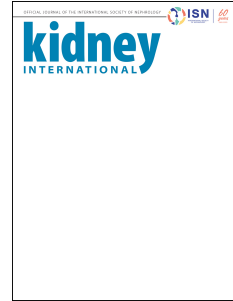


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A pre-specified analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial on the incidence of abrupt declines in kidney function.

Hiddo J.L. Heerspink, PhD, David Cherney, MD, Douwe Postmus, PhD, Bergur V. Stefánsson, MD, Glenn M. Chertow, MD, Jamie P. Dwyer, MD, Tom Greene, PhD, Mikhail Kosiborod, MD, Anna Maria Langkilde, MD, John J.V. McMurray, MD, Ricardo Correa-Rotter, MD, Peter Rossing, MD, C David Sjöström, MD, Robert D. Toto, MD, David C. Wheeler, MD, for the DAPA-CKD trial committees and investigators

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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.

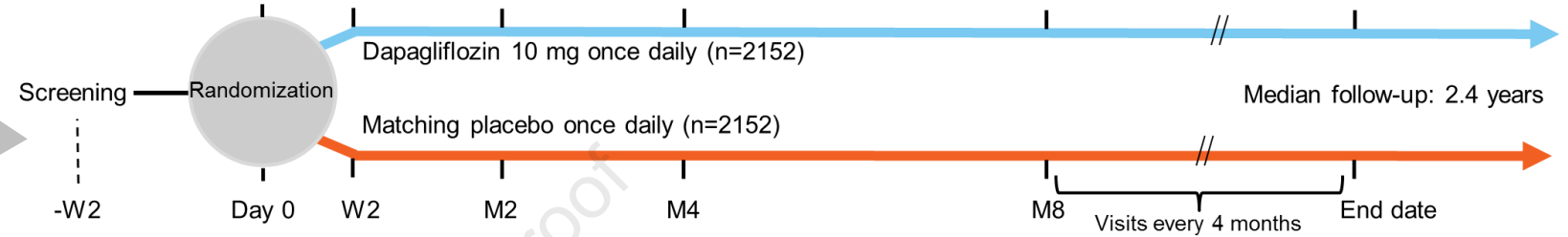
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kidney
INTERNATIONAL



Study design

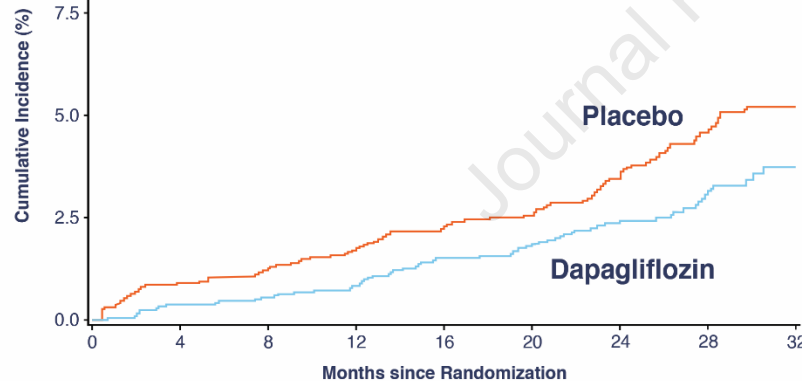
- eGFR 25–75 mL/min/1.73m²
- UACR 200–5000 mg/g
- With/without type 2 diabetes
- Stable, maximally-tolerated ACEi/ARB dose



Outcomes

- Abrupt declines in kidney function, defined as a doubling of serum creatinine between two subsequent visits (median time-interval, 100 days)
- Investigator-reported SAEs of acute kidney injury (pre-defined list)

Sub-distribution hazard ratio, 0.69 (95% CI, 0.50–0.95)



No. at Risk	0	4	8	12	16	20	24	28	32
Dapagliflozin	2152	2031	2017	1998	1965	1881	1484	1000	375
Placebo	2152	2015	1989	1958	1930	1850	1445	969	358

Results

- Dapagliflozin reduced the risk of abrupt declines in kidney function in patients with chronic kidney disease with increased albuminuria (Figure)
- No heterogeneity in effect of dapagliflozin versus placebo across baseline subgroups
- SAEs of acute kidney injury occurred less frequently with dapagliflozin versus placebo

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eGFR=estimated glomerular filtration rate; SAE=serious adverse event; UACR=urinary albumin-to-creatinine ratio

CONCLUSION: Dapagliflozin reduced the risk of abrupt declines in kidney function in patients with chronic kidney disease and substantial albuminuria, with and without type 2 diabetes

[QUERY TO AUTHOR: title and abstract rewritten by Editorial Office – not subject to change]

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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Abstract (1540/1500 characters including spaces)

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 severe albuminuria. DAPA-CKD was a randomized, double-blind, placebo-controlled trial 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/1.73m²) 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.

