*Supplementary Material*

# Kidney outcomes of SGLT2 inhibitors among older patients with diabetic kidney disease in real-world clinical practice: the Japan Chronic Kidney Disease Database Ex

Brief title: Kidney outcomes associated with SGLT2 inhibitors in the older

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**Table S1. Variables included in propensity score matching**

| |
|---|
| Age, years |
| Women, % |
| Hemoglobin A1c, % |
| eGFR, mL/min/1.73m$^2$ |
| Rate of eGFR change prior to index, ml/min/1.73m$^2$/year |
| Proteinuria, % |
| Glucose-lowering medications:<br>DPP-4 inhibitors, %<br>Biguanide, %<br>α-glucosidase inhibitors, %<br>Glinides, %<br>Sulfonylureas, %<br>Insulin, %<br>GLP-1 analogs, %<br>Thiazolidinedione, % |
| Blood pressure-lowering medications, %<br>ACE inhibitors, %<br>ARBs, %<br>Calcium channel blockers, %<br>Diuretics, %<br>β blockers, %<br>α blockers, % |
| Statins, % |
| Length of follow-up, months |

**Table S2. Clinical characteristics at index date prior to propensity score**

| Characteristics | SGLT-2 inhibitor group (n=368) | Other glucose-lowering drugs group (n=899) | Standardized mean difference (%) |
|---|---|---|---|
| Age, years, mean ± SD | 77.6±4.3 | 78.7±4.8 | 24.3 |
| Women, n (%) | 143 (38.9) | 388 (43.2) | 8.8 |
| Hemoglobin A1c, %, mean ± SD | 7.7±1.0 | 7.4±1.2 | 29.6 |
| Hemoglobin A1c, mmol/mol, mean ± SD | 60.8±11.4 | 57.1±13.5 | |
| eGFR, mL/min/1.73m$^2$, mean ± SD | 59.4±13.8 | 57.8±16.3 | 10.9 |
| eGFR ≥ 60, n (%) | 207 (56.3) | 496 (55.2) | |
| eGFR < 60, n (%) | 161 (43.8) | 403 (44.8) | |
| Rate of eGFR change prior to index, ml/min/1.73m$^2$/year, mean ± SD | -1.6±3.6 | -2.0±7.8 | 6.3 |
| Proteinuria, n (%) | 119 (32.3) | 262 (29.1) | 6.9 |
| Glucose-lowering medications: | | | |
| Canagliflozin, n (%) | 65 (17.7) | 0 | − |
| Dapagliflozin, n (%) | 56 (15.2) | 0 | − |
| Empagliflozin, n (%) | 107 (29.1) | 0 | − |
| Ipragliflozin, n (%) | 54 (14.7) | 0 | − |
| Luseogliflozin, n (%) | 57 (15.5) | 0 | − |
| Tofogliflozin, n (%) | 29 (7.9) | 0 | − |
| DPP-4 inhibitor, n (%) | 262 (71.2) | 750 (83.4) | 29.5 |
| Biguanide, n (%) | 134 (36.4) | 261 (29.0) | 15.8 |
| α-glucosidase inhibitors, n (%) | 63 (17.1) | 295 (32.8) | 36.9 |
| Glinides, n (%) | 34 (9.2) | 168 (18.7) | 27.5 |
| Sulfonylureas, n (%) | 99 (26.9) | 286 (31.8) | 10.8 |
| Insulin, n (%) | 0 (0.0) | 28 (3.1) | 25.4 |
| GLP-1 analogs, n (%) | 0 (0.0) | 1 (0.1) | 4.7 |
| Thiazolidinedione, n (%) | 58 (15.8) | 109 (12.1) | 10.5 |
| Blood pressure-lowering medications, n (%) | 279 (75.8) | 602 (67.0) | 19.7 |
| ACE inhibitor, n (%) | 31 (8.4) | 39 (4.3) | 16.8 |
| ARBs, n (%) | 205 (55.7) | 421 (46.8) | 17.8 |
| Calcium channel blocker, n (%) | 185 (50.3) | 414 (46.1) | 8.5 |
| Diuretics, n (%) | 49 (13.3) | 76 (8.5) | 15.7 |
| β blocker, n (%) | 83 (22.6) | 121 (13.5) | 23.8 |
| α blocker, n (%) | 10 (2.7) | 34 (3.8) | 6.0 |
| Statins, n (%) | 11 (3.0) | 17 (1.9) | 7.1 |

