Correlates and consequences of an acute change in eGFR in response to the SGLT2 inhibitor dapagliflozin in patients with chronic kidney disease

Niels Jongs, PhD[1]; Glenn M. Chertow, MD[2], Tom Greene, PhD[3], Prof. John J. V. McMurray, MD[4]; Anna Maria Langkilde, MD[5]; Ricardo Correa-Rotter, MD[6]; Naoki Kashihara;[7] Peter Rossing, MD[8,9]; C. David Sjöström, MD[5]; Bergur V. Stefansson, MD[5]; Robert D. Toto, MD[10]; David C. Wheeler, MD[11,12]; Hiddo J.L. Heerspink, PhD[1,12] for the DAPA-CKD Trial Committees and Investigators

1. Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands
2. Departments of Medicine and Epidemiology and Population Health, Stanford University School of Medicine, Stanford, USA
3. Study Design and Biostatistics Center, University of Utah Health Sciences, Salt Lake City, USA
4. Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow
5. Late-Stage Development, Cardiovascular, Renal, and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden
6. The National Medical Science and Nutrition Institute Salvador Zubiran, Mexico City, Mexico
7. Department of Nephrology and Hypertension, Kawasaki Medical School, Kurashiki, Japan
8. Steno Diabetes Center Copenhagen, Herlev, Denmark
9. Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
10. Department of Internal Medicine, UT Southwestern Medical Center, Dallas, USA
11. Department of Renal Medicine, University College London, London, UK
12. The George Institute for Global Health, Sydney, Australia

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Address for correspondence:
Prof. Dr. Hiddo J.L. Heerspink
Department of Clinical Pharmacy and Pharmacology
De Brug 50D-1-015; EB70
University Medical Centre Groningen

PO BOX 30001
9700 AD Groningen
The Netherlands
Tel: +31 50 361 7859
Email: h.j.lambers.heerspink@umcg.nl

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Significance statement

Dapagliflozin reduces the risk of kidney failure in patients with chronic kidney disease (CKD) but can result in a reversible acute reduction in estimated glomerular filtration rate (eGFR) on initiation of treatment. In this post-hoc analysis of the DAPA-CKD trial we demonstrated that patients who experienced an acute reduction in eGFR >10% after 2 weeks treatment with dapagliflozin had slower rates of long-term eGFR decline compared to patients who experienced a less pronounced decline or increase in eGFR. Adverse event rates in patients randomized to dapagliflozin were unrelated to the acute change in eGFR. These data suggest that a modest acute reduction in eGFR on dapagliflozin initiation should not be reason to discontinue therapy in the majority of patients, and might indicate a more potent therapeutic benefit.

Abstract

Background: Dapagliflozin reduces the risk of kidney failure in patients with chronic kidney disease (CKD) but can result in a reversible acute reduction in estimated glomerular filtration rate (eGFR) on initiation of treatment. Determinants of this initial reduction in eGFR and its associations with efficacy and safety outcomes are unknown.

Methods: The DAPA-CKD trial randomized 4304 adults with CKD and albuminuria to dapagliflozin 10 mg or placebo once daily, added to standard care. We pre-specified an analysis comparing the effects of dapagliflozin among patients who experienced relative reductions in eGFR >10%, >0 to 10%, or an increase in eGFR from baseline to Week 2 and assessed long-term efficacy and safety therafter.

Results: A total of 4157 (96.6%) patients had eGFR data available at baseline and Week 2. In the dapagliflozin and placebo groups, 1026 (49.4%) and 494 (23.7%), respectively, experienced an acute reduction in eGFR >10%. Among patients randomized to dapagliflozin, those with an acute reduction in eGFR >10% experienced slower rates of long-term eGFR decline (-1.6 [SE 0.3] mL/min/1.73m^2/year) compared to patients who experienced a less pronounced decline or increase in eGFR (-2.5 [SE 0.3] and -2.5 [SE 0.4] mL/min/1.73m^2/year, respectively; p-interaction 0.04), a pattern that was not observed in the placebo group. Rates of serious adverse events and adverse events of special interest in patients randomized to dapagliflozin were unrelated to the acute change in eGFR.

Conclusion: Among patients with CKD and albuminuria treated with dapagliflozin, an acute reductions in eGFR (from baseline to Week 2) is associated with lower rates of CKD progression.

Introduction

Randomized controlled trials demonstrated the efficacy of sodium glucose cotransporter 2 (SGLT2) inhibitors to slow decline in kidney function and reduce the incidence of end-stage kidney disease in patients with type 2 diabetes, heart failure, and chronic kidney disease (CKD).[1-5] SGLT2 inhibitors are thought to exert nephroprotective effects in part by reducing intraglomerular pressure and glomerular hyperfiltration.[6] This protective mechanism is similar to that described with other proven nephroprotective treatments such as angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs).

Clinically, a reduction in intraglomerular pressure is manifested as a decline in estimated glomerular filtration rate (eGFR) on treatment initiation which is completely reversible after treatment discontinuation, even after several years of treatment.[7] [8] However, the acute reduction in eGFR observed after initiation of SGLT2 inhibitors has led to concerns about the long-term safety of these agents and may prevent clinicians from initiating or continuing SGLT2 inhibitors despite their well-established safety and efficacy profiles. Emerging data in patients with type 2 diabetes demonstrate that acute reductions in eGFR of up to 30% soon after SGLT2 initiation are not associated with an increased risk of adverse events (AEs), supporting the continued use of these agents despite the acute reduction in eGFR often seen.[9, 10] Moreover, several studies with ACEi and ARBs have suggested that the degree of initial reduction in eGFR is associated with attentuation of CKD progression during prolonged treatment, suggesting that the initial acute reduction in eGFR may serve as a marker of therapeutic benefit.[11, 12]

We performed a pre-specified analysis of the Dapagliflozin and Prevention of Adverse Outcomes in CKD (DAPA-CKD) trial to assess correlates and consequences of an acute reduction in eGFR after initiation of dapagliflozin. We hypothesized that patients treated with dapagliflozin who experienced larger relative and absolute reductions in eGFR would experience slower rates of eGFR decline over long term than patients with less pronounced or no acute reductions in eGFR.

Methods

DAPA-CKD was a randomized, double-blind, placebo-controlled, multicenter clinical trial with patients recruited at 386 clinical sites over 21 countries from February 2017 to June 2020. Details about the trial design, baseline characteristics, primary results and trial protocol have been previously published.[4, 13] All participants provided written informed consent before commencement of any study-specific procedure. Safety of participants in the trial was overseen by an independent data and safety monitoring committee. DAPA-CKD is registered with clinicaltrials.gov, NCT03036150.

