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ORIGINAL RESEARCH

A Real-World Observational Study Evaluating the Probability of Glycemic Control with Basal Insulin or Glucagon-Like Peptide-1 Receptor Agonist in Japanese Patients with Type 2 Diabetes

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ABSTRACT

Introduction: The effectiveness of basal insulin (BI) or glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in providing glycemic control in patients with type 2 diabetes (T2D) in Japanese routine practice is not well known. This real-world observational study evaluated the probability of achieving glycemic control in Japanese patients with T2D uncontrolled by oral antidiabetic drugs (OADs) who initiated BI or GLP-1 RA therapy.

Methods: Patients with T2D aged ≥ 18 years initiating BI or GLP-1 RA therapy following treatment with OADs were selected from real-world data (RWD) retrieved from a large electronic medical record database in Japan, using data from 01 January 2010 to 30 June 2019. Patients were required to have glycated hemoglobin (HbA1c) ≥ 7% within 90 days prior to the first prescription of BI or GLP-1 RA. The probability of reaching first HbA1c < 7% was assessed over a 24-month period in cohorts of patients who initiated BI (n = 3477) or GLP-1 RA (n = 780) and in subcohorts by number of OADs at baseline (1, 2, or ≥ 3), HbA1c at baseline (≥ 7 to < 8%, ≥ 8 to < 9%, or ≥ 9%), and age (< 65 or ≥ 65 years).

Results: Mean (standard deviation) baseline HbA1c was 9.4% (1.8%) and 8.8% (1.4%) in patients initiating BI or GLP-1 RA therapy,

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respectively. The cumulative probability of achieving glycemic control was 50.1% with BI and 60.3% with GLP-1 RA therapy, respectively, at 12 months, and 60.8% and 66.6%, respectively, at 24 months. Quarterly (3-month intervals) conditional probabilities of achieving glycemic control decreased over time and were < 10% after 12 months. Patients with more OADs or higher HbA1c at baseline had a lower probability of achieving glycemic control.

Conclusion: Among Japanese patients with T2D who initiated BI or GLP-1 RA therapy after treatment with OADs, the probability of reaching first glycemic control diminished over time. Further therapy intensification is warranted in patients who do not achieve glycemic control within 6–12 months with BI or GLP-1 RA, particularly those with high HbA1c or taking multiple OADs.

PLAIN LANGUAGE SUMMARY

Patients with type 2 diabetes (T2D) who are taking oral antidiabetic drugs (OADs) but still have high blood glucose often require injectable drugs, such as basal insulin (BI) or glucagon-like peptide-1 receptor agonists (GLP-1 RAs). While BI and GLP-1 RAs have been shown to be effective in controlled clinical trials, it is unclear how well they improve blood glucose in real-world routine practice. Here, we report the results of an observational study that used data retrieved from a large electronic medical records database in Japan to explore how well BI and GLP-1 RAs allow patients to achieve glycemic control [glycated hemoglobin (HbA1c) < 7%].

In Japanese patients with T2D receiving treatment with OADs and initiating BI or GLP-1 RA therapy, the probability of achieving glycemic control in the first quarter (3 months) after initiation was 20.3% with BI and 38.6% with GLP-1 RA. Among those patients who had not previously reached glycemic control, the probability of achieving first glycemic control declined over time, as evidenced in each quarterly assessment, and it was < 10% after the first year. Patients who had higher HbA1c levels or were taking multiple OADs were less likely to achieve glycemic control compared with those with lower HbA1c or taking fewer OADs. Our findings suggest that patients who have not achieved their glycemic goals within the first 6–12 months after starting BI or GLP-1 RA therapy have a low likelihood of achieving their target by maintaining the same therapy. For such patients, intensification with additional medication (e.g., combined BI and GLP-1 RA therapy) should be considered early in treatment.

Keywords: Basal insulin; GLP-1 RA; Real-world evidence; Type 2 diabetes

Key Summary Points

Why carry out this study?

Although basal insulin (BI) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have demonstrated efficacy in randomized controlled trials, it remains unclear whether these agents, when used individually, are sufficient to provide glycemic control in patients with type 2 diabetes (T2D) in real-world practice.

Real-world evidence from patients with T2D in the USA and UK suggests that patients not achieving glycemic targets within 6–12 months following initiation of BI or GLP-1 RA therapy may benefit from treatment intensification (options include combined BI and GLP-1 RA and basal-bolus regimens); however, the relevance of these data to Japanese patients is unknown.

This real-world observational study was conducted to evaluate the probability of achieving glycemic control in Japanese patients with T2D uncontrolled on oral antidiabetic drugs (OADs) alone who initiate BI or GLP-1 RA therapy.

What was learned from the study?

In Japanese patients with T2D uncontrolled on OADs alone, the conditional probability (percentage of patients who achieved glycemic control among those who had not previously reached glycemic control) of reaching first glycated hemoglobin (HbA1c) < 7% was 20.3% with BI and 38.6% with GLP-1 RA therapy in the first quarter (3-month interval) after BI or GLP-1 RA initiation; the conditional probability in each subsequent quarter declined over time, and it was < 10% for both treatments after the first year. Throughout the 2-year follow-up period, subgroups of patients who initiated BI or GLP-1 RA therapy with HbA1c ≥ 9% or who were taking ≥ 3 OADs had a lower probability of achieving glycemic control compared with those with lower baseline HbA1c or fewer OADs.

Treatment intensification should be considered for patients who have not achieved glycemic goals within the first 6–12 months of initiating BI or GLP-1 RA treatment.

Patients taking BI or GLP-1 RA therapy who have higher baseline HbA1c or who are taking multiple OADs are less likely to be successful in achieving adequate glycemic control after intensification with single injectable therapy.