*Standardized difference >10% is considered a non-negligible difference. Diuretics include thiazide diuretics and aldosterone antagonists. SD=standard deviations; ACE=angiotensin converting enzyme; ARB=angiotensin Ⅱ receptor blockers; DPP-4=Dipeptidyl peptidase-4 inhibitors; GLP-1=Glucagon-like peptide-1.

**Table S3. The trajectories for eGFR measurements at each month before and after initiation of index date**

| Month | SGLT-2 inhibitor group | | | Other glucose-lowering drugs group | | |
|---|---|---|---|---|---|---|
| | n | Lsmeans±SE | (Lower, Upper) | n | Lsmeans±SE | (Lower, Upper) |
| -12 | 153 | 61.5±1.0 | (59.6, 63.4) | 111 | 60.7±1.1 | (58.6, 62.9) |
| -11 | 135 | 61.8±1.0 | (59.9, 63.7) | 110 | 60.3±1.1 | (58.1, 62.5) |
| -10 | 147 | 61.9±1.0 | (60.0, 63.8) | 110 | 61.1±1.1 | (58.9, 63.3) |
| -9 | 147 | 61.9±1.0 | (60.0, 63.8) | 116 | 60.5±1.1 | (58.3, 62.7) |
| -8 | 147 | 61.5±1.0 | (59.6, 63.4) | 122 | 61.0±1.1 | (58.8, 63.1) |
| -7 | 139 | 61.2±1.0 | (59.3, 63.1) | 97 | 60.4±1.1 | (58.2, 62.6) |
| -6 | 155 | 60.7±1.0 | (58.8, 62.6) | 139 | 60.4±1.1 | (58.2, 62.5) |
| -5 | 130 | 61.0±1.0 | (59.1, 63.0) | 93 | 60.7±1.1 | (58.5, 63.0) |
| -4 | 149 | 60.0±1.0 | (58.1, 61.9) | 126 | 59.6±1.1 | (57.5, 61.8) |
| -3 | 130 | 60.9±1.0 | (58.9, 62.8) | 114 | 59.7±1.1 | (57.6, 61.9) |
| -2 | 176 | 60.8±1.0 | (58.9, 62.7) | 141 | 59.2±1.1 | (57.0, 61.3) |
| -1 | 106 | 60.3±1.0 | (58.4, 62.3) | 83 | 58.6±1.2 | (56.4, 60.9) |
| 0 | 236 | 60.3±0.9 | (58.4, 62.1) | 183 | 59.4±1.1 | (57.3, 61.5) |
| 1 | 129 | 56.8±1.0 | (54.8, 58.7) | 104 | 59.5±1.1 | (57.3, 61.7) |
| 2 | 174 | 57.6±1.0 | (55.7, 59.5) | 146 | 58.7±1.1 | (56.6, 60.8) |
| 3 | 145 | 57.9±1.0 | (56.0, 59.9) | 105 | 58.8±1.1 | (56.6, 60.9) |
| 4 | 147 | 56.7±1.0 | (54.7, 58.6) | 136 | 57.9±1.1 | (55.8, 60.1) |
| 5 | 128 | 57.7±1.0 | (55.8, 59.7) | 90 | 58.6±1.1 | (56.4, 60.9) |
| 6 | 164 | 58.0±1.0 | (56.1, 59.9) | 136 | 57.5±1.1 | (55.4, 59.6) |
| 7 | 132 | 58.3±1.0 | (56.4, 60.3) | 104 | 56.6±1.1 | (54.4, 58.8) |
| 8 | 148 | 57.7±1.0 | (55.8, 59.6) | 118 | 56.8±1.1 | (54.6, 59.0) |
| 9 | 131 | 58.0±1.0 | (56.0, 59.9) | 97 | 56.7±1.1 | (54.4, 58.9) |
| 10 | 120 | 57.4±1.0 | (55.4, 59.4) | 109 | 56.7±1.1 | (54.5, 58.9) |
| 11 | 113 | 58.1±1.0 | (56.1, 60.1) | 87 | 55.8±1.1 | (53.6, 58.1) |
| 12 | 125 | 57.0±1.0 | (55.0, 58.9) | 96 | 56.5±1.1 | (54.3, 58.7) |
| 13 | 95 | 58.3±1.0 | (56.3, 60.4) | 66 | 56.7±1.2 | (54.4, 59.0) |
| 14 | 105 | 57.6±1.0 | (55.6, 59.6) | 89 | 56.8±1.1 | (54.6, 59.1) |
| 15 | 91 | 56.7±1.0 | (54.6, 58.7) | 59 | 56.7±1.2 | (54.3, 59.1) |
| 16 | 104 | 56.6±1.0 | (54.6, 58.6) | 67 | 56.3±1.2 | (53.9, 58.6) |
| 17 | 81 | 57.0±1.1 | (55.0, 59.1) | 66 | 55.4±1.2 | (53.1, 57.8) |
| 18 | 96 | 56.3±1.0 | (54.2, 58.3) | 63 | 55.5±1.2 | (53.1, 57.8) |

