Supplementary Material

Kidney outcomes associated with SGLT2 inhibitors versus other glucose-lowering drugs in real-world clinical practice: The Japan Chronic Kidney Disease Database

Brief title: SGLT2 inhibitors and kidney

Hajime Nagasu;[1] Yuichiro Yano;[2,3] Hiroshi Kanegae;[4] Hiddo J.L. Heerspink[5]
Masaomi Nangaku;[6] Yosuke Hirakawa;[6] Yuka Sugawara;[6]
Naoki Nakagawa;[7] Yuji Tani,[8] Jun Wada;[9] Hitoshi Sugiyama;[10] Kazuhiko Tsuruya;[11]
Toshiaki Nakano; [12] Shoichi Maruyama;[13] Takashi Wada;[14] Kunihiro Yamagata;[15]
Ichiei Narita;[16] Kouichi Tamura;[17] Motoko Yanagita;[18] Yoshio Terada;[19]
Takashi Shigematsu;[20] Tadashi Sofue;[21] Takafumi Ito;[22] Hirokazu Okada;[23]
Naoki Nakashima;[24] Hiromi Kataoka;[25] Kazuhiko Ohe;[26] Mihoko Okada;[27]
Seiji Itano;[1] Akira Nishiyama;[28] Eiichiro Kanda;[29]
Kohjiro Ueki;[30] and Naoki Kashihara[1]

1. Department of Nephrology and Hypertension, Kawasaki Medical School, Kurashiki, Okayama, Japan
2. Center for Novel and Exploratory Clinical Trials, Yokohama City University, Kanagawa, Japan
3. Department of Family Medicine and Community Health, Duke University, Durham, NC, USA
4. Genki Plaza Medical Center for Health Care, Tokyo, Japan
5. The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia
6. Division of Nephrology and Endocrinology, University of Tokyo Graduate School of Medicine, Tokyo, Japan
7. Division of Cardiology, Nephrology, Pulmonology and Neurology, Department of Internal Medicine, Asahikawa Medical University, Hokkaido, Japan
8. Department of Medical Informatics and Hospital Management, Asahikawa Medical University, Hokkaido, Japan
9. Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.

10. Department of Human Resource Development of Dialysis Therapy for Kidney Disease, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan
11. Department of Nephrology, Nara Medical University, Nara, Japan
12. Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
13. Department of Nephrology, Nagoya University Graduate School of Medicine, Aichi, Japan
14. Department of Nephrology and Laboratory Medicine, Kanazawa University, Kanazawa, Japan
15. Department of Nephrology, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan
16. Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan
17. Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine, Kanagawa, Japan
18. Department of Nephrology, Graduate School of Medicine, Kyoto University, Kyoto, Japan.
19. Department of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi University, Kochi, Japan.
20. Division of Nephrology, Rinku General Medical Center, Oosaka, Japan
21. Division of Nephrology and Dialysis, Department of Cardiorenal and Cerebrovascular Medicine, Kagawa University, Kagawa, Japan.
22. Division of Nephrology, Faculty of Medicine, Shimane University, Shimane, Japan.
23. Department of Nephrology, Faculty of Medicine, Saitama Medical University, Saitama, Japan.
24. Medical Information Center, Kyushu University Hospital, Fukuoka, Japan
25. Faculty of Health Science and Technology, Kawasaki University of Medical Welfare, Okayama, Japan
26. Department of Healthcare Information Management, The University of Tokyo Hospital, Tokyo, Japan
27. Institute of Health Data Infrastructure for All, Tokyo, Japan.
28. Department of Pharmacology, Faculty of Medicine, Kagawa University, Kagawa, Japan
29. Department of Medical Science, Kawasaki Medical School, Kurashiki, Okayama, Japan.

30. Diabetes Research Center, National Center for Global Health and Medicine, Tokyo, Japan.

Corresponding author:
Yuichiro Yano, MD, PhD
Associate Professor
Yokohama City University
Center for Novel and Exploratory Clinical Trials, Kanagawa, Japan.

Adjunct Associate Professor
Duke University
Department of Community and Family Medicine, Durham, NC, USA

1-1-1, Fukuura, Kanazawa-ku, Yokohama, Kanagawa, Japan, 236-0004
Tell: +81-045-370-7949
yyano@jichi.jp OR yuichiro.yano@duke.edu

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: Metformin, % DPP-4 inhibitors, % Sulfonylureas, % Insulin, % GLP-1 receptor agonists, % Thiazolidinedione, % Others, %
Blood pressure-lowering medications, % ACE inhibitors, % ARBs, % Calcium channel blockers, % Diuretics, % β blockers, % 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=1,246)	Other glucose-lowering drugs group (n=2,492)	Standard-ized mean difference (%)
Age, years, mean ± SD	62.1±12.4	69.8±11.3	65.1
Women, n (%)	466 (37.4)	892 (35.8)	3.3
Hemoglobin A1c, %, mean (SD)	8.0±1.3	7.4±1.3	40.8
Hemoglobin A1c, mmol/mol, mean (SD)	63.5±14.7	57.6±13.9	40.8
eGFR, mL/min/1.73m^2, mean (SD)	70.4±18.0	61.3±19.7	48.1
eGFR ≥ 60, n (%)	940 (75.4)	1520 (61.0)	31.4
eGFR < 60, n (%)	306 (24.6)	972 (39.0)	31.4
Rate of eGFR change prior to index, ml/min/1.73m^2/year, mean (SD)	−1.2±5.1	−1.5±8.2	4.0
Proteinuria, n (%)	371 (29.8)	675 (27.1)	6.0
Glucose-lowering medications:			
Canagliflozin, n (%)	154 (12.4)	0	−
Dapagliflozin, n (%)	239 (19.2)	0	−
Empagliflozin, n (%)	249 (20.0)	0	−
Ipragliflozin, n (%)	258 (20.7)	0	−
Luseogliflozin, n (%)	218 (17.5)	0	−
Tofogliflozin, n (%)	128 (10.3)	0	−
Metformin, n (%)	706 (56.7)	983 (39.4)	35.0
DPP-4 inhibitor, n (%)	768 (61.6)	2053 (82.4)	47.5
Sulfonylurea, n (%)	271 (21.7)	697 (28.0)	14.4
Insulin, n (%)	226 (18.1)	803 (32.2)	32.9
GLP-1 receptor agonist, n (%)	19 (1.5)	21 (0.8)	6.3
Thiazolidinedione, n (%)	190 (15.2)	363 (14.6)	1.9
Others, n (%)	182 (14.6)	683 (27.4)	31.8
Blood pressure-lowering medications, n (%)	804 (64.5)	1521 (61.2)	6.9
ACE inhibitor, n (%)	97 (7.8)	139 (5.6)	8.8
ARB, n (%)	479 (38.4)	919 (36.9)	3.2
Calcium channel blocker, n (%)	485 (38.9)	979 (39.3)	0.7
Diuretics, n (%)	135 (10.8)	218 (8.7)	7.0
β blocker, n (%)	152 (12.2)	239 (9.6)	8.4
α blocker, n (%)	85 (6.8)	160 (6.4)	1.6
Statins, n (%)	594 (47.7)	920 (36.9)	21.9

Data are expressed as means (standard deviations) or percentages. *Standardized difference >10% is considered a non-negligible difference. Other glucose-lowering medications include acarbose and epalrestat. Diuretics include thiazide diuretics and aldosterone antagonists. ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; DPP-4=Dipeptidyl peptidase-4 inhibitors; GLP-1=Glucagon-like peptide-1.

