A pre-specified analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial on the incidence of abrupt declines in kidney function

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This pre-specified analysis of DAPA-CKD assessed the impact of sodium-glucose cotransporter 2 inhibition on abrupt declines in kidney function in high-risk patients based on having chronic kidney disease (CKD) and substantial albuminuria. DAPA-CKD was a randomized, double-blind, placebo-controlled trial that had a median follow-up of 2.4 years. Adults with CKD (urinary albumin-to-creatinine ratio 200–5000 mg/g and estimated glomerular filtration rate 25–75 mL/min/1.73m^2) were randomized to dapagliflozin 10 mg/day matched to placebo (2152 individuals each). An abrupt decline in kidney function was defined as a pre-specified endpoint of doubling of serum creatinine between two subsequent study visits. We also assessed a post-hoc analysis of investigator-reported acute kidney injury–related serious adverse events. Doubling of serum creatinine between two subsequent visits (median time-interval 100 days) occurred in 63 (2.9%) and 91 (4.2%) participants in the dapagliflozin and placebo groups, respectively (hazard ratio 0.68 [95% confidence interval 0.49, 0.94]). Accounting for the competing risk of mortality did not alter our findings. There was no heterogeneity in the effect of dapagliflozin on abrupt declines in kidney function based on baseline subgroups. Acute kidney injury–related serious adverse events were not significantly different and occurred in 52 (2.5%) and 69 (3.2%) participants in the dapagliflozin and placebo groups, respectively (0.77 [0.54, 1.10]). Thus, in patients with CKD and substantial albuminuria, dapagliflozin reduced the risk of abrupt declines in kidney function.

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Acute kidney injury (AKI) occurs in approximately 13 million individuals globally per year, mainly in hospitalized patients.[1] Although more severe chronic kidney disease (CKD) is known to be associated with elevated AKI risk, emerging data from large epidemiologic studies have demonstrated that episodes of AKI also increase the risk of CKD progression.[2–4] Moreover, AKI is associated with adverse clinical outcomes, including dialysis, cardiovascular disease, and mortality, especially in patients with diabetes and those with significant albuminuria.[4,5]

Large randomized controlled trials in patients with type 2 diabetes have shown that sodium–glucose co-transporter

2 (SGLT2) inhibitors slow progression of the decline in kidney function and reduce the risk of kidney failure. During the early stages of development of SGLT2 inhibitors, concerns were raised that these agents could increase the risk of AKI resulting from hypovolemia, treatment-induced acute reduction in glomerular filtration rate (GFR), and the potential to trigger kidney medullary hypoxic injury. These concerns were supported by early case reports suggesting that risk of AKI is higher among patients with type 2 diabetes mellitus and preserved kidney function who initiated SGLT2 inhibitors.[6] However, large cardiovascular and kidney outcome trials demonstrated that SGLT2 inhibitors could in fact reduce the risk of AKI. The consistency of this finding across multiple trials suggests that this is a class effect and not limited to a specific SGLT2 inhibitor. Moreover, subsequent work has identified biologically plausible mechanisms by which SGLT2 inhibition could reduce AKI risk.[7,8]

Understanding the relationship between SGLT2 inhibition and risk of AKI in patients with CKD and albuminuria is important, as patients with CKD experience higher rates of AKI than patients with normal or near-normal kidney function. The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial demonstrated that the SGLT2 inhibitor dapagliflozin reduced the risk of kidney failure and heart failure hospitalization, and prolonged survival in patients with CKD with and without type 2 diabetes.[9] In this analysis, we report the effect of dapagliflozin on abrupt declines in kidney function. These events were captured in the DAPA-CKD trial as a pre-specified exploratory outcome, defined as the doubling of serum creatinine between 2 subsequent visits. We also compare the frequency of serious AKI adverse events (as reported by investigators) in patients randomized to receive either dapagliflozin or placebo.

METHODS

Study design and participants

DAPA-CKD was a randomized, double-blind, placebo-controlled, multicenter, international trial conducted in 21 countries at 386 study sites. The study design and the primary results have been published previously.[9] Briefly, DAPA-CKD participants were ≥18 years of age, with an estimated GFR (eGFR) ≥25 and <75 ml/min per 1.73 m^2, and a urinary albumin:creatinine ratio (UACR) ≥200 and <5000 mg/g. Patients either with or without type 2 diabetes were eligible for participation. Patients with type 1 diabetes, polycystic kidney disease, lupus nephritis, or anti-neutrophil cytoplasmic antibody–associated vasculitis, as well as those receiving immunotherapy for primary or secondary kidney disease within 6 months prior to enrollment, were excluded. All participants were receiving treatment with a stable dose of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) for ≥4 weeks prior to randomization, unless they had a documented intolerance to these agents. The trial protocol was approved by a central or local ethics committee at each trial site, and all participants provided written informed consent. This study was prospectively registered on ClinicalTrials.gov (NCT03036150) and was posted online on January 30, 2017, prior to enrollment of the first patient.

