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Transitional changes in medication-initiator cohort profiles in persons with chronic kidney disease and type 2 diabetes—A hospital-based cohort study in Japan

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Abstract

Aims: To describe temporal changes in the characteristics of medication-initiator cohorts in persons with chronic kidney disease (CKD) and type 2 diabetes (T2D).

Materials and Methods: Adults with CKD and T2D initiating sodium-glucose cotransporter-2 inhibitors (SGLT-2i) or glucagon-like peptide-1 receptor agonists (GLP-1RA) were identified in the Japan Chronic Kidney Disease Database Extension in each of the two study periods (Period I: 1 January 2014–30 June 2021; Period II: 1 July 2021–31 December 2022). For each cohort, baseline characteristics and the standard mean differences (SMD) between periods I and II were assessed.

Results: During study periods I and II, 1157 and 1122 SGLT-2i, and 329 and 369 GLP-1RA new users were identified, respectively. All four cohorts had similar age, sex and comorbidity patterns, with a mean age spanning 66.1–69.5 years and 60%–70% being male. More than 80% of persons had hypertension and 60% had congestive heart failure. In the SGLT-2i cohorts, we observed a decrease in prior metformin and dipeptidyl peptidase-4 inhibitor use (SMD ≥0.5 and <0.8), and an increase in the number of persons with no T2D medications other than insulin between

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periods (SMD >0.8). In the GLP-1RA cohorts, there was a medium decrease in persons using insulin.

Conclusions: With the introduction of new treatments and emerging evidence supporting cardio-renal protective effects in people with CKD and T2D, notable changes in baseline treatment were observed in the medication-initiator cohort characteristics. These findings suggest the earlier use of cardio-renal protective medications in the course of T2D.

KEYWORDS

chronic kidney disease, diabetes, glucagon-like peptide-1 receptor agonist, real-world, sodium-glucose cotransporter-2 inhibitor, treatment pattern

1 | INTRODUCTION

Type 2 diabetes (T2D) represents a global disease burden and is one of the leading causes of death and disability worldwide.[1,2] Chronic kidney disease (CKD) is a major complication in persons with T2D. Globally, approximately 160 million individuals were suffering from CKD and T2D in 2019.[3] Persons with CKD and T2D have significant risks of mortality and morbidity (e.g., kidney failure and cardiovascular events).[4,5] Diabetes with CKD accounts for nearly half of the causes of kidney failure in the developed world,[6] and numerous studies have reported elevated cardiovascular mortality risks in people with CKD and T2D.[7,8]

Until recently, renin-angiotensin-aldosterone system blockade using angiotensin-converting enzyme inhibitors (ACEis) and angiotensin-receptor blockers (ARBs) was the sole available therapy for reducing the risk of CKD progression in people with T2D.[9] However, the clinical landscape for the treatment of people with CKD and T2D has evolved rapidly with the introduction of new treatments (e.g., sodium-glucose cotransporter-2 inhibitors (SGLT-2i), glucagon-like peptide-1 receptor agonists (GLP-1RA) and the non-steroidal mineralocorticoid receptor antagonist, finerenone). SGLT-2i were initially authorised as glucose-lowering drugs.[10] Since then, their beneficial effects on preventing kidney disease progression and reducing the risk of cardiovascular events have been established in numerous clinical trials,[11–13] leading to regulatory approval for use in persons with CKD in several countries, including Japan. GLP-1RAs are currently approved for the treatment of T2D and obesity. Recent cardiovascular outcome trials[14–17] and a kidney outcome trial[18] have shown the benefits of this medication class in reducing the risk of cardiovascular and kidney outcomes. The ADA's Standard of Care in Diabetes recommends GLP-1RA and SGLT-2i for the pharmacological treatment of hyperglycaemia in persons with T2D who have established atherosclerotic cardiovascular disease or kidney disease.[19] The proposed algorithm for pharmacotherapy in persons with T2D by the Japan Diabetes Society (JDS) incorporates a step for a consideration of the additional benefits of T2D medications, based on the results of large clinical trials of SGLT-2is and GLP-1RAs.[20]

Given the rapid development of new pharmacological treatments and emerging evidence, it is of particular interest to study how the treatment landscape in persons with CKD and T2D has evolved over time. It is often stated that the pace at which new evidence is implemented in practice is not always consistent with expectations.[21] Thorough evaluations of the transitional changes in the treatment landscape may assist in gaining an understanding of how, and to what extent the benefits of new treatments observed in clinical trials have reached the patients. However, there is limited evidence available to support an understanding of the recent transitions of the treatment landscape in persons with CKD and T2D.

The FINEGUST study (EUPAS48148; NCT05526157) is a multinational observational study using population-based secondary data sources in Europe, Japan and the United States, which was conducted in the FOUTAIN research platform.[22] It aims to describe the drug utilization and temporal changes of different treatments in persons with CKD and T2D. In this country-specific analysis of the FINEGUST study using a nationwide multicentre registry in Japan, we aimed to describe temporal changes in the characteristics of medication-initiator cohorts in persons with CKD and T2D initiating SGLT-2is or GLP-1RAs.