There is a need for different intensification strategies for those patients who are taking multiple OADs or have high baseline HbA1c.

INTRODUCTION

Type 2 diabetes (T2D) is a chronic disease characterized by insulin resistance and progressive decline in β-cell function and insulin secretion, resulting in hyperglycemia [1, 2]. Persistent hyperglycemia is associated with an increased risk of microvascular complications, such as neuropathy, retinopathy, and nephropathy; therefore, attaining ongoing glycemic control is critical to T2D management [3, 4]. In standard clinical practice, glycemic control is assessed using glycated hemoglobin (HbA1c) levels, and HbA1c < 7% has become an accepted therapeutic target based on the reduced risk of diabetic complications in patients achieving this target [5–7].

Current guidelines, including those set forth by the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), and Japan Diabetes Society (JDS), recommend stepwise treatment approaches to help patients achieve and maintain glycemic control [5, 6]. In patients whose glycemic levels are inadequately controlled on oral antidiabetic drugs (OADs), escalation to injectable therapy is required. Current JDS guidelines recommend that initial injectable therapies should focus on basal insulin (BI) or glucagon-like peptide-1 receptor agonists (GLP-1 RAs). In the 2018 ADA/EASD consensus report, GLP-1 RAs are recommended as the first injectable for managing T2D for most patients [5]. Combination therapy with both BI and GLP-1 RAs is an option for patients who do not achieve glycemic control on either agent alone [5, 6].

The efficacy and safety of BI and GLP-1 RAs have been well established in randomized controlled trials (RCTs) [8–11]; however, in real-world practice, monotherapy with either agent may be insufficient to provide glycemic control in many patients with T2D. A retrospective, observational study found that among patients in the USA initiating BI therapy following OADs, the cumulative probability of reaching glycemic control (HbA1c < 7%) was 38% in the first year and only increased by a further 8% in the second year [12]. Similar trends were observed in a UK-based retrospective database study of patients initiating BI or GLP-1 RA therapy, with the cumulative probability of reaching HbA1c < 7% within 12 months being 18% with BI and 30% with GLP-1 RA therapy, with a low rate of increase over the second year (11% and 12%, respectively) [13]. These studies

suggest that intensification should be considered for patients not achieving glycemic control within 6–12 months of BI or GLP-1 RA initiation, and highlight the need for treatment approaches that allow more patients to achieve glycemic goals [12, 13]. However, it is not known whether lessons from these data are applicable outside of the USA or UK.

Here, we report the results of our real-world observational study, which evaluated the probability of achieving glycemic control in Japanese patients with T2D uncontrolled by oral antidiabetic drugs (OADs) who initiated BI or GLP-1 RA therapy, using data retrieved from a large electronic medical record (EMR) database in Japan. We also investigated the association between glycemic control and patient baseline characteristics, including number of OADs and baseline HbA1c.

METHODS

Study Design and Cohort Construction

This was a population-based, retrospective, observational cohort study using the RWD database maintained by the Health, Clinic, and Education Information Evaluation Institute (HCEI; Kyoto, Japan) with support from Real World Data, Co., Ltd. (Kyoto, Japan). The HCEI authorized the use of data for the current study. This database has collected EMRs of about 20 million patients from approximately 160 medical institutions across Japan since 2000, and includes information on patient demographics, diagnoses, prescriptions, procedures, and laboratory results from both outpatient and inpatient services. Data were automatically extracted from EMRs at each medical institution and anonymized using unique identifiers for each patient.

Data in the EMRs from 01 January 2010 to 30 June 2019 were used for this analysis. Patients were included in the study cohort if they had a confirmed diagnosis of T2D and had initiated BI or GLP-1 RA therapy following treatment with OADs. The date of first prescription of BI or GLP-1 RA was defined as the index date. Full inclusion criteria were: (1) diagnosis of T2D identified using ICD-10 [10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD)] codes; (2) at least one prescription for an OAD before initiation of BI or GLP-1 RA therapy; (3) at least one prescription of BI or GLP-1 RA; (4) intensification from OAD to BI or GLP-1 RA (first antidiabetic medication was not a BI or GLP-1 RA); (5) at least one HbA1c measurement $\geq$ 7% within 90 days prior to and including the index date; (6) at least one HbA1c measurement within 720 days after the initiation date of BI or GLP-1 RA therapy; (7) at least 180 days of recorded medical history prior to the index date (baseline period), during which no insulin or GLP-1 RA was prescribed; (8) age $\geq$ 18 years on the index date; and (9) study entrance at least 720 days prior to the data cutoff date to ensure up to 720 days of follow-up. Exclusion criteria were: (1) ICD-10/Japanese disease codes for type 1 diabetes, gestational diabetes, or polycystic ovarian syndrome; (2) an index date and end date (last date of BI or GLP-1 RA prescription) within 30 days; and (3) initiation of BI and GLP-1 RA therapies on the same date (same index date) or the addition of one medication within 3 months of the index date of the other medication (i.e., initiated BI and added a GLP-1 RA within 3 months of initiation of BI, or vice versa).

The patient selection process was designed based on the original objective of the study, which was to assess glycemic control in patients who initiated BI or GLP-1 RA (without sequential therapy with the other agent) and in those who received sequential therapy with BI and GLP-1 RA (added BI to GLP-1 RA, or vice versa). As the number of patients with records of sequential therapy was low, the cohorts of patients with sequential therapy were excluded from the present analyses. Therefore, the main study cohorts in this study consisted of patients who initiated BI or GLP-1 RA, without sequential therapy.

Within the study cohorts of patients initiating BI or GLP-1 RA (without sequential therapy), subcohorts of patients were constructed based on: (1) the number of OADs taken at baseline (1, 2, or $\geq$ 3 OADs); (2) the last HbA1c value prior to and up to the BI or GLP-1 RA initiation date (7 to $<$ 8%, 8 to $<$ 9%, and

≥ 9%); and (3) age on index date (< 65 or ≥ 65 years).

