STUDY REPORT SYNOPSIS

OPTIMISE-CKD

A multinational, observational, secondary data study describing management and treatment with dapagliflozin in routine clinical practice among patients with chronic kidney disease

Milestones:	Final Study Protocol	07 April 2022
	Initiation of Data Extraction	04 May 2022
	Study Protocol Version 2.0 Finalized	24-Mar-2023
	Final Analytic Dataset	28 September 2023
	Statistical Analysis Complete	28 September 2023
	Final Study Report	19 December 2023
Phase of development:	Not Applicable	
Sponsor:	AstraZeneca	

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This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents.

Background/rationale:

CKD has been recognized as a global public health problem and affects 8% to 16% of the general population. Until recently, renin-angiotensin system inhibitors [RASi, defined as angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs)] were the only medications known to reduce the decline in kidney function in CKD patients, primarily in the setting of T2D and proteinuria. Sodium-glucose cotransporter-2 inhibitors (SGLT-2i; dapagliflozin and empagliflozin) have been demonstrated to impart clinically significant cardiorenal protective effects. The placebo-controlled DAPA-CKD trial has recently shown that dapagliflozin, an SGLT-2i, significantly reduced the risk of a composite endpoint comprised of sustained eGFR decline, end stage kidney disease and death from renal or cardiovascular causes in patients with CKD regardless of T2D status. As a result, dapagliflozin was approved for the treatment of CKD in April 2021 by the US Food and Drug Administration (FDA) and in August 2021 by the European Medicines Agency (EMA).

The approved label encompasses all CKD patients at risk of disease progression and thus broader than the DAPA-CKD trial population. It is important to assess the current CKD treatment landscape, dapagliflozin utilisation and effectiveness in order to better understand the opportunities for influencing guideline recommendations, driving guideline implementation and enabling access to dapagliflozin treatment for a broad range of CKD patients.

Objectives:

Primary objective is to characterize dapagliflozin 10mg utilisation in clinical practice, by describing treatment naïve patients who (1) are treated with dapagliflozin 10 mg and (2) who are eligible for CKD treatment with dapagliflozin.

Secondary objectives are to describe the current clinical landscape among incident CKD patients, by:

1 Describing baseline demographic and clinical characteristics, drug utilization, and CKD treatment (RAASi and dapagliflozin 10 mg) patterns

2 Describing selected outcomes among overall, treated and untreated incident CKD patients:

   (a) Measures of CKD progression (eGFR trajectories and slope, advancement in CKD stage)

   (b) Selected health-care resource utilization, e.g., all-cause hospitalizations, heart failure hospitalizations (hHF)

   (c) Cardiorenal events

Exploratory objective is to assess the real-world effectiveness of dapagliflozin in CKD patients:

1 Compare selected outcomes of dapagliflozin 10mg initiation vs not initiating dapagliflozin 10mg (i.e. standard of care (SoC) defined as no CKD treatment or RASi) in CKD patients with or without T2D:

   (a) Measures of CKD progression (eGFR trajectories and slope, advancement in CKD stage)

   (b) Selected health-care resource utilization, e.g., all-cause hospitalizations, heart failure hospitalizations (hHF)

   (c) Cardiorenal events

Study design:

Observational, longitudinal cohort study

Data source:

Optum Clinformatics Data Mart (United States), Medical Data Vision (Japan), Real World Data (Japan), The DAISY study database (Sweden), The CELOSIA CKD study database (Sweden)

Study population:

Patients aged 18 years or older were included if they met the CKD definition at any time during the study periods in each country. CKD was defined as having either of the following: two estimated glomerular filtration rate (eGFR) measurements ≤ 60 ml/min/1.73m2 taken ≥ 90 days apart; or a first eGFR ≤ 60 ml/min/1.73m2 followed by a first CKD diagnosis at any time including chronic, acute, hypertensive, diabetic, tubular, and glomerular renal disease. Patients with CKD stage 5 (based on eGFR < 15 ml/min/1.73m2 or dialysis), dialysis, and type 1 or gestational diabetes were excluded.

Statistical methods:

Continuous variables were summarized using mean and standard deviation, median and interquartile range, and minimum and maximum values. Categorical variables were summarized with number and percentages of patients in each category.