Participants

Adult patients with CKD, estimated glomerular filtration rate (eGFR) 25–75 mL/min/1.73m^2 and urine albumin-to-creatinine ratio (UACR) 200–5000 mg/g, with or without type 2 diabetes, were eligible for participation. We required patients to be treated with a stable maximally-tolerated dose of an ACEi or ARB for ≥4 weeks unless medically contraindicated. Key exclusion criteria included a documented diagnosis of type 1 diabetes, polycystic kidney disease, lupus nephritis, or anti-neutrophil cytoplasmic antibody-associated vasculitis. Recruitment of patients with eGFR 60-75 mL/min/1.73m^2 was limited to no more than 10% of trial participants. A complete list of inclusion and exclusion criteria has been previously published.

Procedures

We randomized participants to dapagliflozin 10 mg once daily or matching placebo. We stratified randomization by diabetes status and UACR (≤ or >1000 mg/g). After randomization, we conducted in-person study visits after 2 weeks; at 2, 4, and 8 months; and at 4-month intervals thereafter. At each follow-up visit, study personnel recorded vital signs, obtained blood and urine samples, and recorded information on potential study endpoints, adverse events, concomitant therapies, and study drug adherence. Participants and all study

personnel (except the Independent Data Monitoring Committee) were masked to treatment allocation.

Kidney function and thresholds of acute eGFR change

We calculated eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and incorporated results from the equation as originally defined, including a term for self-reported race (Black versus non-Black). We included all participants with eGFR measurements at baseline and Week 2 in our analyses. We defined the acute change in eGFR as the percent or absolute change in eGFR at Week 2. The 2-week period was chosen because it was the first time point at which follow-up eGFR measurements were available and prior studies have shown that the acute effect of dapagliflozin on eGFR is fully manifested after 2 weeks. We categorized participants by percentage decline in eGFR at Week 2 as follows: greater than 10% decline (defined as acute eGFR drop); between 0 and 10% decline (acute modest eGFR drop); and no decline (acute eGFR increase). These cut offs were chosen post-hoc with the aim of providing easily understandable thresholds and approximately equal sample sizes for each category. In an additional analysis, we defined the acute change in eGFR as an absolute change in eGFR at Week 2. We stratified patients in the following categories: >3 mL/min/1.73m^2 decline; between 0 and 3 mL/min/1.73m^2 decline; and no decline. We also used finer categories of acute change in eGFR – >30% decrease, >20 to 30% decrease, >10 to 20% decrease, >0 to 10% decrease, or ≥0% increase – to allow for a direct comparison with a prior study. We defined our subgroups by a post-randomization variable (eGFR change at Week 2), and therefore they do not allow for randomized comparison.

Outcomes

The primary outcome of the DAPA-CKD trial was composite endpoint of sustained ≥50% decline in eGFR (confirmed by a second serum creatinine after at least 28 days), onset of end-stage kidney disease (defined as maintenance dialysis for more than 28 days, kidney

transplantation, or estimated GFR <15 mL/min/1.73m^2 confirmed by a second measurement after at least 28 days), or death from kidney or cardiovascular cause. Pre-specified secondary endpoints were (1) a kidney-specific endpoint defined as the primary composite endpoint with exclusion of cardiovascular death, (2) a composite endpoint of cardiovascular death or hospitalization for heart failure, and (3) all-cause mortality. These efficacy endpoints were adjudicated by a masked, independent event adjudication committee. An exploratory endpoint in DAPA-CKD was the rate of eGFR decline. In this study, we calculated the rate of eGFR decline from Month 2 until the end of treatment. Since we categorized patients based on their initial eGFR change, we used the Month-2 value as baseline to avoid potential bias in the chronic eGFR slope due to regression to the mean. This regression to mean could be apparent in the more extreme eGFR change categories (>10% acute reduction in eGFR and no acute reduction in eGFR) with the consequence that a proportion of patients are allocated to these categories due to an unusually high or low eGFR value at Week 2. The Week-2 value may be followed by a more representative value at the subsequent visit (Month 2) which potentially leads to an *overestimation* of the chronic eGFR slope for the >10% acute reduction in eGFR category and an *underestimation* of the chronic eGFR slope for the no acute reduction in eGFR category.

Because of extensive clinical experience with dapagliflozin, safety ascertainment was limited to assessment of serious AEs, AEs resulting in the discontinuation of the study drug, and AEs of special interest (symptoms of volume depletion, kidney-related adverse events, major hypoglycemia, bone fractures, amputations, and diabetic ketoacidosis). All safety outcomes were investigator reported.

Statistical analysis

We summarized baseline characteristics by acute percent reduction in eGFR as follows: >10%, modest acute decline (0% until 10%), and increase in eGFR (>0%). Within these categories and treatment allocation, we described numeric variables with an approximate symmetric distribution by their mean and standard deviation (SD). Variables with skewed

distributions were reported by calculating their median (25th, 75th percentile) or geometric mean; categorical variables were reported as counts and proportions.

We calculated the likelihood with dapagliflozin compared to placebo to experience an acute reduction in eGFR >10% at Week 2 using logistic regression. Subsequently, we assessed if patient characteristics at baseline modified the treatment effect of dapagliflozin versus placebo on this endpoint by adding an interaction between treatment and the respective patient subgroup to the model. The model also included diabetes status, baseline UACR (≤ or >1000 mg/g) and eGFR as covariates. We explored subgroups defined by the following patient characteristics: age, sex, self-reported race, Quételet (body mass) index (BMI), systolic blood pressure, baseline eGFR, baseline UACR, type 2 diabetes, cardiovascular disease history, heart failure history, and use of diuretics, and ACEis or ARBs.