Randomization and follow-up

Eligible participants were randomly assigned to receive either dapagliflozin, 10 mg daily, or matching placebo. This treatment was to be continued until the occurrence of diabetic ketoacidosis, pregnancy, receipt of disallowed therapy, or study completion. Following randomization, in-person study visits were performed after 2 weeks, at 2, 4, and 8 months, and at 4-month intervals thereafter. At each follow-up visit, vital signs were recorded, blood and urine samples were sent for laboratory assessment, and information on potential study endpoints, adverse events, concomitant therapies, and study drug adherence was collected.

Outcomes

The primary pre-specified outcome of the current analysis was an abrupt decline in kidney function, defined as a doubling of serum creatinine (measured by either a local or central laboratory) compared with the most recent central laboratory serum creatinine value, assessed in the intent-to-treat population. The doubling of serum creatinine was adjudicated by the independent event-adjudication committee, which was blinded to study treatment allocation. The event adjudication committee determined whether the doubling of serum creatinine reflected progression of the underlying CKD or was an abrupt deterioration unrelated to the underlying disease, due rather to another cause, such as infection, volume depletion, or cardiovascular disease events. AKI reported by investigators as a serious adverse event (SAE; i.e., an adverse event that required hospitalization, led to prolongation of hospitalization, or was associated with death) was assessed in the safety population. SAEs were derived from a predefined list of kidney-related events from the preferred terms in the Medical Dictionary for Regulatory Activities. These events were not prospectively adjudicated by the event-adjudication committee. However, 2 independent reviewers who were blinded to study drug assignment determined the most likely cause of AKI SAEs by reviewing narratives submitted by study investigators. Any disagreement was resolved by a third reviewer. We also evaluated all episodes of dialysis, institution of maintenance dialysis (for at least 28 days), and mortality following a doubling of serum creatinine or an AKI SAE. Finally, we assessed the proportion of patients with end-stage kidney disease (ESKD) or renal death, and all-cause mortality from the time of an abrupt decline in kidney function event until the end of the trial.

Statistical analyses

We performed all efficacy analyses in accordance with the intention-to-treat principle. We determined the risk of abrupt declines in kidney function (dapagliflozin vs. placebo) by calculating the time-to-first inter-visit doubling of serum creatinine, applying proportional hazards (Cox) regression, stratified by diabetes status and UACR (≤1000 vs. >1000 mg/g). We tested for homogeneity of treatment effects across pre-specified subgroups, defined by patient's demographics and laboratory measurements, by adding interaction terms to the relevant Cox models. We assessed the validity of the proportional hazards assumption by inspection of the log-cumulative hazard function of each treatment group and by including a term for the interaction between treatment assignment and time as a time-varying covariate. We applied the Fine–Gray modification of the Cox model to determine the subdistribution hazard ratio (HR) of an abrupt decline in kidney function, with death as a competing risk. Factors associated with an abrupt decline in kidney function were collected during the trial and summarized by treatment groups. In addition, dialysis and death outcomes after

an abrupt decline in kidney function were collected and summarized by treatment group.

The relative hazard of ESKD or renal death, or mortality, following an abrupt decline in kidney function, was determined in a companion Cox model into which an indicator of the abrupt decline in kidney function event was fitted as a time-varying covariate (with follow-up time starting at the time of randomization). The period of risk prior to the abrupt decline in kidney function event was attributed to the group with no event, so that calculation of incidence rates would reflect patients' time-updated event status. The model was adjusted for treatment assignment, age, sex, race/ethnicity, HbA1c, eGFR, log-transformed UACR, systolic blood pressure, hemoglobin, body mass index, and history of cardiovascular disease.

In an additional analysis, we performed a causal mediation analysis to examine whether the effect of dapagliflozin in reducing the relative risks of ESKD or renal death, or all-cause mortality, could be explained by the prevention of abrupt declines in kidney function. We used study treatment as the exposure variable, and inter-visit doubling of serum creatinine as a binary mediator. We included age, sex, race, type 2 diabetes status, cardiovascular disease, eGFR, UACR, systolic and diastolic blood pressure, body mass index, and hemoglobin as additional covariates in both the outcome model (a Cox proportional hazards model) and the mediator model (a binary logistic regression model).[10] We determined point estimates for the natural direct effect, the natural indirect effect, and the total effect of dapagliflozin using the estimators provided by Valeri and VanderWeele.[11] We obtained 95% confidence intervals (CIs) through bootstrapping with 1000 bootstrap samples. Effects were calculated for the mean level of the continuous confounders and for the mode of the categorical confounders.

We performed all analyses with R, version 4.0.2 (R Foundation for Statistical Computing) or Stata, version 15 (StataCorp).

