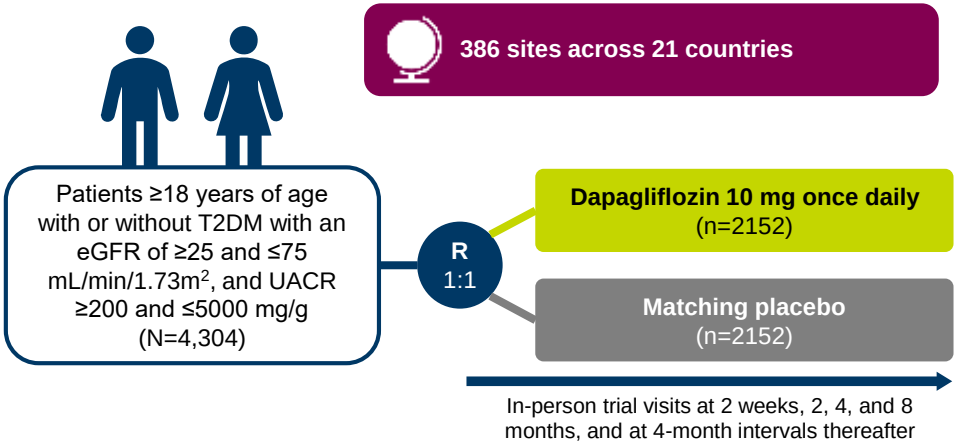
DAPA-CKD trial

Study design

Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) was a randomized, double-blind, placebo-controlled, multicenter trial designed to assess the long-term renal efficacy and safety of the SGLT-2 inhibitor dapagliflozin in patients with CKD, with or without T2DM.



Primary efficacy endpoint:

First occurrence of any of the following:

- A decline of ≥50% in eGFR[a]
- The onset of ESKD[b]
- Death from renal or CV causes

Secondary efficacy endpoints:

- The composite kidney outcome of a sustained decline in eGFR of ≥50%, ESKD, or death from renal causes
- A composite CV outcome defined as hospitalization for HF or death from CV causes
- Death from any cause

[a] Confirmed by a second serum creatinine measurement after ≥28 days; [b] Defined as maintenance dialysis for ≥28 days, kidney transplantation, or an eGFR of <15 mL/min/1.73m² confirmed by a second measurement after ≥28 days.

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CABG; coronary artery bypass grafting; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SGLT2, sodium glucose co-transporter 2; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TIA, transient ischemic attack; UACR, urine albumin to creatinine ratio.

Inclusion criteria

- ✓ Provision of signed informed **consent** prior to any study specific procedures
- ✓ Female or male aged **≥18 years** at the time of consent
- ✓ **eGFR ≥25 and ≤75 mL/min/1.73m²** at visit 1
- ✓ **UACR ≥200 and ≤5000 mg/g** at visit 1
- ✓ Stable, and for the patient maximum tolerated labelled daily dose, **treatment with ACE or ARB ≥4 weeks** before visit 1, if not medically contraindicated

Exclusion criteria

- X A documented **diagnosis of T1DM**; **polycystic kidney disease**; **lupus nephritis**; **antineutrophil cytoplasmic antibody-associated vasculitis**
- X Receiving **cytotoxic therapy**, **immunosuppressive therapy,** or other **immunotherapy** for primary or secondary renal disease within **6 months prior** to enrolment
- X History of **organ transplantation**
- X Receiving therapy with a **SGLT2 inhibitor within 8 weeks prior** to enrolment or previous **intolerance** of an SGLT2 inhibitor
- X **NYHA class IV CHF** at the time of enrolment
- X **MI, unstable angina, stroke, or TIA within 12 weeks prior** to enrolment
- X **Coronary revascularization** (PCI or CABG) or **valvular repair/replacement within 12 weeks prior** to enrolment or planned after randomization

Primary efficacy data

Over a median of 2.4 years, a primary composite endpoint event occurred in **197 patients (9.2%)** in the dapagliflozin group and **312 patients (14.5%)** in the placebo group, with a relative risk reduction (RRR) of 39% in the dapagliflozin group (**HR 0.61**; 95% CI 0.51–0.72; **P<0.001**).

