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Long-term safety and efficacy of alogliptin, a DPP-4 inhibitor, in patients with type 2 diabetes: a 3-year prospective, controlled, observational study (J-BRAND Registry)

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ABSTRACT

Introduction Given an increasing use of dipeptidyl peptidase-4 (DPP-4) inhibitors to treat patients with type 2 diabetes mellitus in the real-world setting, we conducted a prospective observational study (Japan-based Clinical Research Network for Diabetes Registry: J-BRAND Registry) to elucidate the safety and efficacy profile of long-term usage of alogliptin.

Research design and methods We registered 5969 patients from April 2012 through September 2014, who started receiving alogliptin (group A) or other classes of oral hypoglycemic agents (OHAs; group B), and were followed for 3 years at 239 sites nationwide. Safety was the primary outcome. Symptomatic hypoglycemia, pancreatitis, skin disorders of non-extrinsic origin, severe infections, and cancer were collected as major adverse events (AEs). Efficacy assessment was the secondary outcome and included changes in hemoglobin A1c (HbA1c), fasting blood glucose, fasting insulin and urinary albumin.

Results Of the registered, 5150 (group A: 3395 and group B: 1755) and 5096 (3358 and 1738) were included for safety and efficacy analysis, respectively. Group A patients mostly (>90%) continued to use alogliptin. In group B, biguanides were the primary agents, while DPP-4 inhibitors were added in up to ~36% of patients. The overall incidence of AEs was similar between the two groups (42.7% vs 42.2%). Kaplan-Meier analysis revealed the incidence of cancer was significantly higher in group A than in group B (7.4% vs 4.8%, p=0.040), while no significant incidence difference was observed in the individual cancer. Multivariate Cox regression analysis revealed that the imbalanced patient distribution (more elderly patients in group A than in group B), but not alogliptin usage per se, contributed to cancer development. The incidence of other major AE categories was with no between-group difference. Between-group difference was not detected, either, in the incidence of microvascular and macrovascular complications. HbA1c and fasting glucose decreased significantly at the 0.5-year visit and nearly plateaued thereafter in both groups.

Conclusions Alogliptin as a representative of DPP-4 inhibitors was safe and durably efficacious when used alone or with other OHAs for patients with type 2 diabetes in the real world setting.

Significance of this study

What is already known about this subject?

- ► Safety profile was proposed for dipeptidyl peptidase-4 (DPP-4) inhibitors in the previous studies, but the evidence was generally limited to cardiovascular events, hypoglycemia, pancreatitis, and pancreatic cancer, obtained through relatively short-term observations in patients with type 2 diabetes with prior cardiovascular history.
- ► Some of the studies raised a concern about the increased risk of heart failure with DPP-4 inhibitors.

What are the new findings?

- ► Alogliptin, as a representative of DPP-4 inhibitors, was safe and efficacious for a 3-year period.
- ► The results strongly suggest the safe and durably efficacious profile of DPP-4 inhibitors in comparison with other oral hypoglycemic agents including biguanides.

How might these results change the focus of research or clinical practice?

- ► DPP-4 inhibitors can be more recommended for glycemic control in elderly patients with type 2 diabetes mellitus.
- ► Bullous pemphigoid, a possible risk suggested in association with the use of DPP-4 inhibitors, should be further monitored in clinical practice.

INTRODUCTION

Type 2 diabetes mellitus is a pandemic that threatens health and economy worldwide because of its various complications.[1–3] Different classes of agents with different modes of action have become available to treat the disease, such as biguanides, thiazolidinediones, sulfonylureas, glinides, α-glucosidase inhibitors, and insulin therapy, and more recently, incretins and related compounds including glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose cotransporter2 (SGLT2) inhibitors.[4] Among those, DPP-4 inhibitors have been of clinical attention in recent years because of the proposed low risk of hypoglycemic events and weight gain.[5 6]

Several large-scale clinical trials were conducted using DPP-4 inhibitors, such as Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus–Thrombolysis in Myocardial Infarction (SAVOR-TIMI) 53 for saxagliptin,[7] Examination of Cardiovascular Outcomes: Alogliptin vs Standard of Care (EXAMINE) for alogliptin,[8] Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) for sitagliptin,[9] and Cardiovascular and Renal Microvascular Outcome Study with Linagliptin (CARMELINA) for linagliptin,[10] but were to mainly evaluate the safety (particularly on cardiovascular events) and efficacy of the individual drugs. While these trials showed the safe profile of DPP-4 inhibitors in terms of the risk of cardiovascular disease[11] as well as hypoglycemia, pancreatitis, and pancreatic cancer, the study periods were generally short and most of the participants had prior history of cardiovascular disease. Moreover, SAVOR-TIMI53 and EXAMINE raised a concern about the increased risk of heart failure with the drug class,[12] especially saxagliptin,[7] and alogliptin to a lesser extent.[8 13] It is thus important to examine DPP-4 inhibitors for a longer period in the subjects who are not at high cardiovascular risk to entirely clarify the safety issues suggested and unidentified for the drug class. Registry studies must be useful for this purpose, and indeed several reports using registries have shown the safety and efficacy of the class as real-world evidence.[5 14 15] It should be noted, however, that these studies were retrospective[13 14] or non-controlled,[5] or used the short-term claim databases, and lack various important information such as anthropometric and laboratory data.[14]

To more precisely evaluate the safety and efficacy of DPP-4 inhibitors, we conducted a 3-year, large-scale, prospective, controlled, observational study (Japan-based Clinical Research Network for Diabetes Registry: J-BRAND Registry) in the Japanese patients with type 2 diabetes. The study was designed as a concurrently controlled one: patients started the study with initiation of alogliptin (brand name: Nesina) as a representative of DPP-4 inhibitors (group A), while other patients started with initiation of other classes of oral hypoglycemic agents (OHAs) for comparison (group B, see Research design and methods section).[16] The relatively long-term, non-intervening (ie, real world) design of J-BRAND Registry was expected to surpass the limitations associated with the aforementioned, conventional cohort studies. Furthermore, the study allowed the investigators to follow up any safety events including macrovascular as well as microvascular events occurring following the usage of DPP-4 inhibitors and other OHAs. We report here the safety and efficacy profile of alogliptin in the real-world setting.