RESULTS

Study design and participants

A total of 4304 participants were enrolled in the DAPA-CKD trial, of whom 2152 were randomly assigned to receive dapagliflozin, 10 mg once daily, and 2152 to receive placebo, comprising the intent-to-treat population (Supplementary Figure S1). Three patients in each group were randomized but not treated, comprising the safety population (dapagliflozin, n = 2149; placebo, n = 2149). Mean (SD) age was 62 (12) years; 2906 of 4304 (68%) of the cohort had type 2 diabetes; mean eGFR was 43 (12) ml/min per 1.73 m^2; and median UACR was 949 (interquartile range: 477 to 1885) mg/g. Baseline characteristics were balanced between the dapagliflozin and placebo groups (Table 1).

Table 1 | Baseline characteristics of patients randomized to receive dapagliflozin or placebo

Variable	Dapagliflozin (n = 2152)	Placebo (n = 2152)
Age, yr, mean (SD)	61.8 (12.1)	61.9 (12.1)
≤65	1247 (57.9)	1239 (57.6)
>65	905 (42.1)	913 (42.4)
Sex		
Male	1443 (67.1)	1436 (66.7)
Female	709 (32.9)	716 (33.3)
Race		
White	1124 (52.2)	1166 (54.2)
Black or African American	104 (4.8)	87 (4)
Asian	749 (34.8)	718 (33.4)
Other	175 (8.1)	181 (8.4)
Type 2 diabetes	1455 (67.6)	1451 (67.4)
HbA1c, %, mean (SD)	7.1 (1.7)	7.0 (1.7)
Blood pressure, mm Hg, mean (SD)		
Systolic	136.7 (17.5)	137.4 (17.3)
Diastolic	77.5 (10.7)	77.5 (10.3)
eGFR, ml/min per 1.73 m^2, mean (SD)	43.2 (12.3)	43.0 (12.4)
≥45	880 (40.9)	902 (41.9)
<45	1272 (59.1)	1250 (58.1)
Urinary albumin-to-creatinine ratio, mg/g, median (IQR)	965 (472–1903)	934 (482–1868)
≤1000	1104 (51.3)	1121 (52.1)
>1000	1048 (48.7)	1031 (47.9)
Cardiovascular disease diagnosis	813 (37.8)	797 (37.0)
Heart failure diagnosis	235 (10.9)	233 (10.8)
Diuretic use at baseline	928 (43.1)	954 (44.3)
ACEi or ARB use at baseline	2094 (97.3)	2080 (96.7)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IQR, interquartile range.
Values are n (%), unless otherwise indicated.

Effects of dapagliflozin versus placebo on abrupt declines in kidney function

During a median of 2.4 years (interquartile range, 2.0–2.7 years) of follow-up, there were 166 abrupt decline in kidney-function events, with a median time interval between visits of 100 days (interquartile range, 48–130 days) recorded in 154 patients (Supplementary Figure S2)—63 of 2152 patients (2.9%; event rate 1.4 [95% CI, 1.1–1.7] per 100 patient-years) in the dapagliflozin group, and 91 of 2152 patients (4.2%; event rate 2.0 [95% CI, 1.6–2.5] per 100 patient-years) in the placebo group (HR, 0.68 [95% CI, 0.49–0.94; $P = 0.02$]; incidence rate difference 0.64 [95% CI, 0.09–1.20]). Results were similar using the Fine–Gray model, which accounted for the competing risk of death (subdistribution HR, 0.69 [95% CI, 0.50–0.95; $P = 0.02$]; Figure 1). There was no heterogeneity in the effect of dapagliflozin, compared with placebo, on an abrupt decline in kidney function in pre-specified subgroups. Notably, the effects were consistent in patients with versus without type 2 diabetes and were remarkably similar in patients with a baseline eGFR above versus below 45 ml/min per 1.73 m^2, and those with a UACR above versus below 1000 mg/g (Figure 2). Effects were also similar in subgroups created *post hoc*, of those with baseline diuretic use and those with presence of heart failure at baseline (Figure 2).

Patient characteristics and conditions associated with abrupt declines in kidney function

Participants who developed abrupt declines in kidney function were more likely to be White and less likely to be Asian, had higher systolic blood pressure, HbA1c level, and UACR, were more likely to report a diagnosis of type 2 diabetes, have a history of cardiovascular disease or heart failure, and have a prescription for diuretics at baseline (Supplementary Table S1). During follow-up, volume depletion, dehydration, and infections were the most frequently reported factors associated with abrupt declines in kidney function (Table 2).

