DAPAGLIFLOZIN IN PATIENTS WITH CHRONIC KIDNEY DISEASE (DAPA-CKD)

BACKGROUND

SGLT2 Inhibitors and CKD

Chronic kidney disease (CKD) is a common complication of type 2 diabetes. CKD is associated with an increased risk of all-cause and cardiovascular (CV) mortality as well as economic and social burden. As slowing the development and progression of CKD remains an unmet clinical need in this patient population, certain agents have emerged to combat this challenge.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are widely used agents for the treatment of type 2 diabetes, demonstrating improvement in glycemic control with a reduction in body weight and blood pressure. However, past studies have also shown that these agents possess CV benefit and renoprotective effects.[1]

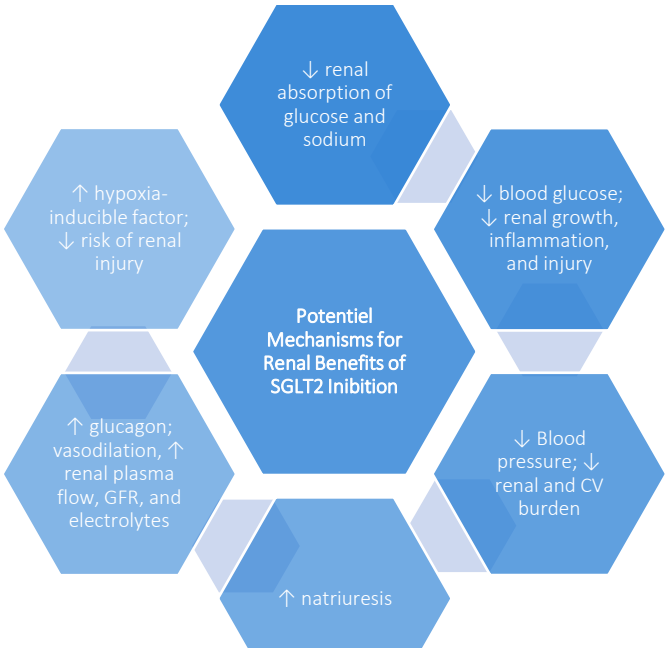

Figure 1. SGLT2 Inhibitor Mechanisms for Renal Benefits

DAPA-CKD Trial

Until recently, the primary medication classes utilized to slow the decline of kidney function in patients with CKD were angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs). However, it is important to note that most evidence was demonstrated in patients with existing type 2 diabetes.

While their predominant effects on glycemic control make SGLT2 inhibitors useful in type 2 diabetes, their renal effects are thought to be independent of their ability to lower blood glucose and may preserve kidney function in the absence of a diabetes diagnosis. These potential mechanisms are listed in Figure 1.[2] Therefore, the Dapagliflozin and Prevention of Adverse Outcomes in CKD (DAPA-CKD) trial was undertaken to evaluate the effect of dapagliflozin on both efficacy and safety outcomes in patients independent of a history of diabetes.[3]

STUDY OVERVIEW

This study was a randomized, double-blind, placebo-controlled trial. The trial was conducted in 21 countries (386 sites) from February 2, 2017 to June 12, 2020 and sponsored by AstraZeneca, the makers of Farxiga® (dapagliflozin).

Study Objective	• To assess the effects of dapagliflozin on reducing the risk of renal and CV events in patients with CKD with and without type 2 diabetes.

METHODS

Key inclusion and exclusion criteria are as follows:

Inclusion Criteria	Exclusion Criteria
• ≥ 18 years old • eGFR 25-75 mL/min/1.73m^2 (CKD-EPI formula) • Urinary albumin-to-creatinine ratio (UACR) of 200-5000 mg/g • Stable dose of ACE inhibitor or ARB for ≥4 weeks (if not contraindicated)	• Type 1 diabetes • Polycystic kidney disease, lupus nephritis, or ANCA-associated vasculitis • Immunotherapy within 6 months prior to enrollment • History of organ transplantation • Receiving SGLT2 inhibitor within 8 weeks prior to enrollment or previous intolerance • NYHA class IV heart failure • MI, unstable angina, stroke or TIA within 12 weeks prior to enrollment

Patients were randomized to receive dapagliflozin 10mg once daily or matching placebo. This is the recommended initial and maintenance dose in diabetic kidney disease as compared to a 5mg once daily initial dose and upward titration to 10mg in patients with hyperglycemia alone. Randomization was stratified by diagnosis of type 2 diabetes (yes or no) and UACR (≤1000 mg/g or >1000 mg/g).