This study was approved by the Research Institute of Healthcare Data Science (RIHD) ethics committee (No. RI2019005). This article is based on an existing EMR database and does not contain any studies with human participants or animals. The manuscript was prepared in line with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines [14].

Outcome Measures

Baseline characteristics and glycemic outcomes were analyzed in the cohorts of patients initiating BI or GLP-1 RA (without sequential therapy). Glycemic control was determined by change in HbA1c over time and cumulative probability of reaching glycemic control (HbA1c < 7%) over 720 days post index date. Other outcome measures included the time to first reaching glycemic control and the conditional probability of reaching glycemic control during each quarter (3-month interval) post index date.

The cumulative probability of reaching glycemic control was also analyzed in the subcohorts of patients stratified by number of OADs used at baseline, HbA1c at baseline, and age on index date.

Statistical Approach

Baseline characteristics and change in HbA1c over time from baseline were analyzed using descriptive statistics. The period used to collect baseline characteristics was over 180 days prior to and up to the index date. The baseline HbA1c value was defined as the last observation within 90 days prior to and including the index date.

The conditional probability of reaching glycemic control was estimated quarterly (3-month intervals post index date) as the proportion of patients reaching first HbA1c < 7% within the specific quarter, among those patients who had not previously achieved glycemic control and were still taking BI or GLP-1 RA therapy and who had at least one valid HbA1c measurement in that quarter. The cumulative probability of reaching first glycemic control over time was estimated using the Kaplan–Meier method, and log-rank tests were used for comparison between subcohort categories. A P value of < 0.05 was considered to indicate statistical significance. Patient data were censored at the end of BI or GLP-1 RA prescription, or when the patient was switched to a new non-BI or non-GLP-1 RA regimen or other insulin therapy. Records of HbA1c < 4% or > 15% were removed.

RESULTS

Patient Cohort Selection

A total of 4356 patients initiating BI or GLP-1 RA therapy following OAD treatment were identified from the EMR database (Fig. 1). Among these patients, 58 and 41 patients, respectively, had records of sequential therapy with BI followed by GLP-1 RA add-on, or GLP-1 RA followed by BI add-on, and were excluded from the analysis. The final analysis cohorts included 3477 patients who initiated BI and did not receive sequential therapy with GLP-1 RA (BI cohort), and 780 patients who initiated GLP-1 RA and did not receive sequential therapy with BI (GLP-1 RA cohort).

Median and range of follow-up time (time between index date and end date of BI or GLP-1 RA prescription) for the study cohorts and subcohorts are shown in Table 1 and Electronic Supplementary Material (ESM) Tables S1 and S2.

Baseline Characteristics

Patient demographics and baseline clinical characteristics of all the study cohorts (whole T2D, BI, and GLP-1 RA) are described in Table 1. BIs and GLP-1 RAs identified in the study are listed in ESM Table S3.

Patients initiating therapy with GLP-1 RA were younger than those initiating BI therapy (median age: 60.5 vs. 65.4 years, respectively). Patients who initiated BI had higher baseline HbA1c than those who initiated GLP-1 RA [mean (standard deviation, SD): 9.4% (1.8%) vs. 8.8% (1.4%), respectively]. Patients in the GLP-1