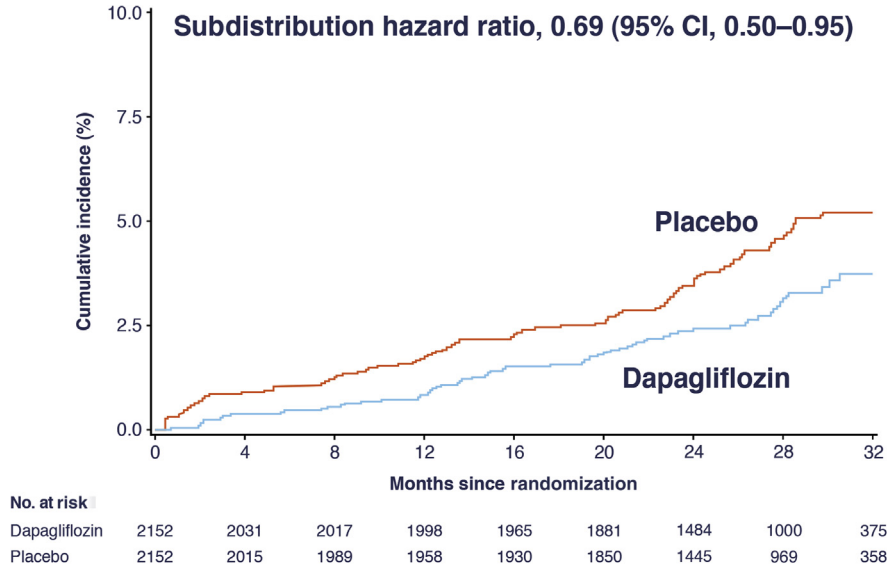


Figure 1 | Shown is the cumulative incidence curve for an abrupt decline in kidney function (at least a doubling of serum creatinine between visits separated by a median of 100 days). Presented are the Aalen–Johansen cumulative incidence estimates, taking into account the competing risk of mortality. CI, confidence interval.

Abrupt decline in kidney function and risk of ESKD and mortality

Following an abrupt decline in kidney function, the rate of ESKD or renal death was 48.7 per 100 patient-years, compared with 2.7 per 100 patient-years for those who did not experience an abrupt decline in kidney function. The risk of death was also increased in those who experienced an abrupt decline in kidney function (Table 3). In a multivariable model including selected baseline variables and treatment assignment, the strong association persisted between doubling of serum creatinine and ESKD or renal death (HR, 13.7 [95% CI, 9.7–19.3]) and mortality (HR, 9.3 [95% CI, 6.6–13.2]; Table 3).

Given that there were fewer doubling of serum creatinine events in the dapagliflozin group compared to the placebo group, and that these events were associated with ESKD and mortality, we explored whether the beneficial effect of dapagliflozin on ESKD and mortality could be explained by its reduction in risk of abrupt declines in kidney function. In a causal mediation analysis model, the direct effect of dapagliflozin (transition from "No AKI" to "ESKD/renal death or mortality" in Figure 3) approximated the total effects, indicating that almost all of the benefit of dapagliflozin on these clinical endpoints occurred through mechanisms distinct from abrupt declines in kidney function (Figure 3).

Effects on AKI-related SAEs

Overall, investigator-reported AKI-related SAEs occurred in 54 of 2149 participants (2.5%; event rate 1.2 per 100 patient-years) in the dapagliflozin group, and 69 of 2149 participants (3.2%; event rate 1.5 per 100 patient-years) in the placebo group (HR, 0.77 [95% CI, 0.54–1.10; $P = 0.15$]; incidence rate difference 0.35 [95% CI, −0.14 to 0.86]). Accounting for the competing risk of mortality did not alter our findings; the effect size for AKI-related SAEs using the Fine–Gray modification of the Cox model was identical (subdistribution HR, 0.77 [95% CI, 0.54–1.10; $P = 0.16$]; Supplementary Figure S3).

DISCUSSION

Initiation of SGLT2 inhibitors is associated[12,13] with an abrupt rise in serum creatinine and a corresponding decline in eGFR of 3–5 ml/min per 1.73 m^2. Prior to the availability of data from cardiovascular safety trials, there was concern among some clinicians that the abrupt rise in creatinine might be a signal of harm related to AKI that had a deleterious effect on survival—an effect amplified in the presence of CKD and increased albuminuria.[4,5] In this analysis from the DAPA-CKD trial, we demonstrated that dapagliflozin, compared with placebo, was associated with a lower risk of an abrupt decline in kidney function. In addition, investigator-reported AKI SAEs occurred less frequently with dapagliflozin, compared with placebo. These data support the favorable benefit–risk profile of dapagliflozin, and endorse the revised clinical practice guidelines recommending the use of SGLT2 inhibitors in patients with CKD.[14]

Long-term safety data from other cardiovascular outcome trials (starting with the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients [EMPA-REG OUTCOME] and subsequently endorsed by other cardiovascular outcome trials) have demonstrated the safety of SGLT2 inhibitors with respect to AKI, and in fact, they have suggested that AKI risk is reduced with these therapies in patients with type 2 diabetes and preserved kidney function.[15] Our observations are also consistent with analyses in patients with type 2 diabetes and CKD from the

