ORIGINAL ARTICLE

Preferential prescribing of linagliptin in type 2 diabetes patients in an expanded post-marketing surveillance study in Japan

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ABSTRACT

Aims/Introduction: To evaluate linagliptin prescribing in type 2 diabetes mellitus patients with different comorbidities, an expanded Japanese post-marketing surveillance also collected baseline data for patients initiating other glucose-lowering drugs.

Materials and Methods: Patients initiating linagliptin monotherapy were enrolled, then the next patient starting monotherapy with another glucose-lowering drug was enrolled (2012–2014). Baseline data were collected and analyzed by the Medical Dictionary for Regulatory Activities system organ class. Analyses were descriptive, and meaningful differences defined as absolute standardized difference >10%.

Results: Over 4,200 type 2 diabetes mellitus patients were enrolled. Most system-organ class comorbidities were more common in patients initiating linagliptin versus other glucose-lowering drugs, with meaningful differences observed for metabolism/nutritional (50.5 *vs* 45.5%, respectively), cardiac (12.2 *vs* 8.6%, respectively), vascular (56.4 *vs* 51.3%, respectively) and renal/urinary disorders (9.9 *vs* 5.7%, respectively).

Conclusions: Expanding the linagliptin Japanese post-marketing surveillance revealed linagliptin prescribing to a type 2 diabetes mellitus population with more comorbidities versus other glucose-lowering drugs. Although such preferential prescribing might be expected, as linagliptin requires no dose adjustment or monitoring in renally or hepatically impaired patients, this innovative post-marketing surveillance approach generated important evidence that could only be shown in such a non-randomized comparative study. These data generated insights important for the design and interpretation of observational studies and spontaneous reports, which are key for public health.

INTRODUCTION

It is estimated that >150 million people in the Western Pacific region have diabetes, with 7.2 million cases in Japan in 2015[1]. Compared with White patients, East Asian patients with type 2 diabetes mellitus generally have greater β-cell dysfunction and reduced insulin secretory capacity, but less obesity and insulin resistance[2]. The 2016–2017 Japanese Diabetes Society Treatment Guide for Diabetes recommends that patients with decreased insulin secretory capacity should be treated with an insulin secretagogue, specifically a sulfonylurea, glinide or dipeptidyl peptidase-4 (DPP-4) inhibitor[3]. Analysis of Japanese health insurance claims database data showed that >70% of patients with type 2 diabetes mellitus received DPP-4 inhibitors[4,5]. Furthermore, 60% of patients initiating DPP-4 inhibitors were drug-naïve, showing the prevalent use of these drugs as first-line treatments[4,5]. This preference can potentially be explained in part by the lower risk of hypoglycemia for DPP-4 inhibitors compared with sulfonylureas or glinides[6]. The particular efficacy of DPP-4 inhibitors in the Asian population was shown in a meta-analysis of 55 randomized, controlled trials, with DPP-4 inhibitors lowering glycated hemoglobin (HbA1c) to a greater extent in studies with ≥50% Asian participants compared with trials with <50% Asian participants[7].

The first DPP-4 inhibitor was launched in Japan in 2009, and has since been followed by eight other drugs from this class, including linagliptin in 2011. Unlike many other

glucose-lowering drugs (GLDs), linagliptin can be administered in patients with renal or hepatic impairment without adjustment of the standard clinical dosage (5 mg once daily)[8–12]. Clinical trials have confirmed the efficacy of linagliptin in patients with kidney disease, liver disease and cardiovascular disease[13–18]. Consequently, in clinical practice, linagliptin might be chosen over other GLDs for patients with type 2 diabetes mellitus and concomitant renal or hepatic impairment. Such preferential prescribing or "channeling" was observed for linagliptin in a USA study of 1,174,476 type 2 diabetes mellitus patients initiating therapy within a commercial insurance dataset[19]. Equivalent data in the Japanese population are currently lacking.