RESEARCH DESIGN AND METHODS

Study treatment and procedures

The overall study procedures were already described[16] in line with the principles of the Declaration of Helsinki and the Harmonised Tripartite Guideline for Good Clinical Practice from the International Council for Harmonisation, and approved centrally by MINS IRB (Tokyo, Japan) and then by the Institutional Review Board set up at each institutional organization. Patients aged 20 years or older with diagnosed type 2 diabetes participated in this study (see box 1 for the detailed patient criteria in our previous article).[16] They provided written informed consent at the time of study registration. Patients were separated into two predefined groups, where they initiated the study with either alogliptin (group A) or non-DPP-4 inhibitor OHAs (group B), respectively, with or without concomitant use of different classes of OHAs primarily depending on their condition. The patients of each group were further sub-grouped according to the type of treatment initiation as “start”, “addition”, or “switch”, where alogliptin or non-DPP-4 inhibitor OHA was newly started, added to the previous treatment, or switched from the previous OHA(s) at the time of or within 3 months prior to the study registration (see figure 2 in our previous article).[16] Treatment with OHA(s) was provided in daily clinical practice and was allowed to change or discontinue as per the package insert for each OHA.[17] For example, Nesina as a representative of DPP-4 inhibitors was administered at a dose of 25 mg once daily, while either 6.25 or 12.5 mg daily was used at physician’s discretion in the patients associated with moderate-to-severe kidney malfunction. Non-OHA antidiabetic therapies and/or treatments for concurrent medical conditions were also provided when needed. The patients were to visit their sites for assessment every 6 months during the 3-year study period and the data were registered via a customized electronic data capture system.

Outcomes

The primary outcome of the present study was all adverse events (AEs). The overall schedule and essential and optional items for observations were as in tables 1 and 2 of our previous article.[16] Any AE was assessed with its term, seriousness, severity, causality to OHA(s) or other treatments used, date of onset, date of resolution, frequency, action taken on OHAs (and other treatments), and consequence. Symptomatic hypoglycemia, pancreatitis (acute or chronic), skin disorders of non-extrinsic origin, severe infections, and cancer were collected as major AEs.[18–22] Microvascular and macrovascular complications were also collected. AE terms were referred to MedDRA V.15.1. The secondary outcome was efficacy of alogliptin and included the levels of hemoglobin A1c (HbA1c), fasting blood glucose, fasting insulin, and urinary albumin.

Other measurements (concurrent medical conditions, laboratory parameters, physical examinations, chest X-ray, and standard 12-lead ECG) were performed as described.[16]

Statistical analysis

Three different patient populations, full analysis set (FAS), safety analysis set (SAS), and efficacy analysis set (EAS), were defined for statistical analysis in the present study.[16] SAS was the primary set for the analysis of safety and microvascular/macrovascular complications, while efficacy was analyzed using EAS.

Cumulative incidence of the major AEs (symptomatic hypoglycemia, pancreatitis acute or chronic, skin disorders of non-extrinsic origin, severe infections, and cancer) and microvascular complications were analyzed by the Kaplan-Meier method and log-rank test for comparison between group A and group B. Cox regression analysis was performed as appropriate. Changes from baseline of HbA1c and other efficacy endpoints were compared between the groups by two-sample t test. All statistical analyses were performed using SAS V.9.4. Note the abbreviation “SAS” was exclusively used to denote “safety analysis set” in the text.

RESULTS

Disposition and baseline characteristics of patients

The study was conducted from April 1, 2012 to December 31, 2017. Although we initially planned to recruit 10,000 patients each in group A and group B,[16] a total of 5969 subjects were registered until September 30, 2014 at 239 institutional sites nationwide.

Figure 1 depicts a diagram of the analysis sets. Of 5969 registered, 5745 were with baseline measurements, and 5208 were included in the FAS population (3424 in group A and 1784 in group B) after 537 excluded mainly due to no drug newly administered for study initiation (344),