Figure S1

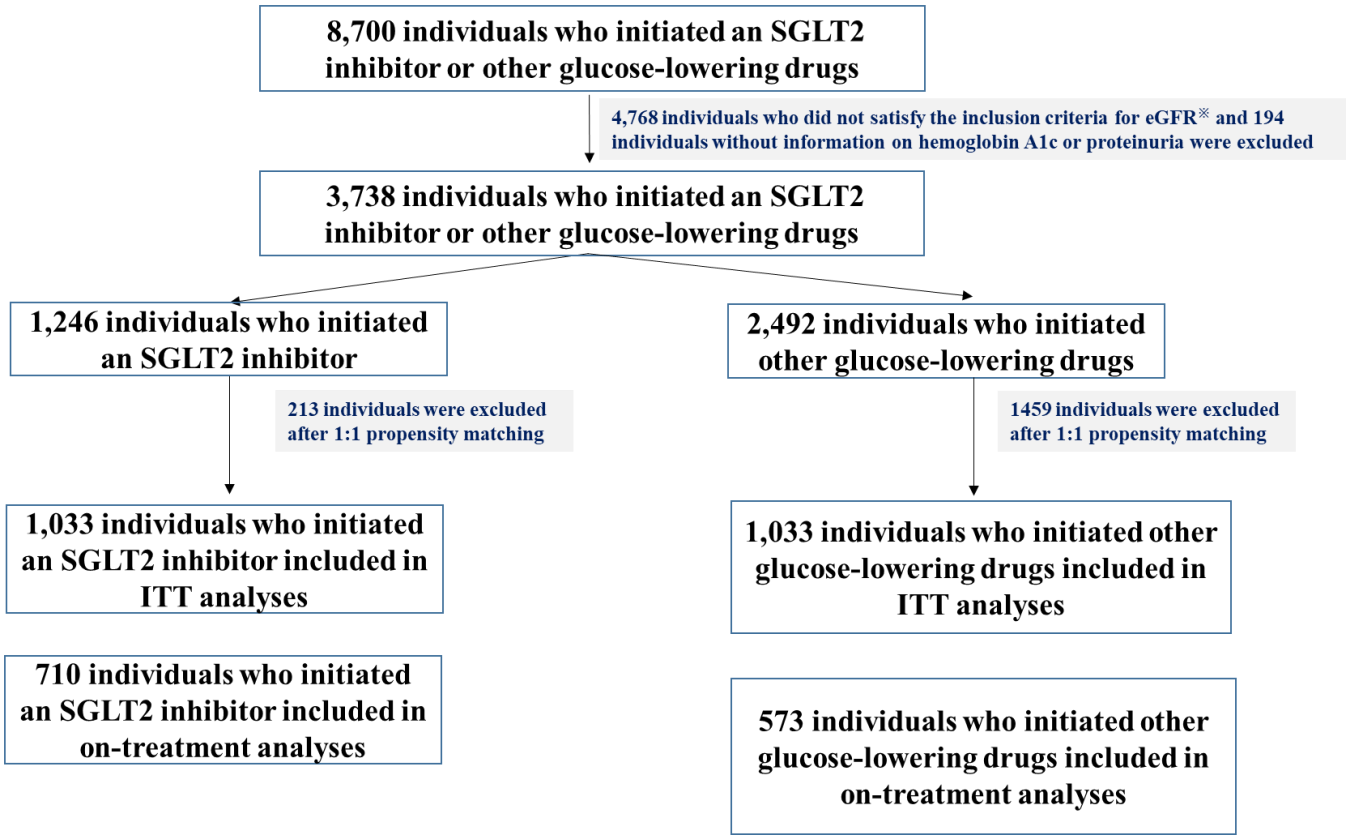
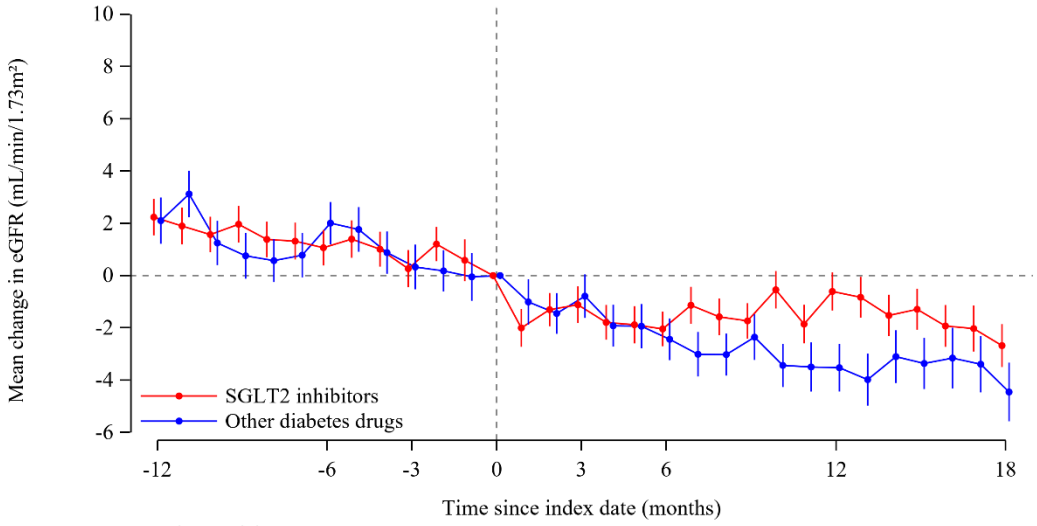

8,700 individuals who initiated an SGLT2 inhibitor or other glucose-lowering drugs
4,768 individuals who did not satisfy the inclusion criteria for eGFR※ and 194 individuals without information on hemoglobin A1c or proteinuria were excluded
3,738 individuals who initiated an SGLT2 inhibitor or other glucose-lowering drugs
1,246 individuals who initiated an SGLT2 inhibitor
2,492 individuals who initiated other glucose-lowering drugs
213 individuals were excluded after 1:1 propensity matching
1459 individuals were excluded after 1:1 propensity matching
1,033 individuals who initiated an SGLT2 inhibitor included in ITT analyses
1,033 individuals who initiated other glucose-lowering drugs included in ITT analyses
710 individuals who initiated an SGLT2 inhibitor included in on-treatment analyses
573 individuals who initiated other glucose-lowering drugs included in on-treatment analyses

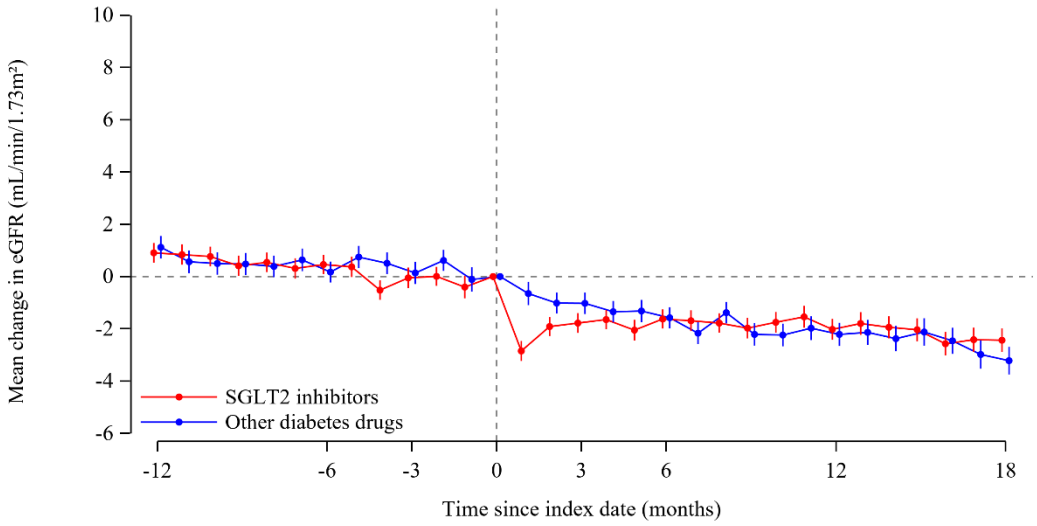
Figure S2

A. With proteinuria at the index date



Number at risk								
SGLT2 inhibitors	124	135	116	207	124	146	109	78
Other diabetes drugs	74	100	83	139	90	104	68	39

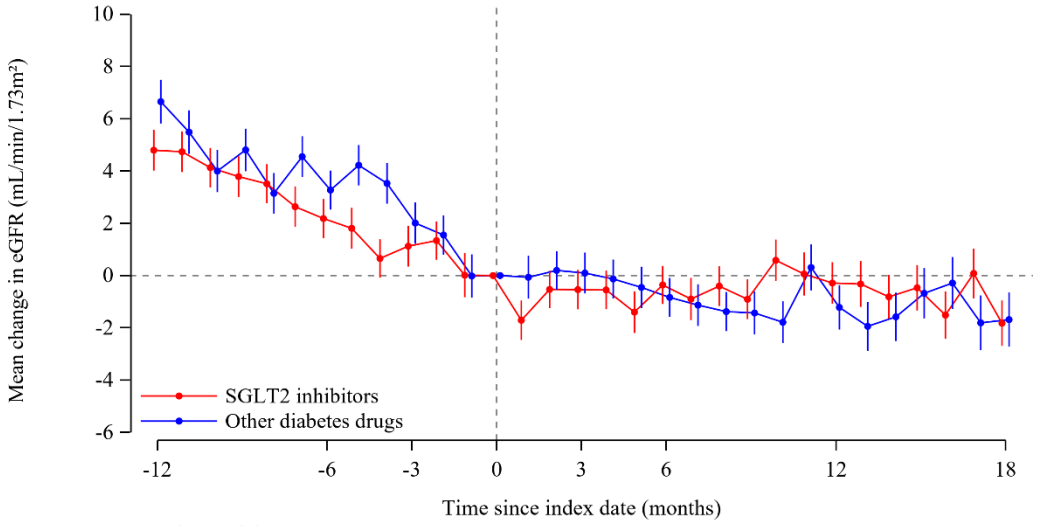
B. Without proteinuria at the index date



Number at risk								
SGLT2 inhibitors	314	345	273	490	307	344	266	183
Other diabetes drugs	228	288	238	409	271	278	212	131

