

## ORIGINAL ARTICLE

# Utilization of glucagon-like peptide-1 receptor agonists and changes in clinical characteristics in patients with type 2 diabetes by chronic kidney disease stage in Japan: A descriptive observational study using a nationwide electronic medical records database

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**Funding information**

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**Abstract**

**Aim:** To describe the utilization of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and changes in clinical characteristics before and after GLP-1 RA initiation in patients with type 2 diabetes (T2D) by chronic kidney disease (CKD) stage.

**Materials and Methods:** In this retrospective descriptive study using a nationwide electronic medical records database in Japan, we included patients with GLP-1 RA prescriptions from June 2010 to October 2019. Clinical characteristics at GLP-1 RA initiation, persistence proportion, and changes in clinical measurements after GLP-1 RA initiation were described for all patients and by CKD stage, defined by baseline estimated glomerular filtration rate (eGFR).

**Results:** We included 8049 patients. During the study period, the proportion of patients with T2D initiating GLP-1 RAs increased from 1.5% in 2010 to 3.3% in 2019. Also, the mean (95% confidence interval) of baseline age and eGFR ranged from 58.6 (56.7-60.4) to 66.3 (65.5-67.2) years and from 72.9 (68.0-77.9) to 64.0 (62.2-65.8) mL/min/1.73m<sup>2</sup>, respectively. The persistence proportion at 12 months was 49.5% overall, 37.8% in T2D patients with CKD with a baseline eGFR of less than 30 mL/min/1.73m<sup>2</sup>, and 34.6% in those undergoing dialysis. The rate of deterioration in renal function reduced after GLP-1 RA initiation.

**Conclusions:** The utilization of GLP-1 RAs has been increasing over the past decade, and GLP-1 RAs have been used in patients with limited treatment options, such as the elderly or those with CKD. In T2D patients with CKD, the persistence proportion of GLP-1 RAs was not low, and the renal dysfunction may be moderated by GLP-1 RA initiation.

**KEYWORDS**

database research, GLP-1, observational study, pharmaco-epidemiology, type 2 diabetes

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## 1 | INTRODUCTION

Type 2 diabetes (T2D) is the leading cause of renal dysfunction in Japan.<sup>1</sup> Patients with T2D are at a higher risk of diabetic nephropathy and chronic kidney disease (CKD).<sup>2</sup> More than 40% of patients with T2D develop CKD and a significant number of them require dialysis or a transplant.<sup>3</sup> The effective therapeutic management of T2D patients with CKD is therefore crucial. In patients with T2D with advanced CKD, some antidiabetic drugs carry an increased risk of hypoglycaemia as a result of decreased insulin clearance, which limits the treatment options for glycaemic control. Patients with T2D with prior cardiovascular disease and CKD also have a higher risk of major adverse cardiac events, cardiovascular death, and all-cause mortality.<sup>4</sup>

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are antidiabetic drugs that reduce hyperglycaemia by inducing satiety and stimulating insulin secretion and postprandial glucagon release in a glucose-dependent manner.<sup>5</sup> GLP-1 RAs are a treatment option for patients with advanced kidney disease because most of them can be prescribed regardless of renal function. Several large randomized controlled trials (RCTs) and meta-analyses have reported the efficacy of GLP-1 RAs in preventing cardiovascular<sup>6-10</sup> and composite renal events in patients with T2D,<sup>11-14</sup> along with their glucose-lowering effects. Accordingly, the American Diabetes Association and European Association for the Study of Diabetes have recommended GLP-1 RAs<sup>15-17</sup> to treat patients with T2D with atherosclerotic cardiovascular disease or CKD.<sup>18-20</sup> Several studies have reported increased utilization of GLP-1 RAs among patients with T2D,<sup>21-23</sup> but not specifically T2D patients with CKD. Further, a Japanese study of the change in estimated glomerular filtration rate (eGFR) with GLP-1 RAs in T2D patients with CKD limited results to only one of the five GLP-1 RAs available in Japan and from a small number and limited type of hospital. Therefore, the utilization of GLP-1 RAs and changes in clinical characteristics around the initiation of GLP-1 RAs in T2D patients with CKD remains unclear.

We aimed to describe the utilization of GLP-1 RAs and changes in clinical characteristics around GLP-1 RA initiation in patients with T2D overall and stratified by CKD stage using a nationwide electronic medical records (EMRs) database in Japan.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and data source

This was a descriptive observational study using the RWD database (RWD-DB) maintained by the Health, Clinic, and Education Information Evaluation Institute (HCEI; Kyoto, Japan) with support from Real World Data Co., Ltd (Kyoto, Japan). This database contains EMRs and medical expenses claims of approximately 20 million patients from approximately 180 medical institutions, from large hospitals to clinics, in a wide range of rural and urban regions across Japan from 2000 to 2019. It includes patient characteristics, diagnoses, prescriptions, procedures, and laboratory test results. Data were automatically

extracted from EMRs in each institution and anonymized using unique identifiers for individuals who are valid within the same institution.

The study was conducted in compliance with the ethical principles of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects and the Amended Act on the Protection of Personal Information. The study protocol was approved by the Research Institute of Healthcare Data Science ethics committee (no. RI2020022).

### 2.2 | Study cohort

The study cohort consisted of adult patients with T2D identified from the RWD-DB who used any GLP-1 RA from 11 June 2010 (after the launch of the first GLP1-RA, liraglutide, in Japan) to 31 October 2019 (end of available data). Patients who met all of the following criteria were included: (a) one or more prescription of any GLP-1 RA (Anatomical Therapeutic Chemical [ATC] code A10BJ) during the study period; (b) aged 20 years or older upon the index date; and (c) at least one data value more than 90 days before the index date. Patients were excluded if they had a disease code for a diagnosis of type 1 diabetes, malnutrition-related diabetes, or secondary diabetes during the study period. The International Classification of Disease 10th Revision (ICD-10 code) was used to identify disease information (Supplemental S1). The index date was defined as the date of first GLP-1 RA prescription during the study period in the RWD-DB, and the baseline period as the period from -60 to 0 days prior to the index date, unless specified otherwise. In addition to the GLP-1RA cohort, we also established the T2D cohort as the population relative to our study cohort to capture the proportion relative to the total number of patients with T2D who initiated oral antidiabetic drugs (OADs) or insulin in each year. The T2D cohort included patients who met the following criteria: (a) a new prescription of any antidiabetic drug (ATC code: A10) (the prescribed date was used as the index date of the T2D cohort); (b) aged 20 years or older upon the index date; and (c) did not have any disease code in the exclusion criteria above. The unit of the T2D cohort was the event of the initiation of a non-previously prescribed antidiabetic drug in each year instead of patient-level unit, which meant that the same patients were included into the cohort more than once if they experienced several antidiabetic drug initiation events in different years (e.g. dipeptidyl peptidase-4 inhibitor [DPP-4i] initiation in 2012, then thiazolidine initiation in 2013).