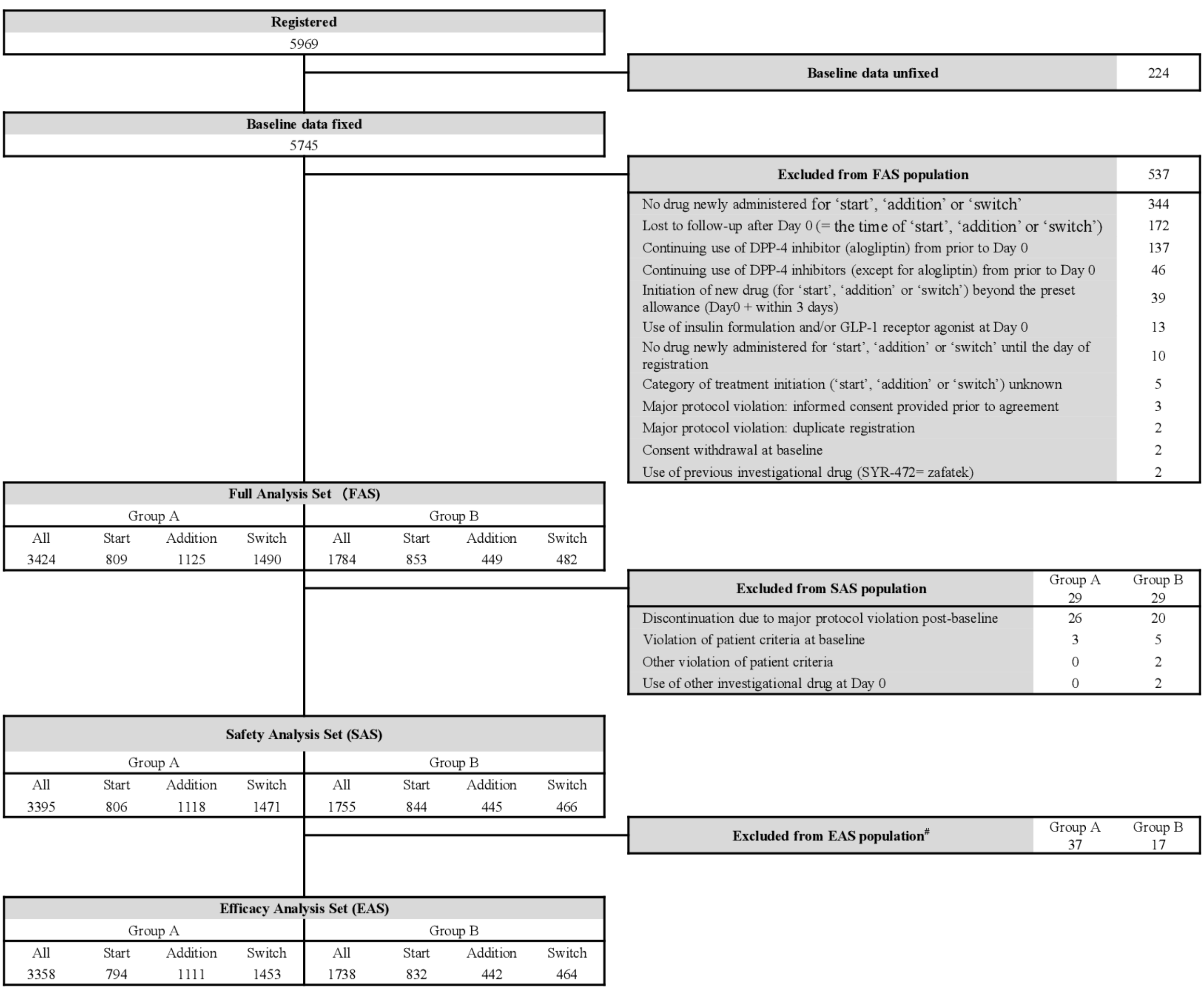

Figure 1 Patient disposition. #Patients were excluded if no visits post-baseline. DPP, dipeptidyl peptidase; GLP-1, glucagon-like peptide-1.

Table 1 Baseline characteristics of study patients

		Group A (N=3395)	Group B (N=1755)	P value†
Sex, n (%)	Male	2098 (61.8)	1074 (61.2)	0.675
	Female	1297 (38.2)	681 (38.8)	
Age (years)		65.0 (11.8)	61.7 (12.5)	<0.001***
Duration of type 2 diabetes (years)		9.55 (8.33)	7.34 (7.70)	<0.001***
Smoking status, n (%)	No	1752 (51.6)	855 (48.7)	<0.001***
	Current	616 (18.1)	402 (22.9)	
	Previous	1027 (30.3)	498 (28.4)	
Height (cm)		161.1 (9.3)	161.8 (9.2)	0.012*
Weight (kg)		65.12 (14.21)	67.98 (15.00)	<0.001***
BMI (kg/m^2)		24.99 (4.45)	25.85 (4.62)	<0.001***
HbA1c (%)‡		7.58 (1.274)	7.86 (1.626)	<0.001***
Fasting blood glucose (mg/dL)		153.9 (51.32)	157.2 (52.15)	0.136
Fasting insulin (μU/mL)		9.33 (9.63)	10.46 (11.71)	0.140
Casual blood glucose (mg/dL)		175.7 (68.71)	186.9 (75.62)	<0.001***
Systolic blood pressure (mmHg)		131.3 (16.90)	133.0 (18.37)	0.009**
Diastolic blood pressure (mmHg)		74.6 (11.50)	76.8 (12.81)	<0.001***
Pulse rate (bpm)		77.3 (12.44)	77.1 (12.80)	0.719
Total cholesterol (mg/dL)		187.9 (34.94)	195.6 (39.50)	<0.001***
HDL cholesterol (mg/dL)		54.8 (17.70)	54.1 (21.70)	0.369
LDL cholesterol (mg/dL)		109.2 (31.11)	115.5 (33.84)	<0.001***
Fasting triglycerides (mg/dL)		136.7 (84.12)	143.7 (92.88)	0.060
Serum creatinine (mg/dL)		0.832 (1.744)	0.796 (0.943)	0.394
Urinary albumin (mg/g·Cre)		91.37 (337.54)	103.12 (355.48)	0.229

Values are mean (SD) unless otherwise specified.
*p<0.05, ** p<0.01 and ≥0.001, and ***p<0.001.
†Patients were compared between group A and group B for sex, and smoking status by χ^2 test, for urinary albumin by Wilcoxon rank-sum test and for the other categories by t-test.
‡% of mean HbA1c was converted to mmol/mol as 59 and 62, respectively.
BMI, body mass index; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

loss to follow-up after day 0 (172; day 0=the time of study initiation), and continuing use of alogliptin from prior to day 0 (137). Following 29 each excluded from the FAS population, 5150 (3395 and 1755) were included in the SAS population. Fifty-four (37 and 17) patients were further excluded due to loss to follow-up and then the EAS population included 5096 (3358 and 1738) patients. The statistical power was 96.6% for group A and 82.7% for group B to detect an AE occurring in SAS population at 0.1% incidence.

The percentage of study completers was comparable between the two groups of SAS population (2374/3395=69.9% and 1239/1755=70.6%). During the study period, 887 (26.1%) group A patients and 471 (26.8%) group B patients discontinued the study mainly due to loss to follow-up (334 (9.8%) and 211 (12.0%)) and voluntary withdrawal (191 (5.6%) and 91 (5.2%)).

Baseline characteristics of the SAS population are summarized in table 1. Mean duration of type 2 diabetes was significantly longer in group A patients than in group B patients (9.55 vs 7.34 years; p<0.001). Statistically significant between-group differences were also found in age (65.0 vs 61.7 years; p<0.001), smoking status (p<0.001), height (161.1 vs 161.8 cm; p=0.012), weight (65.12 vs 67.98 kg; p<0.001), and body mass index (BMI; 24.99 vs 25.85 kg/m^2; p<0.001).

Mean values of HbA1c and casual blood glucose were significantly higher in group B than in group A (7.86 vs 7.58%; 62 vs 59 mmol/mol, p<0.001 and 186.9 vs 175.7 mg/dL, p<0.001). Other efficacy-linked parameters (fasting blood glucose, fasting serum insulin, and urinary albumin) were comparable between the two groups. Systolic and diastolic blood pressures were higher in group B patients (133.0 vs 131.3 mmHg, p=0.009; and 76.8 vs 74.6 mmHg, p<0.001). Total cholesterol and low-density lipoprotein (LDL) cholesterol were also higher in group B (195.6 vs 187.9 mg/dL, p<0.001 and 115.5 vs 109.2 mg/dL, p<0.001, respectively). Other baseline laboratory and vital parameters are listed in online supplemental table 1 and were either with no between-group difference or were deemed clinically less significant even if with statistical difference.