In Japan, post-approval execution of post-marketing surveillance (PMS) is required by the Japanese Pharmaceutical Affairs Law in order to accumulate safety and effectiveness data for re-examination. These studies have a pre-specified design in accordance with Good Post-marketing Surveillance Practice, as specified by the Ministry of Health, Labor and Welfare Ordinance No. 171 (20 December 2004).[20] At the time this PMS was carried out, data were usually requested from approximately 3,000 patients treated with a new DPP-4 inhibitor over a re-examination period of approximately 8 years. The primary aim of PMS studies is to examine drug safety in a wider population treated in daily practice compared with the phase III clinical trial population. Patients are eligible for inclusion according to the Japan package insert for the drug under study. Post-marketing surveillance studies are observational and usually do not include patients treated with comparator drugs. As such, information from these surveillance studies might be challenging to put into context if no additional recent clinical practice data from the respective patient population already exists. Importantly, other studies in Japan have shown that differences among type 2 diabetes mellitus patient age, duration of diabetes, obesity and glycemic control at baseline influenced treatment choice[21], and body-weight and glycemic control differed among metformin, DPP-4 inhibitors and sulfonylureas in accordance with differences in patient clinical features[22]. Furthermore, type 2 diabetes mellitus patients often have a significant burden of comorbid conditions, which might impact treatment choice. Studies carried out in the Japanese population have shown that many patients with type 2 diabetes mellitus have dyslipidemia, hypertension, chronic kidney disease (CKD) and cardiovascular/macrovascular disease[23–26].

The expanded linagliptin PMS study (NCT01650259) is a prospective, observational study to evaluate the safety of linagliptin over a 36-month treatment period based on the standard Japanese Pharmaceutical Affairs Law requirement. As linagliptin might be chosen over other GLDs for type 2 diabetes mellitus patients with concomitant renal or hepatic impairment in clinical practice, the standard PMS study design was expanded to collect baseline demographic and clinical data for patients starting GLDs other than linagliptin. The purpose of the analysis of the baseline data reported herein was to characterize GLD treatment patterns and identify any preferential prescribing that could influence interpretation of the standard PMS safety data.

METHODS

The linagliptin PMS study aimed to gather data from >3,000 type 2 diabetes mellitus patients from hospitals and general clinics across Japan between 2012 and 2014 using a continuous investigation system[27]. For the expansion, sequential enrollment was applied: a patient beginning monotherapy treatment with linagliptin was enrolled, then the patient immediately following who was starting monotherapy with any GLD other than linagliptin (treatment-naïve or switched from prior therapy with a different oral antidiabetic drug) was also enrolled. This sequential enrollment was then repeated. Monotherapy users of other GLDs were the chosen comparator in order to ensure that patients were at a similar stage of diabetes treatment. Patients were eligible for inclusion according to the linagliptin Japan package insert, with no further inclusion/exclusion criteria defined. As an observational study, no study medication was provided to the participants, and treatment decisions were solely at the discretion of the physician and the patient. In accordance with Japanese regulations for PMS studies, institutional review board review was not required, and written informed consent was not required from patients before their participation. However, institutional review boards located in the hospitals participating in this study approved our study before initiation.

In addition to the standard data collected to satisfy the requirements for the PMS, additional baseline characteristics were collected at study entry. These characteristics were analyzed based on the Medical Dictionary for Regulatory Activities (MedDRA® version 16.0) system organ class (SOC) and preferred term (distinct descriptors for symptoms, signs, disease diagnoses, therapeutic indications, investigations, surgical or medical procedures and medical social or family history characteristics) for selected SOCs (Table S1)[28]. Comparisons were made between patients initiating linagliptin versus patients initiating other GLDs, versus patients initiating other drugs within the same treatment class (i.e., other DPP-4 inhibitors), and versus patients initiating drugs from other treatment classes (biguanides, sulfonylureas, thiazolidinediones [TZDs], alpha-glucosidase inhibitors [AGIs] and glinides). Sodium–glucose cotransporter-2 inhibitors were also included, although these have only been available in Japan since 2014.

All statistical analyses were descriptive, and included the mean and standard deviation (SD), median and ranges, and absolute and relative frequencies. Absolute standardized differences (ASDs) for comparing linagliptin with other GLDs were calculated as the difference in mean (or proportion for binary variables) divided by the SD (pooled SD for continuous variables). An ASD >10% was considered a meaningful difference[29,30]. All analyses were carried out using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Patient disposition and baseline characteristics

A total of 4,212 patients with type 2 diabetes mellitus were included in the study, of whom 2,164 (51%) were initiating linagliptin. Of the 2,048 patients beginning other GLDs, 1,325 (65%) were starting a DPP-4 inhibitor other than linagliptin.