We analysed the association of acute reductions in eGFR on the mean on-treatment eGFR slope by fitting a three-slope mixed effects linear spline model (with a knot at 14 days and 2 months) with correlated random intercepts and slopes for each participant over time, incorporating an unstructured covariance matrix). A second knot was added at 2 months to account for potential regression to the mean between the Day 14 and Month 2 visits, as above. We excluded eGFR determinations after treatment discontinuation from the eGFR slope analyses to avoid bias in eGFR slope estimates from hemodynamic changes in eGFR after discontinuation of dapagliflozin. The mixed effects model included fixed effects for categories of acute change in eGFR, time, an interaction term for acute change in eGFR category by time, as well as the following baseline covariates and an interaction term between these covariates and time: age, sex, cardiovascular disease history, baseline eGFR, log transformed UACR, systolic blood pressure, ~~baseline~~ hemoglobin, ~~baseline~~ HBA1c, and change in systolic blood pressure at week 2. With this model, we calculated the acute slope as the mean change in eGFR from baseline to Week 2 and the chronic eGFR slope as the mean rate of change after Month 2 until last on-treatment visit. We fitted models separately for each treatment arm.

In order to visualise trajectories and estimate the mean eGFR for each visit without pre-supposing a linear decline, we fitted a separate set of longitudinal models in which follow-up time was represented by visit as a categorical variable. We fitted these models for the placebo and dapagliflozin arm separately and included fixed effects for category of acute change in eGFR, visit (as a categorical factor), baseline covariates as used in the two-slope model, acute change in eGFR by visit interaction and an interaction between visit and each baseline covariate.

To determine the association between an acute change in eGFR and clinical outcomes, we estimated the hazard ratios (HR) of a large acute reduction in eGFR versus a less pronounced reduction or no reduction (0% until 10%) and acute eGFR decline (>10%) relative to an acute eGFR increase. We used a landmark approach and included only clinical events occurring after Week 2 in the analysis. We calculated HR and 95% confidence intervals (95%CI) using Cox proportional hazards regression adjusting for the following baseline covariates: age, sex, cardiovascular disease history, eGFR, log-transformed UACR, and type 2 diabetes status. We performed the analyses separately for the dapagliflozin and placebo groups. We calculated a p-value for interaction (p-interaction) between treatment and acute change in eGFR change for each clinical endpoint using a combined (dapagliflozin and placebo) model. This model also included interaction terms between category of acute change in eGFR and the above-mentioned baseline covariates. To visualize the association between acute change in eGFR at 2 weeks and clinical outcomes, we repeated the Cox proportional hazards regression analyses in each treatment group separately and fitted acute change in at Week 2 as a continuous variable. In this model, we calculated HR relative to 0% acute eGFR decline using a restricted cubic spline with 3 knots (at the 25, 50 and 75 percentile of the data). We used a Wald-test to calculate a p-value for interaction between acute change in eGFR (with a restricted cubic spline) and treatment using the estimates from the placebo and dapagliflozin model separately. We plotted the treatment effect of dapagliflozin versus placebo for each clinical outcome as function of acute change in eGFR.

Finally, we summarized safety data according to category of acute percent and absolute change in eGFR for dapagliflozin- and placebo-treated particpants. Safety outcomes were described by counts, proportions, and odds ratios (ORs). We calculated ORs and 95% CI for each safety event using a logistic regression model and included fixed effects for category of acute change in eGFRand baseline covariates mentioned above. We calculated the p-interaction using the same approach as described above for estimation of hazard ratios. We performed all analyses with R version 4.1.0 (R-Foundation).

Results

Of the 4304 patients included in the DAPA-CKD trial a total of 4157 (96.6%) had eGFR measurements at baseline and Week 2. Mean (SD) baseline eGFR was 43.2 (12.4) mL/min/1.73m^2. At Week 2, the mean eGFR change was -4.0 (6.7) mL/min/1.73m^2 in the dapagliflozin group and -0.8 (6.8) mL/min/1.73m^2 in the placebo group, corresponding to -9.3% (14.3%) and -1.7% (15%) respectively. An acute reduction in eGFR >10% occurred more frequently in the dapagliflozin group (1026 [49.4%]) compared with the placebo group (494 [23.7%]; **Figure 1**). Few patients experienced an acute reduction in eGFR >30% at Week 2: 97 (4.7%) in the dapagliflozin and 47(2.3%) in the placebo group. The distribution was similar when acute reductions in eGFR were categorized by absolute rather than relative changes (**Figure 1**).

Clinical correlates of acute reduction in eGFR >10% at Week 2

Patients with an acute reduction in eGFR >10% assigned to dapagliflozin were more likely to be older, had a higher BMI, higher systolic blood pressure, and lower hemoglobin, and were more likely to smoke and to use diuretics at baseline (**Table 1**). In the placebo group, patients with an acute reduction in eGFR >10% were more likely to be female, had higher systolic blood pressure, higher UACR and lower hemoglobin. Baseline characteristics

according subgroups defined by acute absolute changes in eGFR are presented in **Supplementary Table S1** and showed a similar pattern

The odds of an acute reduction in eGFR >10% was more than 3-fold higher among patients randomized to dapagliflozin relative to placebo (OR 3.2 [95%CI 2.8, 3.6]; p<0.001]). Results were similar for an absolute decline in eGFR of >3 mL/min/1.73m^2 (OR 3.3 [95%CI 2.9, 3.7]; p<0.001]). The effects of dapagliflozin versus placebo on the acute reduction in eGFR >10% were generally consistent in patients with and without type 2 diabetes as well as in most othert subgroups (**Figure 2**), although the effect was more pronounced among older patients (p-interaction=0.022) and patients who self-identified as white (p-interaction=0.024; **Figure 2**) Subgroup findings were similar among patients who experienced an acute absolute reduction in eGFR >3 mL/min/1.73m^2, with the exception of more pronounced effects in men (p-interaction=0.006) and patients with a history of CV disease (p-interaction=0.020).

eGFR slope over time by acute change categories

Within the dapagliflozin group there was a statistically significant difference in the mean decline in eGFR (eGFR slope), across categories of an acute change in eGFR (p-interaction <0.001). Specifically, after multivariable adjustment, the mean annual decline in eGFR from Month 2 to end-of-treatment was attenuated in patients with an acute reduction in eGFR >10% (eGFR decline ~~OR~~ -1.57 mL/min/1.73m^2/year [95%CI -2.06, -1.08]) compared with those with a modest acute reduction in eGFR (~~OR~~ -2.46 mL/min/1.73m^2/year [95%CI; 3.10, -1.82]; p-value 0.032 vs >10% decline) or no reduction in eGFR (~~OR~~ -2.50 mL/min/1.73m^2/year [95% CI; 3.25, -1.75) p-value 0.043 vs >10% decline; **Figure 3A**). The mean eGFR slope across categories of acute changes in eGFR did not differ when comparing patients with or without type 2 diabetes (p for interaction 0.431). Within the placebo group, there was no statistically significant difference in the mean annual decline in eGFR across categories of acute change in eGFR (p-interaction=0.371; **Figure 3B**). Notably, the rates of eGFR decline were slower in dapagliflozin- than in the placebo-treated

patients across the three categories of acute change in eGFR. Modelling acute changes in eGFR on a continuous scale, we observed attenuated progression of CKD in patients with larger acute reductions in eGFR (**Figure 3C**). Among the 97 participants with an acute reduction in eGFR >30% on dapagliflozin initiation, the long-term eGFR decline was similar compared with those who did not experience an acute reduction in eGFR >30% (**Supplementary Figure 1)**. Results were similar when acute eGFR changes were categorized as absolute changes (**Supplementary Figure 2**).