Table 2 Usage of oral hypoglycemic agents

Group	Drug class	Visit (year) Baseline	3.0
A	Patients	3395 (100.0%)	1839 (100.0%)
	No use of oral hypoglycemic drugs	0 (0.0%)	48 (2.6%)
	Sulfonylureas	1160 (34.2%)	619 (33.7%)
	Rapid-acting insulin secretagogues	100 (2.9%)	128 (7.0%)
	α-Glucosidase inhibitors	539 (15.9%)	321 (17.5%)
	Biguanides	1352 (39.8%)	894 (48.6%)
	Thiazolidinediones	508 (15.0%)	325 (17.7%)
	DPP-4 inhibitors	3395 (100.0%)	1687 (91.7%)
	SGLT2 inhibitors	1 (0.03%)	160 (8.7%)
B	Patients	1755 (100.0%)	965 (100.0%)
	No use of oral hypoglycemic drugs	0 (0.0%)	35 (3.6%)
	Sulfonylureas	505 (28.8%)	235 (24.4%)
	Rapid-acting insulin secretagogues	347 (19.8%)	185 (19.2%)
	α-Glucosidase inhibitors	435 (24.8%)	215 (22.3%)
	Biguanides	1192 (67.9%)	622 (64.5%)
	Thiazolidinediones	342 (19.5%)	157 (16.3%)
	DPP-4 inhibitors	0 (0.0%)	352 (36.5%)
	SGLT2 inhibitors	21 (1.2%)	108 (11.2%)

DPP, dipeptidyl peptidase; SGLT, sodium-glucose cotransporter.

There was a notable difference in OHA usage between the two groups. Before study registration, group A patients used more OHAs compared with group B patients (mean number of OHAs: 1.5 vs 0.8). Nearly twice more patients used two or more OHAs in group A (45.5% vs 23.0%), and a comparable percentage (30.7% vs 28.9%) was with oral monotherapies while a lower percentage (23.7% vs 48.1%) was with no use of OHAs. This tendency was also observed at baseline as 2.1 versus 1.6, while a gradual increase in group B patients as 2.3 versus 2.0 at the 3-year study end. The time-dependent changes of the usage of different OHA classes are profiled in table 2 and online supplemental figure 1. All group A patients received a DPP-4 inhibitor (alogliptin) at baseline as defined in the study protocol.[16] While the real-world setting allowed therapeutic changes with different drug classes, group A patients mostly (>90%) continued to use alogliptin (or other DPP-4 inhibitors) throughout the study. Biguanides and sulfonylureas were the two secondary dominants received by the group A patients, while the group B patients used biguanides as the primary agent at baseline as expected in the current clinical practice. It was interesting that the use of DPP-4 inhibitors gradually increased (up to ~36%) in group B through the study progress and became the second dominant over sulfonylureas at the later stage. Non-OHA therapies (insulin formulations and GLP-1 receptor agonists) were also used in an increasing number of patients in both groups up to ca. 4.2% and 2.4% in group A and 2.7% and 2.0% in group B, respectively.

Primary outcome

AEs were collected as the primary outcome in this study, and all reported AEs are tabulated in online supplemental table 2. The overall incidence of AEs was similar between group A and group B (42.7% vs 42.2%; p=0.744). The

Table 3 Cumulative incidence of major adverse events

	Group A (N=3395) n (%)	Group B (N=1755) n (%)	P value Group A vs B
Symptomatic hypoglycemia	104 (3.9)	45 (3.2)	0.317
Pancreatitis acute	5 (0.2)	3 (0.9)	0.861
Pancreatitis chronic	2 (0.1)	0 (0.0)	0.310
Skin disorders of non-extrinsic origin	201 (7.9)	90 (6.2)	0.240
Severe infections	71 (2.7)	28 (2.0)	0.222
Cancer	162 (7.4)	62 (4.8)	0.040*

Cumulative incidence (%) of major AEs was calculated per observation period by the Kaplan-Meier method (see figure 2). P values were by log-rank test. Potential factors contributing to cancer development were detailed by Cox regression analysis as shown in online supplemental table 3.
*p value with significance level smaller than 0.05.