Following randomization, in-person trial visits were performed at 2 weeks, 2/4/8 months, and at 4-month intervals thereafter.

The co-primary endpoints were:

The first occurrence of:

Decline of ≥50% in eGFR	• Confirmed by a 2nd serum creatinine measurement after ≥28 days
Onset of end-stage renal disease (ESRD)	• Maintenance dialysis for ≥28 days • Kidney transplantation • eGFR <15 mL/min/1.73m^2 confirmed by a 2nd measurement after ≥28 days
Death from renal or CV causes	•Potential CV causes*: Stroke, ACS, CHF, PE, and cardiac arrest •Renal death**: Death due to ESRD when dialysis treatment was deliberately withheld for any reason

* *Not defined within protocol; strictly included to give examples for readers.* ***Defined within study protocol.*

Secondary endpoints included the following:

- Renal composite of a sustained decline in eGFR of ≥50%, ESRD, or death from renal causes
- CV composite of hospitalization for heart failure or death from CV causes
- All-cause mortality

Statistical analysis:

- An estimated 681 primary outcome events were needed to detect a 22% lower relative risk in the dapagliflozin group with 90% power using a two-sided alpha of 0.05.
- Intention-to-treat population
- Cox proportional-hazards regression model used to estimate the hazard ratio (HR) and 95% confidence intervals (CI) for primary and secondary outcomes

RESULTS

Baseline Characteristics

Characteristic	Dapagliflozin (n=2152)	Placebo (n=2152)
Age (years)	61.8 ± 12.1	61.9 ± 12.1
Female – n (%)	709 (32.9)	716 (33.3)
White – n (%)	1124 (52.2)	1166 (54.2)
Mean eGFR (mL/min/1.73m^2)	43.2 ± 12.3	43 ± 12.4
eGFR ≥60 – n (%)	234 (10.9)	220 (10.2)
eGFR 45-<60 – n (%)	646 (30.0)	682 (31.7)
eGFR 30-<45 – n (%)	979 (45.5)	919 (42.7)
eGFR <30 – n (%)	293 (13.6)	331 (15.4)
UACR (mg/g) – n (%)		
>1000	1048 (48.7)	1031 (47.9)
Type 2 diabetes – n (%)	1455 (67.6)	1451 (67.4)
CV disease – n (%)	813 (37.8)	797 (37.0)
Heart failure – n (%)	235 (10.9)	233 (10.8)
Previous medication – n (%)		
ACE inhibitor	673 (31.3)	681 (31.6)
ARB	1444 (67.1)	1426 (66.3)
Diuretic	928 (43.1)	954 (44.3)
Statin	1395 (64.8)	1399 (65.0)

A total of 4,304 patients were randomized from February 2017 through March 2020. Characteristics between the two arms were well-balanced at baseline and greater than half of the participants (67.5%) had a diagnosis of diabetes. Most patients had an eGFR of ≥30 mL/min/1.73m^2 at baseline, with only 14% of subjects falling below this value. Nearly 98% of patients in each group were receiving therapy with an ACE inhibitor or an ARB.

At the conclusion, the median follow-up was 2.4 years with a total of 4,289 subjects completing the trial.

Efficacy Outcomes

Primary Endpoints

- The event rates for each component of the primary outcome favored dapagliflozin, with ≥50% decline in eGFR and ESRD components demonstrating statistical significance.
- Dapagliflozin's effect on the primary outcome was consistent between subgroups, including participants *with and without* type 2 diabetes (HR of 0.64 for subjects with diabetes as compared to 0.50 without).
- To prevent one primary outcome event, 19 patients would need to be treated with dapagliflozin 10mg daily for a duration of 2.4 years.