SE=standard error;

**Figure S1**

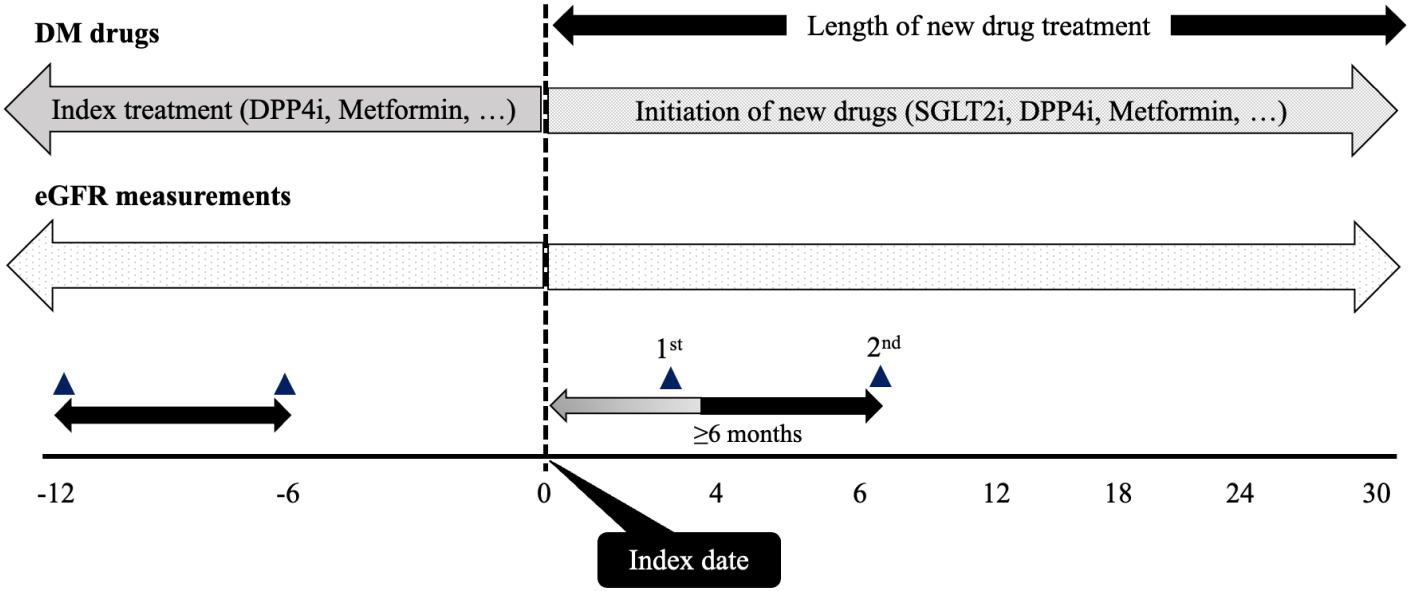

DM drugs
Length of new drug treatment
Index treatment (DPP4i, Metformin, …)
Initiation of new drugs (SGLT2i, DPP4i, Metformin, …)