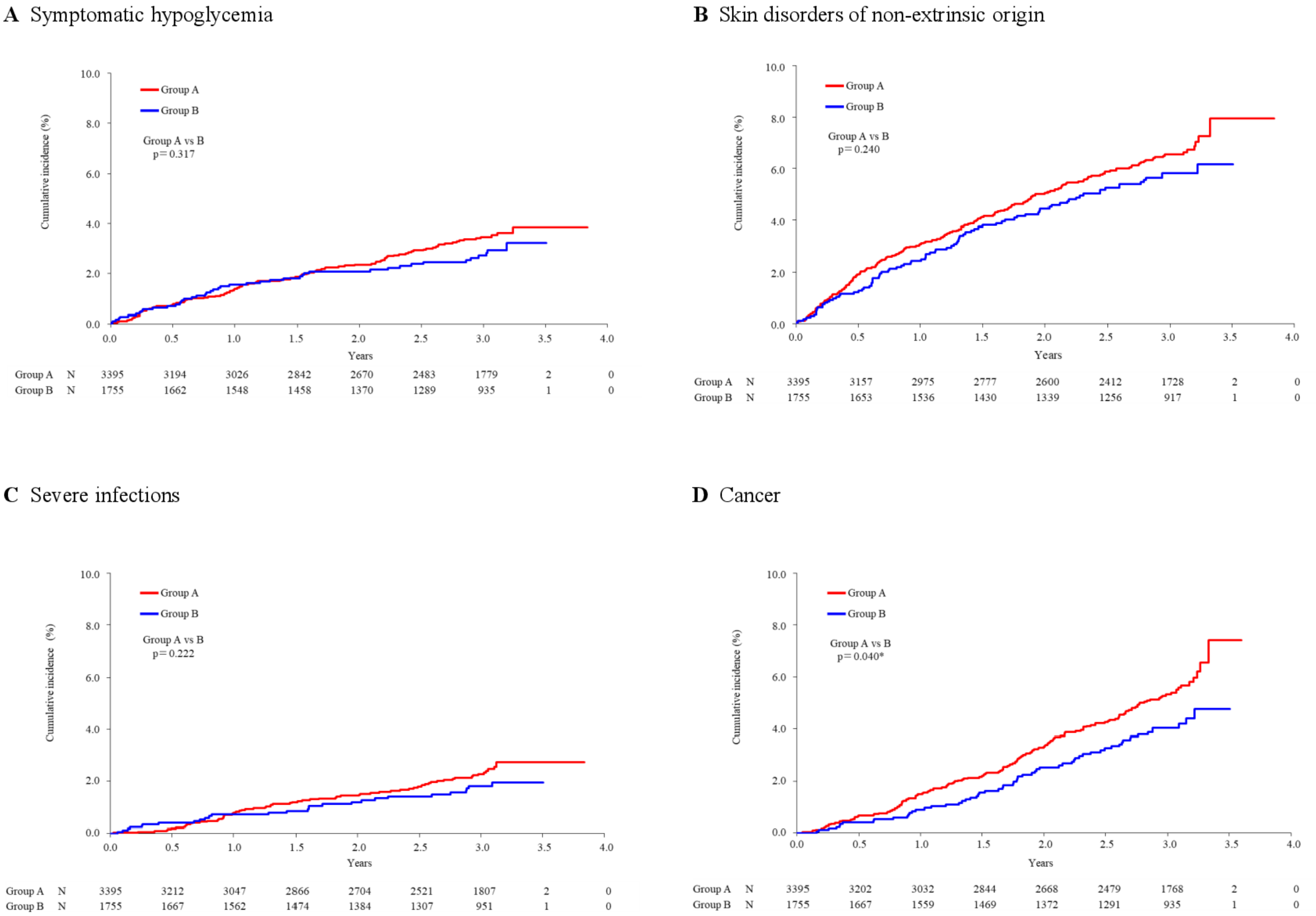

Figure 2 Kaplan-Meier analysis of major adverse events. (A) Symptomatic hypoglycemia, (B) skin disorders of non-extrinsic origin, (C) severe infections, and (D) cancer. Between-group comparisons were performed by log-rank test. Numbers (N) under each time point denote patients at risk.

cumulative incidence of major AEs (see Research design and methods section) is summarized in table 3 with the aid of Kaplan-Meier analysis (figure 2). The difference of the basis for percent incidence calculation should be noted as the Kaplan-Meier method was employed for major AEs (table 3) and microvascular complications (table 4), while the number of patients with AE occurrence was simply divided by SAS population (ie, n=3395 for group A and n=1755 for group B) for individual AEs (see online supplemental table 2), macrovascular complications (table 5), and serious adverse events (SAEs; see online supplemental table 2).

Table 4 Cumulative incidence of onset and progression of microvascular complications

		Group A (N=3395)	Group B (N=1755)	P value
		n (%)	n (%)	Group A vs B
Diabetic retinopathy	Onset/progression	62 (2.3)	27 (2.0)	0.455
	Onset	43 (2.0)	21 (1.9)	0.687
	Progression	19 (3.6)	6 (3.1)	0.661
Diabetic nephropathy	Onset/progression	76 (3.0)	51 (6.0)	0.147
	Onset	49 (2.6)	37 (6.2)	0.117
	Progression	27 (4.2)	14 (4.9)	0.683
Diabetic neuropathy	Onset/progression	30 (1.1)	13 (1.4)	0.588
	Onset	21 (1.0)	12 (1.7)	0.825
	Progression	9 (1.8)	1 (0.4)	0.142

Cumulative incidence (%) of microvascular complications was calculated per observation period by the Kaplan-Meier method (see online supplemental figure 2). P values were by log-rank test.

Table 5 Summary of symptomatic macrovascular events

Category		Group A (N=3395)		Group B (N=1755)		P value
		n (%)	Event	n (%)	Event	Group A vs B
Overall macrovascular events		92 (2.71)	109	52 (2.96)	62	0.594
Acute coronary syndrome		1 (0.03)	1	0 (0.00)	0	1.000
Myocardial infarction		17 (0.50)	17	9 (0.51)	12	1.000
Stroke	Cerebral infarction	29 (0.85)	32	20 (1.14)	20	0.363
	Cerebral hemorrhage	11 (0.32)	11	3 (0.17)	3	0.406
Heart failure		27 (0.80)	33	11 (0.63)	13	0.607
Coronary angioplasty	PCI	2 (0.06)	2	2 (0.11)	3	0.609
	CABG	1 (0.03)	1	0 (0.00)	0	1.000
PAD		8 (0.24)	9	7 (0.40)	8	0.413
Unstable angina		3 (0.09)	3	3 (0.17)	3	0.416

Macrovascular events were selected on symptomatic basis, but events deemed on test/examination basis were not included. The events selected and categorized in the table were acute coronary syndrome, myocardial infarction (acute myocardial infarction and myocardial infarction), cerebral infarction (brain stem infarction, cerebellar infarction, cerebral infarction, cerebral thrombosis, lacunar infarction, thalamic infarction, and thrombotic cerebral infarction), cerebral hemorrhage (brain stem hemorrhage, cerebellar hemorrhage, cerebral hemorrhage, subarachnoid hemorrhage, thalamus hemorrhage, and putamen hemorrhage), heart failure (cardiac failure, cardiac failure acute, cardiac failure chronic, and cardiac failure congestive), PCI (coronary angioplasty and stent placement), CABG (coronary artery bypass), PAD (peripheral arterial occlusive disease), and unstable angina. Incidence (%) was calculated as a division of n for individual AE category by either 3395 (group A) or 1755 (group B). P values were based on Fisher's exact test.
AE, adverse event; CABG, coronary artery bypass grafting; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.

Of major AEs, symptomatic hypoglycemia was cumulatively reported in 104 (point estimate: 3.9%) group A patients and 45 (3.2%) group B patients with no significant difference (p=0.317; table 3 and figure 2A). Pancreatitis was reported at a low rate in both groups, as acute type in 5 (0.2%) and 3 (0.9%) patients and chronic type in 2 (0.1%) and 0 patients with no statistical between-group difference (p=0.861 and p=0.310, respectively, table 3; Kaplan-Meier plots not shown).