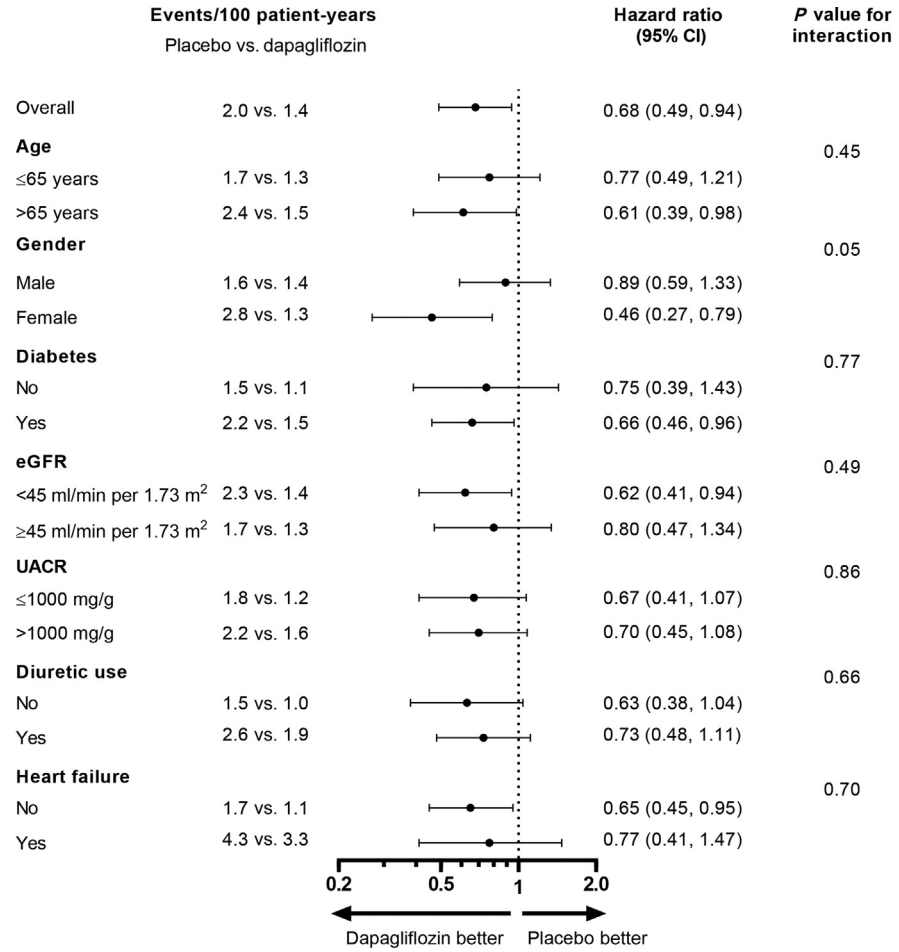


Figure 2 | Forest plot shows the incidence of an abrupt decline in kidney function (at least a doubling of serum creatinine between visits separated by a median of 100 days), by subgroups. CI, confidence interval; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Patients With Diabetic Nephropathy (CREDENCE) trial, in which the HR for AKI SAEs was 0.79 (95% CI, 0.52–1.19).[15] In addition, a network meta-analysis comparing the risk of AKI across different classes of glucose-lowering agents showed that, compared to placebo, SGLT2 inhibitors reduce the risk of AKI, whereas effects were neutral for glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors.[16] Important to note is that the signal for protection against AKI risk was consistent across a range of subgroups, indicating that dapagliflozin is protective even in higher-risk patients, such as those with type 2 diabetes, heart failure, more severe albuminuria, or those already using diuretics. Our results are also in keeping with findings from analyses in the Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (DAPA-HF) trial, in which dapagliflozin reduced the risk of AKI, defined as a doubling of serum creatinine between 2 subsequent visits, by 44%.[17] Finally, this signal of kidney safety in relation to AKI has been mirrored in "real-world evidence" studies involving SGLT2 inhibitors, suggesting that safety in relation to AKI extends to patients who are taking these medications outside of the structure and monitoring integral to clinical trials.[18–21]

These findings have important clinical implications. Estimates indicate that 1,626,098 people in the US meet the DAPA-CKD trial eligibility criteria.[22] When we apply the absolute risk reduction for abrupt declines in kidney function observed in the DAPA-CKD trial to the US population, it would translate into the prevention of 9757 events each year. In the context of the consistent effects of dapagliflozin in preventing abrupt declines in kidney function across regions and patient characteristics, it is expected that many more events would be prevented globally if treatment with dapagliflozin were implemented in clinical practice.