Primary and secondary composite endpoints associated with acute change in eGFR

During a median of 2.3 (IQR 2.0, 2.6) years following the 2-week period during which acute eGFR declines were determined, 494 patients developed the primary outcome. There were 377 kidney-specific outcomes, 228 heart failure hospitalization or cardiovascular deaths, and 235 deaths. In the dapagliflozin group, the multivariable adjusted HR for the primary and three secondary outcomes were similar among patients with an acute reduction in eGFR >10% and an acute reduction in eGFR between 0 and ≤10% or those with no acute reduction in eGFR (**Figure 4**). In contrast, in the placebo group, a larger acute reduction in eGFR was associated with a higher risk of the primary outcome; the multivariable adjusted HR for moderate eGFR decline and large eGFR decline were 1.23 [95%CI 1.02, 1.48] and 1.68 [95%CI 1.28, 2.19], respectively, with evidence of a positive log-linear trend p <0.001 (**Figure 4**). A similar pattern was observed for the kidney-specific outcome and all-cause mortality.

Modelling the acute eGFR change as a continuous variable with a restricted cubic splines model, we observed that a larger acute reduction in eGFR was independently associated with a higher risk of the primary composite and secondary composite outcomes in patients randomized to placebo (**Figure 5**). In contrast, larger acute reductions in eGFR were not associated with a higher risk of the primary composite or secondary composite kidney endpoint in patients randomized to dapagliflozin (**Figure 5**). There was a statistically significant interaction when comparing associations between the acute reduction in eGFR

and the primary composite (p-interaction=0.016; **Supplementary Figure 3A**) and secondary composite kidney endpoint (p-interaction=0.034; **Supplementary Figure 3B**) in the placebo and dapagliflozin groups.

Safety and study drug discontinuation

In the overall dapagliflozin and placebo groups included in this analysis, drug discontinuation due to AEs occurred in 115 (5.5%) and 118 (5.7%) patients, serious AEs in 618 (29.8%) and 711 (34.1%) patients, kidney-related AEs in 152 (7.3%) and 183 (8.8%) patients, and volume depletion events in 122 (5.9%) and 89 (4.3%) patients, respectively. The frequency of serious AEs was similar for dapagliflozin-treated patients regardless of the degree of acute reduction in eGFR (**Figure 6)** whereas the rates of serious AEs increased in the placebo group with larger declines in eGFR. For placebo-treated patients with a decline in eGFR ≥ 30%, there was a suggestion of a higher frequency of kidney-related AEs compared to patients with no eGFR decline, but this was not observed in the dapagliflozin group. Results were similar when we analyzed acute eGFR change as a continuous parameter (**Figure 7**).

Discussion

In this study of patients with CKD and albuminuria enrolled in the DAPA-CKD trial, we demonstrated that an acute reduction in eGFR is more common in patients receiving dapagliflozin compared to placebo. Among dapagliflozin-treated patients, a larger acute reduction in eGFR was associated with an attenuated GFR slope and ~~– in contrast to placebo-treated patients –~~ was not associated with increased risk of the primary composite endpoint or the secondary composite kidney endpoint.

SGLT2 inhibitors frequently induce an acute reversible reduction in eGFR of approximately 3 to 8 mL/min/1.73m^2 by increasing sodium chloride transport to the distal tubule and augmenting tubulo-glomerular feedback.[14] In patients with CKD participating in the DAPA-CKD trial, the mean acute reduction in eGFR was similar to that observed in other

randomized placebo-controlled trials in patients with diabetic kidney disease such as the DELIGHT trial (-4.8 mL/min/1.73m^2) and CREDENCE trial (-3.2 mL/min/1.73m^2).[3, 15] Understanding clinical characteristics associated with a decline in eGFR can help guide optimal use of SGLT2 inhibitors in clinical practice. Within the dapagliflozin group, older patients, those with a higher blood pressure or body mass index or lower hemoglobin, and patients who were using diuretics were more likely to experience a more pronounced reduction in eGFR. Several of these characteristics were also associated with the acute reduction in eGFR in the placebo group.

The acute reduction in eGFR after initiation of dapagliflozin is reminiscent of experience with ACEi and ARBs. In previous studies in patients with CKD, the magnitude of the acute reduction in eGFR following ACE-inhibitor or ARB initiation was associated with the degree of preservation of kidney function in the long term.[11, 12] A post-hoc analysis from the CREDENCE trial in patients with type 2 diabetes and CKD demonstrated that within the canagliflozin group, long-term eGFR trajectories were similar regardless of the acute change in eGFR. In the DAPA-CKD trial, we observed an attenuated chronic eGFR slope in patients with an acute reduction in eGFR >10%.[10] These data suggest that the acute reduction in eGFR could reflect a dapagliflozin-induced reduction in glomerular hyperfiltration. Differences in patient characteristics between the DAPA-CKD and CREDENCE trials may explain these disparate findings. The lower baseline eGFR in DAPA-CKD is noteworthy (43 mL/min/1.73m^2 compared with 56 mL/min/1.73m^2 in CREDENCE). Indeed, within the subgroup of patients in CREDENCE with baseline eGFR similar to the DAPA-CKD cohort, those with an acute reduction in eGFR >10% experienced a less pronounced longer-term eGFR decline (i.e., slower progression) compared to those with a modest or no acute decrease in eGFR upon initiation of canagliflozin.[10]

Not only did we show that the acute eGFR decline was associated with stabilization of long-term kidney function, we also demonstrated that the acute reduction in eGFR during dapagliflozin treatment was not associated with an increased risk of clinical outcomes. In contrast, during placebo treatment a larger acute reduction in eGFR was associated with a

higher risk of kidney and cardiovascular outcomes. Moreover, the benefit of dapagliflozin compared to placebo to prevent kidney outcomes was more pronounced in patients with a larger acute reduction in eGFR. These data support the hypothesis that the acute reduction in eGFR during initiation of treatment with dapagliflozin ~~can~~ may be interpreted as a marker of therapeutic response.

