OVERVIEW	
Citation	▪ Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med.* 2020; 383(15):1436-1446. Doi: 10.1056/NEJMoa2024816
Location	▪ The study was conducted in 386 sites in 21 countries.
Funding	▪ The study was funded by Astra-Zeneca.
INTRODUCTION	
Background	▪ Dapagliflozin (Farxiga®) is an SGLT2i used in conjunction with diet and exercise to enhance glycemic control in adults with T2DM. According to the KDIGO guideline, patients with T2DM, CKD, and an eGFR $\geq$20 ml/min/1.73m^2 should be treated with an SGLT2i.
Objectives	▪ To determine if dapagliflozin (Farxiga®) could be used to enhance the kidney health of patients with CKD in addition to its established use in the management of diabetes.
METHODS	
Study Design	▪ Randomized, double-blind, placebo-controlled, multicenter clinical trial that took place from February 2, 2017 – June 12, 2020. ▪ Patients were stratified according to their T2DM diagnosis and urinary albumin-to-creatinine ratio ($<$1000 or >1000).
Inclusion Criteria	▪ Adults with or without T2DM ▪ Patients must be on an ACE inhibitor or ARB for a minimum of four weeks prior to screening, unless it is documented that they are unable to take the medication ▪ eGFR between 25-75 mL/min/1.73m2 of BSA and a urine albumin-to-creatinine ratio between 200 and 5000
Exclusion Criteria	▪ T1DM ▪ Polycystic kidney disease ▪ Immunotherapy for primary or secondary kidney disease within 6 months of enrollment ▪ Lupus nephritis ▪ Antineutrophil cytoplasmic antibody-associated vasculitis
Interventions	▪ Dapagliflozin 10 mg PO once daily or matching placebo. ▪ Following randomization, patients were evaluated in-person at 2-week, 2-, 4-, and 8-month, and 4-month intervals. During the period of follow-up, the researchers monitored the patients' progression over time and collected data including vital signs, blood and urine samples, concomitant therapies, adverse events, and adherence.
Primary Endpoint	▪ The primary composite outcome was the first occurrence of at least a 50% decline in eGFR, the onset of ESRD, or mortality from renal or cardiovascular complications.
Secondary Endpoints	▪ The secondary composite kidney outcome consisted of a 50% sustained decline in eGFR, ESRD, or death caused by renal complications. The composite cardiovascular outcome consists of hospitalization for heart failure or death from cardiovascular causes, in addition to all cause-mortality.
Safety Endpoints	▪ All adverse events that occurred prior to or during the trial's conclusions were analyzed for safety. This includes severe hypoglycemia, symptoms of volume depletion, renal complications, bone fractures, amputations, and DKA.
Statistical Analyses	▪ The researchers aimed for 90% power and a significance level of 0.05. In addition, a closed testing procedure was used to analyze the primary and secondary outcomes in order to reduce the risk of type 1 error at a two-sided alpha level of 0.05. ▪ The primary efficacy outcome was conducted on the intention-to-treat population, which included all patients who were randomized. ▪ For the primary and secondary outcomes, a cox proportional-hazards regression model was used to find the risk ratio and 95% confidence intervals for dapagliflozin compared to placebo. ▪ A safety analysis was conducted on all adverse effects before or at the trail closure visit.
RESULTS	
Enrollment	▪ 7517 adults were screened, and 4,304 were randomized. ▪ Dapagliflozin (group 1): N=2,152 ▪ Placebo (group 2): N=2,152 ▪ 274 patients (12.7%) in the dapagliflozin group had to discontinue treatment for reasons other than mortality, compared to 309 patients (14.4%) in the placebo group. ▪ 4,289 patients (99.7%) completed the trail.
Baseline Characteristics	▪ The two groups shared similar baseline characteristics. These include medications that the patients were using to treat their CKD and T2DM. The median urinary albumin-to-creatinine ratio was 949, the mean (+SD) age was 61.81±12 years, the mean eGFR was 43.1±12.4 mL/min/1.73m^2, and 2906

participants (67.5%) had been given a T2DM diagnosis.
- ACE inhibitors (31.3% vs. 31.6%), ARBs (67.1% vs. 66.3%), diuretics (43.1% vs. 44.3%), and statins (64.8% vs. 65.0%) were equally distributed between the two groups of patients.