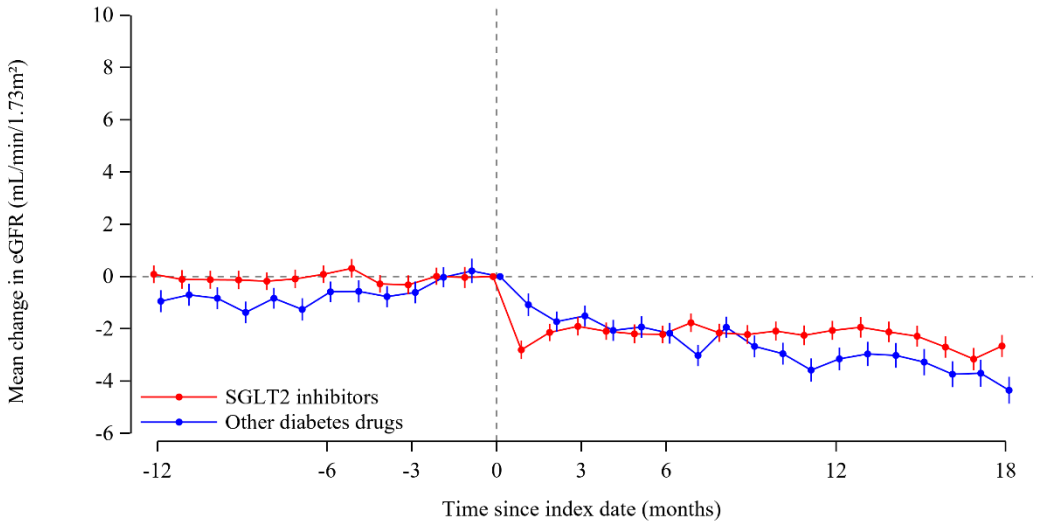
Figure S3

A. With rapid decline in eGFR before initiating treatments



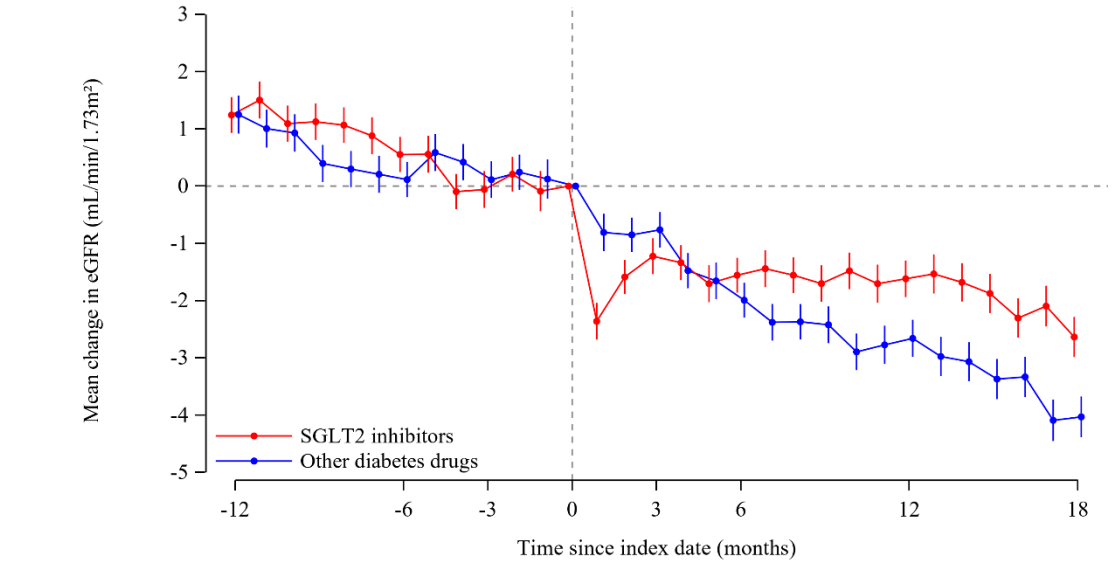
Number at risk								
SGLT2 inhibitors	109	126	107	183	120	136	102	79
Other diabetes drugs	91	129	108	174	111	132	87	50

B. Without rapid decline in eGFR before initiating treatments



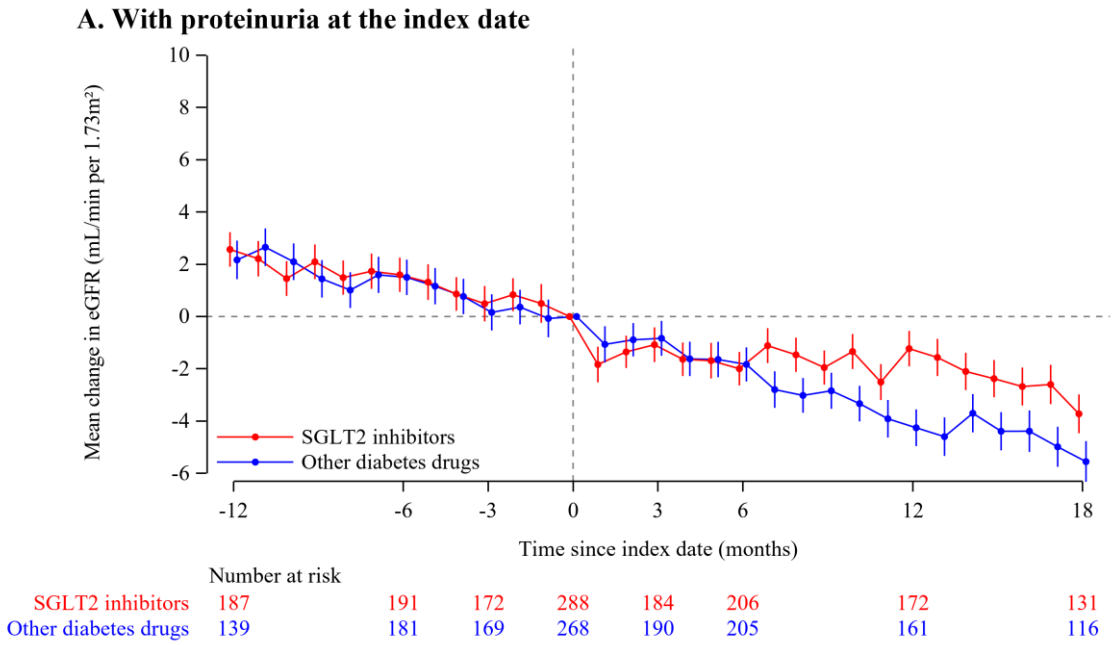
Number at risk								
SGLT2 inhibitors	329	354	282	514	311	354	273	182
Other diabetes drugs	211	259	213	374	250	250	193	120

Figure S4



Number at risk								
SGLT2 inhibitors	653	700	598	1011	649	713	614	460
Other diabetes drugs	546	686	603	999	681	719	580	442

Figure S5


A. With proteinuria at the index date
Mean change in eGFR (mL/min per 1.73m²)
10
8
6
4
2
0
-2
-4
-6
SGLT2 inhibitors
Other diabetes drugs
-12
-6
-3
0
3
6
12
18
Time since index date (months)
Number at risk
SGLT2 inhibitors 187 191 172 288 184 206 172 131
Other diabetes drugs 139 181 169 268 190 205 161 116

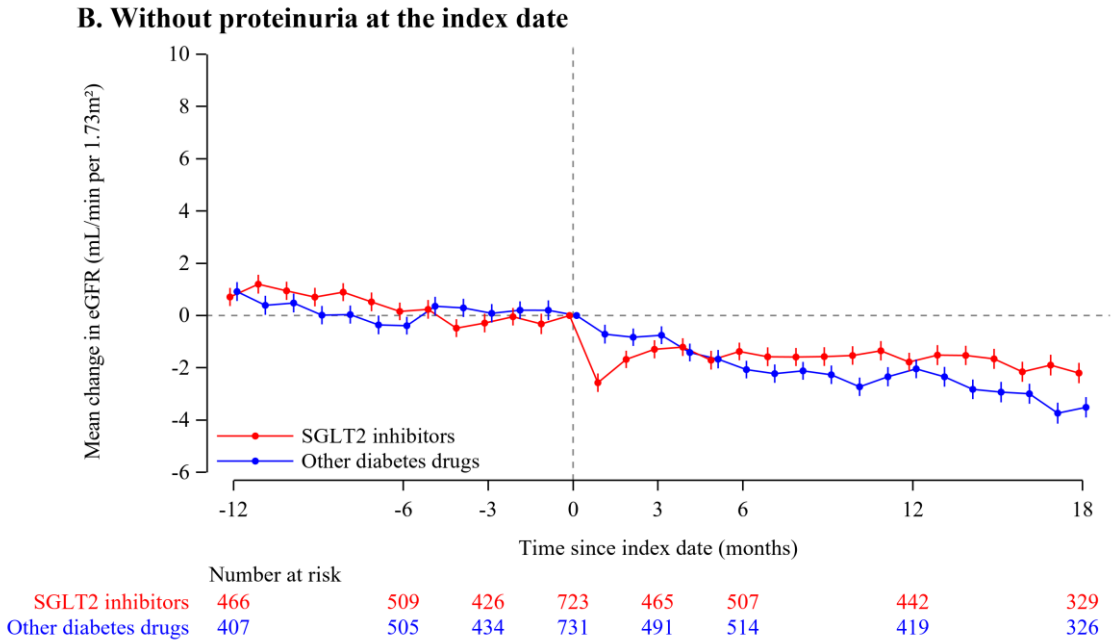

B. Without proteinuria at the index date
Mean change in eGFR (mL/min per 1.73m²)
10
8
6
4
2
0
-2
-4
-6
SGLT2 inhibitors
Other diabetes drugs
-12
-6
-3
0
3
6
12
18
Time since index date (months)
Number at risk
SGLT2 inhibitors 466 509 426 723 465 507 442 329
Other diabetes drugs 407 505 434 731 491 514 419 326