Kaplan-Meier analysis gave a similar profile for skin disorders of non-extrinsic origin observed in 201 (7.9%) group A patients and 90 (6.2%) group B patients (p=0.240; table 3 and figure 2B). Of the observed skin disorder AEs, skin papilloma was with significant between-group difference (0.0% vs 0.2%, p=0.040; see online supplemental table 2). Bullous pemphigoid has been recently suggested in association of the use of DPP-4 inhibitors.[23 24] This AE was observed in three group A patients but no group B patients with no significant difference (p=0.556; see online supplemental table 2).

Severe infections were observed in 71 (2.7%) and 28 (2.0%) patients, respectively, and their Kaplan-Meier analysis was with no between-group difference (p=0.222; table 3 and figure 2C). Of the observed infections, vulvovaginal candidiasis was with between-group difference (0.0% vs 0.2%, p=0.040; see online supplemental table 2).

Cancer occurred more frequently in group A (162 patients; 7.4%) than in group B (62 patients; 4.8%) with a statistical difference (p=0.040; table 3 and figure 2D). Thyroid, lung, stomach, liver, large intestine, and prostate were the frequent sites for the event (see online supplemental table 2). The incidence of pancreatic cancer was low in both groups (0.1% each, p=1.000; see online supplemental table 2). No significant difference was observed between the two groups in the incidence of individual cancer. Multivariate Cox regression analysis showed no significant impact by group, but confirmed an increase of the event as HR (95% CI)=3.34 (2.32 to 4.81; p<0.001) for age ≥65 and <75 years and 5.54 (3.78 to 8.14; p<0.001) for age ≥75 years compared with age <65 years. Previous smoking habit was another factor contributing to the event as HR (95% CI)=1.70 (1.28 to 2.27; p<0.001) compared with the patients with no smoking history (see online supplemental table 3).

SAEs observed during the study period are summarized in online supplemental table 2. Overall incidence of SAEs was 14.6% in group A and 12.5% in group B with a small but significant difference (p=0.046). The table includes serious ones of the reported major AEs (but without defining limitations such as "symptomatic" for hypoglycemia). These major AE categories were of no significant between-group difference in their incidence except for cancer (p=0.037). "Other" SAEs were observed in 10.3% and 9.6% of patients (p=0.463). Of those, System Organ Classes (SOCs) of Cardiac disorders, Gastrointestinal disorders, Injury, poisoning, and procedural complications, Metabolism and nutrition disorders, and Nervous system disorders were the categories frequently reported. Serious cholangitis under SOC of Hepatobiliary disorders was reported in one (0.03%) group A patient and four (0.2%) group B patients with between-group significance (p=0.049, not shown in online supplemental table 2).

We collected information of microvascular complications (diabetic retinopathy, nephropathy, and neuropathy). No significant between-group difference was detected when the onset and progression were analyzed by the Kaplan-Meier method either in combination or separately (table 4 and online supplemental figure 2). Serious microvascular AEs were observed in 0.1% and 0.2% of patients, respectively, with no between-group difference (p=0.239, not shown in online supplemental table 2).

Macrovascular events were tabulated in table 5 on symptomatic basis, but not on test/examination basis. Ninety-two (2.71%) group A patients and 52 (2.96%) group B patients developed macrovascular complications with no significant between-group differences in the categorized events.

There were AEs under "Others" category reported with statistical between-group difference (see online supplemental table 2). Their incidence was higher in group B than in group A, except for iron-deficiency anemia. The incidence of AEs under SOC "Renal and urinary disorders" was high in group A compared with group B, but none of the individual AEs under this organ class were with significant between-group difference.

Efficacy of alogliptin

Since J-BRAND Registry was conducted in the real-world setting, there were patients who received insulin products and/or GLP-1 or related formulations for better glycemic control. Furthermore, the use of DPP-4 inhibitors increased in group B patients (see the section of Disposition and baseline characteristics of patients and online supplemental figure 1). For better clarification of the effectiveness of alogliptin (or other DPP-4 inhibitors), we analyzed the efficacy endpoints mainly in the patient population after excluding those who received insulin products and/or GLP-1 or related formulations (group A) and who received insulin products, GLP-1 or related formulations, and/or DPP-4 inhibitors (group B).

Mean HbA1c was at 7.58% (59 mmol/mol) in group A patients and 7.86% (62 mmol/mol) in group B patients at baseline with significant difference (p<0.001 by two-sample t-test; table 1). The parameter decreased significantly in both groups at 0.5-year visit (7.00%=53 mmol/mol and 6.96%=53 mmol/mol; p<0.001 each by one-sample t-test) and then nearly plateaued up to the end of 3-year treatment period (see online supplemental figure 3). The decrease was larger in group B patients than in group A patients, for example, −0.76% versus −0.60% at 0.5-year visit (p<0.001 by two-sample t-test; figure 3A).

Blood glucose was determined in each patient under a fasting condition. The mean values were 153.9 mg/dL in group A patients and 157.2 mg/dL in group B patients at baseline and significantly decreased at the following visits in either group with changes of −9.9 to −14.5 mg/dL and −16.3 to −18.8 mg/dL (p<0.001; figure 3B). No statistical difference was observed between the groups. Mean fasting serum insulin was 9.33 μU/mL in group A patients and 10.46 μU/mL in group B patients at baseline, and showed no considerable changes at the later visits (figure 3C). In addition, homeostasis model assessment (HOMA)-R and HOMA-β were exploratorily calculated to assess insulin resistance and insulin secretability in the patients. Mean baseline HOMA-R was 3.58 in group A and 4.07 in group B with no significant difference. While group A patients showed a slight change (−0.52 to 0.01) and group B patients showed a significant decrease (−0.80 to −1.06) at 1.0, 2.0, and 3.0 years post-baseline (by one-sample t-test), the changes were with no significant difference between the groups throughout the study period. Similarly, mean HOMA-β was 47.12% and 48.61% with no significant difference at baseline, and its changes were small (1.76% to 15.28% and −2.08% to 5.99%) with no significant between-group difference.