2 | MATERIALS AND METHODS

2.1 | Study design, data source and study population

This was a retrospective cohort study that utilized data collected in the Japan Chronic Kidney Disease Database Extension (J-CKD-DB-Ex). The J-CKD-DB-Ex is a nationwide multicentre registry of persons aged ≥18 years with CKD (proteinuria ≥1+ [dipstick test] and/or estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2), collected at five participating university hospitals in Japan.[23,24] It primarily captures persons treated at university hospitals for any diseases or conditions. The J-CKD-DB-Ex is based on electronic health record data, including inpatient and outpatient encounters, prescriptions, diagnostic codes based on the International Classification of Diseases 10th edition or disease name code, and laboratory measurements. In this study, we aimed to capture the temporal changes of the medication-initiator cohort characteristics in a prospective manner based on registry data. The study period was divided into two separate time periods (Period I: 1 January 2014–30 June 2021; Period II:

1 July 2021–31 December 2022) to assess temporal changes in the characteristics of the medication-initiator cohorts before and after July 2021, when finerenone was first approved for persons with CKD and T2D in the United States.[25] This timepoint was chosen as the latest treatment development in the study population when the multinational study protocol was developed in 2022. The data extraction in this study was originally started in 2023 for the analysis of Period I, covering the period between 1 January 2014, and 31 December 2021. Pre-specified study objectives were planned to describe the medication-initiator cohort characteristics in Period II and assess their temporal changes between Period I and Period II. The analysis of Period II was conducted in June 2024 using a separately extracted dataset, covering the period between 1 January 2014, and 31 December 2022.

The study population included all adult individuals (aged ≥18 years) with at least 12 months of continuous enrollment in J-CKD-DB-Ex, with recorded evidence of CKD and T2D before initiation of SGLT-2i or GLP-1RA. The detailed definitions to ascertain the presence of CKD and T2D are shown in Table S1. In each study period, new-user cohorts of SGLT-2i or GLP-1RA were identified based on the record of a first outpatient prescription of SGLT-2i or GLP-1RA, with no prescription for the same medication class during the previous 12 months. The medication-specific cohorts were not mutually exclusive, and an individual could be included in multiple cohorts. The index date was the date of the first prescription of each medication class. Persons were excluded if they had type 1 diabetes, a diagnosis of kidney cancer, or kidney failure (eGFR <15 mL/min/1.73 m^2, CKD stage 5 or on dialysis, or kidney transplant) on or at any time before the index date.

2.2 | Variables

Demographics, comorbidities and medications, as well as information regarding clinical characteristics related to CKD and T2D (e.g., treatment for CKD or T2D, diabetes complications, insulin use, CKD stage and laboratory test results) were assessed using medical records prior to the index date. The Diabetes Severity Complication Index was calculated based on a previously reported method.[26,27] A list of these variables, along with the time windows for data collection, is shown in Table S1.

2.3 | Statistical analyses

Continuous variables were summarised using mean, standard deviation (SD), median and first and third quartiles (Q1, Q3). Categorical variables were summarised using counts (*n*) and percentages (%). Missing data were not imputed. The absolute and relative number of missing values were calculated and reported. To evaluate the temporal changes in the characteristics of medication-initiator cohorts between Period I and Period II, the standard mean differences (SMDs) for each baseline characteristic were calculated to assess the balance between the baseline covariates in Period I compared with those in Period II, on the same scale. Based on the previous literature,[28] SMDs of 0.2, 0.5 and 0.8 were defined as small, medium and large differences in the level of covariates between the two time periods. All statistical analyses were performed using the SAS software, version 9.4. This study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement,[29] as reported in Table S2.

2.4 | Ethics statement

This study was conducted in accordance with the principle of the Declaration of Helsinki. Informed consent was obtained through an opt-out method on the website of participating university hospitals, in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects.[30] The study protocol was reviewed and approved by the ethics committee of the Shiga University of Medical Science (R2022-143).

3 | RESULTS

3.1 | Characteristics of medication-initiator cohorts in each study period

Out of a total of 251 659 and 385 825 individuals recorded in the J-CKD-DB-Ex datasets for Period I and Period II, respectively, 6394 and 14 422 new users of SGLT-2i, and 2991 and 6051 new users of GLP-1RA were identified. After applying inclusion and exclusion criteria, 1157 and 1122 new SGLT-2i users, and 329 and 369 new GLP-1RA users were included in the analyses for Period I and Period II, respectively. The flow diagrams for individuals included in each cohort can be found in Figure S1. Table 1 shows the distributions of index medications in each study period. In the SGLT-2i cohorts,

TABLE 1 Distribution of newly initiated medications in each medication-initiator cohort.