Other observations about patients exhibiting an acute reduction in eGFR are also clinically relevant. We demonstrated that there was no excess of drug discontinuation due to adverse events among patients with an acute decline in eGFR >10%. Moreover, the risk of AEs or serious AEs were not increased in this subgroup. When we stratified the population in finer subgroups of acute declines in eGFR, the proportion of patients with AEs related to hypoglycemia, renal events and volume depletion was higher in those with more pronounced acute declines in eGFR. However, this was true for both the placebo and dapagliflozin groups indicating that the higher AEs rates cannot be attributed to dapagliflozin initiation. These reassuring efficacy and safety data suggest that it seems reasonable that for the majority of patients there is no need to routinely check electrolytes or kidney function shortly after initiating dapagliflozin unless there is clinical concern for volume depletion such as in elderly patients who are treated with high doses of diuretics.

There are some limitations which should be considered when interpreting the findings. First, this was a post-hoc analysis and we stratified the population based on a post-randomization variable which may have introduced confounding. Second, the intra-individual variability over time in serum creatinine and eGFR is high which may have resulted in misclassification of acute changes in eGFR. Third, we were unable to distinguish whether the acute reduction in the dapagliflozin group represents an acute “hemodynamic induced” reduction in eGFR or an acute reduction in eGFR due to disease progression. This may in part explain why within the dapagliflozin group among patients with an acute eGFR reduction eGFR despite a reduced long-term eGFR decline the risk of clinical outcomes was not different from those with no acute change in eGFR. Finally, we did not collect eGFR after the completion of the trial, which might have accentuated the differences observed among

the dapagliflozin-treated patient groups defined by the acute reduction in eGFR, particularly if the “rebound” in eGFR matched the magnitude of the initial, reversible reduction in eGFR. Other studies with dapagliflozin have however shown that in patients with CKD with and without diabetes the acute decline in eGFR is completely reversible.[15, 16]

In conclusion, among patients with CKD and albuminuria treated with dapagliflozin, acute reductions in eGFR (from baseline to Week 2) associate with lower rates of CKD progression. A modest acute reduction in eGFR following initiation of dapagliflozin should not be reason to discontinue therapy in the majority of patients, and rather, might indicate a more potent therapeutic benefit.

Author contributions

All authors contributed in the design of the trial and data collections. NJ analyzed the data. NJ and HJLH wrote the first draft of the manuscript. All authors contributed with critical revisions. The decision to submit the manuscript was made jointly by all authors. The corresponding author (HJLH) and first author (NJ) had full access to all the data, verified the data, and had the final responsibility to submit for publication.

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NJ has nothing to declare

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Data sharing statement

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.

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Tables:

Table 1: Baseline characteristics by percentage decline in eGFR between baseline and Week 2 in DAPACKD (N=4,157)

	Dapagliflozin (N=2,075)				Placebo (N=2,082)			
	>10% decline	**10% to 0% decline**	**Increase**		**>10% decline**	**10% to 0% decline**	**Increase**	
	n= 1,026	**n=601**	**n= 448**	**p-value**	**n= 494**	**n= 603**	**n= 985**	**p-value**
Age, years	62.9 (11.5)	61.1 (12.1)	61.1 (12.7)	0.003	61.7 (11.9)	62.1 (12.7)	61.9 (11.8)	0.887
Female sex, n (%)	349 (34.0)	182 (30.3)	153 (34.2)	0.252	194 (39.3)	206 (34.2)	297 (30.2)	0.002
Race*, n (%)				0.005				0.068
White	570 (55.6)	302 (50.2)	226 (50.4)		254 (51.4)	324 (53.7)	560 (56.9)	
Black or African American	63 (6.1)	28 (4.7)	13 (2.9)		25 (5.1)	25 (4.1)	35 (3.6)	
Asian	308 (30.0)	224 (37.3)	171 (38.2)		161 (32.6)	214 (35.5)	309 (31.4)	
Other	85 (8.3)	47 (7.8)	38 (8.5)		54 (10.9)	40 (6.6)	81 (8.2)	
Current smoker, n (%)	115 (11.2)	92 (15.3)	64 (14.3)	0.042	59 (11.9)	90 (15)	141 (14.3)	0.321
Body mass index (kg/m^2)	29.8 (6.4)	29.3 (5.7)	28.7 (5.5)	0.003	29.6 (6.3)	29.4 (6.6)	30.0 (6.1)	0.222
Blood pressure, mmHg								
Systolic	138.1 (18.4)	136.4 (16.3)	134.7 (16.5)	0.002	139.1 (17.7)	138.5 (17.5)	136.1 (16.9)	0.001
Diastolic	77.2 (10.7)	77.8 (11.2)	77.6 (10.0)	0.607	77.8 (10.1)	77.7 (10.3)	77.3 (10.4)	0.570
HbA1c, %	7.1 (1.7)	6.9 (1.6)	7.2 (1.9)	0.001	7.1 (1.6)	7.0 (1.8)	7.0 (1.7)	0.479
Median urinary albumin-to-creatinine ratio†	999	959	893	0.110	1098	925	859	<0.001
(Q1–Q3)	(492, 1921)	(467, 1846)	(443, 1819)		(525, 2181)	(489, 1771)	(448,1690)	
Estimated glomerular filtration rate (mL/min/1.73m^2)	43.0 (12.3)	43.4 (12.3)	43.9 (12.5)	0.380	43.1 (12.6)	43.2 (12.0)	42.9 (12.6)	0.846
Type 2 diabetes, n (%)	737 (71.8)	378 (62.9)	292 (65.2)	<0.001	351 (71.0)	403 (66.8)	657 (66.7)	0.202

Cardiovascular disease‡, n (%)	404 (39.4)	222 (36.9)	164 (36.6)	0.478	175 (35.4)	228 (37.8)	367 (37.3)	0.696
Heart failure, n (%)	109 (10.6)	59 (9.8)	60 (13.4)	0.163	53 (10.7)	55 (9.1)	117 (11.9)	0.228
Prior medication, n (%)								
ACE inhibitor	333 (32.5)	171 (28.5)	149 (33.3)	0.160	153 (31.0)	202 (33.5)	299 (30.4)	0.412
ARB	681 (66.4)	421 (70.0)	289 (64.5)	0.137	334 (67.6)	387 (64.2)	664 (67.4)	0.350
Diuretic	490 (47.8)	250 (41.6)	161 (35.9)	<0.001	245 (49.6)	259 (43.0)	421 (42.7)	0.030