### 2.3 | Variables

Baseline characteristics at index date, including age, sex, clinical characteristics, co-morbidities, and duration of T2D (from the first date of T2D recorded in the RWD-DB to the index date), were described. Clinical characteristics were HbA1c, glycoalbumin (GA), urine albumin-to-creatinine ratio (UACR), urine protein-to-creatinine ratio (UPCR), eGFR, aspartate aminotransferase (AST), alanine aminotransferase

(ALT), total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglycerides (TG), uric acid (UA), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and body mass index (BMI). BMI values were only available after 2013 as a consequence of changes in the claim system. Additionally, because there were only two measurements of BMI in 2013, we used BMI data for 2014–2019. For patients with multiple measurements during the baseline period, the one closest to the index date was used. If there was more than one measurement on the same day, the measurement providing the most conservative estimate of treatment effect was used. The co-morbidities were hypertension, ischaemic heart disease, heart failure, stroke, dyslipidaemia, hyperuricaemia, diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy, defined by the presence of ICD-10 code at baseline. Concomitant use of OADs and insulin (ATC code: A10), antihypertensive drugs (ATC codes: C02–C09 and C11), and drugs for dyslipidaemia (ATC codes: C10–C11) at the index date was evaluated. Regarding antidiabetic drugs, treatment patterns before and after the index date were also described.

## 2.4 | Statistical methods

Baseline characteristics, clinical characteristics, co-morbidities, and concomitant drugs in the baseline period were summarized with means  $\pm$  standard deviations (SDs) for continuous variables and percentages for categorical variables. Antidiabetic medications were concomitant with GLP-1 RAs if the index date was included in the prescription period of these medications and their subsequent prescription was recorded within 30 days after the index date. This latter criterion was because patients possibly switched from antidiabetic medications to GLP-1 RAs if there was no subsequent prescription after the index date.

We described the number of patients with T2D who initiated GLP-1 RAs and the proportion relative to total patients with T2D who initiated any OADs or insulin in each year. The mean, standard error (SE), and 95% confidence interval (CI) of baseline age, HbA1c, eGFR, and BMI of patients with T2D who initiated GLP-1RAs were also evaluated annually from 2010 to 2019.

We evaluated changes in the treatment patterns of antidiabetic medications before and after the index date. The proportion of patients whose prescription of OADs or insulin overlapped the pre-index period (from  $-60$  to  $0$  days before the index date) was compared with that whose prescription overlapped the postindex period (from  $1$  to  $60$  days after the index date).

The persistence of GLP-1 RA prescription was defined as the number of days from the index date to the first occurrence of GLP-1 RA discontinuation or censoring date. Patients who remained taking GLP-1 RAs but changed to a different agent were considered as continuing GLP-1 RA treatment. GLP-1 RA treatment was considered as discontinued if there was no subsequent prescription of a GLP-1 RA, a greater than 60-day gap between two consecutive prescriptions of a GLP-1 RA, or if the patient died, because most patients with diabetes

in Japan regularly visit outpatient clinics once every 1 or 2 months. The date of censoring was defined as the last day of presence in the database or 360 days after index date, whichever occurred first. The persistence of GLP-1 RA prescription within 12 months after the index date was evaluated using a Kaplan–Meier plot.

We evaluated changes in laboratory test measurements, vital signs, and BMI from 0 to 24 months after the index date, divided into intervals of 3 months. Means and SEs within each interval were described. To avoid limiting the cohort to those who could maintain renal function to continue GLP-1RAs, clinical variables were followed, irrespective of continuation or discontinuation of GLP-1RAs. This analysis limited the number of patients who had more than one measurement at the index date  $\pm 1.5$  months or also had more than one measurement during the 24 months from this 3-month point. For UACR and UPCR, if the laboratory test was switched from UACR to UPCR or from UPCR to UACR during follow-up, then only the measurement before switching was used, to ensure the consistency of the population.

eGFR data from 9 months before and 12 months after the index date were extracted, regardless of GLP-1 RA prescription status. Trends in eGFR by month were evaluated with longitudinal data analysis. Linear mixed-effects models using eGFR as the outcome, number of months from the index date as the explanatory variable, and individual as a random effect, were fitted separately before (from  $-270$  to  $0$  days) and after (from  $1$  to  $360$  days) the index date. This analysis limited the number of patients who had more than one measurement during the preindex period ( $-270$  to  $-1$  days) and more than one measurement during the postindex period ( $1$  to  $360$  days).

Subgroup analyses according to baseline CKD stage were performed for all the aforementioned analyses, with CKD stage stratified as grade 1 and grade 2 (G1 + G2), grade 3 (G3), grade 4 (G4) or grade 5 (G5) (G4 + G5), and undergoing dialysis. In this study, patients were classified by CKD stage based on baseline eGFR ( $\geq 60$  mL/min/1.73m<sup>2</sup> for G1 + G2;  $<60$  and  $\geq 30$  mL/min/1.73m<sup>2</sup> for G3;  $<30$  and  $\geq 15$  mL/min/1.73m<sup>2</sup> for G4; and  $<15$  mL/min/1.73m<sup>2</sup> for G5). Patients undergoing maintenance dialysis each month within 3 months prior to the index date were classified as part of the dialysis group, regardless of eGFR level. Patients with missing baseline eGFR values were excluded from the subgroup analysis.

The current study aimed to describe the distribution or patterns of prescription or clinical characteristics; therefore, no testing of hypotheses was performed. Additionally, no imputation was conducted for missing data. All analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC).

## 3 | RESULTS

### 3.1 | Baseline characteristics

We identified 8049 patients with T2D (Supplemental S2). Table 1 describes their baseline characteristics. Overall, the mean age of patients was 63.5 years, and 43.1% were women. The mean of HbA1c