eGFR measurements
1st
2nd
≥6 months
-12
-6
0
4
6
12
18
24
30
Index date

**Figure S2**

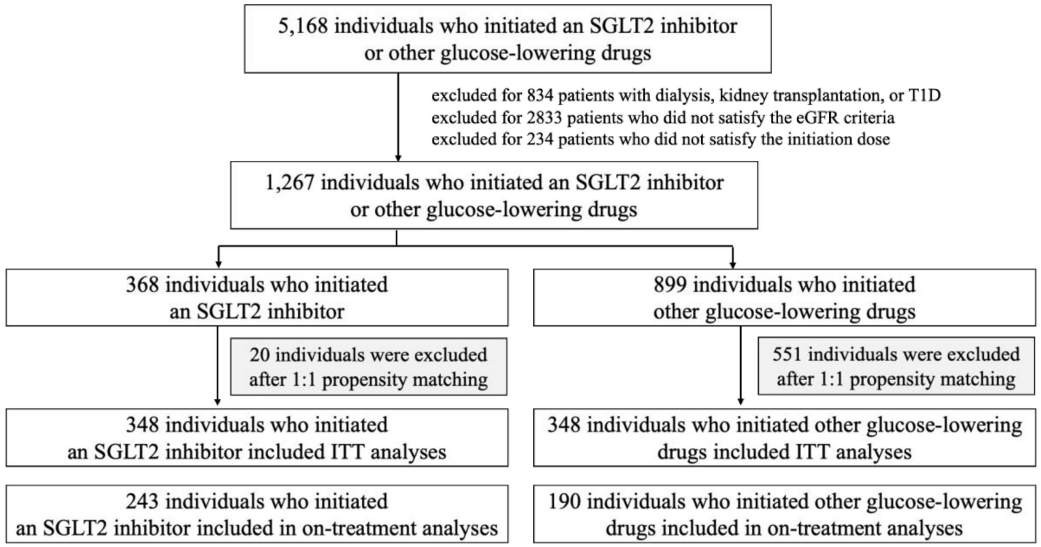
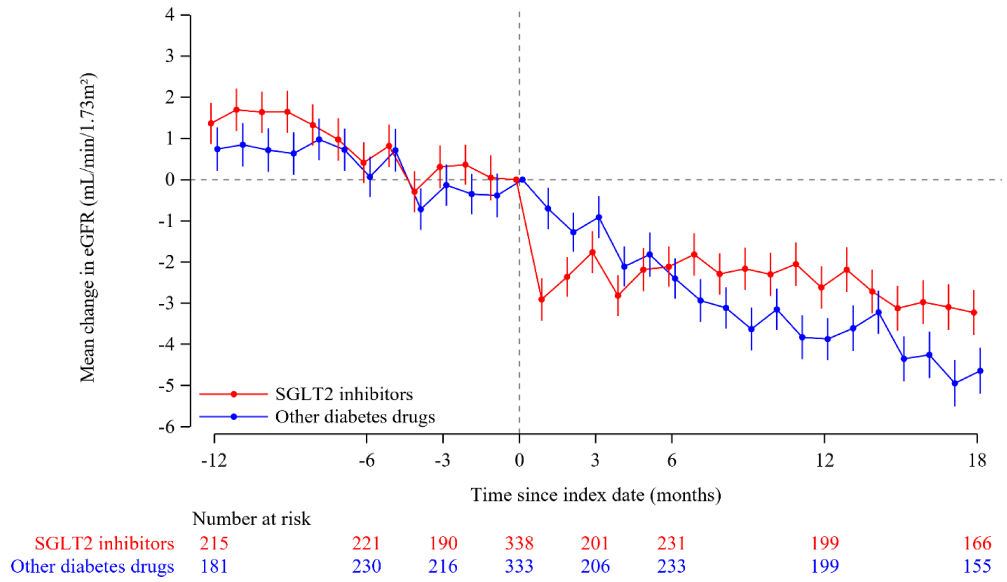