Figure S6

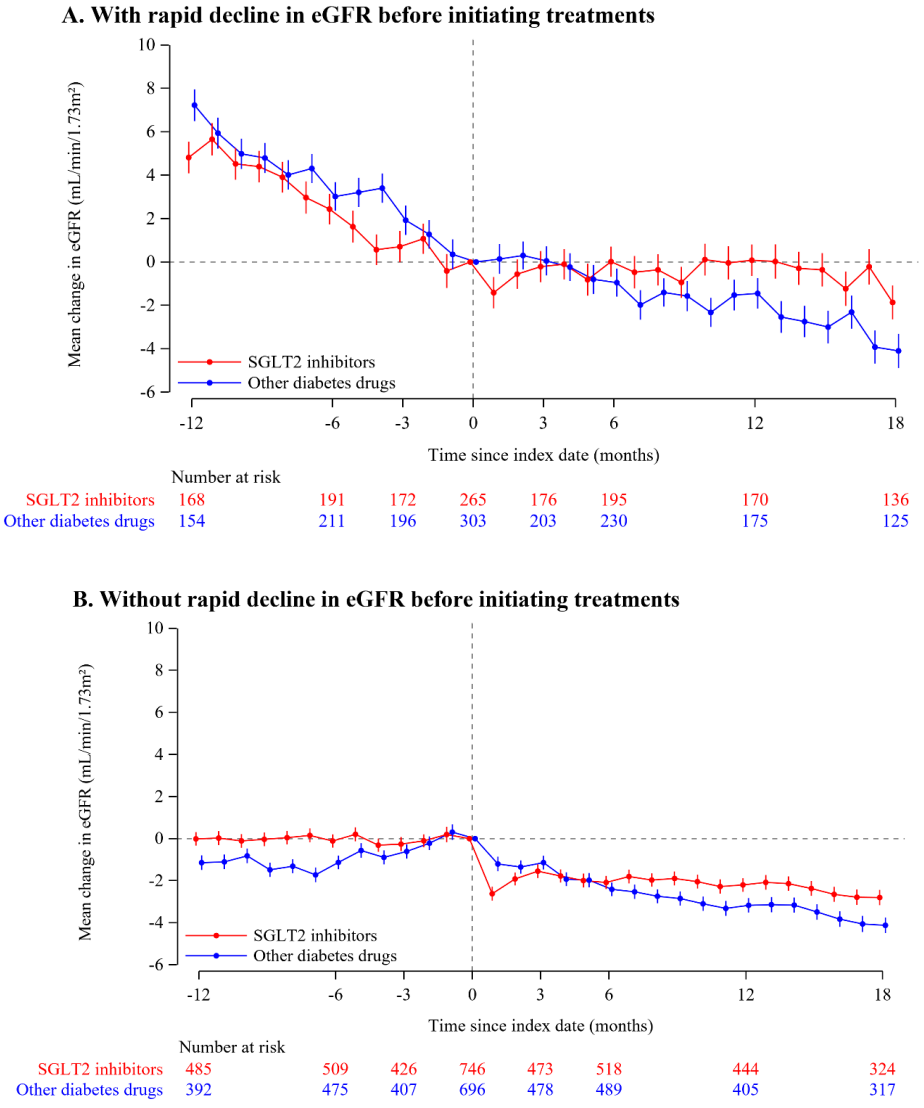

A. With rapid decline in eGFR before initiating treatments
Mean change in eGFR (mL/min/1.73m²)
10
8
6
4
2
0
-2
-4
-6
SGLT2 inhibitors
Other diabetes drugs
-12
-6
-3
0
3
6
12
18
Time since index date (months)
Number at risk
SGLT2 inhibitors 168 191 172 265 176 195 170 136
Other diabetes drugs 154 211 196 303 203 230 175 125
B. Without rapid decline in eGFR before initiating treatments
Mean change in eGFR (mL/min/1.73m²)
10
8
6
4
2
0
-2
-4
-6
SGLT2 inhibitors
Other diabetes drugs
-12
-6
-3
0
3
6
12
18
Time since index date (months)
Number at risk
SGLT2 inhibitors 485 509 426 746 473 518 444 324
Other diabetes drugs 392 475 407 696 478 489 405 317

Figure S7

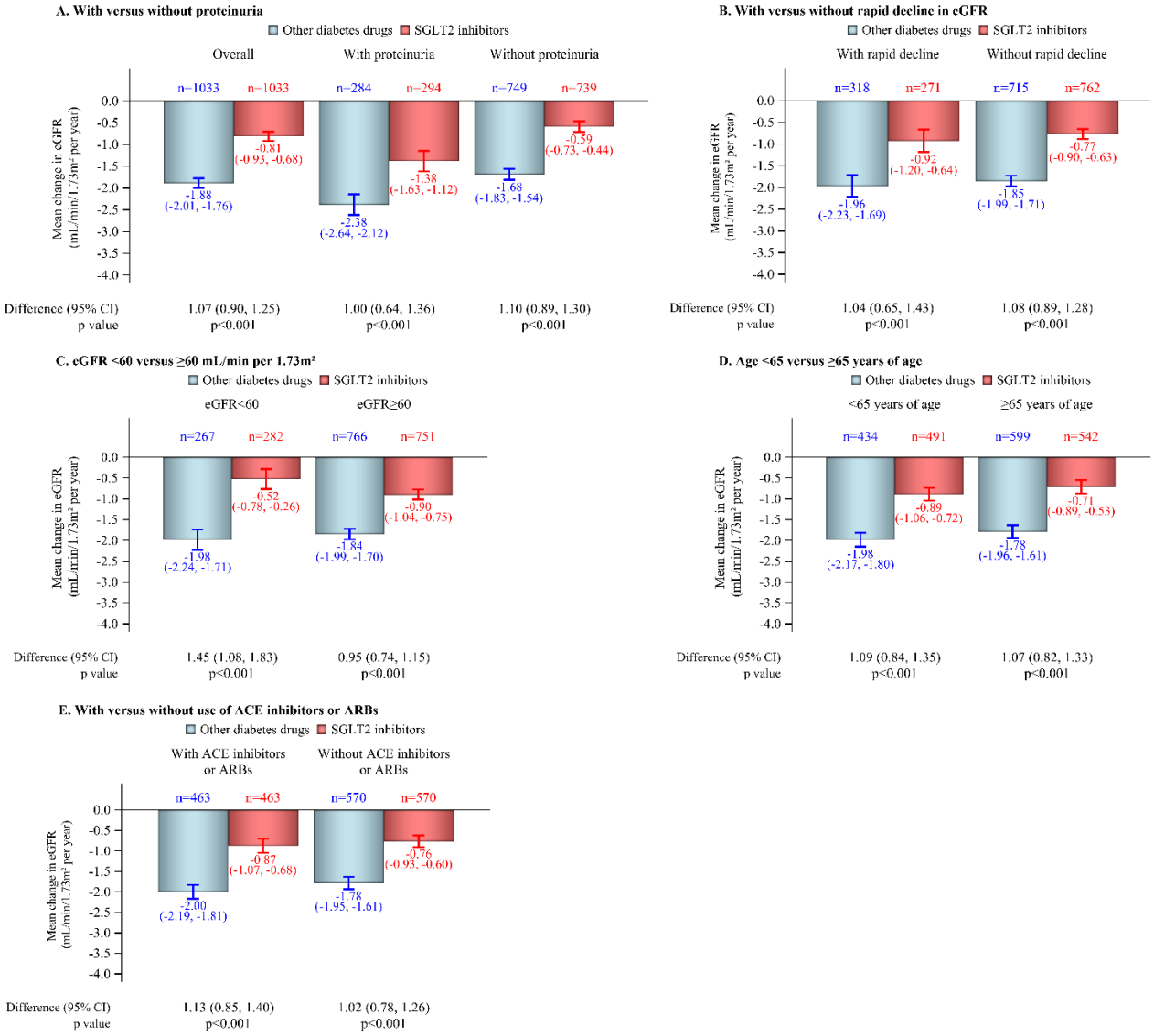
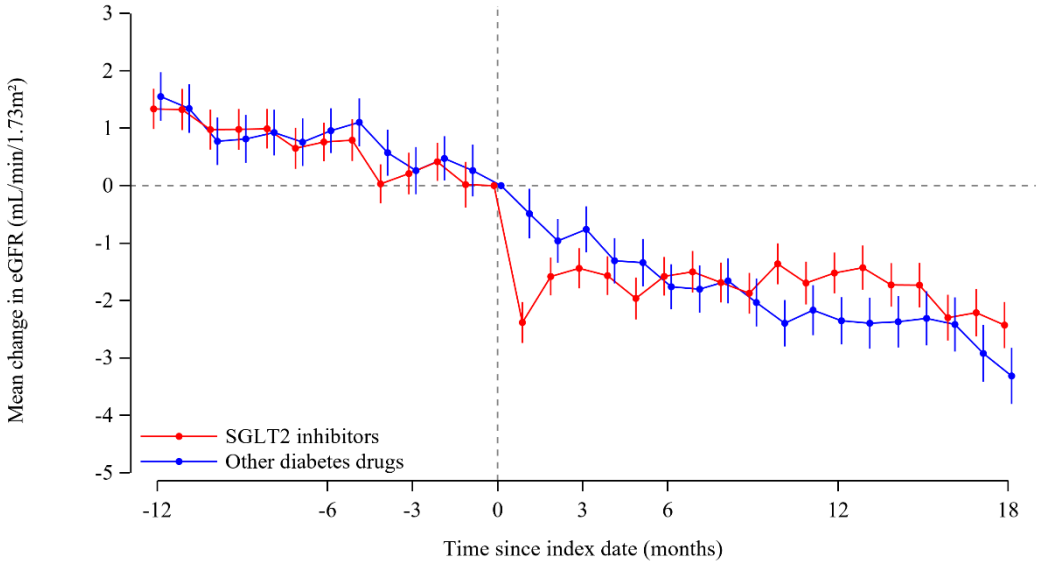