Keywords

Dapagliflozin, SGLT2 inhibitors, chronic kidney disease, acute kidney injury

Introduction

Acute kidney injury (AKI) occurs in approximately 13 million individuals globally per year, of which the majority occur in hospitalized patients.¹ While it is known that more severe chronic kidney disease (CKD) is associated with elevated AKI risk, emerging data from large epidemiological studies have also demonstrated that episodes of AKI 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 in 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 earlier 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 of triggering kidney medullary hypoxic injury. These concerns were supported by early case reports suggesting increased risk of AKI 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 whereby SGLT2 inhibition could reduce AKI risk.^{7,8}

Understanding the relation between SGLT2 inhibition and risk of AKI in patients with CKD and albuminuria is relevant since 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 doubling of serum creatinine between two subsequent visits. We also compare the frequency of serious AKI adverse events (as reported by investigators) in patients randomized to dapagliflozin or placebo.

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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 estimated GFR (eGFR) ≥ 25 and < 75 mL/min/1.73m² and urinary albumin:creatinine ratio (UACR) ≥ 200 and < 5000 mg/g. Patients with and without type 2 diabetes were eligible for participation. Patients with type 1 diabetes, polycystic kidney disease, lupus nephritis, or ANCA-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 there was 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 posted online on the 30 January 2017, prior to enrolment of the first patient.

Randomization and follow-up

Eligible participants were randomly assigned to receive dapagliflozin 10 mg daily or matching placebo. Study drug 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, 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 were 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 (either a local or central laboratory result) since 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 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 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 which required hospitalization, led to prolongation of hospitalization or was associated with death) was assessed in the safety population. SAEs were derived from a pre-defined list of kidney-related events from the Medical Dictionary for Regulatory Activities preferred terms. These events were not prospectively adjudicated by the event adjudication committee. However, two 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 versus placebo) by calculating the time-to-first inter-visit doubling of serum creatinine, applying proportional hazards

(Cox) regression, stratified by diabetes status and UACR ($\leq 1\ 000$ vs $>1\ 000$ 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 an interaction term 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 of an abrupt decline in kidney function with death as a competing risk. Factors associated with the occurrence of 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 end-stage kidney disease or renal death, or mortality following an abrupt decline in kidney function was determined in a companion Cox model where an indicator of the abrupt decline in kidney function event was fitted into the model 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 for calculation of incidence rates that 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 through 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 estimated 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% CIs through bootstrapping with 1,000 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) or Stata version 15 (StataCorp 2017 College Station TX).

Results

Study design and participants

A total of 4304 participants were enrolled in DAPA-CKD of whom 2152 were randomly assigned to dapagliflozin 10 mg once daily and 2152 to placebo, comprising the intent-to-treat population (**Figure S1**). Three patients in each group were randomized but not treated, comprising the safety population (dapagliflozin n=2149; placebo n=2149). Mean (standard deviation) age was 62 (12) years, 2906/4304 (68%) of the cohort had type 2 diabetes, mean eGFR was 43 (12) mL/min/1.73m² and median UACR was 949 (interquartile range [IQR] 477 to 1885) mg/g. Baseline characteristics were balanced between the dapagliflozin and placebo group (**Table 1**).

Effects of dapagliflozin compared to placebo on abrupt declines in kidney function

During a median of 2.4 [IQR 2.0 to 2.7] years of follow-up, there were 166 abrupt decline in kidney function events, with a median time-interval between visits of 100 [IQR 48 to 130] days recorded in 154 patients (**Figure S2**); 63/2152 patients (2.9%, event rate 1.4 [95%CI 1.1 to 1.7] per 100 patient-years) in the dapagliflozin group and 91/2152 patients (4.2%, event rate 2.0 [95%CI 1.6 to 2.5] per 100 patient-years) in the placebo group (hazard ratio 0.68 [95% CI 0.49 to 0.94; $P=0.02$]; incidence rate difference 0.64 [95%CI 0.09 to 1.20]). Results were similar using the Fine-Gray model, which accounted for the competing risk of death (sub-distribution hazard ratio 0.69 [95% CI 0.50 to 0.95; $P=0.02$]; **Figure 1**). There was no heterogeneity in the effect of dapagliflozin compared to placebo on an abrupt decline in kidney function in pre-specified subgroups. Notably, the effects were consistent in patients with and without type 2 diabetes, and were remarkably similar in patients with a baseline eGFR above or below 45 mL/min/1.73m², or UACR above or below 1000 mg/g (**Figure 2**). Effects were also similar in *post-hoc* created subgroups of baseline diuretic use or 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 a higher systolic blood pressure, HbA1c, and UACR, were more likely to report a diagnosis of type 2 diabetes, a history of cardiovascular disease or heart failure, and have a prescription for diuretics at baseline (**Table S1**).