Baseline demographic and clinical characteristics are shown in Table 1. Patients starting linagliptin were older compared with those initiating any other GLD (66.7 ± 12.5 vs 65.3 ± 12.5 years, respectively; ASD 10.8%), with lower HbA1c (7.4 ± 1.4% [57 ± 15 mmol/mol] vs 7.7 ± 1.6% [61 ± 18 mmol/mol], respectively; ASD 16.8%) and estimated glomerular filtration rate (eGFR; 70.8 ± 24.1 vs 76.4 ± 22.6 mL/min/1.73 m^2, respectively; ASD 23.9%). Patients initiating linagliptin were of similar age to those starting other DPP-4 inhibitors, but had lower HbA1c (7.4 ± 1.4% [57 ± 15 mmol/mol] vs 7.6 ± 1.5% [60 ± 16 mmol/mol], respectively; ASD 11.9%) and eGFR (70.8 ± 24.1 vs 75.4 ± 22.7 mL/min/1.73 m^2, respectively; ASD 19.4%). Patients initiating linagliptin were older and had lower HbA1c and eGFR than those starting biguanides or sulfonylureas, but had higher HbA1c than patients beginning TZDs and AGIs, and higher eGFR compared with patients starting glinides (Table 1).

The proportion of patients in the different diabetes duration categories (≤1, 1–5, ≥5 years) was generally similarly distributed among the different GLDs, although more patients beginning sulfonylureas were in the ≥5 years category compared with patients initiating linagliptin (24.3 vs 17.0%, respectively; ASD 18.1%). Fewer patients starting AGIs were in the ≥5-years category compared with patients initiating linagliptin (12.9 vs 17.0%, respectively; ASD 11.5%).

Pre-existing comorbidities by SOC

The proportions of patients with pre-existing comorbidities by SOC are shown in Table 2. Most SOC comorbidities were more common in patients initiating linagliptin compared with all other GLDs, with meaningful differences (linagliptin vs any other GLDs; ASD >10%) observed for metabolism and nutritional disorders (50.5 vs 45.5%), cardiac disorders (12.2 vs 8.6%), vascular disorders (56.4 vs 51.3%), and renal and urinary disorders (9.9 vs 5.7%; Table 2). Renal and urinary disorders were more common in patients initiating linagliptin versus patients starting any other DPP-4 inhibitor (9.9 vs 5.1%; ASD 18.5%), although all other comorbidities were similarly frequent (Table 2). Metabolism and nutritional disorders were more common (ASD >10%) in patients beginning linagliptin (50.5%) than in patients initiating biguanides (44.6%), sulfonylureas (41.1%), TZDs (43.2%) and glinides (39.0%; Table 2). Cardiac disorders were more frequent (ASD >10%) in patients starting linagliptin (12.2%) than patients initiating biguanides (6.6%), sulfonylureas (5.9%) and AGIs (5.4%; Table 2). Renal and urinary disorders were more common (ASD >10%) among patients initiating linagliptin (9.9%) than patients starting biguanides (4.9%) and TZDs (4.2%; Table 2). In contrast, hepatobiliary disorders were less frequent (ASD >10%) among patients initiating linagliptin (7.3%) than those starting biguanides (13.9%; Table 2).

Pre-existing comorbidities by preferred term

With the exception of arrhythmia, all preferred term comorbidities were more common with linagliptin compared with all other GLDs, with meaningful differences (ASD >10%) observed for angina pectoris (5.0 vs 3.0%, respectively) and CKD (4.4 vs 2.1%, respectively), as well as compared with other DPP-4 inhibitors, with meaningful differences in angina pectoris (5.0 vs 3.0%, respectively), CKD (4.4 vs 2.3%, respectively) and diabetic nephropathy (2.7 vs 1.0%, respectively; Table S1).