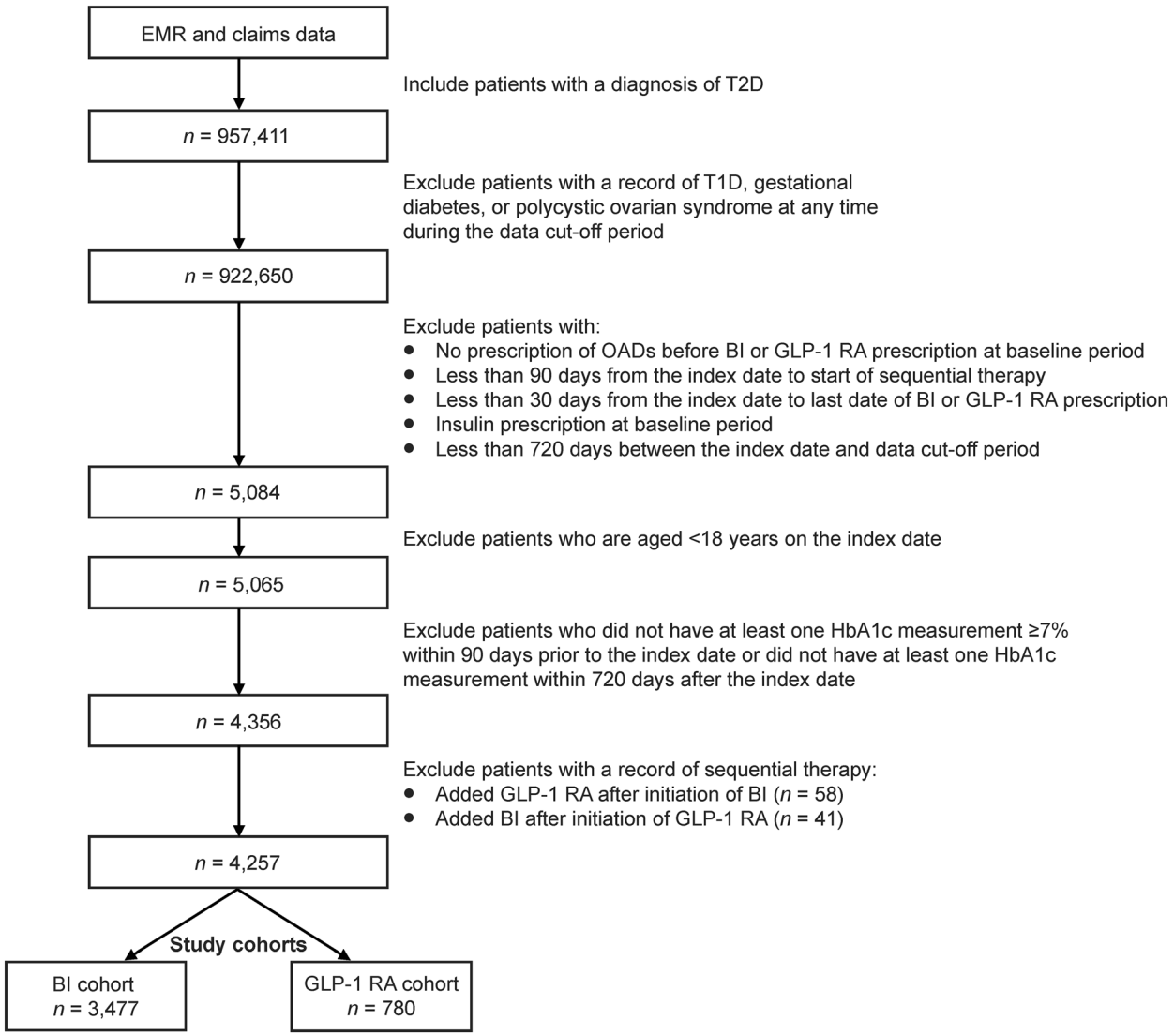

Fig. 1 Flow diagram of patient cohort selection. *BI* basal insulin, *EMR* electronic medical record, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *HbA1c* glycated hemoglobin, *OAD* oral antidiabetic drug, *T1D* type 1 diabetes, *T2D* type 2 diabetes

RA cohort appeared to have a higher body mass index (BMI) than those in the BI cohorts (mean: 28.2 vs. 24.1 kg/m^2, respectively). Regarding common comorbidities, hypertension, dyslipidemia, and obesity were more common in the GLP-1 RA cohort than in the BI cohort (hypertension: 73.2 vs. 63.9%, respectively; dyslipidemia: 77.3 vs. 65.2%, respectively; obesity: 14.2 vs. 4.2%, respectively). Over one third of patients in the BI and GLP-1 RA cohorts were taking ≥ 3 OADs. Higher percentages of patients in the BI cohort compared with the GLP-1 RA cohort were taking sulfonylureas (62.2 vs. 54.9%, respectively) or alpha-glucosidase inhibitors (34.7 vs. 24.2%, respectively). A higher percentage of patients in the GLP-1 RA cohort versus the BI cohort were taking metformin (56.3 vs. 38.9%, respectively), a dipeptidyl peptidase-4 (DPP-4) inhibitor (63.6 vs. 48.9%, respectively), or a sodium-glucose cotransporter 2 inhibitor (8.5 vs. 1.2%, respectively). Additional details on patient demographics and baseline clinical characteristics in patient subcohorts by number of OADs (1, 2, or ≥ 3) and

Table 1 Baseline characteristics and follow-up time for the whole T2D, BI, and GLP-1 RA cohorts

	Whole T2D cohort ***n*** **= 272,813**	**BI cohort** ***n*** **= 3,477**	**GLP-1 RA cohort** ***n*** **= 780**
Age			
Mean (SD)	69.9 (13.8)	64.3 (12.4)	59.7 (13.5)
Median	72.2	65.4	60.5
≥ 65 years, *n* (%)	196,152 (71.9)	1782 (51.3)	287 (36.8)
Female, *n* (%)	120,477 (44.2)	1,316 (37.8)	345 (44.2)
HbA1c, %			
Mean (SD)	6.5 (1.1)[a]	9.4 (1.8)	8.8 (1.4)
Median (range)	6.0 (2.4–6.9)[a]	9.1 (7.0–20.2)	8.5 (7.0–15.8)
HbA1c category			
7–< 8%, *n*	21,055	745	253
Median (range)	7.3 (7.0–7.9)	7.4 (7.0–7.9)	7.5 (7.0–7.9)
8–< 9%, *n*	6758	888	241
Median (range)	8.3 (8.0–8.9)	8.4 (8.0–8.9)	8.4 (8.0–8.9)
≥ 9%, *n*	4357	1844	286
Median (range)	9.8 (9.0–18.7)	10.4 (9.0–20.2)	10.0 (9.0–15.8)
Mean (SD) BMI[b], kg/m^2	23.4 (4.5)	24.1 (4.2)	28.2 (5.8)
Mean (SD) T2D duration, years	7.3 (6.1)	6.5 (6.3)	6.5 (5.9)
Follow-up time[c], days (Q1–Q3)	NA	720 (622–720)	720 (627–720)
Comorbidity[d], *n* (%)			
Hypertension	14,397 (5.3)	2223 (63.9)	571 (73.2)
Dyslipidemia	10,977 (4.0)	2268 (65.2)	603 (77.3)
Obesity	2467 (0.9)	146 (4.2)	111 (14.2)
Renal impairment	4896 (1.8)	391 (11.2)	105 (13.5)
Atherosclerotic cardiovascular disease	25,167 (9.2)	1903 (54.7)	421 (54.0)
Number of OADs, *n* (%)			
1	216,636 (79.4)	1114 (32.0)	194 (24.9)
2	25,329 (9.3)	1127 (32.4)	250 (32.1)
≥ 3	17,698 (6.5)	1236 (35.5)	336 (43.1)
Prescription of OAD, *n* (%)			
Metformin	22,468 (8.2)	1352 (38.9)	439 (56.3)
Sulfonylureas	13,031 (4.8)	2164 (62.2)	428 (54.9)
DPP-4 inhibitors	41,647 (15.3)	1701 (48.9)	496 (63.6)