A. With versus without proteinuria
Other diabetes drugs
SGLT2 inhibitors
Overall
With proteinuria
Without proteinuria
n=1033
n=1033
n=284
n=294
n=749
n=739
Mean change in eGFR (mL/min/1.73m² per year)
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
-1.88 (-2.01, -1.76)
-0.81 (-0.93, -0.68)
-2.38 (-2.64, -2.12)
-1.38 (-1.63, -1.12)
-1.68 (-1.83, -1.54)
-0.59 (-0.73, -0.44)
Difference (95% CI) 1.07 (0.90, 1.25) 1.00 (0.64, 1.36) 1.10 (0.89, 1.30)
p value p<0.001 p<0.001 p<0.001
B. With versus without rapid decline in eGFR
Other diabetes drugs
SGLT2 inhibitors
With rapid decline
Without rapid decline
n=318
n=271
n=715
n=762
Mean change in eGFR (mL/min/1.73m² per year)
-1.96 (-2.23, -1.69)
-0.92 (-1.20, -0.64)
-1.85 (-1.99, -1.71)
-0.77 (-0.90, -0.63)
Difference (95% CI) 1.04 (0.65, 1.43) 1.08 (0.89, 1.28)
p value p<0.001 p<0.001
C. eGFR <60 versus ≥60 mL/min per 1.73m²
Other diabetes drugs
SGLT2 inhibitors
eGFR<60
eGFR≥60
n=267
n=282
n=766
n=751
Mean change in eGFR (mL/min/1.73m² per year)
-1.98 (-2.24, -1.71)
-0.52 (-0.78, -0.26)
-1.84 (-1.99, -1.70)
-0.90 (-1.04, -0.75)
Difference (95% CI) 1.45 (1.08, 1.83) 0.95 (0.74, 1.15)
p value p<0.001 p<0.001
D. Age <65 versus ≥65 years of age
Other diabetes drugs
SGLT2 inhibitors
<65 years of age
≥65 years of age
n=434
n=491
n=599
n=542
Mean change in eGFR (mL/min/1.73m² per year)
-1.98 (-2.17, -1.80)
-0.89 (-1.06, -0.72)
-1.78 (-1.96, -1.61)
-0.71 (-0.89, -0.53)
Difference (95% CI) 1.09 (0.84, 1.35) 1.07 (0.82, 1.33)
p value p<0.001 p<0.001
E. 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=463
n=463
n=570
n=570
Mean change in eGFR (mL/min/1.73m² per year)
-2.00 (-2.19, -1.81)
-0.87 (-1.07, -0.68)
-1.78 (-1.95, -1.61)
-0.76 (-0.93, -0.60)
Difference (95% CI) 1.13 (0.85, 1.40) 1.02 (0.78, 1.26)
p value p<0.001 p<0.001

Figure S8



Number at risk								
SGLT2 inhibitors	394	437	354	629	389	449	375	261
Other diabetes drugs	257	331	278	472	305	326	280	170

Figure S9

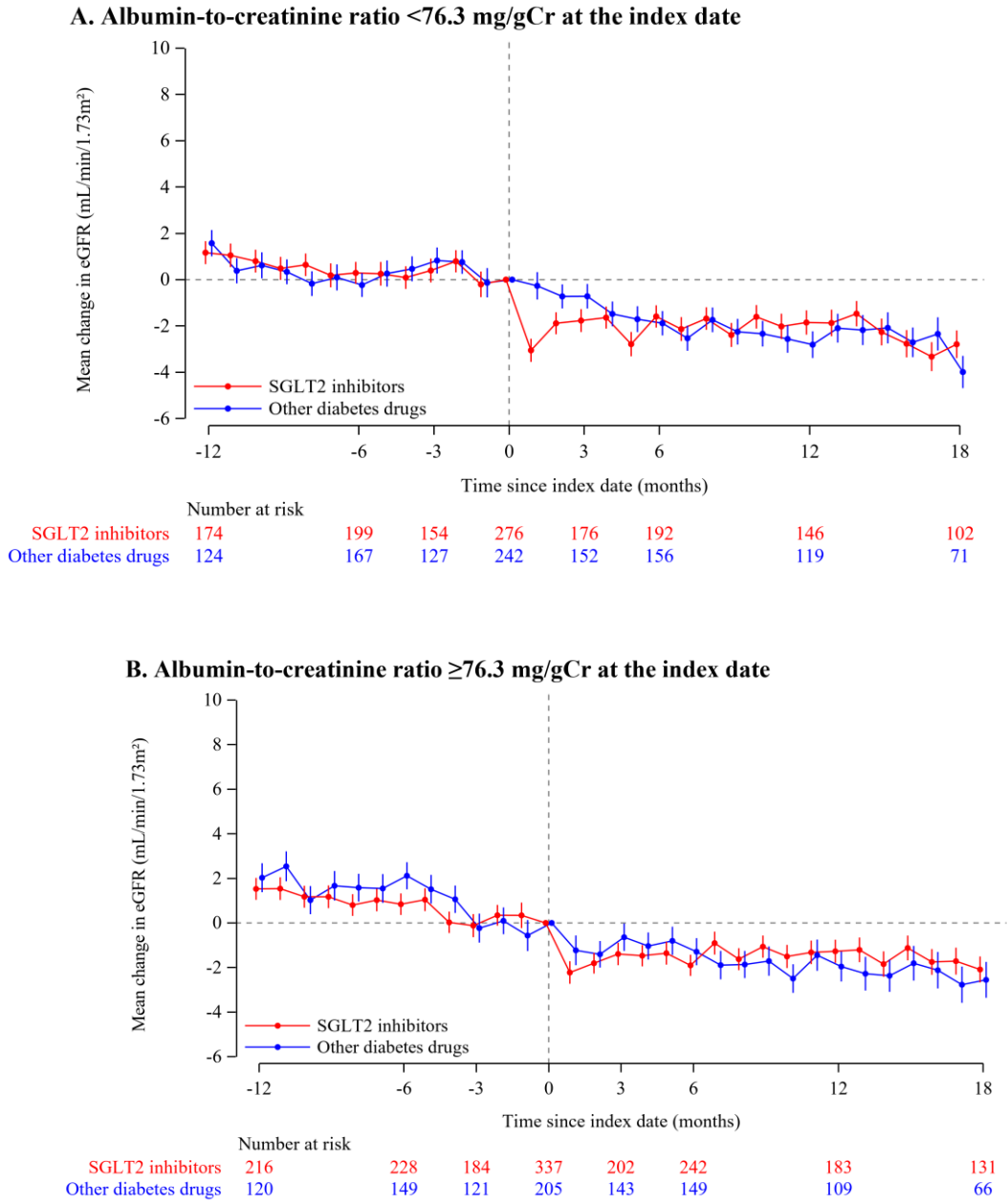
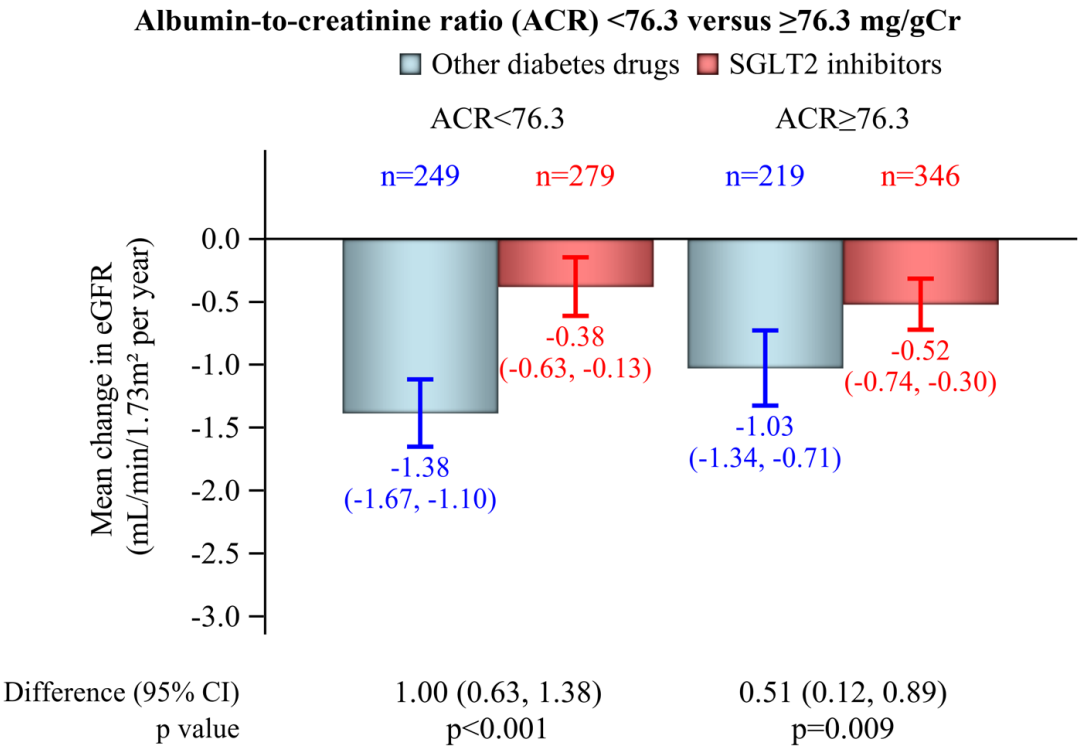
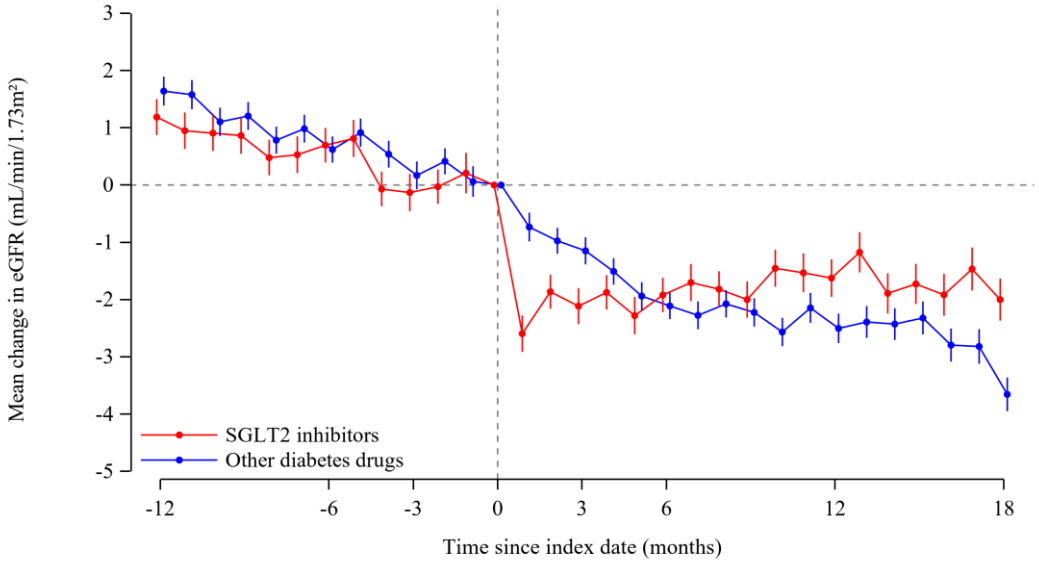