5,168 individuals who initiated an SGLT2 inhibitor or other glucose-lowering drugs
excluded for 834 patients with dialysis, kidney transplantation, or T1D
excluded for 2833 patients who did not satisfy the eGFR criteria
excluded for 234 patients who did not satisfy the initiation dose
1,267 individuals who initiated an SGLT2 inhibitor or other glucose-lowering drugs
368 individuals who initiated an SGLT2 inhibitor
899 individuals who initiated other glucose-lowering drugs
20 individuals were excluded after 1:1 propensity matching
551 individuals were excluded after 1:1 propensity matching
348 individuals who initiated an SGLT2 inhibitor included ITT analyses
348 individuals who initiated other glucose-lowering drugs included ITT analyses
243 individuals who initiated an SGLT2 inhibitor included in on-treatment analyses
190 individuals who initiated other glucose-lowering drugs included in on-treatment analyses

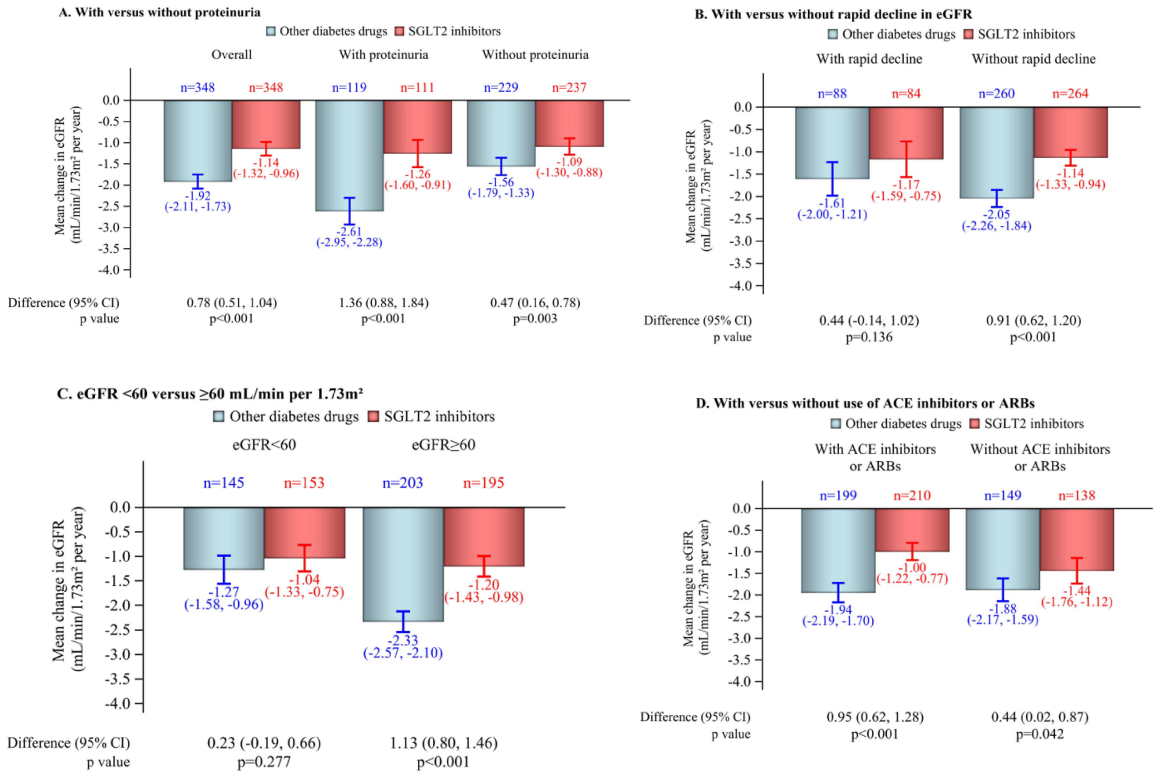
**Figure S3**




Number at risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| SGLT2 inhibitors | 215 | 221 | 190 | 338 | 201 | 231 | 199 | 166 |
| Other diabetes drugs | 181 | 230 | 216 | 333 | 206 | 233 | 199 | 155 |

## Figure S4


A. With versus without proteinuria
Other diabetes drugs
SGLT2 inhibitors
Overall
With proteinuria
Without proteinuria
n=348
n=348
n=119
n=111
n=229
n=237