TABLE 1 Characteristics of patients at baseline

	Overall												CKD stage												
	G1 + G2				G3				G4				G5				G4 + G5				Dialysis				
	N		Mean ± SD		N		Mean ± SD		N		Mean ± SD		N		Mean ± SD		N		N		N		N		
	N = 8049 (100%)																								
Female, n (%)	3466 (43.1)	1478 (42.4)	682 (40.5)	132 (46.0)	287 (3.6%)	73 (34.8)	205 (41.2)	15 (33.3)																	
Age at index date (y)	8049	0	63.5 ± 14.4	3487	0	60.1 ± 14.6	1685	0	70.8 ± 11.2	287	0	70.8 ± 11.6	210	0	66.3 ± 12.0	497	0	68.9 ± 12.0	45	0	67.5 ± 9.6				
Duration of diabetes at index date (y) <sup>b</sup>	8049	0	5.3 ± 5.9	3487	0	4.8 ± 5.7	1685	0	6.5 ± 6.5	287	0	6.4 ± 6.4	210	0	6.7 ± 7.1	497	0	6.5 ± 6.7	45	0	7.7 ± 5.8				
BMI (kg/m <sup>2</sup> )	2155	5894	26.2 ± 5.7	1035	2452	26.4 ± 6.0	603	1082	26.2 ± 5.4	112	175	25.8 ± 5.3	103	107	24.9 ± 5.1	215	282	25.4 ± 5.2	12	33	21.7 ± 4.6				
HbA1c (%)	6802	1247	8.77 ± 1.87	3359	128	8.89 ± 1.91	1609	76	8.64 ± 1.74	259	28	8.41 ± 1.66	150	60	7.39 ± 1.65	409	88	8.04 ± 1.73	30	15	7.66 ± 1.49				
Glycoalbumin (%)	1716	6333	25.1 ± 7.7	651	2836	24.9 ± 7.9	331	1354	24.6 ± 7.2	64	223	24.9 ± 7.6	83	127	23.6 ± 7.9	147	350	24.1 ± 7.8	33	12	28.0 ± 9.2				
UACR (mg/g Cre)	2249	5800	205.0 ± 688.5	1078	2409	124.2 ± 405.8	446	1239	319.2 ± 709.7	55	232	1141.2 ± 2442.2	13	197	1864.3 ± 2042.2	68	429	1279.5 ± 2374.0	0	45	Not available				
UPCR (g/g Cre)	553	7496	1.7 ± 2.8	235	3252	0.6 ± 1.5	170	1515	1.2 ± 2.0	64	223	3.8 ± 3.6	38	172	5.5 ± 4.0	102	395	4.4 ± 3.8	0	45	Not available				
eGFR (mL/min/1.73m <sup>2</sup> )	5690	2359	67.6 ± 29.1	3487	0	85.3 ± 20.7	1685	0	46.7 ± 8.4	287	0	23.7 ± 4.1	210	0	7.9 ± 3.4	497	0	17.0 ± 8.7	21	24	6.3 ± 3.5				
AST (IU/L)	6803	1246	27.4 ± 22.3	3394	93	28.7 ± 24.7	1623	62	25.1 ± 14.7	279	8	25.0 ± 28.8	203	7	19.4 ± 21.5	482	15	22.6 ± 26.1	42	3	12.5 ± 5.1				
ALT (IU/L)	6828	1221	31.4 ± 31.0	3391	96	34.9 ± 34.6	1626	59	24.9 ± 18.5	275	12	22.3 ± 27.9	203	7	19.3 ± 38.0	478	19	21.0 ± 32.6	42	3	11.5 ± 8.5				
Total cholesterol (mg/dL)	4881	3168	181.9 ± 42.5	2411	1076	184.8 ± 42.1	1102	583	176.8 ± 41.3	195	92	177.9 ± 44.7	129	81	165.0 ± 50.2	324	173	172.8 ± 47.3	28	17	146.6 ± 33.4				
HDL (mg/dL)	6016	2033	48.7 ± 14.4	3011	476	49.8 ± 14.4	1397	288	48.1 ± 14.8	228	59	44.9 ± 15.2	134	76	42.8 ± 15.0	362	135	44.1 ± 15.2	26	19	40.8 ± 11.1				
LDL (mg/dL)	5373	2676	105.6 ± 34.1	2618	869	108.9 ± 33.3	1253	432	99.5 ± 32.7	196	91	101.0 ± 40.6	120	90	91.7 ± 38.7	316	181	97.5 ± 40.1	20	25	77.5 ± 27.1				
TG (mg/dL)	6306	1743	177.1 ± 142.8	3169	318	176.9 ± 150.7	1471	214	172.5 ± 113.6	243	44	200.8 ± 162.0	151	59	161.8 ± 131.1	394	103	185.8 ± 151.9	26	19	126.9 ± 102.4				
UA (mg/dL)	6329	1720	5.5 ± 1.6	3160	327	5.0 ± 1.4	1538	147	6.0 ± 1.6	268	19	6.9 ± 1.8	180	30	6.4 ± 2.1	448	49	6.7 ± 2.0	42	3	6.3 ± 1.2				
SBP (mmHg)	93	7956	142.2 ± 20.1	27	3460	140.7 ± 19.5	13	1672	150.1 ± 21.2	2	285	134.0 ± 19.8	1	209	165 ± not available	3	494	144.3 ± 22.7	2	43	143.0 ± 43.8				
DBP (mmHg)	93	7956	76.3 ± 13.1	27	3460	77.8 ± 13.4	13	1672	75.4 ± 14.1	2	285	68.0 ± 8.5	1	209	75 ± not available	3	494	70.3 ± 7.2	2	43	66.5 ± 20.5				
HR (bpm)	149	7900	79.5 ± 13.5	60	3427	80.1 ± 12.1	29	1656	77.6 ± 14.9	3	284	68.0 ± 6.6	2	208	79.0 ± 15.6	5	492	72.4 ± 10.9	2	43	96.5 ± 37.5				

(Continues)

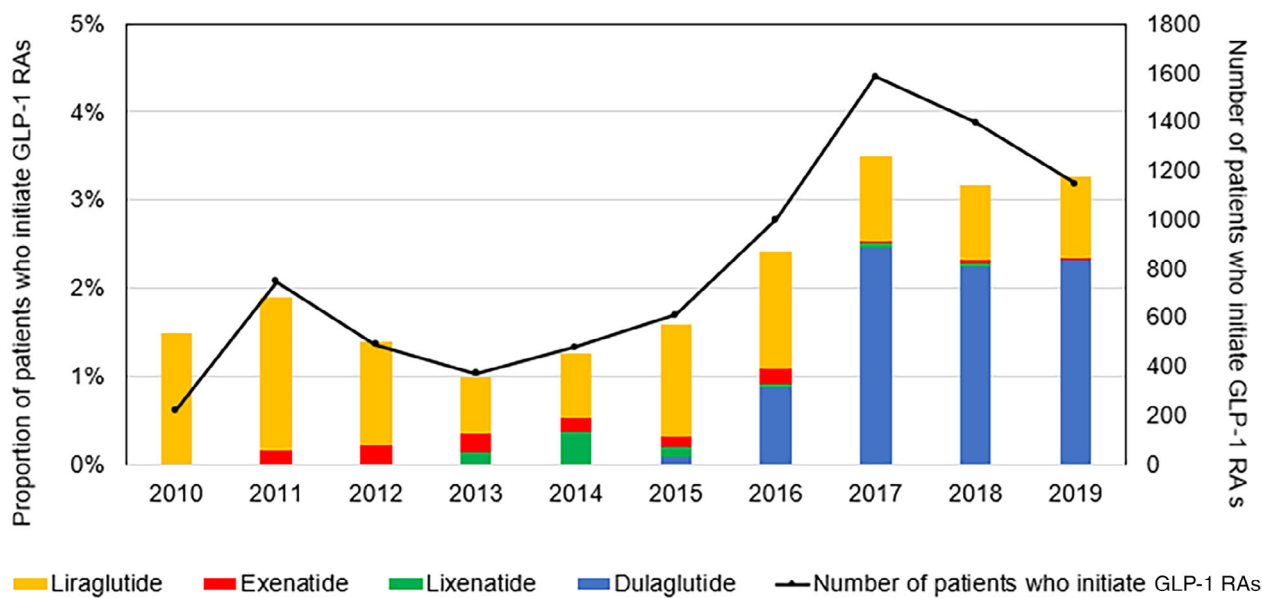
TABLE 1 (Continued)