A. Albumin-to-creatinine ratio <76.3 mg/gCr at the index date
Mean change in eGFR (mL/min/1.73m²)
10
8
6
4
2
0
-2
-4
-6
SGLT2 inhibitors
Other diabetes drugs
-12
-6
-3
0
3
6
12
18
Time since index date (months)
Number at risk
SGLT2 inhibitors 174 199 154 276 176 192 146 102
Other diabetes drugs 124 167 127 242 152 156 119 71
B. Albumin-to-creatinine ratio ≥76.3 mg/gCr at the index date
Mean change in eGFR (mL/min/1.73m²)
10
8
6
4
2
0
-2
-4
-6
SGLT2 inhibitors
Other diabetes drugs
-12
-6
-3
0
3
6
12
18
Time since index date (months)
Number at risk
SGLT2 inhibitors 216 228 184 337 202 242 183 131
Other diabetes drugs 120 149 121 205 143 149 109 66

Figure S10



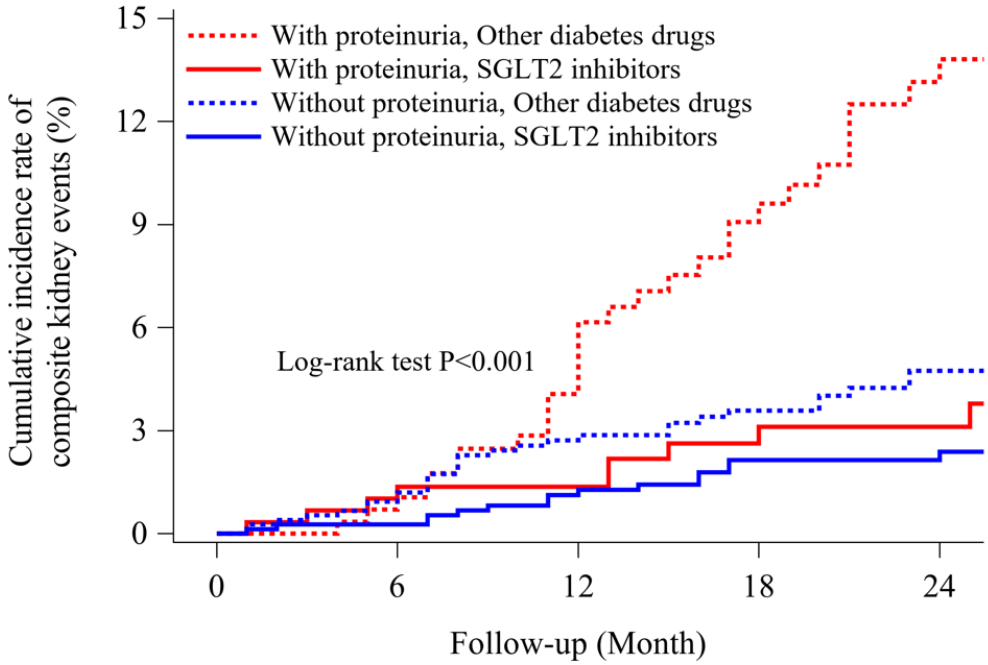
Difference (95% CI)	1.00 (0.63, 1.38)	0.51 (0.12, 0.89)
p value	p<0.001	p=0.009

Figure S11



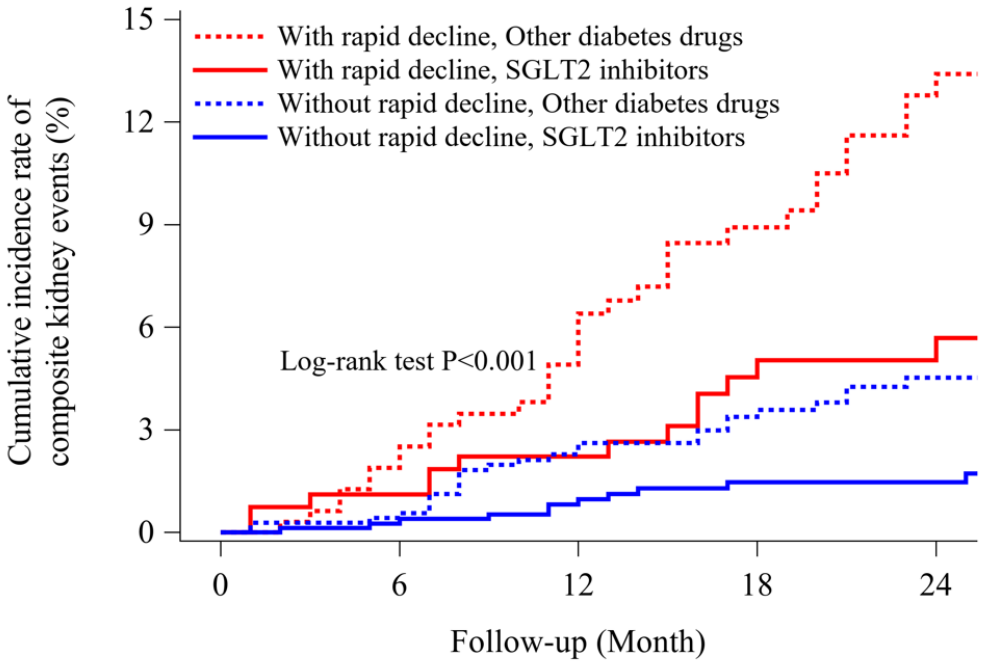
Number at risk								
SGLT2 inhibitors	534	577	476	848	525	594	442	302
Other diabetes drugs	751	1026	855	1406	908	998	724	501

Figure S12



UP(+), Others	284	282	229	171	131
UP(+), SGLT2i	294	291	255	200	153
UP(-), Others	749	742	620	500	365
UP(-), SGLT2i	739	737	651	522	404

Figure S13



Decline(+), Others	318	312	256	189	141
Decline(+), SGLT2i	271	268	236	190	145
Decline(-), Others	715	712	593	482	355
Decline(-), SGLT2i	762	760	670	532	412