During follow-up, volume depletion and dehydration and infections were the most frequently reported factors associated with abrupt declines in kidney function (**Table 2**).

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 between doubling of serum creatinine and ESKD or renal death (hazard ratio 13.7 [95% CI 9.7 to 19.3]) and mortality (hazard ratio 9.3 [95% CI 6.6 to 13.2]), persisted (**Table 3**).

Since there were fewer doubling of serum creatinine events in the dapagliflozin compared to placebo group and 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 serious adverse events

Overall, investigator-reported AKI SAEs occurred in 54/2149 participants (2.5%; event rate 1.2 per 100 patient-years) in the dapagliflozin group and 69/2149 participants (3.2%; event rate 1.5 per 100 patient-years) in the placebo group (hazard ratio 0.77 [95% CI: 0.54 to 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 SAEs using the Fine-Gray modification of the Cox model was identical (sub-distribution hazard ratio 0.77 [95% CI: 0.54 to 1.10; $P=0.16$] Figure S3).

Discussion

Initiation of SGLT2 inhibitors is associated with an abrupt rise in serum creatinine and a corresponding decline in eGFR of between 3–5 mL/min/1.73m².^{12,13} Prior to the availability of data from cardiovascular safety trials, there was concern among some clinicians that the abrupt rise in creatinine reflected a possible signal of harm related to AKI which has a deleterious effect on survival - an effect that is amplified in the presence of CKD and increased albuminuria.^{4,5} In this analysis from the DAPA-CKD trial, we demonstrated that dapagliflozin compared to 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 to placebo. These data support the favorable benefit-risk profile of dapagliflozin and endorse evolving 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 EMPA-REG OUTCOME trial and subsequently endorsed by other cardiovascular outcome trials have demonstrated the safety of SGLT2 inhibitors with respect to AKI, and in fact 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 CREDENCE trial where the hazard ratio for AKI SAEs was 0.79 (95% CI 0.52 to 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, while effects were neutral for glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors.¹⁶ Importantly, 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 analyses from the DAPA-HF trial in which dapagliflozin reduced the risk of AKI, defined as a doubling of serum creatinine between two subsequent visits, by 44%.¹⁷ Finally, this signal of kidney safety around the issue

of AKI has been mirrored in “real-world evidence” studies involving SGLT2 inhibitors, suggesting that safety around AKI extends to patients taking these medications outside of the structure and monitoring that is integral to clinical trials.¹⁸⁻²¹

These findings have important clinical implications. It has been estimated that 1,626,098 people in the United States meet the DAPA-CKD 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 participants who experienced abrupt declines in kidney function experienced an approximately 14-fold higher risk of ESKD or renal death and 9-fold higher risk of mortality compared to those who did not. These findings are in accord with 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 in patients with infection at high risk of developing AKI.² The DARE-19 trial demonstrated that dapagliflozin was well tolerated in hospitalized patients with COVID-19 infection, and although not statistically significant, AKI events were numerically lower in the dapagliflozin (3.4%) compared to the placebo group (5.5%).²³

While the mechanisms responsible for reducing AKI risk with SGLT2 inhibitors are not known, several possibilities exist.⁸ Firstly, SGLT2 inhibitors reduce tubular ischemia by attenuating energy-intensive solute reabsorption, akin to how beta-blockers are used to reduce myocardial ischemia by reducing cardiac workload.²⁴ Secondly, SGLT2 inhibition is associated

with a rise in hematocrit, thereby increasing 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 Thirdly, 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 involves multiple AKI episodes that eventually lead to chronic progression of disease.²⁹ Since dapagliflozin reduced the incidence of abrupt declines in kidney function, we assessed whether the benefits of dapagliflozin on ESKD or renal death and 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 two 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. Firstly, studying AKI in the outpatient setting, where laboratory testing is not uniform and often driven only by 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. Secondly, although we use an objective definition of abrupt declines in kidney function, we may have missed some events if they occurred and resolved within the ~3-month time interval between visits. Thirdly, we did not measure biomarkers of AKI and structural tubular damage, such as kidney injury molecular-1 or

interleukin-18. Fourthly, we recognize that the DAPA-CKD 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 DAPA-CKD but they are clinically important since they required hospitalizations, prolonged hospitalizations 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, which has to be confirmed in a dedicated randomized controlled trial.

