.4% were on the pre-mixed regimen, 20.6% were on the basal-only regimen, 13.6% on basal-plus or basal-bolus and 1.8% on bolus only. Information on treatment regimen was not available in the remaining 5.6% of patients. The respective spread of insulin regimen in the originator insulin-treated patients was 58.1%, 26.3%, 8.7% and 6.3%, and 0.7% had missing information on regimen type.

Lists of biosimilar insulin and insulin analogs

Table 2 lists the 16 biosimilar insulin brands used in these four countries including their distribution and availability in each country. Different countries have different predominant types of biosimilar insulin, while some biosimilar insulin brands were prescribed in more than one country.

Patients treated with biosimilar or originator insulin

Both originator and biosimilar insulin groups had similar distributions of type 1 diabetes and disease duration. Both groups had similar proportions of patients who carried out self-monitoring of blood glucose and adhered to a balanced diet. Compared with the originator insulin group, patients treated with biosimilar insulin were younger; less likely to be college-educated; had higher body mass index, HbA1c and insulin doses; and were more likely to receive diabetes education. They were less likely to attain HbA1c <7.0%, report hypoglycemia or receive concurrent non-insulin antidiabetic drugs. Biosimilar-insulin treated patients had a lower frequency of cardiovascular complications, with higher proportions of them attaining blood pressure (<130/80 mmHg) and lipid targets (LDL-C < 2.6 mmol/L). They were less likely to have retinopathy, but more likely to have microalbuminuria and peripheral neuropathy (Table 3).

Biosimilar insulin and quality of glycemic control

Table 4 shows the regression analysis, which explored the associations of biosimilar insulin with quality of glycemic control. We first carried out a univariate regression analysis to identify clinical factors associated with HbA1c, insulin dosage and self-reported hypoglycemia. Factors with a P-value of <0.05 were selected into a final multivariate regression analysis to determine the statistical significance of their independent associations, if any, with HbA1c, insulin dosage and hypoglycemia. Only patients with type 2 diabetes with complete data on insulin dose, HbA1c and self-reported hypoglycemia were included in this analysis. After adjustments for confounders, no independent association of biosimilar insulin with HbA1c, insulin dosage or hypoglycemia was found.

Table 2 | List of different biosimilar insulin used in the Joint Asia Diabetes Evaluation Program

	China, n = 58 (%)	India, n = 593 (%)	Philippines, n = 106 (%)	Vietnam, n = 126 (%)
Basalog (glargine)	0	119 (20.0)	0	0
Biosulin (human insulin NPH)	0	1 (0.2)	0	0
Diamisu (human insulin isophane)	0	0	0	34 (27.0)
Glaritus (glargine)	0	11 (1.9)	0	2 (1.6)
Humstard (human insulin NPH)	0	83 (14.0)	0	0
Insucare (human insulin isophane)	0	9 (1.5)	0	0
Insugen (human insulin NPH)	0	326 (55.0)	0	0
Insuget (human insulin Isophane)	0	0	35 (33.0)	0
Insulinum Lente (porcine insulin)	0	0	0	7 (5.6)
Insunova (human insulin isophane)	0	0	0	6 (4.8)
Lupinsulin (human insulin isophane)	0	0	10 (9.4)	0
Mixulin (human insulin isophane)	0	3 (0.5)	0	0
Recosulin (human insulin isophane)	0	7 (1.2)	0	0
Scilin (human insulin)	0	0	32 (30.2)	77 (61.1)
Wosulin (human insulin)	2 (3.4)	34 (5.7)	29 (27.4)	0
Gansulin (human insulin)	56 (96.6)	0	0	0

Table 3 | Clinical and biochemical characteristics of patients treated with biosimilar or originator insulin from India, China, Vietnam and the Philippines