	Period I	Period II
SGLT-2i, *n* (%)		
Empagliflozin	356 (30.8)	321 (28.6)
Dapagliflozin	222 (19.2)	594 (52.9)
Luseogliflozin	181 (15.6)	57 (5.1)
Ipragliflozin	166 (14.3)	47 (4.2)
Canagliflozin	146 (12.6)	71 (6.3)
Tofogliflozin	86 (7.4)	32 (2.9)
GLP-1RA, *n* (%)		
Liraglutide	198 (60.2)	56 (15.2)
Dulaglutide	110 (33.4)	67 (18.2)
Lixisenatide	10 (3.0)	1 (0.3)
Semaglutide	9 (2.7)	245 (66.4)
Exenatide	2 (0.6)	0 (0)

Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

TABLE 2 Baseline characteristics of the medication-initiator cohorts of SGLT-2i new users and GLP-1RA new users in each study period.

	SGLT-2i			GLP-1RA		
	Period I ($N = 1157$)	Period II ($N = 1122$)	SMD in SGLT-2i[a]	Period I ($N = 329$)	Period II ($N = 369$)	SMD in GLP-1RA[a]
Age (years)						
Mean ± SD	67.1 ± 11.7	69.5 ± 12.9	0.19	66.1 ± 13.6	68.2 ± 11.9	0.16
Gender, male, *n* (%)	726 (62.7)	812 (72.4)	0.21	196 (59.6)	240 (65.0)	0.11
Index year, *n* (%)						
2015	83 (7.2)	0 (0)	–	24 (7.3)	0 (0)	–
2016	186 (16.1)	0 (0)	–	41 (12.5)	0 (0)	–
2017	172 (14.9)	0 (0)	–	44 (13.4)	0 (0)	–
2018	186 (16.1)	0 (0)	–	45 (13.7)	0 (0)	–
2019	184 (15.9)	0 (0)	–	65 (19.8)	0 (0)	–
2020	208 (18.0)	0 (0)	–	75 (22.8)	0 (0)	–
2021[b]	131 (11.9)	393 (35.0)	–	35 (10.6)	110 (29.8)	–
2022	0 (0)	729 (65.0)	–	0 (0)	259 (70.2)	–
Type of initiation of the index medication[c]						
Switched from GLP-1RA	4 (0.3)	3 (0.3)	0	0 (0)	0 (0)	–
Switched from SGLT-2i	0 (0)	0 (0)	–	7 (2.1)	7 (1.9)	−0.01
Add-on to GLP-1RA	75 (6.5)	47 (4.2)	−0.10	0 (0)	0 (0)	–
Add on to SGLT-2i	0 (0)	0 (0)	–	89 (27.1)	177 (48.0)	0.44
Medications for T2D[d], *n* (%)						
SGLT-2i	0 (0)	0 (0)	0	174 (52.9)	255 (69.1)	0.34
GLP-1RA	203 (17.5)	114 (10.2)	−0.21	0 (0)	(0)	0
Metformin	604 (52.2)	244 (21.7)	−0.67	199 (60.5)	222 (60.2)	−0.01
Sulfonylureas	341 (29.5)	147 (13.1)	−0.41	115 (35.0)	154 (41.7)	0.14
Alpha glucosidase inhibitors	298 (25.8)	149 (13.3)	−0.32	129 (39.2)	107 (29.0)	−0.22
Thiazolidinediones	197 (17.0)	74 (6.6)	−0.33	56 (17.0)	65 (17.6)	0.02
Dipeptidyl peptidase inhibitors	860 (74.3)	473 (42.2)	−0.69	255 (77.5)	291 (78.9)	0.03
Meglitinides	223 (19.3)	118 (10.5)	−0.25	118 (35.9)	79 (21.4)	−0.32
Number of T2D drug classes[e], *n* (%)						
No therapy	145 (12.5)	557 (49.6)	0.88	18 (5.5)	19 (5.1)	−0.01
Mono therapy	218 (18.8)	181 (16.1)	−0.07	32 (9.7)	33 (8.9)	−0.03
Dual therapy	272 (23.5)	157 (14.0)	−0.25	61 (18.5)	70 (19.0)	0.01
Triple therapy	251 (21.7)	129 (11.5)	−0.28	82 (25.2)	83 (22.5)	−0.06
Quadruple therapy or more	271 (23.4)	98 (8.7)	−0.41	135 (41.0)	164 (44.4)	0.07
Insulin use[c], *n* (%)	562 (48.6)	329 (29.3)	−0.40	281 (85.4)	202 (54.7)	−0.71
HbA1c, *n* (%)						
≤7%	412 (35.6)	610 (54.4)	0.38	67 (20.4)	62 (16.8)	−0.09
>7% and ≤8%	382 (33.0)	218 (19.4)	−0.31	82 (24.9)	136 (36.9)	0.26
>8% and ≤9%	204 (17.6)	96 (8.6)	−0.27	76 (23.1)	97 (26.3)	0.07
>9%	131 (11.3)	54 (4.8)	−0.24	98 (29.8)	71 (19.2)	−0.25
Missing	28 (2.4)	144 (12.8)	0.40	6 (1.8)	3 (0.8)	−0.09
Diabetes Severity Complication Index						
Mean ± SD	3.6 ± 2.1	3.8 ± 2.0	0.10	4.1 ± 2.2	3.5 ± 2.3	−0.27
Key diagnosis for scoring at the index date, *n* (%)						
Retinopathy	231 (20.0)	226 (20.1)	0	82 (24.9)	82 (22.2)	−0.06
Nephropathy	390 (33.7)	518 (46.2)	0.26	130 (39.5)	106 (28.7)	−0.23