*Race was reported by the investigators; 'other' includes Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and other. †The albumin-to-creatinine ratio was calculated with albumin measured in milligrams and creatinine measured in grams. ‡Cardiovascular disease was defined as a history of peripheral artery disease, angina pectoris, myocardial infarction, percutaneous coronary intervention, coronary-artery bypass grafting, heart failure, valvular heart disease, abdominal aorta aneurysm, atrial fibrillation, atrial flutter, ischemic stroke, transient ischemic attack, hemorrhagic stroke, carotid artery stenosis, cardiac-pacemaker insertion, vascular stent, coronary-artery stenosis, ventricular arrhythmia, implantable cardioverter–defibrillator, noncoronary revascularization, or surgical amputation.

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker

Figure 1: Distribution of eGFR decline

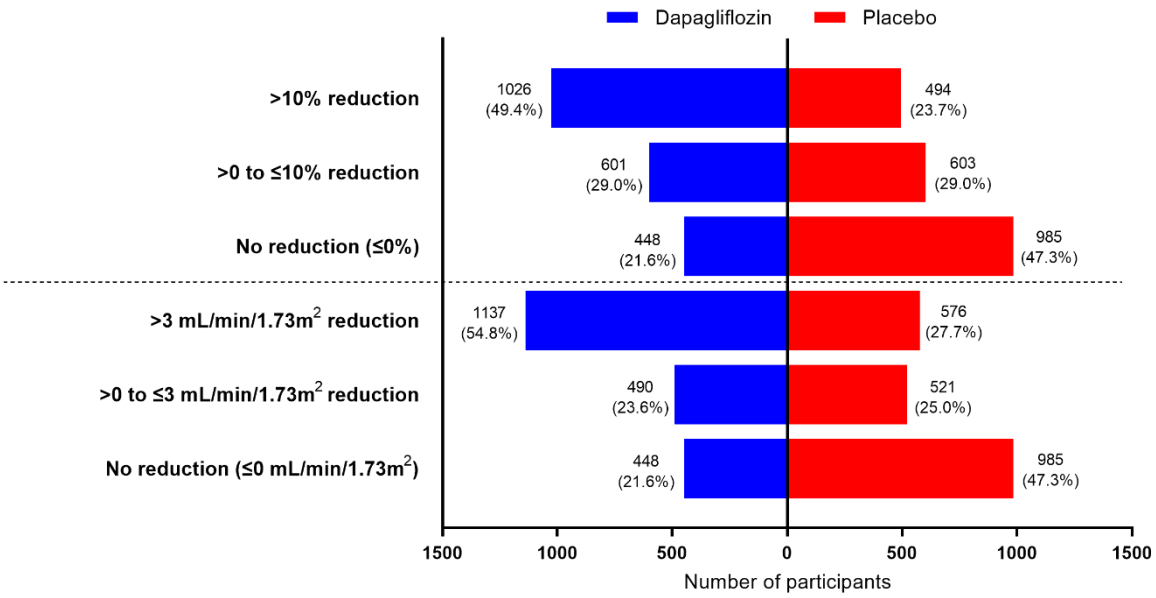


Figure 2: Odds ratios and 95% confidence intervals (95% CI) of dapagliflozin versus placebo for the risk of an acute decline (>10% or >3 mL/min/1.73m^2) in eGFR across participant subgroups defined by baseline characteristics

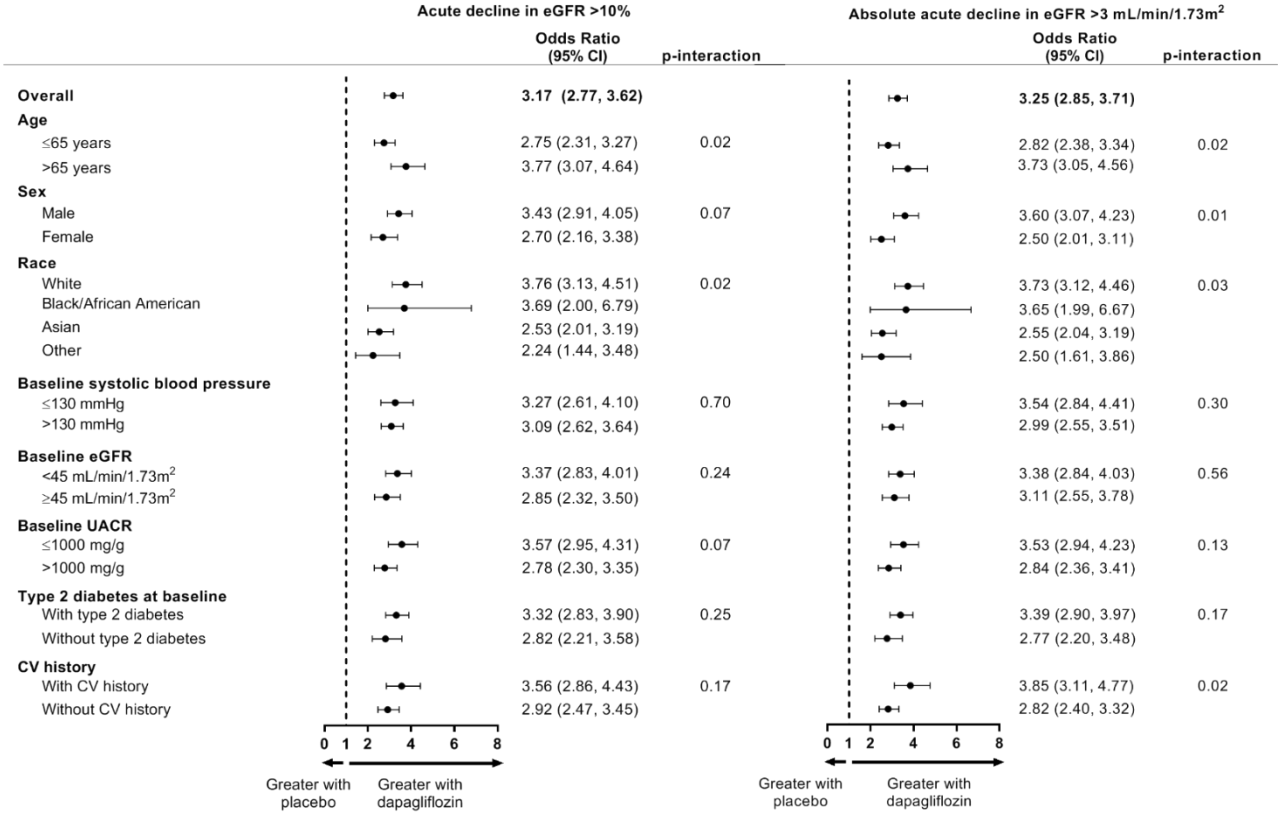
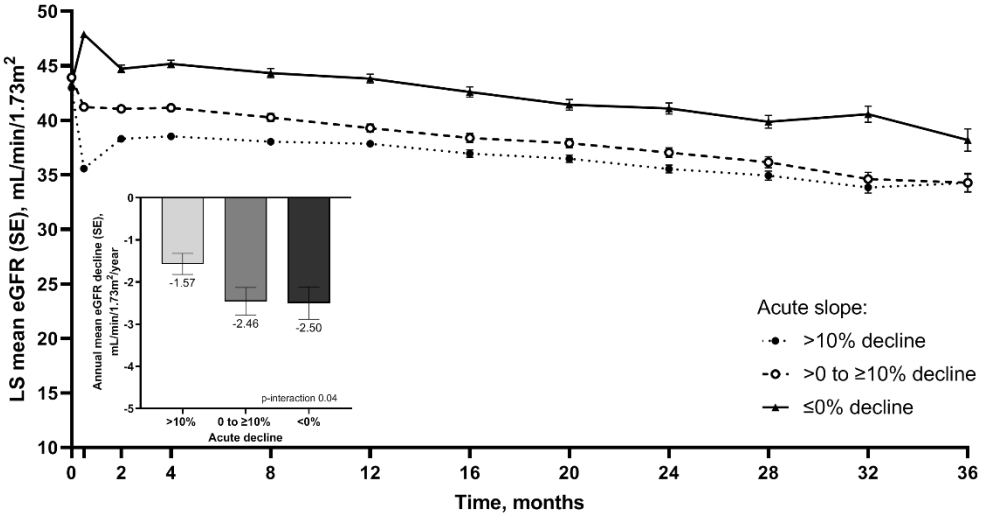