Figure S14

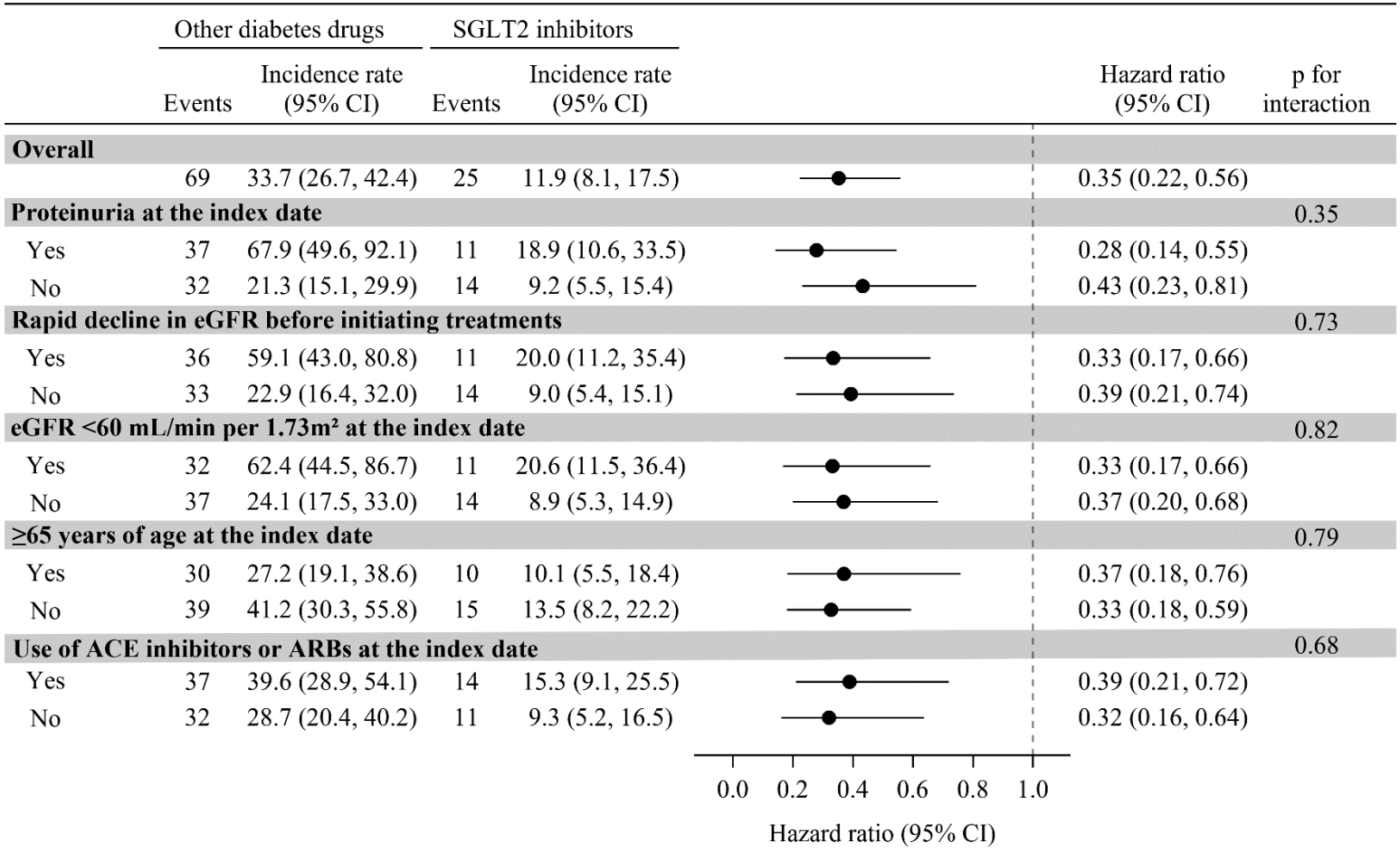

Other diabetes drugs
SGLT2 inhibitors
Events
Incidence rate (95% CI)
Events
Incidence rate (95% CI)
Hazard ratio (95% CI)
p for interaction
Overall
69 33.7 (26.7, 42.4) 25 11.9 (8.1, 17.5) 0.35 (0.22, 0.56)
Proteinuria at the index date 0.35
Yes 37 67.9 (49.6, 92.1) 11 18.9 (10.6, 33.5) 0.28 (0.14, 0.55)
No 32 21.3 (15.1, 29.9) 14 9.2 (5.5, 15.4) 0.43 (0.23, 0.81)
Rapid decline in eGFR before initiating treatments 0.73
Yes 36 59.1 (43.0, 80.8) 11 20.0 (11.2, 35.4) 0.33 (0.17, 0.66)
No 33 22.9 (16.4, 32.0) 14 9.0 (5.4, 15.1) 0.39 (0.21, 0.74)
eGFR <60 mL/min per 1.73m² at the index date 0.82
Yes 32 62.4 (44.5, 86.7) 11 20.6 (11.5, 36.4) 0.33 (0.17, 0.66)
No 37 24.1 (17.5, 33.0) 14 8.9 (5.3, 14.9) 0.37 (0.20, 0.68)
≥65 years of age at the index date 0.79
Yes 30 27.2 (19.1, 38.6) 10 10.1 (5.5, 18.4) 0.37 (0.18, 0.76)
No 39 41.2 (30.3, 55.8) 15 13.5 (8.2, 22.2) 0.33 (0.18, 0.59)
Use of ACE inhibitors or ARBs at the index date 0.68
Yes 37 39.6 (28.9, 54.1) 14 15.3 (9.1, 25.5) 0.39 (0.21, 0.72)
No 32 28.7 (20.4, 40.2) 11 9.3 (5.2, 16.5) 0.32 (0.16, 0.64)
0.0 0.2 0.4 0.6 0.8 1.0
Hazard ratio (95% CI)