DISCUSSION

The collection of baseline characteristic data from patients initiating treatment other than linagliptin represents a novel approach for a standard required Japanese PMS study. The expansion of the linagliptin Japan PMS study to include collection of baseline characteristics in patients who were eligible for linagliptin treatment, but initiating GLDs other than linagliptin, showed the spectrum of patients receiving linagliptin, and enabled the identification of preferential prescribing of linagliptin in patients with cardiac, vascular, renal/urinary and metabolism/nutritional disorders. Although preferential prescribing could be anticipated based on pharmacokinetic data (indicating that dose adjustment is not required) and clinical trial data reflected in the prescribing information (showing safety and efficacy in these patients[8–18]), this phenomenon can only be determined in a real-world data study with comparator data.

DPP-4 inhibitors are well established in clinical practice in Japan[4,5], as reflected by 65% of patients among those who did not start linagliptin, but initiated another DPP-4 inhibitor. In contrast with treatment guidelines in the USA and Europe[31,32], the Japanese Diabetes Society Treatment Guide for Diabetes during the study and at the present time does not give precedence to first-line treatment with biguanides, such as metformin, over other GLDs[3]. In terms of patient age, body mass index, HbA1c, eGFR and cardiovascular disease history, the patients who received linagliptin in the present study were comparable with the wider Japanese type 2 diabetes mellitus patient population described by Yokoyama et al.[26]

Although the data reported here are most relevant to Japan (given the distinct patient population, health system and diabetes treatment paradigm compared with other countries), similar "channeling" has been observed for linagliptin in the USA population[19]. In that study, the prevalence of baseline kidney disease (overall kidney dysfunction, any stage of CKD, respectively) was higher among patients initiating linagliptin (22.4%, 12.9%), glinides (28.7%, 16.7%) or insulin (27.0%, 13.5%) compared with other DPP-4 inhibitors (16.7%, 8.6%), sulfonylureas (second generation; 16.9%, 8.5%), glitazones (18.6%, 10.1%), glucagon-like peptide-1 receptor agonists (13.4%, 6.1%), sodium–glucose co-transporter-2 inhibitors (10.3%, 4.1%) or

Table 1 | Baseline characteristics of study participants: individuals treated with linagliptin versus all other glucose-lowering drugs and specific glucose-lowering drug classes

Patient characteristic	Linagliptin	Other GLDs[†]		Other DPP-4is		Biguanides		Sulfonylureas		TZDs		AGIs		Glinides	
	Value	Value	ASD (%)	Value	ASD (%)	Value	ASD (%)	Value	ASD (%)	Value	ASD (%)	Value	ASD (%)	Value	ASD (%)
Patients (n)	2,164	2,048	–	1,325	–	287	–	185	–	95	–	93	–	59	–
Mean age, years (SD)	66.7 (12.5)	65.3 (12.5)	10.8	66.4 (12.2)	1.9	59.2 (12.2)	60.3	64.6 (12.6)	16.4	67.3 (11.8)	5.5	66.9 (12.8)	1.7	67.1 (13.6)	3.2
Male (%)	58.5	57.3	2.5	56.5	4.2	59.9	2.8	56.2	4.7	62.1	7.3	60.2	3.4	55.9	5.3
Mean BMI, kg/m² (SD)	25.2 (4.2)	25.3 (4.3)	2.1	25.0 (4.1)	5.2	27.2 (4.6)	45.4	24.6 (3.8)	15.7	26.0 (5.3)	17.7	24.6 (3.9)	14.1	23.3 (3.4)	50.4
Mean HbA1c, % (SD)	7.4 (1.4)	7.7 (1.6)	16.8	7.6 (1.5)	11.9	7.9 (1.8)	28.7	8.7 (2.1)	73.8	6.9 (0.9)	43.7	7.0 (1.0)	35.0	7.4 (1.1)	0.7
Mean HbA1c, mmol/mol (SD)	57 (15)	61 (18)		60 (16)		63 (20)		72 (23)		52 (10)		53 (11)		57 (12)	
Mean eGFR, mL/min/1.73 m² (SD)	70.8 (24.1)	76.4 (22.6)	23.9	75.4 (22.7)	19.4	82.9 (20.8)	53.5	82.1 (24.1)	46.6	70.7 (15.6)	0.5	71.7 (23.1)	3.8	68.4 (21.8)	10.5
Hepatic dysfunction (%)[‡]	7.9	9.3	4.9	8.9	3.6	13.9	19.4	8.6	2.7	6.3	6.2	7.5	1.4	5.1	11.5
Cardiovascular history, yes (%)[§]	14.2	9.2	15.6	9.8	13.6	6.3	26.5	8.1	19.5	13.7	1.6	7.5	21.7	10.2	12.4
Duration of diabetes (%)															
≤1 year	22.3	21.8	1.3	21.4	2.1	26.5	9.7	16.8	14.1	22.1	0.5	24.7	5.7	18.6	9.1
>1–5 years	20.7	19.5	2.9	20.2	1.1	20.2	1.1	17.3	8.6	17.9	7.0	17.2	8.8	13.6	18.9
≥5 years	17.0	16.8	0.4	16.0	2.7	16.7	0.7	24.3	18.1	20.0	7.7	12.9	11.5	13.6	9.6
Unknown	40.0	41.9	–	42.3	–	36.6	–	41.6	–	40.0	–	45.2	–	54.2	–