TABLE 2 (Continued)

	SGLT-2i			GLP-1RA		
	Period I ($N = 1157$)	Period II ($N = 1122$)	SMD in SGLT-2i[a]	Period I ($N = 329$)	Period II ($N = 369$)	SMD in GLP-1RA[a]
Neuropathy	295 (25.5)	281 (25.0)	−0.01	113 (34.3)	99 (26.8)	−0.16
Cerebrovascular	484 (41.8)	444 (39.6)	−0.04	171 (52.0)	137 (37.1)	−0.30
Cardiovascular	947 (81.8)	935 (83.3)	0.04	276 (83.9)	290 (78.6)	−0.14
Peripheral vascular disease	170 (14.7)	157 (14.0)	−0.02	57 (17.3)	58 (15.7)	−0.04
Metabolic complications	20 (1.7)	18 (1.6)	−0.01	7 (2.1)	16 (4.3)	0.13
CKD stage[f], *n* (%)						
Stage 1	48 (4.1)	12 (1.1)	−0.19	21 (6.4)	12 (3.3)	−0.14
Stage 2	454 (39.2)	262 (23.4)	−0.35	110 (33.4)	137 (37.1)	0.08
Stage 3	569 (49.2)	669 (59.6)	0.21	155 (47.1)	187 (50.7)	0.07
Stage 3a	374 (32.3)	388 (34.6)	0.05	83 (25.2)	102 (27.6)	0.05
Stage 3b	192 (16.6)	279 (24.9)	0.21	71 (21.6)	85 (23.0)	0.03
Stage 3 not specified	3 (0.3)	2 (0.2)	−0.02	1 (0.3)	0 (0)	−0.08
Stage 4	78 (6.7)	172 (15.3)	0.28	38 (11.6)	25 (6.8)	−0.17
Stage 5	5 (0.4)	3 (0.3)	−0.02	5 (1.5)	4 (1.1)	−0.04
Not assessed in the 1 year before the index date	3 (0.3)	4 (0.4)	0.02	0 (0)	4 (1.1)	0.15
UACR, *n* (%)						
A1: <30 mg/g	180 (15.6)	87 (7.8)	−0.24	78 (23.7)	98 (26.6)	0.07
A2: 30–300 mg/g	215 (18.6)	103 (9.2)	−0.27	78 (23.7)	80 (21.7)	−0.05
A3: >300 mg/g	121 (10.5)	51 (4.5)	−0.23	48 (14.6)	34 (9.2)	−0.17
Not assessed in the 1 year before the index date	641 (55.4)	881 (78.5)	0.51	125 (38.0)	157 (42.5)	0.09
Clinical conditions associated with CKD, *n* (%)						
Hypertension	957 (82.7)	993 (88.5)	0.17	293 (89.1)	325 (88.1)	−0.03
Glomerulonephritis	233 (20.1)	350 (31.2)	0.26	67 (20.4)	55 (14.9)	−0.14
Renovascular disease	36 (3.1)	56 (5.0)	0.10	9 (2.7)	7 (1.9)	−0.05
Autoimmune disease	327 (28.3)	460 (41.0)	0.27	99 (30.1)	104 (28.2)	−0.04
Polycystic kidney disease	1 (0.1)	6 (0.5)	0.07	0 (0)	0 (0)	0
Comorbidities, *n* (%)						
Hypercholesterolaemia	887 (76.7)	813 (72.5)	−0.09	278 (84.5)	299 (81.0)	−0.28
Congestive heart failure	717 (62.0)	781 (69.6)	0.20	194 (59.0)	212 (57.5)	0.26
Coronary heart disease	677 (58.5)	679 (60.5)	0.04	197 (59.9)	216 (58.5)	0.01
Cerebrovascular disease	484 (41.8)	444 (39.6)	0.12	171 (52.0)	137 (37.1)	−0.09
Gout or hyperuricaemia	381 (32.9)	474 (42.2)	0.19	117 (35.6)	128 (34.7)	−0.02
Peripheral vascular disease	199 (17.2)	156 (13.9)	−0.13	72 (21.9)	57 (15.4)	−0.25
Obesity	97 (8.4)	40 (3.6)	−0.20	51 (15.5)	38 (10.3)	−0.16
Hyperkalaemia	73 (6.3)	91 (8.1)	0.07	44 (13.4)	26 (7.0)	−0.21
Alcohol abuse	35 (3.0)	25 (2.2)	−0.05	10 (3.0)	12 (3.3)	0.02
Comedications, *n* (%)						
ACEi	135 (11.7)	149 (13.3)	0.05	21 (6.4)	23 (6.2)	−0.01
ARB	615 (53.2)	635 (56.6)	0.07	181 (55.0)	212 (57.5)	0.05
ARNI	8 (0.7)	92 (8.2)	0.37	0 (0)	15 (4.1)	0.29
Direct renin inhibitors	2 (0.2)	7 (0.6)	0.06	1 (0.3)	0 (0)	−0.08
Calcium channel blockers	471 (40.7)	449 (40.0)	−0.01	176 (53.5)	170 (46.1)	−0.15
Beta-blockers	309 (26.7)	405 (36.1)	0.20	83 (25.2)	87 (23.6)	−0.04