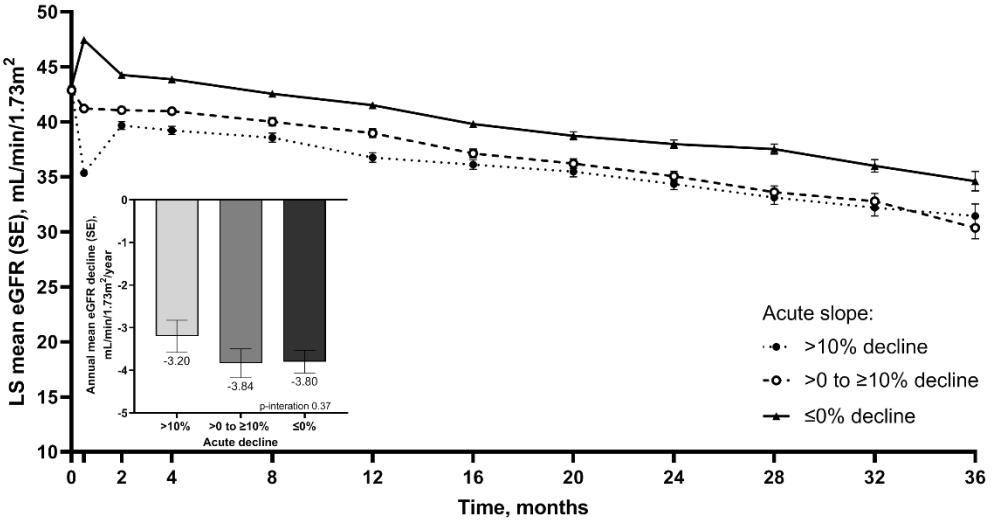
Figure 3: eGFR by acute percent decline categories for dapagliflozin and placebo. Panel A shows the dapagliflozin group; panel B the placebo group and panel C the annual eGFR decline from Week 2 to end of treatment as a function of acute changes in eGFR in the placebo and dapagliflozin group.