- The number of patients who needed to be treated during the trial period to prevent one primary outcome event was **19** (95% CI 15–27)
- The hazard ratio for all components of the composite endpoint favored dapagliflozin
- The effect of dapagliflozin on the primary composite endpoint was consistent across pre-specified subgroups:
  - Patients with T2DM: RRR: 36% **HR 0.64** (95% CI 0.52 to 0.79)
  - Patients without T2DM: RRR: 50% **HR 0.50** (95% CI 0.35 to 0.72)

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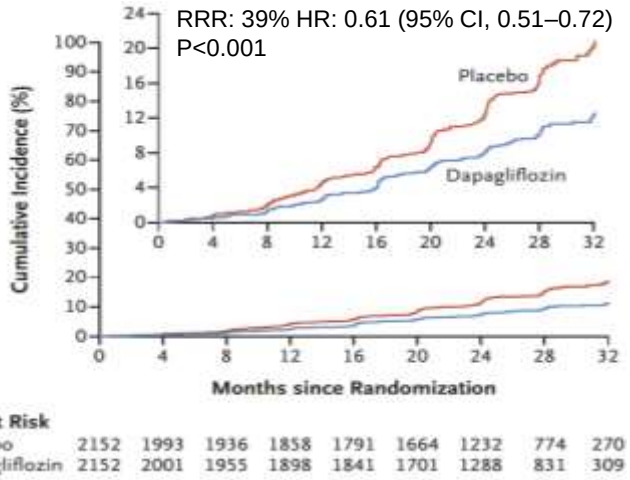

Secondary efficacy data

The incidence of each secondary outcome was **lower in the dapagliflozin group** than in the placebo group.

Outcome	Dapagliflozin (n=2152) Patients, n (%)	Dapagliflozin (n=2152) Events/ 100 pt-yr	Placebo (n=2152) Patients, n (%)	Placebo (n=2152) Events/ 100 pt-yr	HR (95% CI)	P value
Composite of decline in eGFR of ≥50%, ESKD, or death from renal causes	142 (6.6)	3.3	243 (11.3)	5.8	0.56 (0.45–0.68)	<0.001
Composite of death from CV causes or hospitalization for HF	100 (4.6)	2.2	138 (6.4)	3.0	0.71 (0.55–0.92)	0.009
Death from any cause	101 (4.7)	2.2	146 (6.8)	3.1	0.69 (0.53–0.88)	0.004

AE, adverse event; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; HR, hazard ratio; SE, standard error; T2DM, type 2 diabetes mellitus.

- The **mean eGFR at baseline in the dapagliflozin group was 43.2 ml/min/1.73m²** of body-surface area and 43.0 ml/min/1.73m² in the placebo group
- The least-squares mean (±SE) eGFR slopes from baseline to 30 months in the dapagliflozin and placebo groups were –2.86±0.11 and –3.79±0.11 ml/min/1.73m²/year, respectively, resulting in a **between-group difference of 0.93 ml/min/1.73m²/year** (95% CI, 0.61 to 1.25)
  - During the **first 2 weeks, there was a greater reduction in the eGFR in the dapagliflozin group** than in the placebo group
  - The **annual change in the mean eGFR was smaller with dapagliflozin** than placebo

Safety

The incidences of **AEs and serious AEs were similar** overall in the dapagliflozin and placebo groups.

Outcome‡	Dapagliflozin (n=2149) Patients, n (%)	Placebo (n=2149) Patients, n (%)	P value
Discontinuation due to AE	118 (5.5)	123 (5.7)	0.79
Any serious AE	633 (29.5)	729 (33.9)	0.002
Amputation§	35 (1.6)	39 (1.8)	0.73
Any definite or probable diabetic ketoacidosis	0	2 (<0.1)	0.50
Fracture¶	85 (4.0)	69 (3.2)	0.22
Renal-related adverse event¶	155 (7.2)	188 (8.7)	0.07
Major hypoglycemia‖	14 (0.7)	28 (1.3)	0.04
Volume depletion¶	127 (5.9)	90 (4.2)	0.01

‡Safety analyses included all the participants who had undergone randomization and received at least one dose of dapagliflozin or placebo. §Shown are cases of surgical amputation or spontaneous or nonsurgical amputation, excluding amputation due to trauma. ¶These outcomes are based on a predefined list of preferred terms. ‖The following criteria were confirmed by the investigator: symptoms of severe impairment in consciousness or behavior, need of external assistance, intervention to treat hypoglycemia, and prompt recovery from acute symptoms after the intervention.

- **Diabetic ketoacidosis** was not reported in any participants who received dapagliflozin and in 2 patients who received placebo
- Neither **diabetic ketoacidosis nor severe hypoglycemia** was observed in participants **without T2DM**
- There was **1 confirmed case of Fournier's gangrene** in the placebo group

1. Heerspink HJL et al. Dapagliflozin in patients with chronic kidney disease. *NEJM* 2020; 383: 1436-1446. 2. Heerspink HJL et al. Dapagliflozin in patients with chronic kidney disease (Supplementary Appendix). *NEJM* 2020; 1-54.