	Biosimilar insulin	Originator insulin	*P*-value
Total	719 (7.3%)	9,130 (92.7%)	–
China	62	2,052	
India	507	4,749	
Philippines	90	1,201	
Vietnam	60	1,128	
Demographics			
Age (years)	56.5 ± 11.0	58.2 ± 11.8	<0.001
Sex (male)	54.2%	54.2%	0.967
Type 1 diabetes	2.6%	2.4%	0.807
Disease duration (years)	11.9 (6–16)	11.5 (5–16)	0.189
Smoking status			<0.001
Never	76.6%	69.9%	
Ex-smoker	15.9%	18.4%	
Current	7.4%	11.7%	
Alcohol consumption			0.052
Never	71.6%	68.1%	
Ex-drinker	10.7%	11.9%	
Occasional	15.0%	15.3%	
Regular	2.7%	4.7%	
Education			<0.001
Primary or illiterate (<6 years)	13.4%	12.9%	
Middle school (6–11 years)	20.7%	17.8%	
Higher school (>11 years)	26.7%	21.3%	
College	35.3%	42.7%	
Waist circumference (cm)			
Male	92.1 ± 12.4	90.9 ± 11.5	0.088
Female	91.8 ± 12.2	88.3 ± 12.8	<0.001
Body mass index (kg/m^2)	26.1 ± 4.8	25.7 ± 4.5	0.042
Systolic blood pressure (mmHg)	130.8 ± 18.2	131.6 ± 17.1	0.266
Diastolic blood pressure (mmHg)	77.8 ± 8.7	78.5 ± 9.3	0.045
Laboratory Tests			
HbA1c (%)	9.3 ± 2.3	8.9 ± 2.1	<0.001
HbA1c (mmol/mol)	78	74	
Fasting plasma glucose (mmol/L)	9.9 ± 4.3	9.4 ± 3.9	0.007
Total cholesterol	4.6 ± 1.4	4.7 ± 1.3	0.141
LDL-C (mmol/L)	2.6 ± 1.1	2.7 ± 1.0	0.017
HDL-C (mmol/L)	1.1 ± 0.3	1.1 ± 0.3	0.025
Triglyceride (mmol/L)	1.6 (1.2–2.2)	1.7 (1.2–2.2)	0.143
Estimated GFR (mL/min per 1.73 m²)	75.6 ± 29.2	77.6 ± 33.6	0.136
Spot urine albumin:creatinine ratio (mg/mmol)	3.4 (2.1–14.8)	3.1 (1.0–14.6)	0.517
Hypoglycemia in the past 3 months			0.002
Less than once monthly	84.9%	79.8%	
At least once monthly	15.1%	20.1%	
Nature of hypoglycemia			0.285
Mild	91.0%	87.5%	
Moderate	8.5%	11.0%	
Severe	0.5%	1.5%	
Microvascular complications	54.2%	51.1%	0.159
Microalbuminuria (%)	39.9%	32.0%	0.002
Macroalbuminuria (%)	18.1%	18.9%	0.721
Chronic kidney disease	28.0%	30.0%	0.313
End stage renal disease	3.1%	2.2%	0.138
Diabetic retinopathy	8.7%	12.1%	0.010
Peripheral sensory neuropathy	25.1%	20.8%	0.006
Macrovascular complications	24.3%	27.6%	0.065

Table 3 | (*Continued*)

	Biosimilar insulin	Originator insulin	*P*-value
Coronary heart disease	8.6%	15.7%	<0.001
Heart failure	2.9%	5.0%	0.013
All heart events	8.7%	15.6%	<0.001
Stroke	2.1%	3.2%	0.106
Self-care and health education			
Self monitoring of blood glucose in the past 3 months	79.6%	80.9%	0.428
Adherence to balanced diet in the past 3 months	85.1%	84.98%	0.814
Regular exercise in the past 3 months (at least 3 times/week)	37.3%	41.4%	0.033
Education by dietitian	76.4%	57.7%	<0.001
Education by diabetes nurses	68.8%	49.7%	<0.001
Current medication use			
Insulin dosage (unit/kg)	0.52 (0.27–0.79)	0.47 (0.28–0.70)	0.001
Oral antidiabetic drugs			
Biguanides	25.7%	31.3%	0.002
Sulphonylureas	17.7%	16.2%	0.321
Alpha glucosidases inhibitor	7.5%	10.5%	0.012
DPP4 inhibitors	14.9%	13.4%	0.258
Meglitinides	0.1%	1.2%	0.008
Thiazolidinediones	4.5%	4.3%	0.853
Lipid-regulating drugs	45.5%	50.6%	0.011
Antihypertensive drugs	58.3%	60.2%	0.302
Attainment of treatment targets			
HbA1c <7.0%	12.4%	18.3%	<0.001
BP <130/80 mmHg	31.0%	25.1%	0.001
LDL-C < 2.6 mmol/L	57.6%	50.5%	<0.001

Data presented as mean ± standard deviation and median (interquartile range). BP, blood pressure; DPP4, dipeptidyl peptidase-4; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high density-lipoprotein cholesterol; LDL-C, low density-lipoprotein cholesterol.

Independent variables associated with high HbA1c included young age, living in the Philippines, higher insulin dosage, higher lipid levels, history of peripheral vascular disease and consultation with dietitians. College education and education by a podiatrist were associated with lower insulin dosage. Use of lipid-lowering drugs, regular exercise and frequent hypoglycemia were associated with both high insulin dosage and low HbA1c. A history of coronary heart disease was associated with a higher insulin dose, and a history of congestive cardiac failure was associated with a lower HbA1c. High insulin dosage, low HbA1c, history of heart failure and use of lipid-lowering drugs were independently associated with increased frequency of hypoglycemia.