(Continues)

TABLE 2 (Continued)

	SGLT-2i			GLP-1RA		
	Period I ($N = 1157$)	Period II ($N = 1122$)	SMD in SGLT-2i[a]	Period I ($N = 329$)	Period II ($N = 369$)	SMD in GLP-1RA[a]
Loop diuretics	159 (13.7)	235 (20.9)	0.19	52 (15.8)	43 (11.7)	−0.12
Thiazide diuretics	74 (6.4)	68 (6.1)	−0.01	28 (8.5)	23 (6.2)	−0.09
Other antihypertensives	51 (4.4)	33 (2.9)	−0.08	33 (10.0)	19 (5.1)	−0.19
Statins	504 (43.6)	441 (39.3)	−0.09	160 (48.6)	197 (53.4)	0.10
Lipid-lowering agents other than statins	187 (16.2)	157 (14.0)	−0.06	67 (20.4)	67 (18.2)	−0.06
Anticoagulants	207 (17.9)	247 (22.0)	0.10	34 (10.3)	44 (11.9)	0.05
Antiplatelets (including aspirin)	318 (27.5)	264 (23.5)	−0.09	110 (33.4)	81 (22.0)	−0.26
Nitrates and other vasodilators	77 (6.7)	95 (8.5)	0.07	28 (8.5)	18 (4.9)	−0.14
Digoxin	14 (1.2)	9 (0.8)	−0.04	1 (0.3)	3 (0.8)	0.07

[a]Standard mean differences between Periods I and II.
[b]Period I started from 1 January 2014, to 30 June 2021, while Period II started from 1 July 2021, to 31 December 2022.
[c]Assessed based on the prescription record during the 90 days prior to and 90 days post index date.
[d]Ever prescribed from 180 days before and on the index date.
[e]Does not count the index medication class (SGLT-2i or GLP-1RA) and insulin.
[f]Based on the International Classification of Disease 10th revision codes and estimated glomerular filtration rate, in accordance with the KDIGO definition.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin-receptor blocker neprilysin inhibitor; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, haemoglobin A1c; HIV, human immunodeficiency virus; NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SMD, standard mean difference; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

empagliflozin (30.8%), dapagliflozin (19.2%) and luseogliflozin (15.6%) were the three most prescribed medications in Period I, while dapagliflozin (52.9%), empagliflozin (28.6%) and canagliflozin (6.3%) were the three most prescribed medications in Period II. In the GLP-1RA cohorts, most individuals were prescribed liraglutide (60.2%) or dulaglutide (33.4%) in Period I, while semaglutide was the most prescribed medication (66.4%), followed by dulaglutide (18.2%) and liraglutide (15.2%) in Period II.

Table 2 shows the baseline characteristics of the medication-initiator cohorts of SGLT-2i new users and GLP-1RA new users in each study period. The mean (SD) ages were similar across the medication-initiator cohorts, ranging from 66.1 (13.6) years in the GLP-1RA cohort in Period I to 69.5 (12.9) years in the SGLT-2i cohort in Period II. The proportion of males ranged from approximately 60%–72% across the medication-initiator cohorts and was slightly higher in Period II compared to Period I. Comorbidity patterns were similar across the medication-initiator cohorts in each study period. Hypertension was the most frequently observed comorbidity in approximately 83%–89% of individuals in each cohort. Hypercholesterolaemia was observed in approximately 73%–85% of individuals, 60%–70% had congestive heart failure and approximately 60% had coronary heart disease. Likewise, the patterns of comedications were similar across the medication-initiator cohorts in each study period. The proportions of individuals receiving prescriptions for ARBs and ACEis ranged from 53%–58% to 6%–13% across cohorts, respectively, and Approximately 40%–53% and 22%–33% of individuals received prescriptions for statins and antiplatelets (including aspirin), respectively.

In the SGLT-2i cohorts, notable differences between Period I and Period II were observed in the percentages of individuals already treated with several medication classes for T2D, including dipeptidyl peptidase-4 inhibitors (74.3% vs. 42.2%), metformin (52.2% vs. 21.7%), sulfonylurea (29.5% vs. 13.1%) and alpha glucosidase inhibitors (25.8% vs. 13.3%) (Period I vs. Period II). Similarly, the percentages of individuals treated with multiple T2D medication classes other than insulin were lower in Period II than in Period I. In contrast, the number of persons treated with no T2D medication classes other than insulin increased from 12.5% in Period I to 49.6% in Period II. The CKD stages were largely similar between Period I and Period II, with a certain degree of increases in the numbers of individuals with Stage 3b (16.6% vs. 24.9%) and stage 4 (6.7% vs. 15.3%) (Period I vs. Period II). In the GLP-1RA cohorts, most of these characteristics were similar between Period I and Period II, except for insulin use before GLP-1RA initiation and HbA1c category. The number of individuals with prior insulin use decreased from 85.4% in Period I to 54.7% in Period II, while the number of individuals with prior use of SGLT-2is increased from 52.9% in Period I to 69.1% in Period II.