[†]Includes biguanides, sulfonylureas, thiazolidinediones (TZDs), alpha-glucosidase inhibitors (AGIs) and glinides. Four patients initiated glucose-lowering drugs (GLDs) other than dipeptidyl peptidase-4 inhibitors (DPP-4is), biguanides, sulfonylureas, TZDs, AGIs or glinides. [‡]Standardized Medical Dictionary for Regulatory Activities (MedDRA) queries 20000005 (hepatic disorders) and 20000118 (biliary disorders) – narrow search terms. [§]Standardized MedDRA queries 20000043 (ischemic heart disease), 20000004 (cardiac failure), 20000060 (cerebrovascular disorders) and 20000001 (torsade de pointes/QT prolongation) – regardless of presence at baseline. ASD, absolute standardized difference versus linagliptin; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; SD, standard deviation.

Table 2 | Proportion of patients with pre-existing comorbidities by system organ class: individuals treated with linagliptin compared with specific glucose-lowering drug classes

Disorder by SOC	Linagliptin (n = 2,164) % Of patients	Other GLDs§ (n = 2,048)		Other DPP-4is (n = 1,325)		Biguanides (n = 287)		Sulfonylureas (n = 185)		TZDs (n = 95)		AGIs (n = 93)		Glinides (n = 59)	
		% Of patients	ASD (%)	% Of patients	ASD (%)	% Of patients	ASD (%)	% Of patients	ASD (%)	% Of patients	ASD (%)	% Of patients	ASD (%)	% Of patients	ASD (%)
Infections and infestations	1.3	2.0	4.8	2.3	7.4	0.7	6.4	2.7	9.7	1.1	2.6	1.1	2.4	0	16.5
Neoplasms (benign, malignant and unspecified)	1.9	1.0	7.7	0.9	8.4	1.0	7.1	0.5†	12.4†	1.1	7.0	3.2	8.4	0†	19.7†
Blood and lymphatic system	3.6	2.5	6.5	2.6	6.0	2.4	6.8	2.2	8.6	1.1†	17.0†	3.2	2.1	3.4	1.2
Endocrine	1.9	1.2	5.4	1.2	5.6	0.3†	14.7†	0.5†	12.4†	2.1	1.5	1.1	6.8	6.8‡	24.2‡
Metabolism and nutritional	50.5	45.5†	10.0†	46.6	7.7	44.6†	11.9†	41.1†	19.0†	43.2†	14.8†	49.5	2.1	39.0†	23.3†
Psychiatric	5.7	5.2	2.0	5.7	0.1	1.7†	21.0†	4.3	6.2	8.4‡	10.7‡	9.7‡	15.0‡	3.4†	11.0†
Nervous system	9.2	7.1	7.7	7.4	6.7	4.9†	17.1†	7.6	6.0	9.5	0.8	8.6	2.2	5.1†	16.2†
Eye	1.8	1.3	3.6	1.1	5.9	1.4	2.9	3.8‡	12.4‡	0†	18.9†	0†	18.9†	3.4‡	10.3‡
Cardiac	12.2	8.6†	12.0†	9.4	9.1	6.6†	19.3†	5.9†	22.0†	10.5	5.4	5.4†	24.4†	10.2	6.6
Vascular	56.4	51.3†	10.3†	53.5	5.9	46.7†	19.6†	44.9†	23.3†	48.4†	16.1†	48.4†	16.1†	54.2	4.4
Respiratory, thoracic and mediastinal	4.9	4.7	1.0	4.7	1.2	3.8	5.4	4.9	0.4	9.5‡	17.6‡	5.4	2.0	1.7†	18.2†
Gastrointestinal	12.1	9.8	7.4	10.3	5.7	5.6†	23.0†	7.6†	15.1†	8.4‡	12.0‡	22.6‡	28.1‡	8.5†	11.8†
Hepatobiliary	7.3	8.5	4.8	7.9	2.5	13.9‡	21.8‡	8.1	3.2	6.3	3.7	6.5	3.2	5.1	9.0
Skin and subcutaneous tissue	1.1	0.9	1.4	0.8	3.2	1.7	5.8	1.1	0.2	0†	14.7†	1.1	0.1	1.7	5.4
Musculoskeletal and connective tissue	6.0	5.7	1.1	6.6	2.5	2.4†	17.6†	4.9	4.8	3.2†	13.5†	6.5	2.0	8.5	9.7
Renal and urinary	9.9	5.7†	15.8†	5.1†	18.5†	4.9†	19.3†	7.6	8.2	4.2†	22.3†	10.8	2.8	11.9	6.3
Reproductive system and breast	2.2	1.6	4.8	1.7	3.5	1.0	9.3	0.5†	14.4†	2.1	0.8	3.2	6.2	0†	21.3†