	Overall																				
	CKD stage																				
	G1 + G2		G3		G4		G5		G4 + G5		Dialysis										
	N = 8049 (100%)		N = 3487 (43.3%)		N = 1685 (20.9%)		N = 287 (3.6%)		N = 210 (2.6%)		N = 497 (6.2%)		N = 45 (0.6%)								
GLP-1 RA formulations, total N and n (%)	Total	Missing n (%)	Total	Missing n (%)	Total	Missing n (%)	Total	Missing n (%)	Total	Missing n (%)	Total	Missing n (%)	Total	Missing n (%)							
Liraglutide	8049	0	4019 (49.9)	3487	0	1684 (48.3)	1685	0	727 (43.2)	287	0	147 (51.2)	210	0	88 (41.9)	497	0	235 (47.3)	45	0	5 (11.1)
Dulaglutide	8049	0	3303 (41.0)	3487	0	1476 (42.3)	1685	0	852 (50.6)	287	0	128 (44.6)	210	0	117 (55.7)	497	0	245 (49.3)	45	0	40 (88.9)
Exenatide	8049	0	419 (5.2)	3487	0	171 (4.9)	1685	0	46 (2.7)	287	0	4 (1.4)	210	0	0 (0.0)	497	0	4 (0.8)	45	0	0 (0.0)
Lixisenatide	8049	0	308 (3.8)	3487	0	156 (4.5)	1685	0	60 (3.6)	287	0	8 (2.8)	210	0	5 (2.4)	497	0	13 (2.6)	45	0	0 (0.0)
Co-morbidity, n (%)	Total	Missing n (%)	Total	Missing n (%)	Total	Missing n (%)	Total	Missing n (%)	Total	Missing n (%)	Total	Missing n (%)	Total	Missing n (%)	Total	Missing n (%)	Total	Missing n (%)	Total	Missing n (%)	
Hypertension	8049	0	3761 (46.7)	3487	0	1605 (46.0)	1685	0	936 (55.5)	287	0	164 (57.1)	210	0	86 (41.0)	497	0	250 (50.3)	45	0	24 (53.3)
Dyslipidaemia	8049	0	3684 (45.8)	3487	0	1498 (43.0)	1685	0	1014 (60.2)	287	0	204 (71.1)	210	0	124 (59.0)	497	0	328 (66.0)	45	0	44 (97.8)
Hyperuricaemia	8049	0	792 (9.8)	3487	0	184 (5.3)	1685	0	277 (16.4)	287	0	97 (33.8)	210	0	56 (26.7)	497	0	153 (30.8)	45	0	14 (31.1)
Ischaemic heart disease	8049	0	1551 (19.3)	3487	0	530 (15.2)	1685	0	471 (28.0)	287	0	83 (28.9)	210	0	64 (30.5)	497	0	147 (29.6)	45	0	23 (51.1)
Heart failure	8049	0	1359 (16.9)	3487	0	407 (11.7)	1685	0	435 (25.8)	287	0	115 (40.1)	210	0	92 (43.8)	497	0	207 (41.6)	45	0	32 (71.1)
Stroke	8049	0	600 (7.5)	3487	0	221 (6.3)	1685	0	169 (10.0)	287	0	28 (9.8)	210	0	26 (12.4)	497	0	54 (10.9)	45	0	3 (6.7)
Diabetic nephropathy	8049	0	1323 (16.4)	3487	0	459 (13.2)	1685	0	350 (20.8)	287	0	108 (37.6)	210	0	70 (33.3)	497	0	178 (35.8)	45	0	20 (44.4)
Diabetic retinopathy	8049	0	1151 (14.3)	3487	0	490 (14.1)	1685	0	258 (15.3)	287	0	50 (17.4)	210	0	42 (20.0)	497	0	92 (18.5)	45	0	9 (20.0)
Diabetic neuropathy	8049	0	971 (12.1)	3487	0	387 (11.1)	1685	0	275 (16.3)	287	0	57 (19.9)	210	0	31 (14.8)	497	0	88 (17.7)	45	0	13 (28.9)
Concomitantly used antidiabetic drugs, n (%)	Total	Missing n (%)	Total	Missing n (%)	Total	Missing n (%)	Total	Missing n (%)	Total	Missing n (%)	Total	Missing n (%)	Total	Missing n (%)	Total	Missing n (%)	Total	Missing n (%)	Total	Missing n (%)	
Monotherapy of GLP-1 RA	8049	0	1824 (22.7)	3487	0	684 (19.6)	1685	0	322 (19.1)	287	0	61 (21.3)	210	0	94 (44.8)	497	0	155 (31.2)	45	0	17 (37.8)
Biguanide	8049	0	2750 (34.2)	3487	0	1554 (44.6)	1685	0	431 (25.6)	287	0	15 (5.2)	210	0	1 (0.5)	497	0	16 (3.2)	45	0	0 (0.0)
SU	8049	0	1810 (22.5)	3487	0	766 (22.0)	1685	0	351 (20.8)	287	0	34 (11.8)	210	0	3 (1.4)	497	0	37 (7.4)	45	0	0 (0.0)
SGLT2i	8049	0	3487	0	1685	0	1685	0	287	0	25 (8.7)	210	0	6 (2.9)	497	0	31 (6.2)	45	0	0 (0.0)	



and GA was 8.77% and 25.1%, respectively. The breakdown of GLP-1 RAs was as follows: liraglutide (49.9%), dulaglutide (41.0%), exenatide (5.2%), and lixisenatide (3.8%). Because exenatide is contraindicated in patients with severe CKD, the proportion taking exenatide was 0% in these groups. Common co-morbidities were hypertension (46.7%), dyslipidaemia (45.8%), ischaemic heart disease (19.3%), heart failure (16.9%), and stroke (7.5%). We found that GLP-1 RAs were prescribed as monotherapy in 22.7% of patients

and were comparatively higher in patients at the G5 CKD stage (44.8%) and in the dialysis group (37.8%). Frequent concomitant antidiabetic drugs were biguanide (34.2%), insulin (33.6%), sulphonylurea (22.5%), sodium-glucose co-transporter-2 inhibitors (SGLT2is) (13.5%), and DPP-4is (10.2%). The proportions for CKD stage were 43.3%, 20.9%, 3.6%, 2.6%, 0.6%, and 29.0% for G1 + G2, G3, G4, G5, dialysis group patients, and patients with missing baseline eGFR data, respectively.