Our data add to an emerging body of evidence demonstrating that acute episodes precede and predict accelerated irreversible decline in kidney function and mortality. DAPA-CKD trial participants who experienced abrupt declines in kidney function experienced an approximately 14-fold higher risk of ESKD or renal death, and a 9-fold higher risk of

Table 2 | Factors associated with abrupt decline-in-kidney-function events

	Total	Dapagliflozin	Placebo
Patients who had an event	154 (3.6)	63 (2.9)	91 (4.2)
Predisposing factors associated with event[a]			
Event adjudicated to be related to underlying disease, n	38	13	25
Event adjudicated to be unrelated to underlying disease,[b] n	116	50	66
Dehydration/volume depletion	21 (20.2)	9 (21.4)	12 (19.4)
Medication-associated	11 (10.6)	2 (4.8)	9 (14.5)
Trauma	1 (1.0)	0 (0.0)	1 (1.6)
Cardiovascular event	6 (5.8)	2 (4.8)	4 (6.5)
Infection/septic shock	24 (23.1)	12 (28.6)	12 (19.4)
Acute exacerbation of existing kidney disease	2 (1.9)	1 (2.4)	1 (1.6)
Other	5 (4.8)	2 (4.8)	3 (4.8)
Unknown	50 (43.1)	22 (44.0)	28 (42.4)
Event			
Requiring dialysis	59 (38.3)	23 (36.5)	36 (39.6)
Requiring maintenance dialysis after AKI	32 (20.8)	13 (20.6)	19 (20.9)
Death after AKI	43 (27.9)	16 (25.9)	27 (29.7)
Recovery of kidney function: Δ serum creatinine at next central laboratory measurement,[c] %			
>25 (no recovery)	55 (56.1)	23 (54.8)	32 (57.1)
0 to ≤25 (partial recovery)	27 (27.6)	12 (28.6)	15 (26.8)
≥0 (full recovery)	16 (16.3)	7 (16.6)	9 (16.1)

AKI, acute kidney injury.
[a]Predisposing factors are reported for patients with available data and in whom the event was unrelated to underlying kidney disease as adjudicated by the independent event-adjudication committee.
[b]Four participants in the placebo group had more than 1 predisposing factor.
[c]Serum creatinine data at the next central laboratory measurement were available in 98 participants.
Seven patients (2 in the dapagliflozin and 5 in the placebo group) discontinued study medication within 28 days after the abrupt decline-in-kidney-function event.
Values are n (%), unless otherwise indicated.

mortality, compared to those who did not. These findings are in accord with those from a meta-analysis of 13 cohort studies demonstrating that patients with AKI had a higher risk of ESKD and mortality.[2] Dedicated studies are needed to examine the possibility that SGLT2 inhibitors could be a viable therapeutic option to prevent AKI and subsequent outcomes for high-risk patients, including those undergoing major surgery, or those with infection at high risk of developing AKI.[2] The Dapagliflozin in Respiratory Failure in Patients with COVID-19 (DARE-19) trial demonstrated that dapagliflozin was well tolerated in hospitalized patients with COVID-19 infection, and AKI events were numerically lower in the dapagliflozin (3.4%) compared to the placebo group (5.5%), although this difference was not statistically significant.[23]

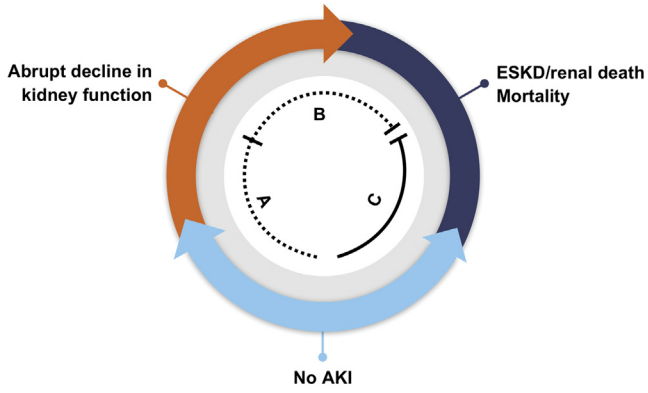
Although the mechanisms by which SGLT2 inhibitors reduce AKI risk are not known, several possibilities exist.[8] First, SGLT2 inhibitors reduce tubular ischemia by attenuating energy-intensive solute reabsorption, a process akin to how beta-blockers reduce myocardial ischemia by reducing cardiac workload.[24] Second, SGLT2 inhibition is associated with a rise in hematocrit, which increases oxygen-carrying capacity and kidney oxygenation, thereby reducing ischemia. Renal oxygenation may be further preserved through optimization of left ventricular filling, thereby maintaining adequate kidney perfusion.[25] Third, SGLT2 inhibitor use is associated with a reduction in the use of loop diuretics, thereby avoiding circulating volume contraction and pre-renal ischemia.[26] Finally, SGLT2 inhibition may preserve capillary architecture and parenchymal perfusion, and protect against apoptosis and ischemia-reperfusion, thereby helping to preserve kidney perfusion and avoid AKI.[27,28]

It has been suggested that the progression of kidney function decline, in some instances, is not linear over time but rather involves multiple AKI episodes that eventually lead to chronic progression of disease.[29] Given that dapagliflozin reduced the incidence of abrupt declines in kidney function, we assessed whether the benefits of dapagliflozin on ESKD or