†Meaningful differences for comorbidities that are more common with linagliptin versus comparator glucose-lowering drug (GLD); ‡meaningful differences for comorbidities that are more common with the comparator GLD versus linagliptin. All system organ classes (SOCs) with ≥1% of patients starting treatment with either linagliptin or "all other GLDs" affected are shown. §Includes biguanides, sulfonylureas, thiazolidinediones (TZDs), alpha-glucosidase inhibitors (AGIs) and glinides. Four patients initiated GLDs other than dipeptidyl peptidase-4 inhibitors (DPP-4is), biguanides, sulfonylureas, TZDs, AGIs or glinides. ASD, absolute standardized difference.

metformin (9.4%, 3.9%)[19]. Similar observations have also been noted for other GLDs in the USA population[33–36].

The novel approach of expanding a standard, required PMS to collect baseline data from patients initiating other medications for the same indication shows the importance and potential impact if data on a newly marketed product are considered in isolation. In the absence of comparator data, the presence and extent of preferential prescribing cannot be assessed. Consequently, in the setting of a standard single-arm PMS program, interpretation of safety and effectiveness data of a new medication might be difficult. Expansion of such studies to include at least the collection of baseline characteristics of patients initiating other medications for the same indication could be a critical step in the identification and quantification of preferential prescribing, and in strengthening the interpretability of the safety and effectiveness of newly marketed medications, which is key for public health.

The strengths of these data from the expanded linagliptin PMS study include the large number of patients overall, the real-world, routine clinical practice setting and minimal exclusion criteria. The setting did, however, result in a small imbalance in the number of patients initiating linagliptin compared with other GLDs, as it was not always possible to follow recruitment of a patient initiating linagliptin with a patient initiating any other GLD. The study was limited by the small patient numbers for individual drug classes other than DPP-4 inhibitors; however, this reflects treatment patterns in Japan at the time of the study. In addition, we did not collect specific information on the category of physician. The ratio of hospital : primary care physicians was 1:7. Therefore, the vast majority of prescribing physicians in the PMS were in primary care. It would be reasonable to assume that most of the hospital-based physicians were specialists; however, we do not have the data to support this notion. Furthermore, although no study medication was provided and treatment decisions were solely at the discretion of the physician and patient, it could be argued that participation in the study might have altered physician and/or patient behavior. While this is a limitation, the results from the present study are consistent with other findings from studies using existing data[19], suggesting that any study participation bias in the current study was minimal.

In conclusion, the novel approach of expanding the linagliptin PMS enabled detection of linagliptin prescribing to a type 2 diabetes mellitus patient population with more comorbidities, specifically renal, vascular, cardiac, and metabolism and nutritional disorders, compared with patients prescribed other GLDs. Such preferential prescribing needs to be accounted for when comparing safety and effectiveness data for linagliptin with those of other GLDs in a non-randomized study to avoid biased comparisons and erroneous conclusions. Thus, the findings from the present study generate insights that are important for the design and interpretation of observational studies and spontaneous reports.