3.2 | Temporal changes in the characteristics of medication-initiator cohorts

The SMDs of variables related to the treatment of T2D and CKD between Periods I and II are shown in Table 2 and Figure 1. In the SGLT-2i cohorts, medium decreases in the numbers of individuals with prior use of metformin (SMD −0.67) and dipeptidyl peptidase-4

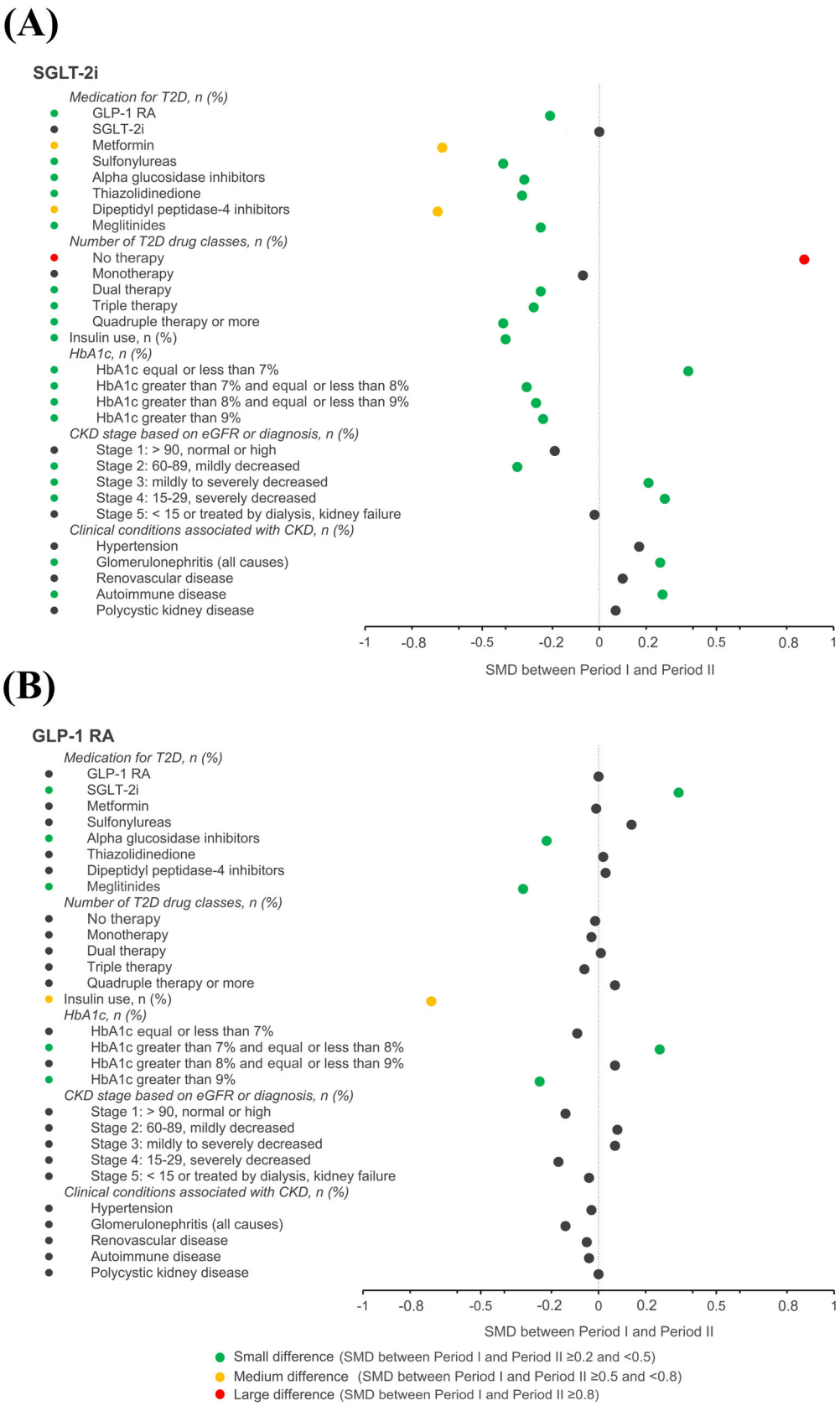

FIGURE 1 Standard mean differences of variables between Period I and Period II related to the treatment of T2D and CKD. Panel (A) shows the standard mean differences in the SGLT-2i cohort, while Panel (B) shows the standard mean differences in GLP-1RA cohorts. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, haemoglobin A1c; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SMD, standard mean difference; T2D, type 2 diabetes.

inhibitors (SMD −0.69), and a large increase in the number of persons with no T2D medications other than insulin in the 180 days before the index date (SMD 0.88) were observed. Small (SMD ≥0.2 and <0.5) differences were observed in several variables, including the numbers of individuals with prior use of other T2D medications, number of T2D drug classes, prior insulin use, HbA1c category, CKD stages and

clinical conditions associated with CKD. In the GLP-1RA cohorts, there was a medium decrease in the number of individuals with prior insulin use (SMD −0.71). There were small differences in the number of individuals with prior SGLT-2i use, prior alpha glucosidase inhibitor use and prior meglitinides use, and in some HbA1c categories.