Urinary albumin and serum creatinine were determined and their ratio (ACR) was calculated. The baseline values were 91.4 mg/g·Cre and 103.1 mg/g·Cre, respectively, with no statistical difference (p=0.229; table 1). The parameter showed no notable changes throughout the study period in both groups (figure 3D).

Over-time changes in other related parameters

Changes of body weight, ECG abnormalities, total/high-density lipoprotein (HDL)/LDL cholesterol, and fasting triglycerides are summarized in online supplemental table 4.

Mean weight was higher in group B patients than in group A patients at baseline (p<0.001, table 1) and then significantly decreased at 0.5-year and later visits (group A: −0.17 to −0.81 kg, group B: −0.37 to −0.92 kg). Higher weight of group B patients was throughout the study period. The changes from baseline were not significantly different between the two groups (see online supplemental table 4).

ECG abnormalities were found in 7.3% of group A patients and 4.4% of group B patients at baseline with significant difference (p=0.032 by χ^2 test). However, this between-group difference disappeared with stable percentage of abnormalities at 0.5-year and later visits (see online supplemental table 4).

Mean total cholesterol was higher in group B patients than in group A patients at baseline (p<0.001, table 1), and then significantly decreased at later visits (group A: −5.1 to −6.4 mg/dL, group B: −6.7 to −10.8 mg/dL). The higher level of total cholesterol was throughout the study period in group B, but the difference of changes from baseline were generally insignificant between the two groups (see online supplemental table 4). HDL cholesterol was not largely different between the two groups with only minor changes throughout the study period (see online supplemental table 4). Mean LDL cholesterol was higher in group B patients than in group A patients at baseline (p<0.001, table 1) and then significantly decreased at later visits (group A: −4.9 to −7.1 mg/dL, group B: −7.3 to −12.3 mg/dL). The higher level of LDL cholesterol in group B patients was up to 2.0-year

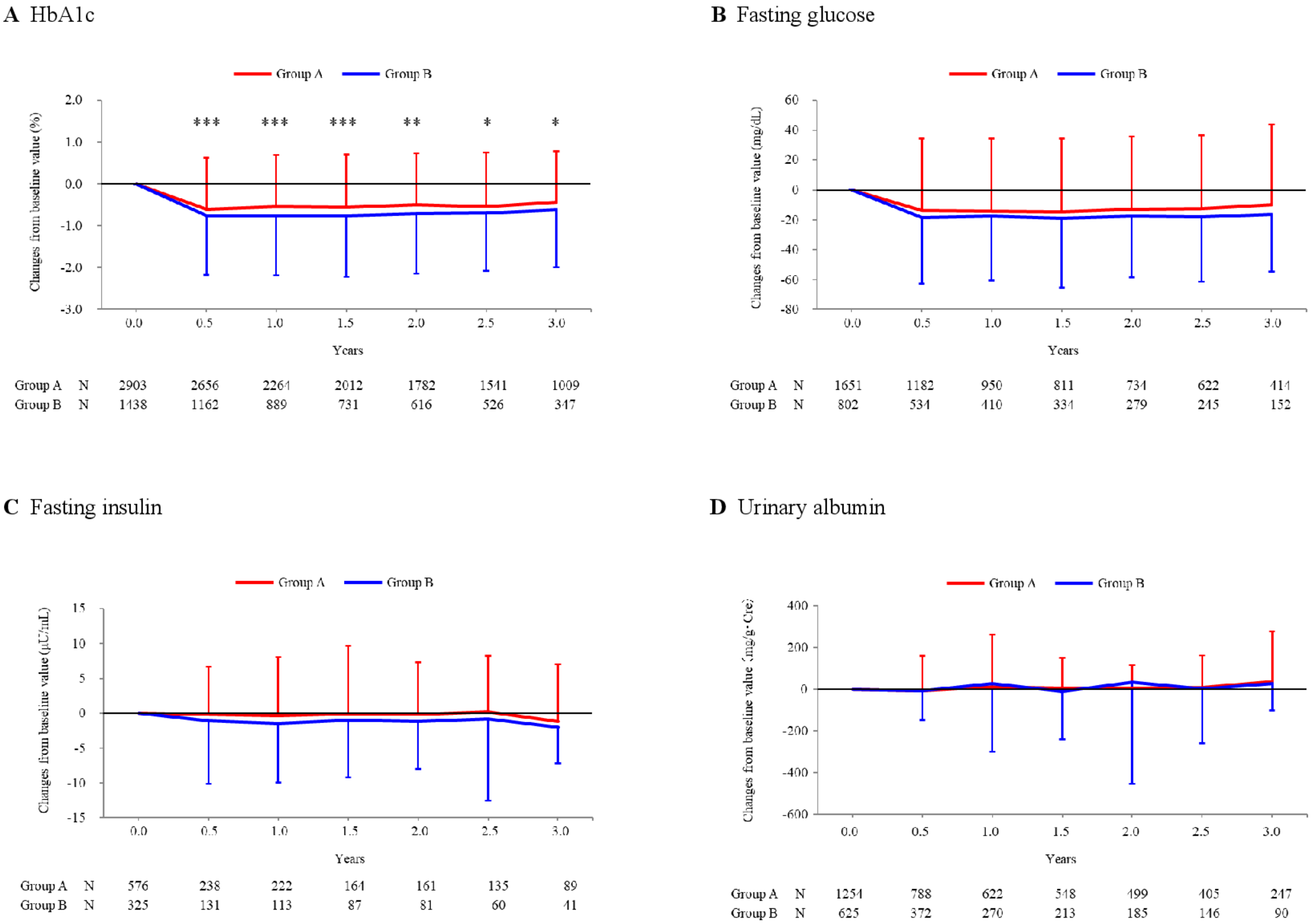

Figure 3 Over-time changes of efficacy endpoints. HbA1c (A), fasting glucose (B), fasting insulin (C), and urinary albumin (D) were determined at baseline and following visits. Changes of these parameters from baseline (mean±SD) were plotted against each visit. Note the patients were excluded from the analysis if they received insulin products and/or GLP-1 or related formulations (group A), and received insulin products, GLP-1 or related formulations, and/or DPP-4 inhibitors (group B). Between-group difference was examined at each visit by two-sample t-test, giving significant p values only for HbA1c as ***p<0.001, ***p<0.001, ***p<0.001, **p=0.001, *p=0.026, and *p=0.027, respectively. Also note that mean HbA1c was 7.58% in group A patients and 7.86% in group B patients at baseline with significant difference (p<0.001 by 2-sample t-test; table 1). DPP, dipeptidyl peptidase; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c.

visit and with greater changes from baseline throughout the study period (see online supplemental table 4).