Supplementary Material

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. *N Engl J Med*. 2020;**383**(15):1436-1446. Copyright © 2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

Figure S2: Distribution of time-interval between two subsequent visits to determine doubling of serum creatinine

Exclusion of 16 patients in whom the time difference between two serum creatinine measurements was more than 8 months did not change the primary result (sub-distribution hazard ratio for effect of dapagliflozin compared with placebo on abrupt declines in kidney function was 0.70 (95%CI 0.50, 0.98))

Figure S3: Cumulative incidence curve for the incidence of AKI, defined as an SAE of AKI

AKI, acute kidney injury; SAE, serious adverse event

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

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IQR, interquartile range

Supplementary information is available at Kidney International's website

Disclosures

HJLH is consultant for AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Pharma, Gilead, Janssen, Merck, Mundipharma, Mitsubishi Tanabe, Novo Nordisk, and Retrophin. He received research support from Abbvie, AstraZeneca, Boehringer Ingelheim and Janssen.

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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, research grants from NIDDK, and Amgen; he is on the board of directors for Satellite Healthcare, has received fees for advisory boards for Baxter, Cricket, DiaMedica, and Reata; and 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 DSMB service from Angion, Bayer and ReCor.

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Author Contribution

HJLH and DC were involved in the study design, conduct of the study, data analysis, interpretation of the data and wrote the first draft of the manuscript. DCW, GMC, JJVMcM, TG, FFH, 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 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.

Data sharing

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at

<https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure>.

Figure legends:

Figure 1: Cumulative incidence curve for the incidence of an abrupt decline in kidney function (at least doubling of serum creatinine between visits separated by median 100 days).

Presented are the Aalen-Johansen cumulative incidence estimates taking into account the competing risk of mortality.

Figure 2: Forest plot for the incidence of an abrupt decline in kidney function (at least doubling of serum creatinine between visits separated by median 100 days), by subgroups

eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

Figure 3: Mediation of effect of dapagliflozin treatment on the 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 decomposed into the indirect effect (A and 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 the 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; ESKD, end-stage kidney disease

Table 1: Baseline characteristics of patients randomized to dapagliflozin or placebo

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

ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IQR, interquartile range

Table 2. Factors associated with abrupt decline in kidney function events

	Total	Dapagliflozin	Placebo
Patients with event, n (%)	154 (3.6)	63 (2.9)	91 (4.2)
Predisposing factors associated with event^a			
Event adjudicated to be related to underlying disease	38	13	25
Event adjudicated not to be related to underlying disease ^b	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, n (%)	59 (38.3)	23 (36.5)	36 (39.6)
Requiring maintenance dialysis after AKI, n (%)	32 (20.8)	13 (20.6)	19 (20.9)
Death after AKI, n (%)	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 \leq 25% (Partial recovery)	27 (27.6)	12 (28.6)	15 (26.8)
\geq 0% (Full recovery)	16 (16.3)	7 (16.6)	9 (16.1)

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.

^aPredisposing factors are reported for patients with available data and in whom the event was not related to underlying kidney disease as adjudicated by the independent event adjudication committee; ^bFour participants in the placebo group had more than one predisposing factor; ^cSerum creatinine data at the next central laboratory measurement were available in 98 participants; AKI, acute kidney injury.

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

Outcome	Without an abrupt decline in kidney function		With an abrupt decline in kidney function		Hazard Ratio (95% CI)
	Events	Event rate, 95% CI (events per 100 patient- years)	Events	Event rate, 95% CI (events per 100 patient- years)	
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)

AKI, acute kidney injury; ESKD, end-stage kidney disease.

The multivariable adjusted hazard ratio for the association between doubling of serum creatinine events which 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