4 | DISCUSSION

In this contemporary study, we describe the changes in the demographic and clinical profiles of the persons with CKD and T2D, who initiated SGLT-2is or GLP-1RAs therapy in two different time periods. The notable changes observed in the profiles of the medication-initiator cohorts in the two different time periods provide novel population-based insights into the evolving landscape of treatments for persons with CKD and T2D in real-world settings in Japan.

In the present study, the individuals were of similar ages across the two study periods. Cardiovascular complications such as heart failure and coronary heart disease were commonly observed in more than half of the individuals in the study populations. Likewise, the comedication patterns were similar across medication-initiator cohorts in each study period, with ARBs or ACEis prescribed in more than half, and statins prescribed in approximately 50% of the individuals in the study populations. These results are aligned with recent observational studies reporting the use of SGLT-2is or GLP-1RAs in Japan,[31–34] suggesting that the findings from this study reflect a broad range of persons with CKD and T2D initiating the new treatments in clinical practice. Notable differences were identified in the characteristics of the medication-initiator cohorts. Previous observational studies conducted in Japan in the 2010's indicated that dipeptidyl peptidase-4 inhibitors and metformin were the two most-used glucose-lowering drug classes for first-line treatment in persons with T2D.[35,36] Taken together with the large increase in the number of individuals with no T2D medications prior to SGLT-2i initiation after July 2021, the decreases in the number of individuals with prior use of dipeptidyl peptidase-4 inhibitors or metformin suggest that SGLT-2i began to be prescribed earlier in the course of T2D. Until recently, metformin was the most prescribed first-line glucose-lowering drug in several regions.[37,38] One recent study reported a marked shift towards the use of SGLT-2i in persons with T2D with high cardiovascular risk over decades.[39] Hence, the present study confirmed this trend in persons with T2D and CKD. In Japan, dapagliflozin was approved for use in persons with CKD in August 2021.[40] Of the persons initiating a SGLT2i, the percentage with dapagliflozin increased greatly (19.2%–52.9%) in Period II (after July 2021), coinciding with the approval of the indication for CKD. The small increase in the number of individuals with advanced CKD stages (Stage G3–4) and HbA1c <7% in Period II suggests that SGLT-2is were also used for the treatment of CKD. Likewise, a moderate decrease in the number of individuals with prior insulin use observed in the GLP-1RA cohort suggests its increased use prior to insulin therapy in persons with CKD and T2D. Oral semaglutide has become available in Japan from February 2021, which may also influence the use patterns of GLP-1RAs, particularly in Period II. In Period II, approximately 70% of individuals had prior use of SGLT-2is, suggesting that the concomitant use of SGLT-2i and GLP-1RA had increased. This finding was supported by the small to medium increase in the number of persons initiating GLP-1RA as add-on therapy to SGLT-2i in Period II. The enhanced efficacy in glycaemic control and renal protection by complementary mechanisms of action of SGLT-2i and GLP-1RA has been attracting attention.[41] The increased combination use of cardio-renal protective medications was also reported in a recent study reporting the characteristics of persons who initiated finerenone,[32] where 70% and 30% of the individuals were concomitantly prescribed with SGLT-2i and GLP-1RA, respectively. In the present study, GLP-1RAs were more likely to be introduced after the initiation of SGLT-2is. The sequence of introducing a combination therapy is another topic that needs to be clarified. A recent study has evaluated the effect of preceding treatment on renal outcomes in persons with T2D and CKD who received combination therapy of SGLT-2i and GLP-1RA.[42] In the study, the renal composite outcomes did not differ between the two groups, though further studies are required to elucidate the optimal sequence and timing of introduction of the combination therapy.