Mean change in eGFR (mL/min/1.73m² per year)
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
-1.92 (-2.11, -1.73)
-1.14 (-1.32, -0.96)
-2.61 (-2.95, -2.28)
-1.26 (-1.60, -0.91)
-1.56 (-1.79, -1.33)
-1.09 (-1.30, -0.88)
Difference (95% CI)
p value
0.78 (0.51, 1.04)
p<0.001
1.36 (0.88, 1.84)
p<0.001
0.47 (0.16, 0.78)
p=0.003
B. With versus without rapid decline in eGFR
Other diabetes drugs
SGLT2 inhibitors
With rapid decline
Without rapid decline
n=88
n=84
n=260
n=264
Mean change in eGFR (mL/min/1.73m² per year)
-1.61 (-2.00, -1.21)
-1.17 (-1.59, -0.75)
-2.05 (-2.26, -1.84)
-1.14 (-1.33, -0.94)
Difference (95% CI)
p value
0.44 (-0.14, 1.02)
p=0.136
0.91 (0.62, 1.20)
p<0.001
C. eGFR <60 versus ≥60 mL/min per 1.73m²
Other diabetes drugs
SGLT2 inhibitors
eGFR<60
eGFR≥60
n=145
n=153
n=203
n=195
Mean change in eGFR (mL/min/1.73m² per year)
-1.27 (-1.58, -0.96)
-1.04 (-1.33, -0.75)
-2.33 (-2.57, -2.10)
-1.20 (-1.43, -0.98)
Difference (95% CI)
p value
0.23 (-0.19, 0.66)
p=0.277
1.13 (0.80, 1.46)
p<0.001
D. With versus without use of ACE inhibitors or ARBs
Other diabetes drugs
SGLT2 inhibitors
With ACE inhibitors or ARBs
Without ACE inhibitors or ARBs
n=199
n=210
n=149
n=138
Mean change in eGFR (mL/min/1.73m² per year)
-1.94 (-2.19, -1.70)
-1.00 (-1.22, -0.77)
-1.88 (-2.17, -1.59)
-1.44 (-1.76, -1.12)
Difference (95% CI)
p value
0.95 (0.62, 1.28)
p<0.001
0.44 (0.02, 0.87)
p=0.042