Table 1 continued

	Whole T2D cohort *n* = 272,813	BI cohort *n* = 3,477	GLP-1 RA cohort *n* = 780
TZDs	4811 (1.8)	650 (18.7)	129 (16.5)
SGLT-2 inhibitors	6866 (2.5)	42 (1.2)	66 (8.5)
Alpha-GI	10,746 (3.9)	1205 (34.7)	189 (24.2)
Glinide	4936 (1.8)	351 (10.1)	71 (9.1)

Alpha-GI alpha-glucosidase inhibitor, *BI* basal insulin, *BMI* body mass index, *DPP-4* dipeptidyl peptidase-4, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *HbA1c* glycated hemoglobin, *ICD* International Classification of Diseases, *NA* not applicable, *OAD* oral antidiabetic drug, *Q1* lower quartile, *Q3* upper quartile, *SD* standard deviation, *SGLT-2* sodium-glucose cotransporter 2, *T2D* type 2 diabetes, *TZD* thiazolidinedione

[a] Data are for HbA1c < 7%

[b] *n* = 589 (BI cohort) and 120 (GLP-1 RA cohort). BMI is available for inpatients only

[c] Follow-up time for probability of glycemic control analyses (index date to last date of BI or GLP-1 RA prescription)

[d] Obesity was defined as a BMI ≥ 30 kg/m^2 or the presence of ICD-10 codes for obese/morbidly obese; the other comorbidities were based on ICD-10 codes

baseline HbA1c (7 to < 8%, 8 to < 9%, or ≥ 9%) within the BI and GLP-1 RA cohorts are shown in ESM Tables S2 and S3.

HbA1c Change Over Time

Distributions of HbA1c values from 6 months before to 24 months after initiation of BI or GLP-1 RA therapy are shown in Fig. 2. For both cohorts, mean HbA1c levels tended to be higher during the 3 months prior to the index date, followed by a rapid decrease within 2–4 months post index date, without further improvement thereafter.

HbA1c change from baseline by quarter (3-month time intervals) after the initiation of BI or GLP-1 RA therapy are shown in ESM Table S4. For both cohorts, mean (SD) HbA1c reduction from baseline peaked at 3–6 months following initiation, at − 1.85% (2.03%) for BI and − 1.26% (1.64%) for GLP-1 RA.

Cumulative Probability of Patients Achieving Glycemic Control

The Kaplan–Meier curves for the cumulative probability of patients reaching their first HbA1c < 7% over time showed similar trends in the BI and GLP-1 RA cohorts (Fig. 3a, b), with a sharp increase in probability within 6 months following the initiation of BI or GLP-1 RA therapy and only a slight increase thereafter. In the BI cohort, approximately 28.6, 40.7, 50.1, and 60.3% of patients achieved their first HbA1c < 7% within 3, 6, 12, and 24 months, respectively; these proportions were 39.5, 50.9, 60.8, and 66.6%, respectively, in the GLP-1 RA cohort.

In both the BI and GLP-1 RA cohorts, patients taking greater numbers of OADs at baseline showed a lower cumulative probability of achieving their first HbA1c < 7% throughout the 24-month follow-up period (Fig. 3c, d). For both the BI and GLP-1 RA cohorts, differences between subcohorts by number of OADs at baseline were significant according to log-rank test ($P < 0.05$ for all pair-wise comparisons between subcohorts). In both cohorts, the subcohorts of patients with baseline HbA1c ≥ 9% had the lowest cumulative probability of achieving glycemic control, while those with HbA1c 7– < 8% had the highest probability (Fig. 3e, f); all pair-wise comparisons between subcohorts showed significant differences ($P < 0.01$) by the log-rank test. No