Percentages of patients using RASi or SGLT-2i after index were calculated as the actual number of patients with a prescription for these treatments covering each day, divided by the total number of patients still in the database on that day. One-year event rates were calculated as events per 100 patient-years (PY) based on time to first event.

The average costs related to each of the diagnoses were summarized as the arithmetic mean for each month, and the cumulative cost was the sum of the mean values from month 1 to the month of interest.

Change in eGFR relative to baseline was described as the mean change at each timepoint with 95% confidence intervals (CI) based on observed values. The individual patient slopes of post eGFR measurements were analyzed using quantile regression, where the median slopes (per year) were estimated and presented with 95% CI.

The time to clinical outcomes was analyzed using Cox regression models, where time since index was the primary timescale. The results were presented as the hazard ratio with 95% CI for the relative risk of high UACR relative to low UACR.

A quantile regression analysis was performed to evaluate the effect of dapagliflozin 10 mg initiation versus no initiation on estimated glomerular filtration rate (eGFR) slope in a propensity score-matched cohort, using a prevalent new user design.

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Results:

Dapagliflozin initiators (n = 20 407) were mostly in stage 3–4 CKD (69–81% across databases). The most common comorbidities were T2D, hypertension, and cardiovascular disease. At baseline, a RASi

was prescribed in 53–81% of patients. Eligible but untreated patients were older, had a higher eGFR and a lower comorbidity burden than initiators.

Among 449 232 incident CKD patients (across-country median age range 74–81 years), 69% did not have T2D. Prevalence ranges for atherosclerotic cardiovascular disease (ASCVD) and heart failure (HF) were 20–36% and 17–31%, respectively. Baseline kidney-protective treatment (RASi and/or SGLT2i) use was limited, especially among patients without T2D. Event rates were high for CKD (11.4–44.4/100 P-Y) and HF (7.4–22.3/100 P-Y). Up to 14.6% of patients had died at 1 year. Hospital costs for CKD and HF were higher than for ASCVD. Following incident CKD, kidney-protective treatment initiation was low (7–15%) and discontinuation was high (16–27%), especially among patients without T2D.

In total, 1160 non-diabetic dapagliflozin initiators had low (n=633) and high (n=527) UACR. The two groups were similar at baseline, aged 74 and 75 years, and 38% and 41% female, respectively. After dapagliflozin initiation, an acute eGFR dip of 3 ml/min/1.73 m2 was observed, followed by a flat development in both groups. The eGFR slope (95% confidence interval [CI]) for patients with low UACR was 0.53 ml/min/1.73 m2 per year (–0.64, 2.88), and similar to patients with high UACR (0.46 ml/min/1.73 m2 per year [–0.32, 2.28]). Cardiorenal event rates per 100 patient-years were 29.7 and 23.5 in the low and high UACR groups, respectively (adjusted hazard ratio 0.93 [95% CI 0.66, 1.29]). Analogous results were found in those with normal/mildly elevated UACR.

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Conclusion:

After its approval for CKD treatment in the USA and Japan, dapagliflozin 10 mg was prescribed to a broad range of patients with CKD.

Incident CKD was associated with substantial morbidity, mortality, costs, and undertreatment, especially in patients without T2D, who represented the majority of patients. This highlights an urgent need for early CKD detection and improved kidney-protective treatment among patients with moderate CKD

Dapagliflozin in non-diabetic patients for the treatment of CKD demonstrated similar kidney protection and cardiorenal risk across UACR levels. This suggest that the efficacy of dapagliflozin found in clinical trials expands to real-world CKD patients regardless of albuminuria levels.

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Publications:

- Tangri. N. et al. Dapagliflozin Utilization in Chronic Kidney Disease and its Real-World Effectiveness Among Patients with Lower Levels of Albuminuria in the US and Japan (submitted to Advances in Therapy – September 2023)
- Tangri, N. et al. Mortality, healthcare burden and treatment of chronic kidney disease: the OPTIMISE-CKD study (submitted to Kidney360 – October 2023)

- Svensson, M.K. et al. Dapagliflozin treatment of non-diabetic patients with chronic kidney disease and low or high albuminuria (submitted to CKJ – November 2023)