REFERENCES

1. International Diabetes Federation. IDF Western Pacific members: Japan, 2015. Available from: https://www.idf.org/our-network/regions-members/western-pacific/members/105-japan.html Accessed July 24, 2018.
2. Yabe D, Seino Y, Fukushima M, et al. β cell dysfunction versus insulin resistance in the pathogenesis of type 2 diabetes in East Asians. Curr Diab Rep 2015; 15: 602.
3. Japan Diabetes Society. Treatment Guide for Diabetes 2016–2017. Available from: http://www.fa.kyorin.co.jp/jds/uploads/Treatment_Guide_for_Diabetes_2016-2017.pdf Accessed January 7, 2019.
4. Seino Y, Kuwata H, Yabe D. Incretin-based drugs for type 2 diabetes: focus on East Asian perspectives. J Diabetes Investig 2016; 7(Suppl 1): 102–109.
5. Yabe D, Kuwata H, Nishikino R, et al. Use of the Japanese health insurance claims database to assess durability of DPP-4 inhibitors in patients with diabetes: comparison with other anti-diabetic drugs. Diabetologia 2015; 58(Suppl 1): S389.
6. Grunberger G. Should side effects Influence the selection of antidiabetic therapies in type 2 diabetes? Curr Diab Rep 2017; 17: 21.
7. Kim YG, Hahn S, Oh TJ, et al. Differences in the glucose-lowering efficacy of dipeptidyl peptidase-4 inhibitors between Asians and non-Asians: a systematic review and meta-analysis. Diabetologia 2013; 56: 696–708.
8. Boehringer Ingelheim. Tradjenta® (linagliptin) prescribing information (12/2016), 2015. Available from: http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Tradjenta/Tradjenta.pdf?DMW_FORMAT=pdf Accessed November 20, 2017.
9. Doupis J. Linagliptin: from bench to bedside. Drug Des Devel Ther 2014; 8: 431–446.
10. McKeage K. Linagliptin: an update of its use in patients with type 2 diabetes mellitus. Drugs 2014; 74: 1927–1946.
11. Graefe-Mody U, Rose P, Retlich S, et al. Pharmacokinetics of linagliptin in subjects with hepatic impairment. Br J Clin Pharmacol 2012; 74: 75–85.
12. Graefe-Mody U, Friedrich C, Port A, et al. Effect of renal impairment on the pharmacokinetics of the dipeptidyl peptidase-4 inhibitor linagliptin. Diabetes Obes Metab 2011; 13: 939–946.

13. Laakso M, Rosenstock J, Groop PH, *et al*. Treatment with the dipeptidyl peptidase-4 inhibitor linagliptin or placebo followed by glimepiride in patients with type 2 diabetes with moderate to severe renal impairment: a 52-week, randomized, double-blind clinical trial. *Diabetes Care* 2015; 38: e15–e17.

14. McGill JB, Barnett AH, Lewin AJ, *et al*. Linagliptin added to sulphonylurea in uncontrolled type 2 diabetes patients with moderate-to-severe renal impairment. *Diab Vasc Dis Res* 2014; 11: 34–40.

15. Groop PH, Del Prato S, Taskinen MR, *et al*. Linagliptin treatment in subjects with type 2 diabetes with and without mild-to-moderate renal impairment. *Diabetes Obes Metab* 2014; 16: 560–568.

16. Lehrke M, Leiter LA, Hehnke U, *et al*. Safety and efficacy of linagliptin in patients with type 2 diabetes mellitus and coronary artery disease: analysis of pooled events from 19 clinical trials. *J Diabetes Complications* 2016; 30: 1378–1384.

17. von Eynatten M, Gong Y, Emser A, *et al*. Efficacy and safety of linagliptin in type 2 diabetes subjects at high risk for renal and cardiovascular disease: a pooled analysis of six phase III clinical trials. *Cardiovasc Diabetol* 2013; 12: 60.

18. Inagaki N, Sheu WH, Owens DR, *et al*. Efficacy and safety of linagliptin in type 2 diabetes patients with self-reported hepatic disorders: a retrospective pooled analysis of 17 randomized, double-blind, placebo-controlled clinical trials. *J Diabetes Complications* 2016; 30: 1622–1630.

