Use of SGLT2 Inhibitors in Patients With Type 2 Diabetes and Chronic Kidney Disease: A Multicountry Report From the FOUNTAIN Platform

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DISCLOSURES

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BACKGROUND

- Currently available therapies to slow chronic kidney disease (CKD) progression and reduce cardiovascular disease risk in patients with type 2 diabetes (T2D) and CKD include sodium-glucose cotransporter 2 inhibitor(s) (SGLT2i), renin-angiotensin system inhibitor drugs (e.g., angiotensin-converting enzyme inhibitors [ACEi], angiotensin receptor blockers [ARBs]), glucagon-like peptide-1 receptor agonists, and nonsteroidal mineralocorticoid receptor antagonists such as finerenone.
- SGLT2i were first introduced in 2012 for lowering glucose in patients with T2D, but indications were added in 2020 and 2021 for reduction of the risk of sustained decline in estimated glomerular filtration rate (eGFR), end-stage kidney disease, and cardiovascular death.
- The SGLT2i are now recommended as first-line drug therapy for people with T2D and CKD for the prevention of CKD progression and cardiovascular events, regardless of other glucose-lowering treatment (KDIGO, 2022).
- The clinical landscape for the treatment of patients with CKD and T2D is rapidly evolving.

OBJECTIVES

- As part of the FOUNTAIN platform (NCT05526157; EUPAS48148), describe the following in patients with a dual diagnosis of CKD and T2D initiating an SGLT2i before the launch of finerenone:
  - Baseline characteristics, comorbidities, and comedication
  - Treatment changes over time

RESULTS

- The characteristics of eligible SGLT2i initiators in each data source are shown in Table 1.
  - Patients were predominantly male.
  - Cardiovascular comorbidities and treatments were common.
  - The most commonly used CKD-protective medication classes before SGLT2i initiation were ACEi and ARBs.
- Most patients initiated SGLT2i while in CKD stage 2 or 3 (Figure 2).
  - Severe CKD (stage 4) occurred in < 7% of patients.
- Characteristics of SGLT2i use are shown in Table 2.
  - Median duration of the initial SGLT2i exposure episode ranged from 2.8 months to 11.6 months.
  - 50.2% to 82.9% of SGLT2i initiators had only 1 current-use episode of the index medication.
  - 6.6% to 42.7% had a treatment interruption lasting ≥ 90 days.
- Treatment states over time are summarized in Figure 3.
  - The largest decreases in use occurred between 90 and 180 days after SGLT2i initiation.
  - At the 1-year timepoint, 50% or more of patients in all data sources were currently receiving SGLT2i treatment.

CONCLUSIONS

- SGLT2i use was dynamic in patients with CKD and T2D in all data sources with patients frequently interrupting, restarting, or discontinuing SGLT2i treatment. At 1 year of follow-up, half or more of patients who initiated an SGLT2i were currently receiving SGLT2i treatment.
- The study period captured use largely before SGLT2i received approval for the indications CKD and cardiovascular disease. Most patients had cardiovascular risk factors, fewer than half of patients were CKD stage 3, and the majority received guideline-recommended treatment.
- Understanding the characteristics and patterns of use of existing treatments for patients with CKD and T2D is a first step in designing future studies to compare the incidence of kidney and cardiovascular outcomes related to new and existing treatments for CKD.

METHODS

Study Design

- Multinational, multidatabase descriptive study using real-world data from 5 participating data sources: Danish National Health Registers (DNHR), PHARMO Data Network in The Netherlands, Valencia Health System Integrated Database (VID) in Spain, Japan Chronic Kidney Disease Database Extension (J-CKD-DB-Ex), and Optum's de-identified Clinformatics® Data Mart Database (CDM) in the United States.

Study Population

- Adults (aged ≥ 18 years) with at least 12 months of continuous enrollment or registration in the data source with recorded evidence of CKD and T2D before SGLT2i use and who initiated an SGLT2i from 1 January 2012 (1 January 2014 in Japan) through 30 June 2021.

Index Date

- Date of first SGLT2i prescription/dispensing that meets eligibility criteria (Figure 1).

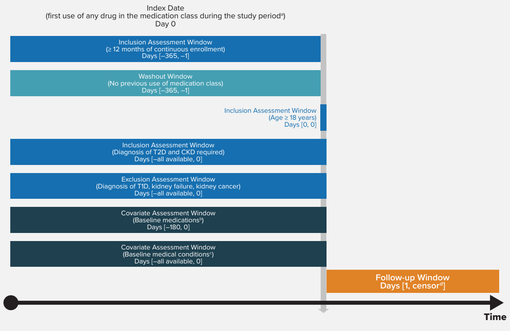
Characteristics

- Baseline (characteristics including use of other medication classes with potential CKD-protective effects) were measured on or before the index date.
- Patterns of SGLT2i utilization and treatment changes were described during follow-up.