		YEAR									
		2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Patients who have newly prescription records with any antidiabetic drug or add another class of antidiabetic drugs in each year	N	14 883	39 332	35 181	37 772	37 812	38 755	41 590	45 219	43 968	35 130
Patients who initiate GLP-1 RAs	N	223	746	488	372	479	613	1002	1583	1397	1146
	%	1.5%	1.9%	1.4%	1.0%	1.3%	1.6%	2.4%	3.5%	3.2%	3.3%
Liraglutide	N	223	686	415	237	280	488	554	436	378	322
	%	1.5%	1.7%	1.2%	0.6%	0.7%	1.3%	1.3%	1.0%	0.9%	0.9%
Exenatide	N	0	60	73	79	62	45	70	7	17	6
	%	0.0%	0.2%	0.2%	0.2%	0.2%	0.1%	0.2%	0.0%	0.0%	0.0%
Lixisenatide	N	—	—	—	56	137	47	18	27	19	4
	%	—	—	—	0.1%	0.4%	0.1%	0.0%	0.1%	0.0%	0.0%
Dulaglutide	N	—	—	—	—	—	33	360	1113	983	814
	%	—	—	—	—	—	0.1%	0.9%	2.5%	2.2%	2.3%

**FIGURE 1** The 2010-2019 trend in patients who initiate glucagon-like peptide-1 receptor agonists (GLP-1 RAs). Year 2010 includes 7 months, from 11 June to 31 December, and year 2019 includes 10 months, from 1 January to 31 October; the other years include the full 12 months. The number of denominators includes patients with type 2 diabetes (T2D) who satisfied the following items in each year: (1) for any of the diabetic drugs, prescription had been made for the current year without prescription for the previous year; and (2) patients aged 20 years or older who had no disease code for exclusion criteria. The number of numerators includes patients with T2D who satisfied the following items in each year: (1) prescription of GLP-1 RAs had been made for the current year without prescription before the year and study period; (2) patients aged 20 years or older who had no disease code for exclusion criteria; and (3) at least one data value more than 90 days before the index date. The launch dates for GLP-1 RAs in Japan were June 2010 for liraglutide, December 2010 for exenatide, September 2013 for lixisenatide, and September 2015 for dulaglutide

### 3.2 | 2010-2019 trend in patients who initiate GLP-1 RAs

The proportion of patients with T2D who initiated GLP-1RAs increased from 1.5% in 2010 to 1.9% in 2011, decreased to 1.0% in 2013, then increased to more than 3% after 2017 (Figure 1). From 2010 to 2019, the mean (95% CI) age at GLP-1 RA initiation increased from 58.6 (56.7-60.4) to 66.3 (65.5-67.2) years, and the mean (95% CI) eGFR decreased from 72.9 (68.0-77.9) to 64.0 (62.2-65.8) mL/min/1.73m<sup>2</sup>. Mean (95% CI) BMI decreased from 28.9 (27.5-30.2) to 25.5 (25.0-26.0) kg/m<sup>2</sup> (Supplemental S3).

### 3.3 | Treatment patterns for antidiabetic drugs before and after GLP-1 RA initiation

Use of DPP-4is and insulin substantially decreased from 47.1% to 12.2% and from 51.6% to 33.3%, respectively, after the initiation of GLP-1 RAs (Supplementary S4). Other drugs showed no significant tendency.

### 3.4 | Persistence proportion of GLP-1 RA initiation

Figure 2 shows the Kaplan-Meier plot of the persistence of GLP-1RA in patients overall and stratified by CKD stage. For patients overall,

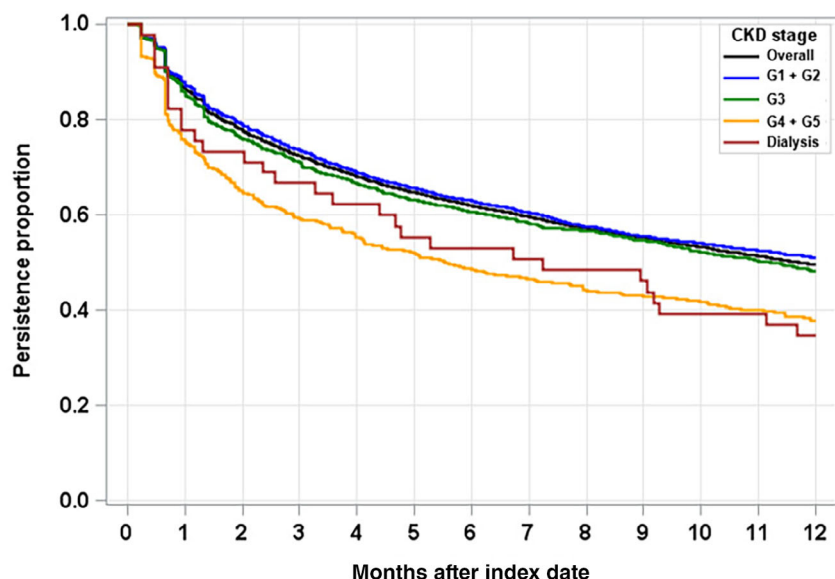
the persistence proportion at 6 months was 61.9% (95% CI: 60.8%-63.0%), and 49.5% (48.3%-50.6%) at 12 months. Subgroup analyses showed that the persistence proportions at 12 months were 50.9%, 48.3%, 37.8%, and 34.6% for G1 + G2, G3, G4 + G5, and the dialysis group, respectively.

### 3.5 | Description of changes in clinical measurements after GLP-1 RA initiation

Figure 3 shows that average eGFR gradually declined across all CKD stages after GLP-1 RA initiation. Although Figure 3 includes the average UACR and UPCR, the number of these measurements was small, and accordingly, we describe them for reference only. Average HbA1c and GA values decreased 0 to 3 months after GLP-1 RA initiation across all CKD stages (Supplementary S5). Another noticeable change was that the average LDL level declined initially and then remained stable (Supplementary S6).