DISCUSSION

To our knowledge, this is the first large-scale cross-sectional survey on the use of biosimilar insulin in real-world practice. In the JADE Program, one in five adult patients with diabetes in Asia were treated with insulin. Amongst the four countries with high usage of biosimilar insulin, including India, Philippines, Vietnam and China, 3–10% of insulin-treated patients were using 16 different brands of biosimilar insulin. Of note, 3% of insulin-treated patients in these countries were excluded from the analysis due to incomplete or unclear information on the insulin brands. Biosimilar insulin users had higher HbA1c, insulin dosage and frequency of hypoglycemia than originator insulin users. However, these differences were rendered non-significant after adjustment of confounding variables in the multivariate regression analysis. That said, as a large number of patients had been excluded due to an incomplete set of co-variables for adjustments, these findings will need to be confirmed in a larger cohort.

Taken together, the present results highlight the multiple variables associated with good glycemic control, with types of insulin being one possible variable. Although the quality of glycemic control was similar between biosimilar users and originator insulin users after adjustment, more real-world data regarding patterns of biosimilar insulin usage and their independent associations with quality of glycemic control are required to inform practice and policy. In Asia, where young-onset diabetes, delayed diagnosis, β-cell insufficiency and poor risk factor control are predominant features[3], the number of patients requiring insulin is expected to continue to rise. In a recent study from India, it was opined that biosimilar insulin

Table 4 | Multivariate regression analysis for glycated hemoglobin, insulin dosage and hypoglycemia (adjusted for countries)

HbA1c (n = 1,530)	β	95% CI	*P*-value
Independent variables			
Biosimilar insulin use	0.231	−0.034, 0.495	0.087
China	1.068	−0.337, 2.472	0.136
Philippines	0.653	0.076, 1.230	0.028*
Vietnam	0.050	−0.393, 0.494	0.824
College education	−0.003	−0.189, 0.183	0.974
Smoking status	0.168	−0.052, 0.387	0.134
Education by dietician	0.722	0.310, 1.134	0.001*
Education by podiatry	−0.155	−0.416, 0.106	0.243
Education by diabetes nurse	0.028	−0.211, 0.267	0.818
Physical activity ≥3 times a week	−0.264	−0.454, −0.075	0.006*
Presence of hypoglycemia ≥1 a month	−0.293	−0.5453, −0.057	0.021*
On lipid regulating medications	−0.255	−0.453, −0.057	0.012*
History of coronary heart disease	−0.175	−0.498, 0.147	0.287
History of peripheral vascular disease	0.404	0.055, 0.754	0.023
History of congestive cardiac failure	−1.341	−2.180, −0.502	0.002*
History of diabetic retinopathy	−0.235	−0.598, 0.128	0.204
Age	−0.023	−0.032, −0.015	<0.001*
Body mass index	−0.003	−0.021, 0.016	0.794
Low-density lipoprotein cholesterol	0.289	0.203, 0.376	<0.001*
Insulin dose (unit/kg)	0.187	0.091, 0.283	<0.001*

Insulin dosage (n = 2,009)	β	Exp (β)	95% CI	*P*-value
Independent variables				
Biosimilar insulin use	0.034	1.035	0.919, 1.164	0.573
China	−0.036	0.965	0.494, 1.886	0.917
Philippines	−0.100	0.905	0.693, 1.181	0.462
Vietnam	0.080	1.083	0.931, 1.261	0.303
College education	−0.112	0.894	0.826, 0.968	0.006*
Education by dietician	0.061	1.063	0.912, 1.239	0.435
Education by podiatry	−0.128	0.880	0.788, 0.983	0.023*
Education by diabetes nurse	−0.053	0.939	0.849, 1.039	0.224
Physical activity ≥3 times a week	0.148	1.160	1.070, 1.257	<0.001*
Presence of hypoglycemia ≥1 a month	0.177	1.193	1.075, 1.325	<0.001*
Concurrent oral hypoglycemic agent	−0.061	0.940	0.870, 1.016	0.122
On lipid regulating medications	0.126	1.134	1.043, 1.233	0.003*
History of coronary heart disease	0.216	1.241	1.082, 1.424	0.002*
History of congestive heart failure	0.175	1.192	0.861, 1.649	0.290
Age	0.001	1.001	0.998, 1.005	0.493
Body mass index	−0.005	0.995	0.987, 1.004	0.281
HBA1c	0.049	1.050	1.028, 1.072	<0.001*
Low-density lipoprotein cholesterol	0.017	1.017	0.980, 1.055	0.377