Organ-protective treatment has been increasingly integrated into the clinical practice guidelines and the expert consensus statements for persons with CKD and T2D.[19,43] In a joint consensus statement from the Japanese Circulation Society and the JDS for the diagnosis, prevention and treatment of cardiovascular disease in persons with T2D and prediabetes, SGLT-2i is recommended as a glucose-lowering therapy for persons with T2D at high risk of heart failure, including persons with CKD.[44] In the proposed algorithm for pharmacotherapy in persons with T2D by the JDS, cardiovascular disease, heart failure and CKD are the target diseases when considering the additional benefits of pharmacological therapies.[20] More recently, the non-steroidal mineralocorticoid receptor antagonist, finerenone, was introduced in clinical practice in June 2022 in Japan. Currently, finerenone is recommended in the guidelines, alongside ACEis or ARBs, SGLT-2is and GLP-1RA, as part of a holistic approach to reduce the risk of cardiovascular and kidney complications in persons with CKD and T2D.[45,46] The findings in our study suggest that the shift towards the early use of cardio-renal protective medications was at least partially driven by these guideline updates. Despite the availability of newer treatments, persons with CKD and T2D continue to have important residual cardiovascular and kidney risks.[47] A recent study has shown that compliance with the CKD guidelines in clinical practice had a significant association with improved renal outcomes.[48] However, it is often observed that these therapies are not fully implemented in real-world settings.[49]

The reasons behind the low implementation of the evidence-based treatment may be multifold. A previous publication summarized the barriers to adherence to the diabetes guidelines,[21] such as inadequate contextual support (e.g., limited resources) for guideline implementation, therapeutic inertia and poor communication and dissemination strategies. With the assessment of the temporal trends of the medication-initiator cohort profiles in persons with CKD and T2D, this study facilitates a further understanding of the extent to

which the evidence-based treatments are implemented, as well as the remaining gaps to be addressed in clinical practice. Given that the increased use of cardio-renal protective medications in the present study cooccurred with the guideline updates, it is possible that target educational interventions and/or policy changes might further accelerate the adoption of cardio-renal protective therapies. As part of the learning health care system,[50] this study may serve in the continuous feedback cycle of systematic data collection, the creation of real-world evidence and application in clinical practice, in an integrated effort to provide the best possible care for persons with CKD and T2D.

This study has both strengths and limitations. Its strengths included that the analyses were performed using two independently extracted datasets based on the pre-specified protocol. In both datasets, the data were collected at the same institutions, which allowed an evaluation of the temporal changes in the medication-initiator characteristics based on identical source populations. The database collects extensive clinical and demographic data. The source population of the J-CKD-DB-Ex was selected based on age and laboratory test results, which enabled a relatively more comprehensive coverage of individuals with CKD treated at the participating institutions. Several limitations should also be noted. First, the data were collected at the participating university hospitals, where most participants were assumed to have been treated by specialists. Hence, the results did not reflect individuals treated in primary care settings. Second, information regarding prescriptions occurring outside the participating institutions could not be collected. Therefore, there may have been an under-capture of medications if medications were dispensed before entry into a cohort or at a hospital outside the registry. Missing data were not imputed, which could introduce bias. While we selected persons with T2D based on diagnostic codes in combination with exclusion criteria of confirmed diagnosis of type 1 diabetes, other types of diabetes were potentially included in the study population. Third, the datasets did not contain information regarding the condition(s)/indication(s) of the initiated treatment. Therefore, it was not possible to distinguish whether the use of SGLT-2i was for glycaemic control or the treatment of CKD. Likewise, the lack of the GLP-1RA indication information may preclude a more specific and comprehensive comparison of the use of GLP-1RAs between the 2 periods.

5 | CONCLUSION

In this contemporary study, we described the changes in the profiles of persons with CKD and T2D, who initiated SGLT-2is or GLP-1RAs therapy in two different time periods. With the introduction of new treatments and emerging evidence supporting cardio-renal protective effects in persons with CKD and T2D, notable changes in baseline treatment were observed in the medication-initiator cohort characteristics, which suggest the earlier use of cardio-renal protective medications in the course of T2D in the latter time period. These findings should serve as a guiding resource to facilitate the implementation of evidence-based treatment in clinical practice, in thorough efforts to provide the best possible care for persons with CKD and T2D.

AUTHOR CONTRIBUTIONS

Nikolaus G. Oberprieler, **Catherine Johannes** and **David Vizcaya:** Conceptualization; interpretation; writing–review and editing. **Suguru Okami:** Conceptualization; interpretation; writing—original draft; writing—review and editing. **Yuichiro Yano**, **Hiroshi Kanegae** and **Naoki Kashihara:** Conceptualization; data curation; formal analysis; interpretation; writing—review and editing. All authors provided intellectual content of critical importance to the work described and final responsibility in deciding to submit this manuscript for publication.

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CONFLICT OF INTEREST STATEMENT

S.O., N.G.O., K.Y.-R. and S.Y. are employees of Bayer. D.V. was an employee of Bayer when this research was conducted and is now an employee of Alexion Pharma S.L., Barcelona, Spain. Y.Y. reports consultancy for Bayer. H.K. reports no competing interests in conducting this study. C.J. is an employee of RTI Health Solutions, which received research funding for this study from Bayer. C.P.K. received consulting fees from Abbott, Akebia, AstraZeneca, Bayer, Boehringer Ingelheim, Cara Therapeutics, CSL Behring, CSL Vifor, GSK, Pharmacosmos, ProKidney, Renibus and Takeda. N.K. reports research grants from Daiichi Sankyo, AstraZeneca and Bayer.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

All necessary data required to interpret and conclude the findings of this study were included in the main text and Supplementary materials.

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SUPPORTING INFORMATION

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

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