### 3.6 | Longitudinal analysis of change in eGFR before and after GLP-1 RA initiation

Figure 4 shows the results of linear mixed-effect models for eGFR measurement before and after GLP-1 RA initiation. For patients overall, the decline before and after GLP-1 RA initiation decreased from



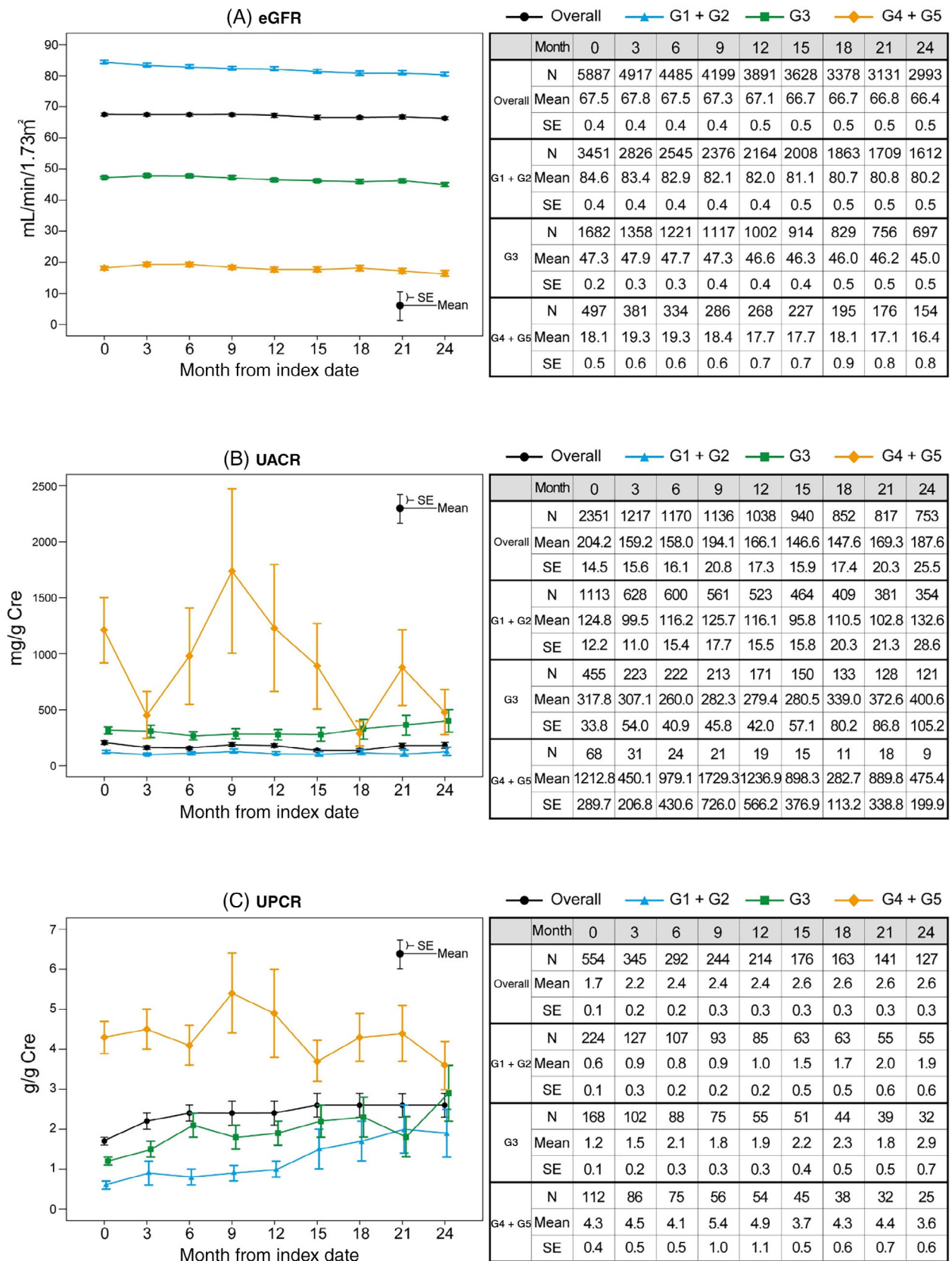
Estimates and 95% CIs of persistency proportion

CKD Stage	Month	Estimates	95% CI	
Overall	6	0.619	0.608	0.630
	12	0.495	0.483	0.506
G1 + G2	6	0.629	0.613	0.645
	12	0.509	0.492	0.526
G3	6	0.605	0.581	0.629
	12	0.483	0.458	0.508
G4 + G5	6	0.485	0.441	0.531
	12	0.378	0.335	0.424
Dialysis	6	0.519	0.380	0.673
	12	0.346	0.223	0.510

	No. at risk													
Overall	8049	6914	6100	5589	5201	4873	4601	4369	4148	3961	3785	3594	3416	
G1 + G2	3487	3031	2691	2461	2283	2137	2021	1917	1810	1733	1667	1592	1524	
G3	1685	1437	1251	1157	1069	1000	951	903	868	822	773	736	696	
G4 + G5	497	370	312	277	257	241	224	213	196	186	179	170	160	
Dialysis	45	35	33	30	27	24	23	22	21	20	17	17	15	

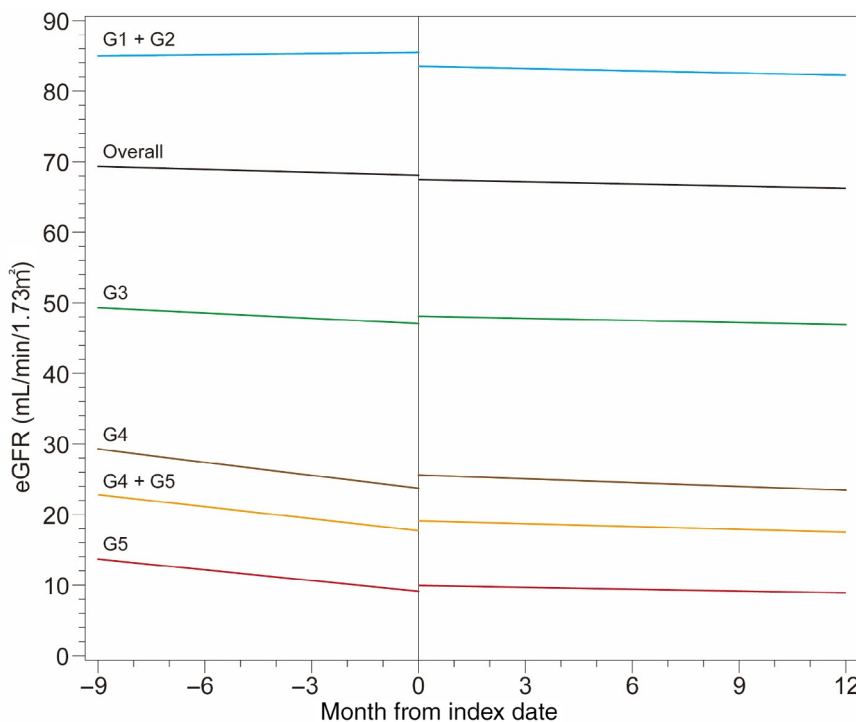
**FIGURE 2** Kaplan-Meier plots for persistence proportion after initiation of glucagon-like peptide-1 receptor agonists (GLP-1 RAs). Black line = overall patients; blue line = G1 + G2 chronic kidney disease (CKD) stage (baseline estimated glomerular filtration rate [eGFR]  $\geq$  60 mL/min/1.73m<sup>2</sup>); green line = G3 CKD stage (baseline eGFR  $<$ 60 and  $\geq$ 30 mL/min/1.73m<sup>2</sup>); orange line = G4 + G5 CKD stage (baseline eGFR  $<$ 30 mL/min/1.73m<sup>2</sup>); brown line = dialysis group. 95% CI, 95% confidence interval