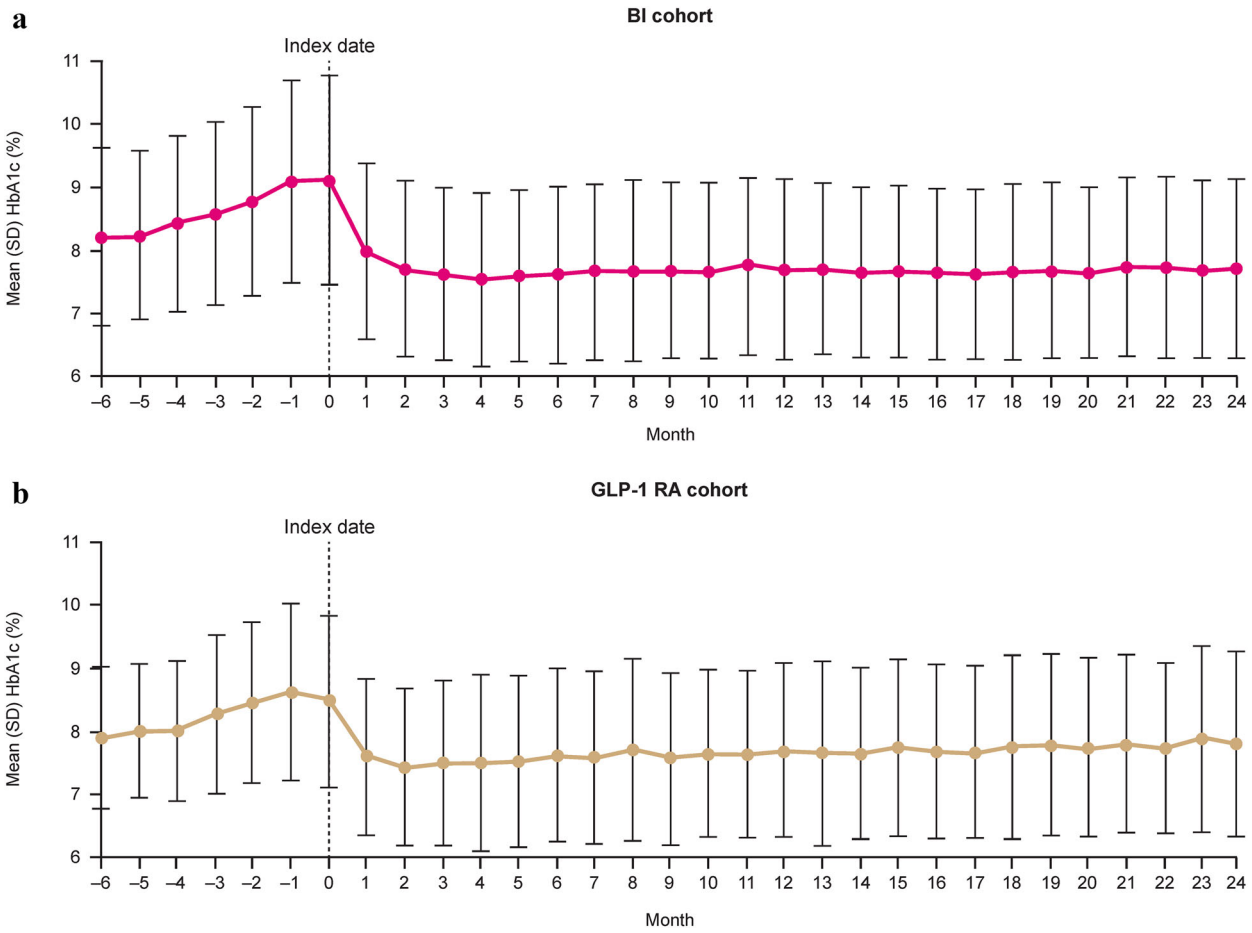

Fig. 2 Monthly HbA1c distributions [mean (SD)] from 6 months before to 24 months after BI or GLP-1 RA initiation (index date) in the BI cohort (**a**) and GLP-1 RA cohort (**b**). Data are presented as the mean with the standard deviation (*SD*). *x*-axis values correspond to the start of the time interval assessed (data at month 1 correspond to the time period of 1 month post index date to < 2 months post index date). Data were not adjusted for censorship or achievement of glycemic control

notable differences were observed in the cumulative probability curves between subcohorts by age (< 65 or ≥ 65 years) in either the BI or the GLP-1 RA cohorts (data not shown).

Estimation of Conditional Probabilities

The proportion of patients who reached their first HbA1c < 7% within the first quarter (0–3 months post index date) was 20.3% in the BI cohort and 38.6% in the GLP-1 RA cohort (Table 2). Among patients who had not reached HbA1c < 7% in the first quarter following the index date, the probability of reaching first glycemic control in the second quarter was 17.3% for the BI cohort and 19.0% for the GLP-1 RA cohort (Table 2). The respective conditional probabilities declined to 8.9% and 9.4% in the third quarter, and remained at < 10% thereafter for both cohorts (other than a 12.9% probability in the fourth quarter for GLP-1 RA).

DISCUSSION

Based on data in the Japanese RWD database between January 2010 and June 2019, approximately fourfold more patients intensified their OAD therapy with BI compared with GLP-1 RA.