Hypoglycemia (n = 1,546)	β	Odds ratio	95% CI	*P*-value
Independent variables				
Biosimilar insulin use	0.001	1.001	0.119, 2.720	0.484
China	−0.079	0.924	0.046, 6.179	0.944
Philippines	−0.877	0.416	0.116, 1.169	0.246
Vietnam	−0.439	0.645	0.329, 1.252	0.198
College education	0.200	1.221	0.921, 1.621	0.165
Smoking status	−0.081	0.922	0.655, 1.282	0.644
Education by dietician	−0.419	0.658	0.350, 1.242	0.194
Education by podiatry	0.049	1.051	0.701, 1.600	0.814

Table 4 | (*Continued*)

Hypoglycemia (n = 1,546)	β	Odds ratio	95% CI	*P*-value
Education by diabetes nurse	0.080	1.083	0.754, 1.569	0.669
Physical activity ≥3 times a week	0.069	1.071	0.802, 1.429	0.446
Concurrent oral hypoglycemic agent	0.035	1.036	0.778, 1.380	0.809
On lipid regulating medications	0.518	1.678	1.222, 2.324	0.002*
History of coronary heart disease	0.306	1.358	0.873, 2.071	0.164
History of peripheral vascular disease	0.100	1.105	0.602, 1.951	0.737
History of congestive heart failure	2.252	9.503	3.233, 32.389	<0.001*
Presence of peripheral neuropathy	–0.222	0.777	0.519, 1.140	0.207
Presence of diabetic retinopathy	–0.083	0.920	0.525, 1.554	0.763
Age	0.009	1.009	0.995, 1.023	0.200
Body mass index	–0.013	0.987	0.957, 1.016	0.378
HbA1c	–0.097	0.908	0.837, 0.983	0.019
Low density lipoprotein cholesterol	–0.098	0.907	0.781, 1.043	0.184
Insulin dose (units/kg)	0.351	1.420	1.185, 1.723	<0.001*

*$P < 0.05$. CI, confidence interval; HbA1c, glycated hemoglobin.

will become an unavoidable option in South-East Asia, given the life-saving nature of insulin and the high cost of diabetes treatments[27]. However, pharmacoepidemiological analysis of biosimilar insulin is hindered by the lack of a uniform system to record the brand names and types of biosimilar insulin[28,29]. The degree of demonstrability of biosimilarity also varies widely amongst different biosimilar insulin brands. These products often do not have easily accessible safety or efficacy data in a public repository.

In the present analysis, 4.8% of biosimilar insulin-treated patients did not have a record of their insulin dose or regimen versus 0.9% for patients treated with originator insulin. This is in keeping with the literature that clinicians have significant knowledge gaps defining biologics, biosimilars and biosimilarity[30]. This missing information might reflect the unfamiliarity of local medical practitioners with the molecule names, brand names, types, dosage, regimens and pen devices in these multitudes of biosimilar insulin.

The present results also highlight the many determinants associated with glycemic control, hypoglycemia and insulin dosage. The increased risk of hypoglycemia in elderly patients with a history of cardiac disease calls for careful selection of insulin regimen in high-risk patients[31,32]. In a similar vein, the higher insulin dosage in the biosimilar insulin group (0.52 unit/kg/day) compared with the originator insulin group (0.47 unit/kg/day) with a difference of 0.05 unit/kg/day was reported in a study where 77 adult patients with either type 1 or type 2 diabetes were switched from their insulin regimen (Actraphane, Humulin 30/70, Insuman) to a biosimilar insulin (Biosulin 30/70). The authors reported similar antiglycemic effects, but there was a small increase in total dose of 0.03 units/kg/day on switching[33].

In the present exploratory analysis, we utilized cross-sectional, multicenter data collected from a diversity of healthcare settings; drug availability; price affordability; patients' attributes; and care practices to learn more about the pattern of use of biosimilar insulin in a convenient sample. We did not pre-specify the need to enter the brand names of insulin in the JADE register. Thus, up to one-quarter of insulin prescriptions analyzed were recorded using generic names, which were excluded from the analysis. We have grouped all biosimilar insulin in one group, although subtle differences might exist between different types of biosimilar insulin. Switching between biosimilar and originator insulin use within the same patient might confound our results. Sampling bias, incomplete data availability due to a lack of coverage of laboratory tests or unwillingness to pay by patients and unmeasured factors, such as variations in the urban-to-rural ratio, care practices, physicians' prescribing habits, insulin initiation and intensification processes, use of pen devices, and supporting services are other confounders. Because of the large number of patients excluded in the multivariable analysis, further studies will be required to elucidate the independent associations of biosimilar insulin with the quality of glycemic control.

In this real-world JADE register, 7.1% of insulin-treated patients in India, the Philippines, Vietnam and China were using biosimilar insulin. With rising costs of insulin, biosimilar insulin use might be an unavoidable option to make healthcare costs affordable. The large number of biosimilar insulin available in Asia calls for concerted efforts amongst policymakers, prescribers and payers to establish high-quality registers to monitor the safety and cost-effectiveness of these biosimilar insulins.

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