**FIGURE 3** Changes in renal function variables after initiation of glucagon-like peptide-1 receptor agonists (GLP-1 RAs). A, Estimated glomerular filtration rate (eGFR); B, Urinary albumin-to-creatinine ratio (UACR); and C, Urinary protein-to-creatinine ratio (UPCR). Black colour = overall patients; blue colour = G1 + G2 chronic kidney disease (CKD) stage (baseline eGFR  $\geq 60$  mL/min/1.73m<sup>2</sup>); green colour = G3 CKD stage (baseline eGFR  $<60$  and  $\geq 30$  mL/min/1.73m<sup>2</sup>); orange colour = G4 + G5 CKD stage (baseline eGFR  $<30$  mL/min/1.73m<sup>2</sup>). SE, standard error

**FIGURE 4** Changes in estimated glomerular filtration rate (eGFR) measurements before and after initiation of glucagon-like peptide-1 receptor agonists (GLP-1 RAs). Black line = overall patients; blue line = G1 + G2 chronic kidney disease (CKD) stage (baseline eGFR  $\geq 60$  mL/min/1.73m<sup>2</sup>); green line = G3 CKD stage (baseline eGFR  $<60$  and  $\geq 30$  mL/min/1.73m<sup>2</sup>); orange line = G4 + G5 CKD stage; brown line = G4 CKD stage (baseline eGFR  $<30$  and  $\geq 15$  mL/min/1.73m<sup>2</sup>); red line = G5 CKD stage (baseline eGFR  $< 15$  mL/min/1.73m<sup>2</sup>). 95% CI, 95% confidence interval



Stage	preindex period					postindex period						
	number of observations	number of patients	Intercept	Estimate	95% CI	number of observations	number of patients	Intercept	Estimate	95% CI		
<b>Overall</b>	33 739	5531	Intercept	68.10	67.34	68.86	44 783	5531	Intercept	67.45	66.70	68.19
			month	-0.13	-0.17	-0.09			month	-0.10	-0.12	-0.07
<b>G1 + G2</b>	17 793	3228	Intercept	85.44	84.70	86.18	24 041	3228	Intercept	83.54	82.81	84.26
			month	0.05	-0.01	0.11			month	-0.11	-0.16	-0.07
<b>G3</b>	10 509	1554	Intercept	47.01	46.48	47.53	13 418	1554	Intercept	48.09	47.51	48.67
			month	-0.25	-0.30	-0.20			month	-0.10	-0.14	-0.06
<b>G4</b>	2438	268	Intercept	23.81	23.05	24.57	3072	268	Intercept	25.62	24.59	26.64
			month	-0.61	-0.69	-0.53			month	-0.18	-0.24	-0.11
<b>G5</b>	1892	190	Intercept	9.13	7.72	10.54	2469	190	Intercept	9.98	8.47	11.49
			month	-0.50	-0.60	-0.41			month	-0.09	-0.13	-0.04
<b>G4 + G5</b>	4330	458	Intercept	17.78	16.79	18.77	5541	458	Intercept	19.11	18.01	20.21
			month	-0.56	-0.63	-0.50			month	-0.13	-0.17	-0.09

-0.13 (95% CI: -0.17, -0.09) to -0.10 (-0.12, -0.07) mL/min/1.73m<sup>2</sup> per month. Specifically, for patients at G3, the decline decreased from -0.25 (-0.30, -0.20) to -0.10 (-0.14, -0.06) mL/min/1.73m<sup>2</sup> per month. Moreover, we observed a greater change in decline—namely, -0.56 (-0.63, -0.50) and -0.13 (-0.17, -0.09) mL/min/1.73m<sup>2</sup> per month before and after the index date, respectively—in patients at the advanced CKD stage (G4 + G5).

## 4 | DISCUSSION

We conducted a retrospective cohort study to describe the utilization of GLP-1 RAs and changes in clinical characteristics before and after GLP-1 RA initiation in patients with T2D by CKD stage.

Regarding the annual trend of the number of patients with T2D who initiated GLP-1 RAs, we found that the proportion of patients initiating GLP-1 RAs more than doubled from 2010 to 2019. The first peak in 2011 was probably attributable to the launch of liraglutide in 2010, and the second peak in 2016 because of the wider use of dulaglutide, which was launched in late 2015. Fadini et al.<sup>23</sup> showed that prescriptions of GLP-1 RAs increased after 2010; a similar paper was published in the United States<sup>21</sup>; both reported that liraglutide use

tended to peak around 2013 then decreased, while dulaglutide use tended to increase after 2015. Our findings of two peaks complement these previous reports. A rapidly increasing trend in the proportion of GLP-1 RA initiation from 2016 may be ascribable to evidence accumulating in the early 2010s that GLP-1 RAs have renoprotective and cardioprotective effects, as well as glycaemic control.<sup>6-9,11-14</sup> Moreover, regarding the increasing trend of dulaglutide use, which accounted for the increment after 2016, we suggest that dulaglutide has been widely used in T2D patients with CKD because of its wider range of adaptation, and easier administration as a result of its simplified dosing (once weekly) using a dose pen.<sup>25,26</sup>

Regarding the baseline characteristics of those patients with T2D who initiated GLP-1 RAs, some patients with advanced CKD were included (G4, 3.6%; G5, 2.6%; dialysis, 0.6%); moreover, these patients had a higher prevalence of ischaemic heart disease, heart failure, and stroke than patients without CKD. Two retrospective cohort studies showed that patients with T2D who received GLP-1 RAs had a higher prevalence of cardiovascular disease history or decreased renal function than those without GLP-1 RA therapy.<sup>27,28</sup> Furthermore, we detected an increasing trend in average baseline age and a reduction in the average baseline eGFR (Supplemental S3). These findings suggest that GLP-1 RAs are increasingly prescribed for elderly

or CKD patients, probably because of accumulating evidence and recommendations in guidelines. Our study also showed a decreasing trend in baseline BMI, which could be explained by the trend of higher age with non-obesity.