Figure S15

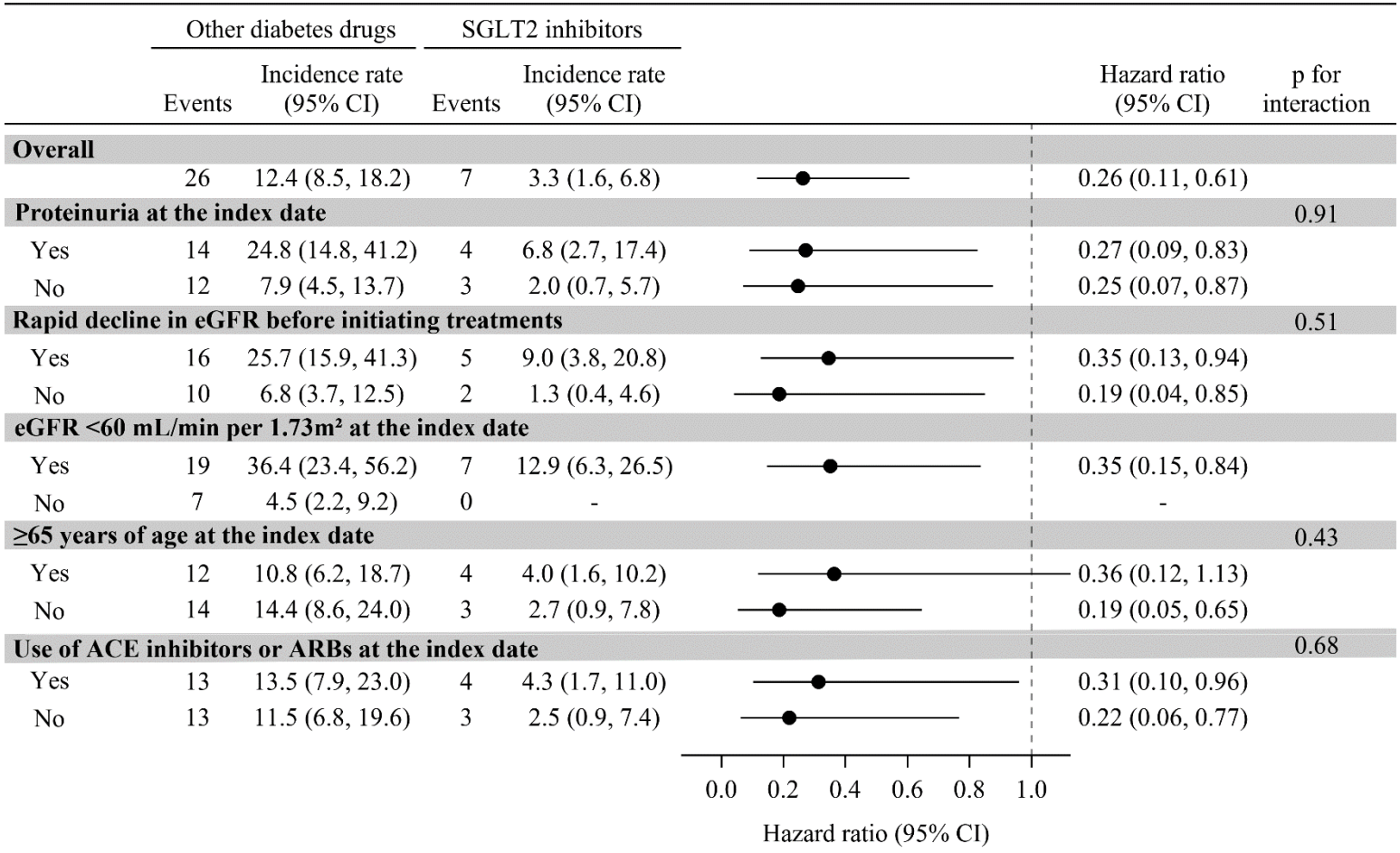

Other diabetes drugs
SGLT2 inhibitors
Events
Incidence rate (95% CI)
Events
Incidence rate (95% CI)
Hazard ratio (95% CI)
p for interaction
Overall
26 12.4 (8.5, 18.2) 7 3.3 (1.6, 6.8) 0.26 (0.11, 0.61)
Proteinuria at the index date 0.91
Yes 14 24.8 (14.8, 41.2) 4 6.8 (2.7, 17.4) 0.27 (0.09, 0.83)
No 12 7.9 (4.5, 13.7) 3 2.0 (0.7, 5.7) 0.25 (0.07, 0.87)
Rapid decline in eGFR before initiating treatments 0.51
Yes 16 25.7 (15.9, 41.3) 5 9.0 (3.8, 20.8) 0.35 (0.13, 0.94)
No 10 6.8 (3.7, 12.5) 2 1.3 (0.4, 4.6) 0.19 (0.04, 0.85)
eGFR <60 mL/min per 1.73m² at the index date
Yes 19 36.4 (23.4, 56.2) 7 12.9 (6.3, 26.5) 0.35 (0.15, 0.84)
No 7 4.5 (2.2, 9.2) 0 - -
≥65 years of age at the index date 0.43
Yes 12 10.8 (6.2, 18.7) 4 4.0 (1.6, 10.2) 0.36 (0.12, 1.13)
No 14 14.4 (8.6, 24.0) 3 2.7 (0.9, 7.8) 0.19 (0.05, 0.65)
Use of ACE inhibitors or ARBs at the index date 0.68
Yes 13 13.5 (7.9, 23.0) 4 4.3 (1.7, 11.0) 0.31 (0.10, 0.96)
No 13 11.5 (6.8, 19.6) 3 2.5 (0.9, 7.4) 0.22 (0.06, 0.77)
0.0 0.2 0.4 0.6 0.8 1.0
Hazard ratio (95% CI)

Figure legends

Figure S1: Flowchart: sample for the analyses, J-CKD-DB Extension

※Based on the inclusion criteria in the current study, we selected records of T2DM patients 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 at least 180 days between the first and last eGFR measurements before the index date were required 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. T2DM=Type 2 diabetes mellitus; eGFR=estimated glomerular filtration rate; ITT=intention-to-treat.

Figure S2: Change in eGFR over time before and after initiation of SGLT2 inhibitors or other diabetes drugs by subgroups (on-treatment analyses)

Error bars show mean ± standard errors among groups with and without proteinuria. 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, accounting for the acute dip in eGFR in the SGLT2 inhibitor group. P values were calculated using a linear mixed regression model. eGFR=estimated glomerular filtration rate; SGLT2=sodium-glucose co-transporter-2.

Figure S3: Change in eGFR over time before and after initiation of SGLT2 inhibitors or other diabetes drugs by subgroups (on-treatment analyses)

Error bars show mean ± standard errors among groups with and without rapid decline in eGFR before initiating treatments. 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, accounting for the acute dip in eGFR in the SGLT2 inhibitor group. P values were calculated using a linear mixed regression model. eGFR=estimated glomerular filtration rate; SGLT2=sodium-glucose co-transporter-2.

Figure S4: 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 S5: Change in eGFR over time before and after initiation of SGLT2 inhibitors or other diabetes drugs by subgroups (ITT analyses)

Error bars show mean ± standard errors among groups with and without proteinuria. 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, accounting for the acute dip in eGFR in the SGLT2 inhibitor group. 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 S6: Change in eGFR over time before and after initiation of SGLT2 inhibitors or other diabetes drugs by subgroups (ITT analyses)

Error bars show mean ± standard errors among groups with and without rapid decline in eGFR before initiating treatments. 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, accounting for the acute dip in eGFR in the SGLT2 inhibitor group. 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 S7: 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, (D) age < 65 versus ≥ 65 years of age at the index date, and (E) with versus without use of ACE inhibitors or ARBs at the index date. eGFR change 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.

Figure S8: Change in eGFR over time before and after initiation of SGLT2 inhibitors

or other diabetes drugs among participants with a follow-up period greater than a year (on-treatment analyses)

Error bars show mean ± standard errors. Numbers below the graph refer to the number of patients at each timepoint. We included only participants with follow-up period greater than a year who also met the criteria for on-treatment analyses (n=641 in the SGLT 2 inhibitor group and n=494 in the other glucose-lowering drugs). Analyses for eGFR slope were conducted from the index date and thereafter, accounting for the acute dip in eGFR in the SGLT2 inhibitor group. P values were calculated using a linear mixed regression model. eGFR=estimated glomerular filtration rate; SGLT2=sodium-glucose co-transporter-2.

Figure S9: Change in eGFR over time before and after initiation of SGLT2 inhibitors or other diabetes drugs by subgroups (on-treatment analyses)

Error bars show mean ± standard errors. Numbers below the graph refer to the number of patients at each timepoint. We included only participants who had a quantitative urinary albumin measurement using ACR and met the criteria for the on-treatment analyses (n=625 in the SGLT2 inhibitors group and n=468 in the other glucose-lowering group). These numbers differ from the text (i.e., 903 participants in the SGLT2 inhibitors group, and 811 participants in the other glucose-lowering group) because some participants who had ACR did not meet the criteria for the on-treatment analyses. eGFR=estimated glomerular filtration rate; SGLT2=sodium-glucose co-transporter-2; ACR=albumin-creatinine ratio.

Figure S10: Annual rate of eGFR change in subgroups (on-treatment analyses)

We included only participants who had a quantitative urinary albumin measurement using ACR and met the criteria for the on-treatment analyses (n=625 in the SGLT2 inhibitors group and n=468 in the other glucose-lowering group). These numbers differ from the text (i.e., 903 participants in the SGLT2 inhibitors group and 811 participants in the other glucose-lowering group) because some participants who had ACR did not meet the criteria for the on-treatment analyses. We assessed whether the effects upon kidney function of SGLT2 inhibitors versus other glucose-lowering drugs differed by subgroups defined as above or below median levels of ACR (i.e., 76.3 mg/g・Cr) in this population. eGFR change was calculated from the post-index eGFR measurements using a linear mixed regression model. eGFR=estimated glomerular filtration rate; SGLT2=sodium-glucose co-transporter-2; ACR=albumin-creatinine ratio.

Figure S11: Change in eGFR over time before and after initiation of SGLT2 inhibitors or other diabetes drugs in IPTW analyses using the propensity score (on-treatment 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, accounting for the acute dip in eGFR in the SGLT2 inhibitor group. P values were calculated using a linear mixed regression model. eGFR=estimated glomerular filtration rate; SGLT2=sodium-glucose co-transporter-2; IPTW=inverse probability of treatment weighting.

Figure S12: Cumulative incidence of composite kidney events among the SGLT2 inhibitors group and other glucose-lowering drugs group (ITT analyses)

The cumulative probability of composite kidney events among subgroups with and without proteinuria was calculated using the Kaplan-Meier method. Composite kidney events included a sustained reduction in eGFR of 50% or more and ESKD (i.e., an eGFR of less than 15 mL/min/1.73 m²). The log-rank test was used to calculate the P value, and the value was <0.001. ESKD=end-stage kidney disease; SGLT2=sodium-glucose co-transporter-2; ITT=intention-to-treat.

Figure S13: Cumulative incidence of kidney events among the SGLT2 inhibitors group and other glucose-lowering drugs group (ITT analyses)

The cumulative probability of composite kidney events among subgroups with and without rapid eGFR decline was calculated using the Kaplan-Meier method. Composite kidney events included a sustained reduction in eGFR of 50% or more and ESKD (i.e., an eGFR of less than 15 mL/min/1.73 m²). The log-rank test was used to calculate the P value, and the value was <0.001. ESKD=end-stage kidney disease; SGLT2=sodium-glucose co-transporter-2; ITT=intention-to-treat. ESKD=end-stage kidney disease; SGLT2=sodium-glucose co-transporter-2; ITT=intention-to-treat.

Figure S14: The frequency of events, corresponding incidence rates, and hazard ratios for a 50% eGFR decline among the SGLT2 inhibitors group and other glucose-lowering drugs group (ITT analyses)

The incidence rate is per 1,000 person-years. Time to first event for SGLT2 inhibitors and other glucose-lowering drugs was compared by use of Cox proportional-hazard models and presented as the HR and 95% CI for a 50% eGFR decline, separately by the subgroups. We tested for heterogeneity in the association between SGLT2 inhibitor use and outcomes

by each subgroup at the index date with the inclusion of multiplicative interaction terms, and a statistically significant interaction was defined as a p-value <0.05. CKD=chronic kidney disease; SGLT2=sodium-glucose co-transporter-2; ITT=intention-to-treat. HR=hazard ratio; CI=confidence intervals; eGFR=estimated glomerular filtration rate.

Figure S15: The frequency of events, corresponding incidence rates, and hazard ratios for ESKD among the SGLT2 inhibitors group and other glucose-lowering drugs group (ITT analyses)

The incidence rate is per 1,000 person-years. Time to-first event for SGLT2 inhibitors and other glucose-lowering drugs was compared by use of Cox proportional-hazard models and presented as the HR and 95% CI for an ESKD, separately by the subgroups. We tested for heterogeneity in the association between SGLT2 inhibitor use and outcomes by each subgroup at the index date with the inclusion of multiplicative interaction terms, and a statistically significant interaction was defined as a p-value <0.05. CKD=chronic kidney disease; SGLT2=sodium-glucose co-transporter-2; ITT=intention-to-treat. HR=hazard ratio; CI=confidence intervals; ESKD=end-stage kidney disease.