Primary Endpoint

Primary Outcome	**Dapagliflozin** *No. /total no. (%)*	**Placebo** *No. /total no. (%)*	**Hazard Ratio (95% CI)**	**P Value**
Primary Composite Outcome	197/2152 (9.2)	312/2152 (14.5)	0.61 (0.51–0.72)	<0.001
Decline in EGFR ≥50%	112/2152 (5.2)	201/2152 (9.3)	0.53 (0.42–0.67)	N/A
EDRD	109/2152 (5.1)	161/2152 (7.5)	0.64 (0.50–0.82)	N/A
Mortality from renal causes	2/2152 (<0.1)	6/2152 (0.3)	N/A	N/A
Morality from CV causes	65/2152 (3.0)	80/2152 (3.7)	0.81 (0.58–1.12)	N/A

Secondary Endpoints

Secondary Outcomes	**Dapagliflozin** *No. /total no. (%)*	**Placebo** *No. /total no. (%)*	**Hazard Ratio (95% CI)**	**P Value**
Composite of decline in eGFR of ≥50%, ESRD, or death from renal causes	142/2152 (6.6)	243/2152 (11.3)	0.56 (0.45–0.68)	<0.001
Composite of death from CV causes or hospitalization for HF	100/2152 (4.6)	138/2152 (6.4)	0.71 (0.55–0.92)	0.009
All-cause mortality	101/2152 (4.7)	146/2152 (6.8)	0.69 (0.53–0.88)	0.004

Safety Endpoints

Adverse Events	**Dapagliflozin** *No. /total no. (%)*	**Placebo** *No. /total no. (%)*	**P Value**
Serious ADE	663/2149 (29.5)	729/2149 (33.9)	0.002
Amputations	35/2149 (1.6)	39/2149 (1.8)	0.73
Definite or probable diabetic ketoacidosis	0/2149	2/2149 (<0.1)	0.50
Fracture	85/2149 (4.0)	69/2149 (3.2)	0.22
Renal-related	155/2149 (7.2)	188/2149 (8.7)	0.07
Severe hypoglycemia	14/2149 (0.7)	28/2149 (1.3)	0.04
Volume depletion	127/2149 (5.9)	90/2149 (4.2)	0.01

AUTHORS' CONCLUSIONS

Dapagliflozin significantly reduced the risk of a sustained decline in eGFR of at least 50%, end-stage kidney disease, and death from kidney or heart disease in patients with chronic kidney disease, with or without diabetes.

OVERALL STUDY EVALUATION

Strengths
- Double-blinded: Both patients and researchers were blinded in the study. Dapagliflozin and placebo were packaged identically, with identical tablet appearance, labeling, and administration schedules, reducing the risk of performance bias.
- Placebo-controlled: Using a placebo was appropriate due to the fact there isn't a particular medication that is frequently combined to an ACE inhibitor or an ARB in CKD.

Limitations
- Results: P values for the individual components of the primary composite endpoints were not provided.
- Inclusion/Exclusion Criteria: Patients with CKD who didn't have albuminuria were excluded from the study. Therefore, this analysis may not be applicable to the patient population classified as having CKD due to reduced eGFR without albuminuria.

Clinical Impact
- Patients receiving dapagliflozin had a lower mortality rate than those who were not (4.7% versus 6.8%). This indicates that these results were not only statistically significant, but also clinically significant, as there were fewer deaths among dapagliflozin-treated patients than among placebo-treated patients. Furthermore, the NNT to prevent one primary outcome was 19.

LEADER'S CONCLUSION

CKD is a chronic, progressive condition, and the kidneys are vital organs that remove waste, excess fluids, and toxins from the blood into the urine. Dapagliflozin can effectively manage CKD in patients with or without type 2 diabetes and enhance long-term outcomes because it decreases albuminuria, slows the decline in eGFR, and is well tolerated.