Regarding the persistence of GLP-1 RAs for patients with T2D, studies reporting the persistence of GLP-1 RAs showed mixed results on the proportion of persistence of GLP-1 RAs, probably because of differences in setting and patient selection. Although 27.1% of patients with T2D are at CKD stage G3-G5 in the current study, the persistence proportions of GLP-1 RAs in our study were comparable with those in previous studies, which reported 51.9%-70.4% persistence at 12 months in all patients with T2D.<sup>29-31</sup> Also, in comparison with the persistence of antidiabetic medications other than GLP-1RAs, the current study showed that the persistence of GLP-1RAs in patients with T2D, including those with CKD, was not low. In those previous studies, the 12-month persistence of antidiabetic medications, such as DPP-4is, alpha-glucosidase inhibitors, SGLT2is, or metformin, ranged from 35.3% to 70.1%.<sup>29,32</sup> Also, when focusing on T2D patients with CKD, the persistence of GLP-1RAs in the current study was also comparable with those for other medications reported previously (50.2% for DPP-4is and 39.7% for thiazolidine in T2D patients with CKD),<sup>33</sup> although those studies did not include dialysis patients and may therefore have comparatively higher persistence. Additionally, because we defined the CKD stage based on eGFR, we may have been able to minimize the misclassification of the CKD category.

With regard to treatment patterns, prescriptions of DPP-4is and insulin substantially decreased after initiation of GLP-1 RAs, suggesting that DPP-4is or insulin might be replaced by GLP-1 RAs. This observation accords with a previous study conducted in Japan.<sup>30</sup> Regarding switching from DPP-4is, DPP-4is and GLP-1 RAs are both incretin-related drug classes with an hypoglycaemic effect via the GLP-1 receptor, and Japanese public insurance often does not approve their prescription in combination. However, we found that 10.2% of patients used a GLP-1 RA and a DPP-4i concomitantly, possibly because some prefectures in Japan allow reimbursement for concomitant use of DPP-4is during GLP-1 RA therapy. Concerning switching from insulin, GLP-1 RAs might improve glycaemic control, thereby allowing a decrease in insulin prescription in favour of GLP-1 RAs.

In the analysis of eGFR decline (Figure 4), we found a gradual moderation in the exacerbation of eGFR decline after GLP-1 RA initiation, especially in G3, G4, G5, and dialysis group patients. This may suggest that GLP-1 RA initiation moderates eGFR decline, particularly in patients at a moderate or advanced CKD stage, as seen in other RCTs<sup>13,34</sup> and an observational study.<sup>24</sup> Although the renal protective effect of GLP-1RAs is effective for all patients with T2D, it is possible that the changes in eGFR decline before and after GLP-1 RA initiation were more pronounced in patients at a moderate or advanced CKD stage than in patients at stage G1 + G2, because they have a greater absolute value of eGFR decline before GLP-1 RA initiation. Another possible explanation for this difference in eGFR decline after GLP-1

RA initiation at G1 + G2 was that the glucose-lowering effect could influence the improvement in glomerular hyperfiltration. Those previous studies mainly focused on only a single formulation and patients with moderate CKD, whereas we included patients with T2D with a wider range of CKD stages from a variety of hospitals. A causal relationship between GLP-1 RAs and slower renal function deterioration cannot be established through the current study, and further studies are warranted.

The current study has several strengths. First, we used measured values of eGFR to determine the CKD stage. Recently, in addition to diabetic nephropathy, a broader concept of diabetes with CKD has also arisen. This concept is associated with decreased renal function, in which eGFR decreases without albuminuria, and it has also been adopted in some guidelines.<sup>3,20</sup> The use of eGFR values might also minimize measurement bias. Second, we used large-scale EMR data collected from a wide range of medical institutions, providing stronger evidence in clinical practice than studies conducted in limited types of facility. Third, the sample size in the current analysis is much larger than in previous studies.

The current study also has some limitations. First, the diagnosis codes for co-morbidities or dialysis procedures were not validated in the RWD-DB. Second, patients who were transferred to other institutions could not be followed up. Third, we did not include an evaluation of adverse events in our objectives because the validity of extracting adverse event information is not yet confirmed. Further research on the validity of safety information is expected in the future. Fourth, the trend of eGFR before and after GLP-1 RA initiation was confirmed only descriptively because one of the purposes of this study was to describe the trend of eGFR around GLP-1 RA initiation. To establish the effect of GLP-1 RAs on the trend of eGFR, further analyses are required, including comparative analyses adjusting for confounding factors. Fifth, we could not collect the information on the reason of the discontinuation of GLP-1 RA. It was possible that patients discontinued GLP-1 RA for reasons other than tolerability so that we need further information to conclude the tolerability of GLP-1 RA in T2DM patients with CKD, although such data collection is not feasible for a large number of patients included in our study. Finally, the approved dose of dulaglutide is 0.75 mg in Japan; in other countries this can be uptitrated to higher dose levels, based on the patient's glycaemic condition. However, the 0.75-mg dose of dulaglutide has also been evaluated in clinical research<sup>14</sup> and is widely used in practice. Therefore, we believe that the generalizability of our study results is not entirely limited.

In conclusion, this is the first study to investigate the use of GLP-1 RAs in patients with T2D, both overall and by their CKD stage. The initiation of GLP-1 RAs has been increasing over the past decade, and GLP-1 RAs have also been used in patients with limited treatment options, such as the elderly or those with CKD. The persistence proportion of GLP-1 RAs was not low compared with that of patients taking other antidiabetic medications, and analysis of the change in eGFR suggests that renal dysfunction may be moderated after GLP-1 RA initiation.

## ACKNOWLEDGEMENTS

Medical writing support was provided by Takeshi Kimura and Sachiko Tanaka of Real World Data Co., Ltd, and editorial assistance was provided by Masakazu Takeuchi of Eli Lilly Japan K. K. The authors thank the Health, Clinic, and Education Information Evaluation Institute, for RWD-DB database development for the study. This study was funded by Eli Lilly Japan K. K.

## CONFLICT OF INTEREST

NH, NT, TK, and RC are employees of Eli Lilly Japan K. K. NT, TK, and RC are minor stockholders of Eli Lilly and Company.

## AUTHOR CONTRIBUTIONS

All named authors met the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, and take responsibility for the integrity of the work as a whole, and provided approval for the final version to be published.

## PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14600>.

## DATA AVAILABILITY STATEMENT

Research data are not shared.

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#### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Hirose N, Tsujimoto N, Katayose T, Chin R. Utilization of glucagon-like peptide-1 receptor agonists and changes in clinical characteristics in patients with type 2 diabetes by chronic kidney disease stage in Japan: A descriptive observational study using a nationwide electronic medical records database. *Diabetes Obes Metab.* 2022;24(3):486–498. doi:10.1111/dom.14600