Table 3 | Association between an abrupt decline in kidney function and ESKD/renal death and mortality

	Without an abrupt decline in kidney function		With an abrupt decline in kidney function		
Outcome	Events	Event rate, 95% CI (events per 100 patient-year)	Events	Event rate, 95% CI (events per 100 patient-year)	Hazard ratio (95% CI)
ESKD or renal death	228	2.7 (2.4–3.1)	44	48.7 (35.4–65.4)	13.7 (9.7–19.3)
Mortality	204	2.2 (1.9–2.6)	43	33.3 (24.1–44.8)	9.3 (6.6–13.2)

CI, confidence interval; ESKD, end-stage kidney disease.
The multivariable adjusted hazard ratio for the association between doubling of serum creatinine events that were not attributed to the underlying disease (n = 116 patients) and subsequent ESKD or renal death was 7.0 (95% CI, 4.4–11.3) and 9.9 (95% CI, 6.8–14.3) for the association with mortality.



Hazard ratio (95% CI)	ESKD/renal death	Mortality
A + B: indirect effect	0.99 (0.95, 1.01)	0.98 (0.96, 1.01)
C: direct effect	0.60 (0.46, 0.75)	0.71 (0.55, 0.93)
Total effect	0.59 (0.45, 0.74)	0.70 (0.55, 0.91)

Figure 3 | Shown is the mediation of effect of dapagliflozin treatment on end-stage kidney disease (ESKD) or all-cause mortality outcomes by abrupt declines in kidney function. The overall effect of dapagliflozin on ESKD/renal death or all-cause mortality can be separated into the indirect effect (**a,b**) and the direct effect (**c**). The direct effect represents the effect of the intervention (dapagliflozin) on these outcomes through pathways unrelated to abrupt declines in kidney function. The indirect effect represents the effect of dapagliflozin on these outcomes as a consequence of its effect on abrupt declines in kidney function. Although the total effect of dapagliflozin can be estimated using the intent-to-treat analysis, estimation of indirect and direct effects requires control of confounding factors that jointly influence abrupt declines in kidney function and the outcomes of ESKD/renal death or all-cause mortality. AKI, acute kidney injury; CI, confidence interval.

renal death, and on mortality, could be explained through its beneficial effect on these acute events. In the multistate model, the direct effect of dapagliflozin on ESKD or renal death and mortality was of the same magnitude as the total effect on these outcomes reported previously, suggesting that the benefit of dapagliflozin on these clinical endpoints was largely independent of its effect on abrupt declines in kidney function.

In this analysis, dapagliflozin reduced the risk of doubling of serum creatinine between 2 subsequent visits. As part of the safety analysis, serious AKI SAEs were also nominally reduced with dapagliflozin. The consistent effects of dapagliflozin on both endpoints support the robustness of our results. This study does have limitations. First, studying AKI in the outpatient setting, in which laboratory testing is not uniform and is often driven by only signs, symptoms, or random tests, may lead to underreporting and differential reporting between groups; however, these limitations apply to any AKI study in the ambulatory setting. Second, although we used an objective definition of abrupt declines in kidney function, we may have missed some events if they occurred and were resolved within the ~3-month time interval between visits. Third, we did not measure biomarkers of AKI and structural tubular damage, such as kidney injury molecular-1 or interleukin-18. Fourth, we recognize that the DAPA-CKD trial dataset does not permit mechanistic insight into why SGLT2 inhibitors reduce AKI risk. Future work should include biomarkers of kidney injury to better elucidate these potential pathways.[23,30] Finally, AKI SAEs were not adjudicated in the DAPA-CKD trial, but they are clinically important as they required hospitalization or prolonged hospitalization, or led to death.

In conclusion, dapagliflozin reduced the risk of an abrupt decline in kidney function in patients with CKD with albuminuria, with and without type 2 diabetes. In the context of similar observations with SGLT2 inhibitors involved in other trials and across different levels of cardiorenal risk, dapagliflozin may be a viable therapeutic option to prevent AKI, a possibility that needs to be confirmed in a dedicated randomized controlled trial.