Outcome	Dapagliflozin		Placebo		HR (95% CI)	P-Value
	n (%)	Events/100 patient-yr	n (%)	Events/100 patient-yr		
Primary Endpoint	**197 (9.2)**	**4.6**	**312 (14.5)**	**7.5**	**0.61 (0.51-0.72)**	**<0.001**
≥50% decline in eGFR	112 (5.2)	2.6	201 (9.3)	4.8	0.53 (0.42-0.67)	
ESRD	109 (5.1)	2.5	161 (7.5)	3.8	0.64 (0.50-0.82)	
Death from renal causes	2 (<0.1)	0.0	6 (0.3)	0.1	-	
Death from CV causes	65 (3.0)	1.4	80 (3.7)	1.7	0.81 (0.58-1.12)	

Secondary Endpoints

- The incidence of each secondary outcome was lower in the dapagliflozin group with each demonstrating statistical significance.

Outcome	Dapagliflozin		Placebo		HR (95% CI)	P-Value
	n (%)	Events/100 patient-yr	n (%)	Events/100 patient-yr		
Secondary Endpoint						
Renal composite	142 (6.6)	3.3	243 (11.3)	5.8	0.56 (0.45-0.68)	<0.001
CV composite	100 (4.6)	2.2	138 (6.4)	3.0	0.71 (0.55-0.92)	0.009
All-cause mortality	101 (4.7)	2.2	146 (6.8)	3.1	0.69 (0.53-0.88)	0.004

Safety Outcomes

- Significant adverse effects were more frequent in the placebo arm, with the exception of volume depletion.
- Neither DKA nor severe hypoglycemia were observed in participants without diabetes.
- To prevent the occurrence of any serious adverse event, 22 patients would need to be treated with dapagliflozin 10mg daily for a duration of 2.4 years.

Safety Endpoint	Dapagliflozin – n (%)	Placebo – n (%)	P-Value
Discontinuation due to adverse event	118 (5.5)	123 (5.7)	0.79
Any serious adverse event	633 (29.5)	729 (33.9)	0.002
Amputations	35 (1.6)	39 (1.8)	0.73
Definite or probable DKA	0 (0.0)	2 (<0.1)	0.50
Fracture	85 (4.0)	69 (3.2)	0.22
Major hypoglycemia	14 (0.7)	28 (1.3)	0.04
Volume depletion	127 (5.9)	90 (4.2)	0.01
Renal-related adverse event	155 (7.2)	188 (8.7)	0.07

AUTHOR'S CONCLUSION

"Among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of composite sustained decline in the estimated GFR of at least 50%, ESRD, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo."

ARTICLE CRITIQUE

Overall Strengths

- Inclusion of patients regardless of type 2 diabetes diagnosis
- Inclusion of patients with reduced renal cutoffs (<30 mL/min/1.73m^2) as compared to previous studies
- Patients were stabilized on maximum tolerated of an ACE inhibitor or ARB
- Established endpoints that were clinically meaningful

Overall Limitations

- Increased potential for bias as study was funded by AstraZeneca
- Use of composite primary outcome
- Exclusion of individuals without evidence of proteinuria and low percentage of black participants
- Early trial conclusion (overestimate primary outcome)

Conclusion and Impact on Practice

- DAPA-CKD builds on the existing body of evidence for the use of SGLT2 inhibitors to enhance renal and CV outcomes. However, this study is unique in that it examined SGLT2 inhibitor use in patients with and without a diagnosis of type 2 diabetes.
- This study supports the use of SGLT2 inhibitors as adjunctive therapy in patients with CKD who are receiving the standard of care to reduce the risk of renal function decline, onset of ESRD leading to transplantation or dialysis, and death from renal or CV causes independent of diabetes diagnosis.

References:

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2. Davidson JA. SGLT2 inhibitors in patients with type 2 diabetes and renal disease: overview of current evidence. *Postgrad Med.* 2019;131(4):251-260.
3. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease (DAPA-CKD). *N Engl J Med*. 2020;383(15):1436-1446.

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