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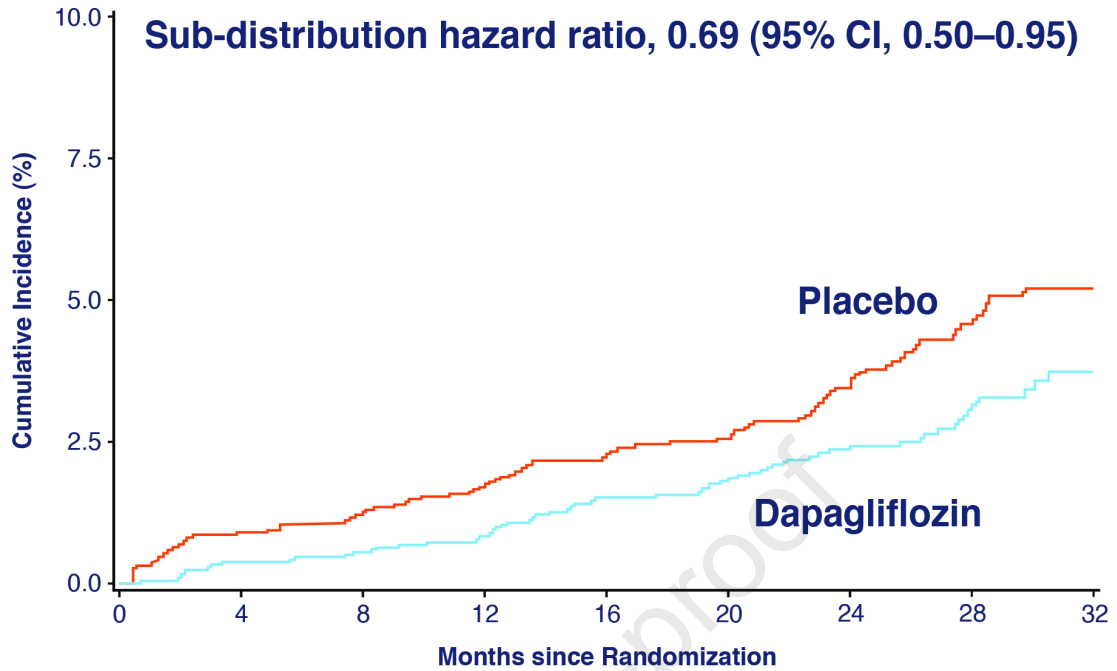
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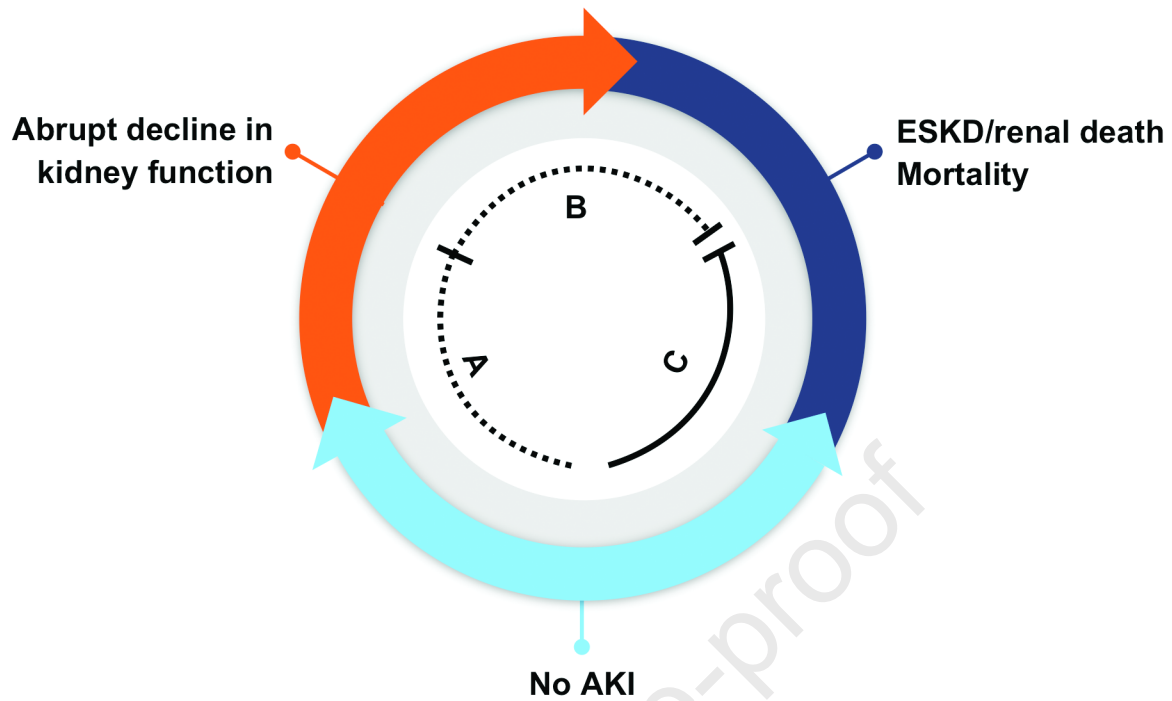
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No. at Risk

Dapagliflozin	2152	2031	2017	1998	1965	1881	1484	1000	375
Placebo	2152	2015	1989	1958	1930	1850	1445	969	358



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)