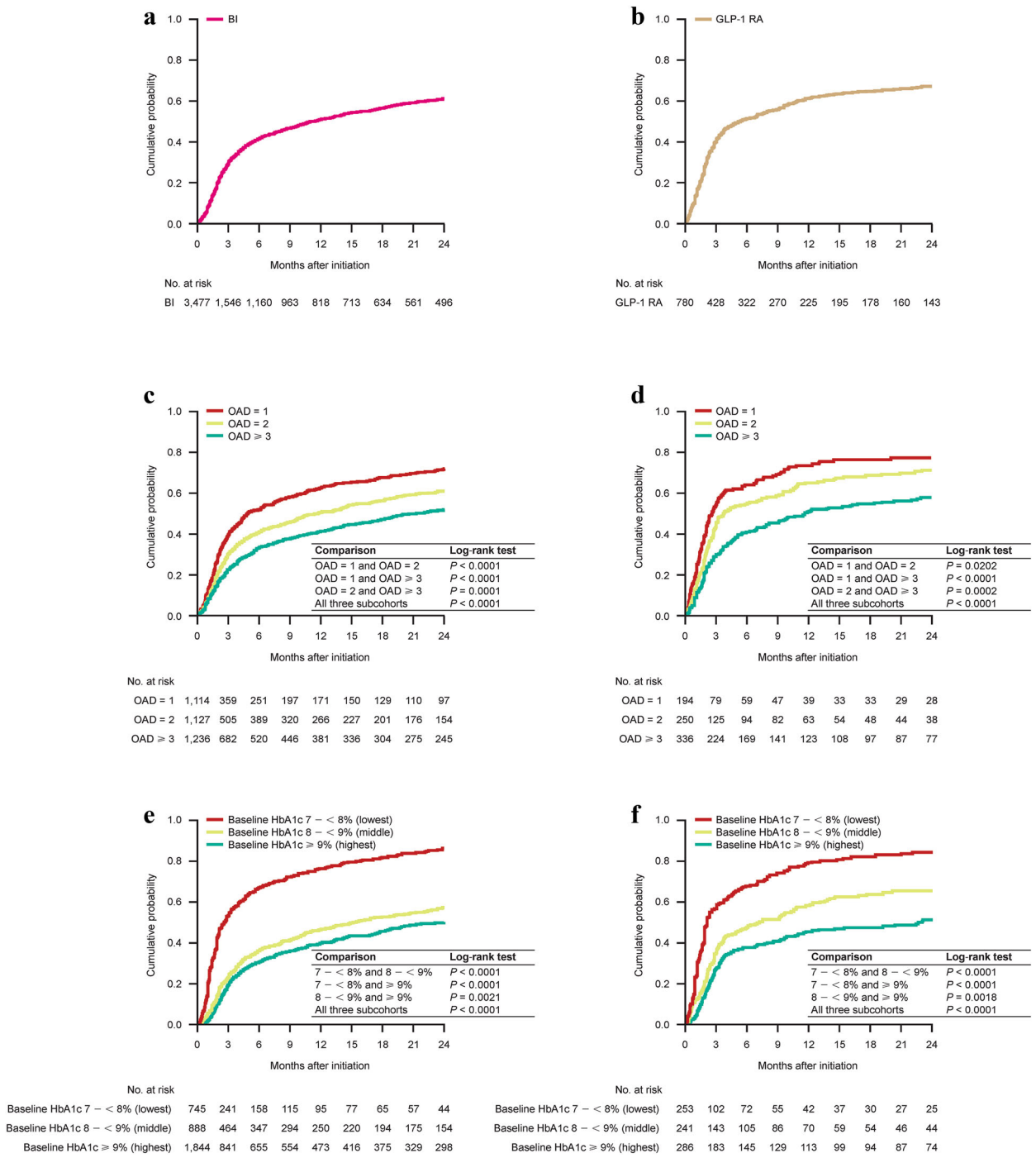

Fig. 3 Overall cumulative probability of reaching first HbA1c < 7% within 2 years post index date in the BI cohort (**a**) and GLP-1 RA cohort (**b**), and in subcohorts by number of OADs among the BI cohort (**c**) or GLP-1 RA cohort (**d**) or by HbA1c at baseline among the BI cohort (**e**) or GLP-1 RA cohort (**f**)

Initiation of BI or GLP-1 RA therapy occurred at an advanced stage of disease, after a mean of 6.5 years with T2D and high HbA1c [mean HbA1c of 9.4% (BI) and 8.8% (GLP-1 RA)], with over one third of patients taking ≥ 3 OADs. The delay in treatment intensification, or clinical

Table 2 Conditional probability of reaching first glycemic control (HbA1c < 7%)

Time after initiation of BI or GLP-1 RA therapy (months)	BI cohort			GLP-1 RA cohort		
	Number of patients who had not reached glycemic control previously and were still on treatment and had at least one valid HbA1c record within this quarter	Number of patients who reached their first glycemic control within this quarter	Estimated conditional probability[a], % (95% CI)	Number of patients who had not reached glycemic control previously and were still on treatment and had at least one valid HbA1c record within this quarter	Number of patients who reached their first glycemic control within this quarter	Estimated conditional probability[a], % (95% CI)
> 0–3	3320	674	20.3 (18.9–21.7)	762	294	38.6 (35.1–42.0)
> 3–6	1453	251	17.3 (15.3–19.2)	406	77	19.0 (15.2–22.8)
> 6–9	1087	97	8.9 (7.2–10.6)	299	28	9.4 (6.1–12.7)
> 9–12	886	72	8.1 (6.3–9.9)	249	32	12.9 (8.7–17.0)
> 12–15	751	52	6.9 (5.1–8.7)	205	13	6.3 (3.0–9.7)
> 15–18	647	34	5.3 (3.5–7.0)	177	6	3.4 (0.7–6.1)
> 18–21	584	36	6.2 (4.2–8.1)	160	6	3.8 (0.8–6.7)
> 21–24	510	26	5.1 (3.2–7.0)	144	5	3.5 (0.5–6.5)

CI Confidence interval

[a] Conditional probability is defined as the percentage of patients achieving glycemic control within the specified time interval, among patients who had not reached glycemic control previously, were still on treatment, and had at least one valid HbA1c record within the time interval

inertia, observed in the present study is consistent with previous real-world studies in Japan, which found that the mean HbA1c of patients initiating BI therapy was 9.4% [15, 16]. Similarly, in the DAWN JAPAN survey study, the mean HbA1c at which insulin therapy was recommended by physicians was 9.6% [17].

Patients initiating GLP-1 RA therapy tended to be younger than those intitiating BI therapy, with a lower mean baseline HbA1c. In addition, consistent with the benefits of body weight associated with the GLP-1 RA class, patients initiating GLP-1 RA therapy had a higher BMI at baseline than those initiating BI. Observed differences in the types of OADs used may reflect differences in disease pathophysiology between patients initiating BI versus GLP-1 RA therapies. The use of sulfonylureas, which are insulin secretagogues suited for patients with insulin deficiency, was higher in patients initiating BI than in those initiating GLP-1 RAs, while metformin, which reduces blood glucose at least in part by improving insulin sensitivity, was used more frequently in patients initiating GLP-1 RAs compared with those initiating BI. The use of alpha-glucosidase inhibitors, which delay the absorption of sugars by inhibiting enzymes, thereby reducing postprandial hyperglycemia, was more common among patients initiating BI than in those initiating GLP-1 RA therapy. DPP-4 inhibitors, which block the degradation of endogenous GLP-1 and promote glucose-dependent insulin secretion, were also more commonly used by patients initiating GLP-1 RA therapy. However, it is worth noting that about half of the patients initiating BI therapy were also being treated with DPP-4 inhibitors, in line

with the prevalent use of this class of drugs in Japanese patients with T2D [18].