APPENDIX
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DISCLOSURE

HJLH is consultant for AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Pharma, Gilead, Janssen Pharmaceuticals, Merck, Mundipharma, Mitsubishi Tanabe, Novo Nordisk, and Retrophin; and has received research support from AbbVie, AstraZeneca, Boehringer Ingelheim, and Janssen Pharmaceuticals. DC has received honoraria from Boehringer Ingelheim, Lilly, Merck, AstraZeneca, Sanofi, Mitsubishi-Tanabe, AbbVie, Janssen Pharmaceuticals, Bayer, Prometic, Bristol Myers Squibb, and Novo Nordisk; and has received operational funding for clinical trials from Boehringer Ingelheim-Lilly, Merck, Janssen Pharmaceuticals, Sanofi, AstraZeneca, and Novo Nordisk. DP has nothing to declare. BVS, CDS, and AML are employees and stockholders of AstraZeneca. GMC has received fees from AstraZeneca for the DAPA-CKD trial steering committee, and research grants from the National Institute of Diabetes and Digestive and Kidney Diseases and Amgen; is on the board of directors for Satellite Healthcare; has received fees for advisory boards for Baxter, Cricket, DiaMedica, and Reata; holds stock options for Ardelyx, CloudCath, Durect, DxNow, and Outset; has received fees from Akebia, Sanifit, and Vertex for trial steering committees; and has received fees for Data Safety Monitoring Board service from Angion, Bayer, and ReCor. JPD has received fees from AstraZeneca for the conduct of this study; has received fees from Sanofi-Aventis and CSL Behring as part of a steering committee; has received fees from Novo Nordisk for outcome adjudication for a trial; has received fees from Goldfinch Bio, Birdrock Bio, and Boehringer Ingelheim for study design; and received personal fees from Bayer. TG has received grants for statistical consulting from AstraZeneca, CSL, and Boehringer Ingelheim; and personal fees from Janssen Pharmaceuticals, DURECT Corporation, and Pfizer for statistical consulting. MK reports receiving research grants from Boehringer Ingelheim and AstraZeneca; other research support from AstraZeneca; and honoraria from Boehringer Ingelheim, AstraZeneca, Sanofi, Amgen, Novo Nordisk, Merck (Diabetes), Janssen Pharmaceuticals, Bayer, GlaxoSmithKline, and Applied Therapeutics. JJVM reports payments to his employer, Glasgow University, for his work on clinical trials, consulting, and other activities from Alnylam, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Cardurion, Cytokinetics, GlaxoSmithKline, Novartis, Pfizer, and Theracos; and personal lecture fees from the Corpus, Abbott, Hickma, Sun Pharmaceuticals, and Medsca. RC-R has received honoraria from AstraZeneca, GlaxoSmithKline, Medtronic, and Boehringer Ingelheim; has lectured for Amgen, Janssen Pharmaceuticals, and Boehringer Ingelheim; and has received research support from GlaxoSmithKline, Novo Nordisk, and AstraZeneca. PR has received honoraria paid to Steno Diabetes Center Copenhagen for consultancy from AstraZeneca, Bayer, Boehringer Ingelheim, Gilead, Novo Nordisk, Sanofi, Eli Lilly, and research support from AstraZeneca and Novo Nordisk. RDT is a consultant for AstraZeneca, Amgen, Akebia, Quest Diagnostic, Bayer, Boehringer Ingelheim, Reata, and Relypsa. DCW provides ongoing consultancy services to AstraZeneca and has received honoraria and/or consultancy fees from Amgen, Astellas, AstraZeneca, Boehringer Ingelheim, Bayer, GlaxoSmithKline, Janssen Pharmaceuticals, Napp, Mundipharma, Merck Sharp and Dohme, Reata, Tricida, and Vifor Fresenius.

DATA AVAILABILITY STATEMENT

Data underlying the findings described in this article may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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AUTHOR CONTRIBUTIONS

HJLH and DC were involved in the study design, conduct of the study, data analysis, and interpretation of the data; and they wrote the first draft of the manuscript. DCW, GMC, JJVM, TG, RC-R, PR, and RDT are members of the study's executive committee and were involved in the study design, data collection, and analysis/interpretation of the data. DP performed the data analyses. AML, CDS, and BVS were involved in the study design, conduct of the study, and interpretation of data. JPD was involved in data collection and interpretation. MK was involved in the interpretation of the data. All the authors reviewed the manuscript drafts for important intellectual content, provided approval of the final version for submission, and take responsibility for the accuracy and integrity of the data, including ensuring that any questions are appropriately investigated and resolved. HJLH is the guarantor and corresponding author, and as such accepts full responsibility for the overall content of the work and conduct of the study, had access to the data, and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Participant flow diagram. From *The New England Journal of Medicine*. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, Mann JFE, McMurray JJV, Lindberg M, Rossing P, Sjöström CD, Toto RD, Langkilde AM, Wheeler DC, for the DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease, volume 383, pages 1436–1446, Copyright © 2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Figure S2. Distribution of time interval between 2 subsequent visits to determine doubling of serum creatinine. Exclusion of 16 patients for whom the time difference between 2 serum creatinine measurements was more than 8 months did not change the primary result (subdistribution hazard ratio for effect of dapagliflozin compared with placebo on abrupt declines in kidney function was 0.70 (95% confidence interval [CI], 0.50–0.98).

Figure S3. Cumulative incidence curve for the incidence of acute kidney injury (AKI), defined as a serious adverse event (SAE) of AKI.

Table S1. Baseline characteristics of patients with and without abrupt declines in kidney function during follow-up.

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