Mean fasting triglycerides was comparable at baseline (table 1). Although the values did not change considerably in group A patients, a significant decrease was observed at 0.5-year, 1.5-year, and 2.0-year visits in group B patients. The difference of this parameter was with no significance between the two groups throughout the study period (see online supplemental table 4).

DISCUSSION

J-BRAND Registry was conducted in patients with type 2 diabetes as a large-scale, multicenter, controlled, prospective, observational study. Given that DPP-4 inhibitors have been extensively used in the patients with the disease during the recent decade, the study constructed a real-world database on the safety and efficacy of the drug class particularly focusing on alogliptin as a representative.[16] Group A patients (n=3395) started the study treatment with alogliptin and group B patients (n=1755) with non-DPP-4 inhibitor OHAs. Of patient backgrounds, age, disease duration, BMI, and so on were different between the two groups. These differences reflected the reasonable drug choice based on the pathogenesis and background of the individual patients by the diabetes specialists participating in this study; DPP-4 inhibitors are suitable for non-obese, older patients whose major pathogenesis is likely to be a defect in insulin secretion (especially in the population of East Asian region including Japan), while biguanides are effective for obese, non-elderly patients who are likely to exhibit insulin resistance. Of baseline parameters, blood pressure, HbA1c, weight, total cholesterol, LDL cholesterol, and casual blood glucose were lower in group A patients than in group B patients.

Of the major safety events, symptomatic hypoglycemia, pancreatitis, skin disorders of non-extrinsic origin, and severe infections were not statistically different in their incidence between the two groups. A risk for pancreatitis, which has been suggested for DPP-4 inhibitors,[19 25] was not detected as previously reported regarding alogliptin and other DPP-4 inhibitors by relatively short-term observations.[5 7–10] Bullous pemphigoid is another concern,[20 23 24 26] given that DPP-4 inhibitor-related bullous pemphigoid has been reported to preferentially occur in elderly patients treated for several years. Although our study did not detect the increased risk with DPP-4 inhibitor treatment, further study might be needed to draw a definitive conclusion. While skin papilloma and vulvovaginal candidiasis were exceptionally observed in group B with a statistical significance over group A, their incidence was low and none of those were reported as treatment related.

Cancer was observed more frequently in group A than in group B, while the incidence of individual cancer was not different. The between-group difference of all cancers was attributable to group A patients being significantly older than group B patients. Presumably due to a similar reason, there was a small increase of SAEs including cancers in group A compared with those in group B. It should be noted the incidence of pancreatic cancer was low in both groups.

Onset and progression of microvascular complications were reported at comparable rates between the two groups when analyzed either in combination or separately. The incidence similarity was also observed for macrovascular events between the groups. Several outcome studies showed no increase in cardiovascular risk by DPP-4 inhibitors.[7–10] The current study confirmed the safe profile of alogliptin in terms of cardiovascular disease in the real-world setting. It should be noted that alogliptin use achieved the similar glycemic control and showed the similar incidence of macrovascular complications to that observed in the group predominantly using metformin, which has been shown to suppress macrovascular complications.[27] Previous studies raised some concern about the risk of heart failure by DPP-4 inhibitor use.[7 8 12] While recent studies have shown the protective effects of SGLT2 inhibitors for heart failure,[28] SGLT2 inhibitor use was very low in both groups and alogliptin use was not associated with the risk in the current study, confirming the safe profile of alogliptin for heart failure.

The low risk of weight gain was also confirmed for DPP-4 inhibitors during long passage of the treatment of patients with diabetes mellitus.

The efficacy profile was similar between the two groups as observed for the time-dependent decrease in HbA1c and fasting blood glucose. Importantly, group A patients achieved and maintained the target HbA1c (7.0%=53 mmol/mol) in average throughout the study with only a slight increase in the number of medications (the mean number of drugs used: from 2.1 to 2.3), while group B patients also maintained the target but with more increase in the number of medications (from 1.6 to 2.0). Moreover, alogliptin use appeared to preserve the ability of insulin secretion as evidenced by the maintained HOMA-β for 3-year study period, different from the decline by sulfonylurea-based therapy in the United Kingdom Prospective Diabetes Study,[29] while group B patients using metformin as a major medication showed no decrease in HOMA-β, either, as shown by the previous study.[30] The effect of alogliptin on albuminuria was not different from that observed in group B, suggesting that achieving the target HbA1c is important for the suppression of diabetic kidney disease rather than using specific medication.

DPP-4 inhibitors are widely used in Japan and other East Asian countries since the incretin-based therapy is more efficacious for the Asian subjects than Caucasians.[31] The current study has shown that DPP-4 inhibitors are more preferentially prescribed to relatively older and thinner patients with longer disease history in the real-world setting as expected. Prevalence of the elderly patients with diabetes has been and will be increasing,[32] and safety profile of medication including low risk of severe hypoglycemia[33] tightly associated with cognitive decline and frailty is important. With this regard, the current study provides the evidence of the safety of DPP-4 inhibitors. It also suggests that the treatment of elderly patients with DPP-4 inhibitors is durable for glucose-lowering and maintenance of the pancreatic β-cell function.

On the other hand, the current study has certain limitations: (1) differences were observed in patients' baseline characteristics, (2) no centralized adjudication system was applied to the safety and efficacy evaluations, and thereby the collection of macrovascular events in particular may have been influenced. These limitations are, however, a reflection of real-world context of type 2 diabetes treatment. Nevertheless, the current study for the first time demonstrated in a prospective fashion that alogliptin is not associated with any risks previously concerned and is durable in terms of glucose-lowering compared with the biguanide-based therapy.

In conclusion, alogliptin, as a representative of DPP-4 inhibitors, was revealed as a safe and efficacious agent for the treatment of patients with type 2 diabetes in the real-world setting.

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