Statistical Analyses

- Research partners at each data source conducted analyses using a common protocol and an analysis plan with data source–specific adaptations.
- The following treatment states were assessed at discrete checkpoints after the index date (90 days, 180 days, 270 days, 1 year, 2 years, and 3 years) after the index date and were displayed with Sankey diagrams:
  - Treated with index medication
  - Untreated with index medication
  - Death
  - Lost to follow-up, end of study, or censored

Figure 1. Variable Assessment Windows Relative to the Study Index Date for the SGLT2i Cohorts



T1D = type 1 diabetes; T2D = type 2 diabetes.

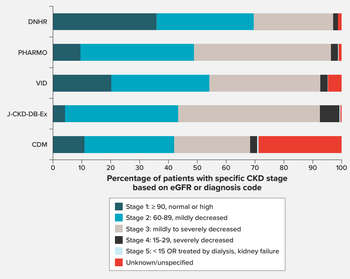
[a] Study period: 1 January 2012 through 30 June 2021.

[b] CKD-protective medications (SGLT2i, GLP 1 RA, sMRA, other nonsteroidal MRA, ACEi, ARB), cardiovascular medications (antihypertensives, beta blockers, direct renin inhibitors, angiotensin receptor-neprilysin inhibitor, lipid-lowering medications, anticoagulants, aspirin and other antiplatelets [e.g., clopidogrel, ticlopidine, prasugrel], digoxin, nitrates), anti-inflammatory drugs, antibiotics, other (acetaminophen, anticonvulsants, antifungals, antituberculars, chemotherapeutic agents).

[c] Baseline conditions: chronic cardiovascular disease, hypertension, diabetes severity and complications, hyperlipidemia, lifestyle cardiovascular disease risk factors (smoking, obesity), stage of CKD, other kidney disorders, liver disease, HIV infection, dementia, COPD, malignancies (other than kidney), glomerulonephritis, renovascular disease, polycystic kidney disease, and autoimmune disease.

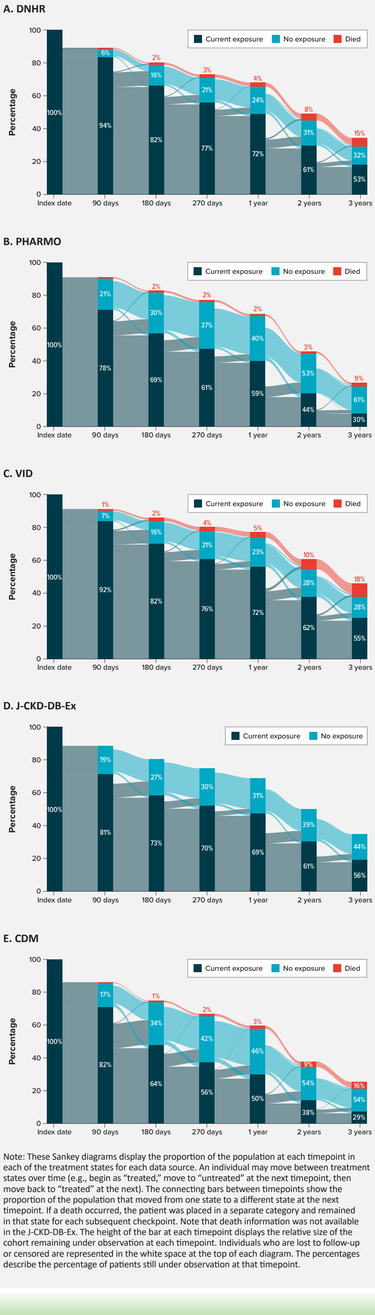
[d] Censored at the earliest of date of death, disenrollment, developing kidney cancer, kidney failure, or end of the study period.

Figure 2. CKD Stage at Index Date Based on eGFR Value or Diagnosis Code



Note: All patients met the inclusion eligibility criteria for CKD, which was defined by (1) ≥ 1 diagnosis code(s) for stage 2, 3, 3a, 3b, 4, or stage unspecified; or (2) occurrence of 2 different eGFR test results ≥ 15 mL/min/1.73 m^2 and < 60 mL/min/1.73 m^2 separated by at least 90 days and no more than 540 days; or (3) 2 different albumin-to-creatinine ratio results ≥ 30 mg/g separated by at least 90 days and no more than 540 days.