19. Patorno E, Gopalakrishnan C, Bartels DB, *et al*. Preferential prescribing and utilization trends of diabetes medications among patients with renal impairment: emerging role of linagliptin and other dipeptidyl peptidase 4 inhibitors. *Endocrinol Diabetes Metab* 2018; 1: e00005.

20. Maeda K, Katashima R, Ishizawa K, *et al*. Japanese physicians' views on drug post-marketing surveillance. *J Clin Med Res* 2015; 7: 956–960.

21. Fujihara K, Igarashi R, Matsunaga S, *et al*. Comparison of baseline characteristics and clinical course in Japanese patients with type 2 diabetes among whom different types of oral hypoglycemic agents were chosen by diabetes specialists as initial monotherapy (JDDM 42). *Medicine (Baltimore)* 2017; 96: e6122.

22. Kanatsuka A, Sato Y, Kawai K, *et al*. Relationship between the efficacy of oral antidiabetic drugs and clinical features in type 2 diabetic patients (JDDM38). *J Diabetes Investig* 2016; 7: 386–395.

23. Nagai A, Hirata M, Kamatani Y, *et al*. Overview of the BioBank Japan Project: study design and profile. *J Epidemiol* 2017; 27: S2–S8.

24. Urushihara H, Taketsuna M, Liu Y, *et al*. Increased risk of acute pancreatitis in patients with type 2 diabetes: an observational study using a Japanese hospital database. *PLoS One* 2012; 7: e53224.

25. Yokomichi H, Nagai A, Hirata M, *et al*. Survival of macrovascular disease, chronic kidney disease, chronic respiratory disease, cancer and smoking in patients with type 2 diabetes: BioBank Japan cohort. *J Epidemiol* 2017; 27: S98–S106.

26. Yokoyama H, Oishi M, Takamura H, *et al*. Large-scale survey of rates of achieving targets for blood glucose, blood pressure, and lipids and prevalence of complications in type 2 diabetes (JDDM 40). *BMJ Open Diabetes Res Care* 2016; 4: e000294.

27. Komeda T, Ishii S, Itoh Y, *et al*. Post-marketing safety evaluation of the intravenous anti-influenza neuraminidase inhibitor peramivir: a drug-use investigation in patients with high risk factors. *J Infect Chemother* 2016; 22: 677–684.

28. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Medical Dictionary for Regulatory Activities. MedDRA® trademark owned by International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) on behalf of ICH. Available from: http://www.meddra.org/ Accessed November 20, 2017.

29. Ali MS, Groenwold RH, Pestman WR, *et al*. Propensity score balance measures in pharmacoepidemiology: a simulation study. *Pharmacoepidemiol Drug Saf* 2014; 23: 802–811.

30. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009; 28: 3083–3107.

31. Inzucchi SE, Bergenstal RM, Buse JB, *et al*. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2012; 55: 1577–1596.

32. Inzucchi SE, Bergenstal RM, Buse JB, *et al*. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 2015; 58: 429–442.

33. Brodovicz KG, Kou TD, Alexander CM, *et al*. Recent trends in the characteristics of patients prescribed sitagliptin and other oral antihyperglycaemic agents in a large U.S. claims database. *Int J Clin Pract* 2013; 67: 449–454.

34. Brodovicz KG, Chen Y, Liu Z, *et al*. Characterization of sitagliptin use in patients with type 2 diabetes and chronic kidney disease by cross-sectional analysis of a medical insurance claims database. *Diabetes Ther* 2015; 6: 627–634.

35. Zhang Q, Rajagopalan S, Mavros P, *et al*. Baseline characteristic differences between patients prescribed sitagliptin vs. other oral antihyperglycemic agents: analysis of a US electronic medical record database. *Curr Med Res Opin* 2010; 26: 1697–1703.

36. Cai B, Katz L, Alexander CM, *et al*. Characteristics of patients prescribed sitagliptin and other oral antihyperglycaemic agents in a large US claims database. *Int J Clin Pract* 2010; 64: 1601–1608.

SUPPORTING INFORMATION

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

Table S1 | Proportion of patients with pre-existing comorbidities by preferred term: individuals treated with linagliptin compared with specific glucose-lowering drug classes.