## Figure legends

**Figure S1: Study design parameters and observational timeframe**

Patients with DKD who were ≥75 years old and had ≥180 days of continuous enrollment history in the database before the initiation of SGLT2 inhibitors or other glucose-lowering drugs were included in the current study. Patients who initiated SGLT2 inhibitors or other glucose-lowering drugs with eGFR measurements at the time of SGLT2 inhibitors or other glucose-lowering drugs initiation were included. The index date was set as the date of the hospital visit when a prescription was made or filled, as either an initial or add-on therapy, for any SGLT2 inhibitors (dapagliflozin, empagliflozin, canagliflozin, ipragliflozin, luseogliflozin, and tofogliflozin) or other glucose-lowering drugs (DPP-4 inhibitors, biguanide, aGI, glinides, SU, TZD, insulin and GLP-1 analogs), including fixed-dose combinations but excepting SGLT2 inhibitor combinations, with no prior prescriptions issued for the medicine class during the lookback period (≥180 days). To estimate eGFR changes reliably before the initiation of treatment, we also required at least one eGFR measurement from the period of 181 to 365 days prior to the index date. We collected baseline data from 180 days before the index date until the index date. At least one eGFR measurement within the first 120 days after the index date was also required. Furthermore, our selection criteria included at least one subsequent eGFR measurement taken more than 180 days after the first post-index date eGFR measurement. Patients were followed up from the initiation of SGLT2 inhibitors or other glucose-lowering drugs until the time of death, emigration, departure from the database, or the last date of data collection, whichever came first. All eGFR measurements obtained during the follow-up period were used to assess eGFR slope and clinical events.

DKD=diabetic kidney diseases; eGFR=estimated glomerular filtration rate; SGLT2=sodium-glucose co-transporter-2; DPP-4=dipeptidyl peptidase-4; GI=glucosidase inhibitors; SU=sulfonylureas; TZD=thiazolidine; GLP-1=Glucagon-like peptide-1.

**Figure S2: Sampling frame for the analyses, J-CKD-DB Extension**

Based on the inclusion criteria in the current study, we selected records of DKD patients aged ≥ 75 years who had at least two eGFR measurements before the index date, with at least one eGFR measurement within 180 days of the index date. We additionally specified that the time between the first and last eGFR measurements before the index date must be at least 180 days to reliably estimate eGFR change before the index date. The on-treatment follow-up timeframe was defined as the time from the index date to

the: 1) end of index treatment; 2) initiation of another new glucose-lowering drug or SGLT2 inhibitor; 3) patient's departure from the practice or database; or 4) date of last data collection, whichever occurred first. The ITT follow-up time was defined as the time from the index date to either the patient's departure from the practice or database, date of last data collection, or death, whichever occurred first.

DKD=diabetic kidney diseases; eGFR=estimated glomerular filtration rate; ITT=intention-to-treat.

**Figure S3: Change in eGFR over time before and after initiation of SGLT2 inhibitors or other diabetes drugs (ITT analyses)**

Error bars show mean ± standard errors. Numbers below the graph refer to the number of patients at each timepoint. Analyses for eGFR slope were conducted from the index date and thereafter, and repeated across multiple timepoints, including pre-index (Period 0), from the index date to Week 4 (Period 1), from Week 4 to Week 24 (Period 2), and from Week 25 and thereafter (Period 3). P values were calculated using a linear mixed regression model.

eGFR=estimated glomerular filtration rate; SGLT2=sodium-glucose co-transporter-2; ITT=intention-to-treat.

**Figure S4: Annual rate of eGFR change in various subgroups (ITT analyses)**

(A) With versus without proteinuria at the index date, (B) with versus without rapid decline in eGFR before initiating treatments, (C) eGFR < 60 versus ≥ 60 mL/min/1.73 m² at the index date, and (D) with versus without use of ACE inhibitors or ARBs at the index date. Change in eGFR was calculated from the post-index eGFR measurements using a linear mixed regression model.

eGFR=estimated glomerular filtration rate; ACE=angiotensin converting enzyme; ARB=angiotensin II receptor blocker; ITT=intention-to-treat.