Figure 3. Treatment States at Specific Timepoints for SGLT2 Initiators for Each Data Source



Note: These Sankey diagrams display the proportion of the population at each timepoint in each of the treatment states for each data source. An individual may move between treatment states over time (e.g., begin as "treated," move to "untreated" at the next timepoint, then move back to "treated" at the next). The connecting bars between timepoints show the proportion of the population that moved from one state to a different state at the next timepoint. If a death occurred, the patient was placed in a separate category and remained in that state for each subsequent checkpoint. Note that death information was not available in the J-CKD-DB-Ex. The height of the bar at each timepoint displays the relative size of the cohort remaining under observation at each timepoint. Individuals who are lost to follow-up or censored are represented in the white space at the top of each diagram. The percentages describe the percentage of patients still under observation at that timepoint.

Table 1. Baseline Characteristics of SGLT2i New Users by Data Source

Characteristic n (%)	DNHR (n = 21,739)	PHARMO (n = 381)	VID (n = 31,785)	J-CKD-DB-Ex (n = 1,157)	CDM (n = 56,219)
Age, mean (SD), years	66.5 (11.4)	69.4 (9.5)	70.7 (10.9)	67.1 (11.7)	68.6 (10.1)
Female sex	7,710 (35.5)	169 (44.4)	12,910 (40.6)	431 (37.3)	25,633 (45.6)
Obesity	5,811 (26.7)	219 (57.5)	21,156 (66.6)	97 (8.4)	26,443 (47.0)
Hypertension	17,575 (80.8)	271 (71.1)	28,846 (90.8)	957 (82.7)	52,558 (93.5)
Hypercholesterolemia	7,369 (33.9)	134 (35.2)	25,186 (79.2)	887 (76.7)	50,291 (89.5)
Coronary heart disease	6,774 (31.2)	129 (33.9)	8,550 (26.9)	677 (58.5)	19,663 (35.0)
Congestive heart failure	3,611 (16.6)	58 (15.2)	1,776 (5.6)	717 (62.0)	12,073 (21.5)
Gout or hyperuricemia	1,051 (4.8)	15 (3.9)	9,397 (29.6)	381 (32.9)	6,046 (10.8)
Hyperkalemia	244 (1.1)	8 (2.1)	2,917 (9.2)	73 (6.3)	3,639 (6.5)
Insulin use	6,657 (30.6)	82 (5.6)	10,088 (31.7)	562 (48.6)	18,447 (32.8)
ACEi	8,252 (38.0)	152 (39.9)	6,728 (21.2)	135 (11.7)	22,793 (40.5)
ARBs	9,702 (44.6)	135 (35.4)	18,984 (59.7)	615 (53.2)	29,637 (52.7)
Thiazide-like diuretics	3,099 (14.3)	76 (19.9)	1,617 (5.1)	74 (6.4)	17,919 (31.9)
Loop diuretics	5,557 (25.6)	77 (20.2)	8,360 (26.3)	159 (13.7)	12,595 (22.4)
Beta blockers	9,195 (42.3)	220 (57.7)	11,552 (36.3)	309 (26.7)	28,416 (50.5)
Calcium channel blockers	8,607 (39.6)	128 (33.6)	8,056 (25.4)	471 (40.7)	18,711 (33.3)
Statins	16,870 (77.6)	292 (76.6)	23,797 (74.9)	504 (43.6)	43,609 (77.6)

SD = standard deviation.

Table 2. Characteristics of the Index SGLT2i at Baseline and During Follow-up

Characteristic	DNHR (n = 21,739)	PHARMO (n = 381)	VID (n = 31,785)	J-CKD-DB-Ex (n = 1,157)	CDM (n = 56,219)
Type of index SGLT2i, n (%)					
Canagliflozin	806 (3.7%)	17 (4.5%)	4,126 (13.0%)	146 (12.6%)	14,974 (26.6%)
Dapagliflozin	7,704 (35.4%)	219 (57.5%)	12,450 (39.2%)	222 (19.2%)	6,516 (11.6%)
Empagliflozin	13,211 (60.8%)	145 (38.1%)	15,107 (47.5%)	356 (30.8%)	34,640 (61.6%)
Duration of initial index exposure episode (months), median	9.7	2.8	11.6	7.7	5.4
Duration of total exposure to an SGLT2i (months), median	12.8	7.5	17.0	11.9	14.5
Number of patients with only 1 distinct current-use treatment episode for index SGLT2i, n (%)	17,801 (81.9%)	316 (82.9%)	23,381 (73.6%)	879 (76.0%)	28,202 (50.2%)
Interruptions of current use lasting ≥ 90 days, n (%)	2,001 (9.2%)	25 (6.6%)	3,769 (11.9%)	494 (42.7%)	18,100 (32.2%)

Note: In J-CKD-DB-EX, other SGLT2i medications used were ipragliflozin (14.3%), luseogliflozin (15.6%), and tofogliflozin (7.4%). Ertugliflozin was used by 0.3% of patients in VID and 0.2% of patients in CDM.

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