In patients initiating BI or GLP-1 RA therapy, HbA1c levels tended to increase rapidly during the 3 months prior to initiation, which may have prompted the initiation of injectable therapy. This trend was then followed by a rapid decrease within 2–4 months of treatment initiation, without further improvement thereafter. Although there was a sharp increase in the cumulative probability of reaching HbA1c < 7% within 6 months of initiation of BI or GLP-1 RA therapy, the rates of increase declined over time. The conditional probability of achieving HbA1c < 7% with BI or GLP-1 RA therapy was highest in the first 3 months following treatment initiation (20.3% for BI and 38.6% for GLP-1 RA), then declined thereafter to < 10% after 6–12 months. These data are consistent with the findings from similar retrospective database studies in the UK [13] and USA [12] and suggest that for Japanese patients who have not reached glycemic goals at early stages of BI or GLP-1 RA treatment, the probability of achieving the target is low, and early treatment escalation is warranted. Reports of factors that might adversely influence the prescribing of GLP-1 RAs in Japan appear to be limited. However, it is possible that the injectable nature of the treatment is a limitation. Furthermore, one of the perceived advantages of GLP-1 RAs in Western countries (namely, weight loss) is not a major clinical objective in Japanese patients with T2D.

Patients initiating BI or GLP-1 RA therapy with higher baseline HbA1c or those who were taking multiple OADs had a lower probability of achieving HbA1c < 7% throughout the 2-year follow-up period compared with those with lower baseline HbA1c or taking fewer OADs. In line with the approach of early intensive therapy in patients with high HbA1c, the 2018 ADA/EASD consensus report recommends initial injectable combination therapy with GLP-1 RA and BI or prandial/BI for patients with HbA1c > 10% and/or > 2% above target [5]. However, while insulin in combination with a GLP-1 RA is listed as a treatment option for patients with inadequate glycemic control, the current JDS guidelines do not make a recommendation for any specific combination to be used as initial injectable therapy [6].

The importance of glycemic control in lowering the risk of diabetes complications is highlighted in the ADA, EASD, and JDS guidelines, and the benefits of aggressive glycemic management have been shown by long-term studies. The UK Prospective Diabetes Study demonstrated over 10 years of follow-up that intensive blood-glucose control substantially decreases the risk of microvascular complications in patients with T2D [4]. In a prospective study in Japan, intensive glycemic control was associated with a delay in the onset and progression of diabetic retinopathy, nephropathy, and neuropathy in patients with T2D [3].

The efficacy and safety of BI and GLP-1 RA therapies in Japanese patients are well established in RCTs [19–26]. While RCTs provide a controlled setting to evaluate the effects of therapeutic interventions using standardized treatments in a well-defined patient cohort, they may not necessarily fully reflect the treatment practices and patient populations seen in real-world practice. Indeed, there is a gap between the efficacy of glycemia-lowering agents reported from RCTs and that reported from real-world studies, with smaller improvements in HbA1c observed in the real world [27]. Real-world data may guide individualized treatment decisions and provide important insights into the challenges that are encountered in routine clinical practice. In our current real-world database study, initiation of BI or GLP-1 RA therapy was insufficient to provide HbA1c control for many Japanese patients intensifying OAD therapy, highlighting the unmet need for alternative treatment strategies in this population.

There are several limitations to this study. General limitations of observational, non-randomized studies include selection bias and the inability to confirm efficacy in the absence of a placebo arm. Nonetheless, real-world data do provide important insights, as discussed above. In this study, our data confirm that initiation of either medication (BI or GLP-1 RA) is considered only after attempts have been made to optimize the use of OADs for at least 6 months. While the large sample size is a strength of the study, the fact that it included primarily the hospital-

based cohort is a limitation; patients who were not part of the participating facilities were not captured in this study. The database consists of a limited number of hospitals and clinics and does not cover all regions of Japan. Furthermore, patients who transferred to other institutions could not be followed up, and data were based on prescriptions written; imperfect adherence could have reduced the effects of treatment. Persistence data are not currently available from this study to enable investigation of this aspect of treatment. The study was originally designed to compare outcomes between patients who received BI or GLP-1 RA but not the other, versus those who received sequential therapy with BI and GLP-1 RA. However, because of the low number of patients in the database with records of sequential therapy, only the cohort of patients initiating BI or GLP-1 RA without sequential therapy was analyzed. Additionally, the treatment options for GLP-1 RAs in Japan were not constant throughout the study period; for example, lixisenatide was approved in 2013, and dulaglutide was approved in 2015. While a 10-year period was considered, this was not a longitudinal study and, although it would have been interesting to investigate how treatment changed over time as different agents became available or more widely used, this was outside the scope of this analysis. Although subgroup analyses were conducted according to potentially relevant patient factors, additional unknown confounders could exist and contribute to any differences between BI and GLP-1 RA cohorts.

CONCLUSIONS

This retrospective, observational study conducted in Japan demonstrated that in patients with T2D inadequately controlled on OADs, escalation to BI or GLP-1 RA therapy occurred after many years of disease, when HbA1c levels had risen far above target values, and often after inadequate response to multiple OADs. Patients who initiated GLP-1 RA therapy tended to be slightly younger and have higher BMI and lower HbA1c at baseline compared with those who initiated BI therapy. The conditional probability of reaching HbA1c $< 7\%$ with BI or GLP-1 RA declined over time, suggesting that treatment intensification should be considered for patients who do not achieve their glycemic goal in the first 6–12 months on BI or GLP-1 RA. In particular, patients with high baseline HbA1c ($\geq 9\%$) or those on multiple OADs (≥ 3) may benefit from early treatment escalation, based on the low probability of achieving target HbA1c in these patient populations. Overall, these results highlight the need for new treatment strategies to allow more patients in Japan with T2D inadequately controlled on OADs to achieve early glycemic control.

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Compliance with Ethics Guidelines. This study was approved by the Research Institute of Healthcare Data Science (RIHD) ethics committee (No. RI2019005). This article is based on an existing EMR database and does not contain any studies with human participants or animals.

Data Availability. These analyses were conducted on medical records data provided under a commercial license, which the authors are unable to share.

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