A

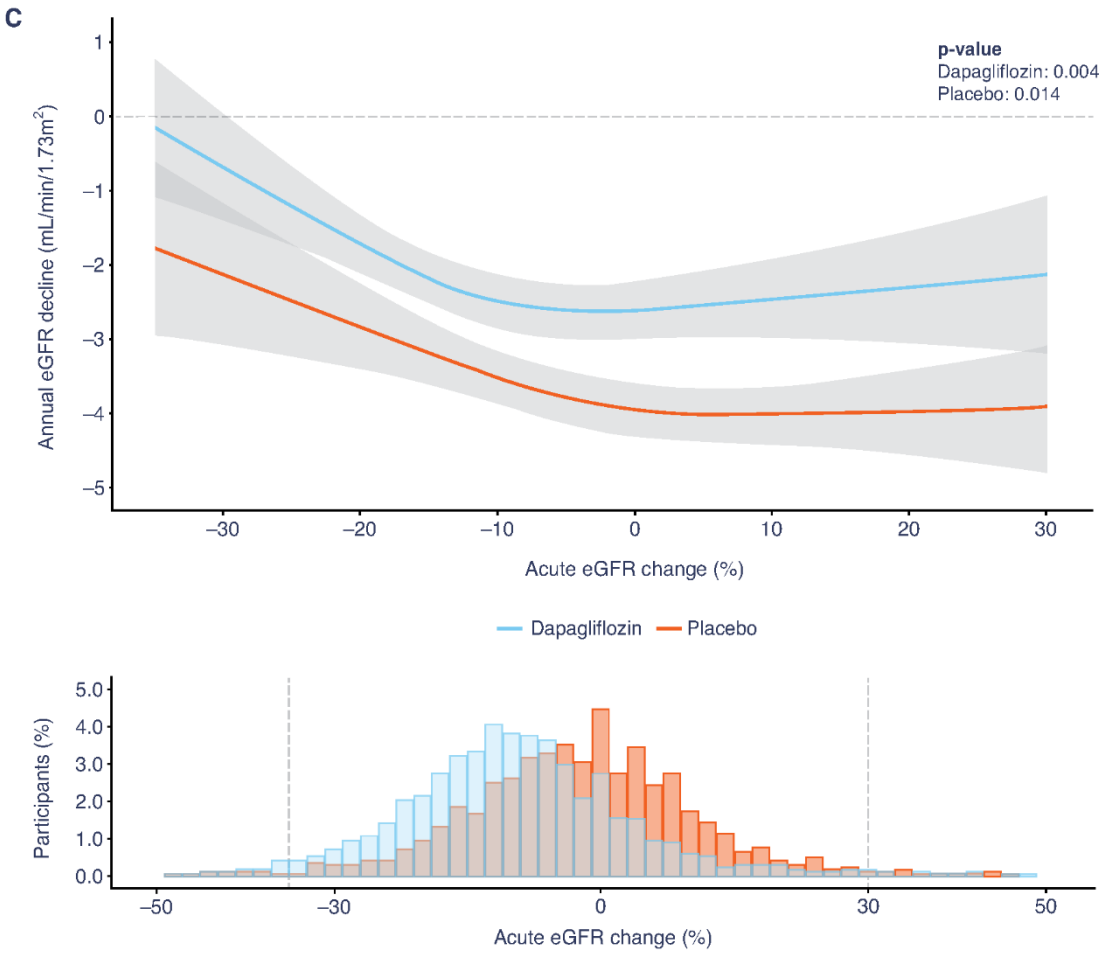


Number of participants												
>10% decline	1026	1026	988	972	931	905	872	835	720	487	251	67
>0 to ≥10% decline	601	601	576	571	543	521	513	499	437	283	149	53
≤0% decline	448	448	428	422	396	381	377	350	309	200	93	37

B



Number of participants												
>10% decline	494	494	470	462	436	421	415	401	337	215	106	37
>0 to ≥10% decline	603	603	581	567	532	512	498	481	417	268	125	52
≤0% decline	985	985	941	916	872	839	817	769	673	436	211	67



P-values in Figure 3C indicate the statistical significance of the association between the acute eGFR change (%) and long-term eGFR decline.

Figure 4: Risk of primary and secondary outcomes according to initial change in eGFR in the dapagliflozin and placebo groups separately. Patients with an increase in eGFR (eGFR decline ≤0%) are used as reference group for the subgroups of patients with modest acute decline (>0 to ≥10%) and acute decline (>10%) .

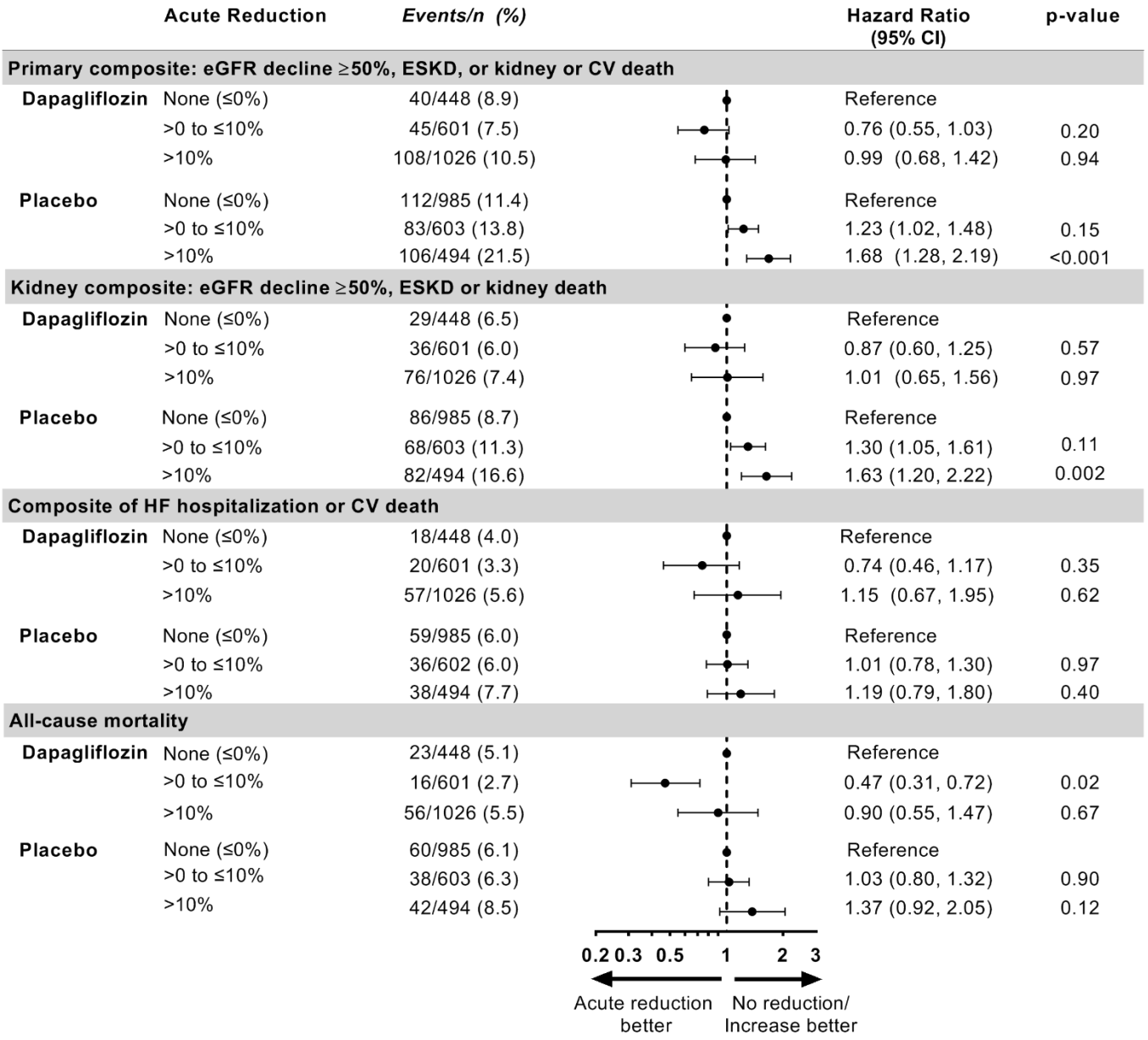
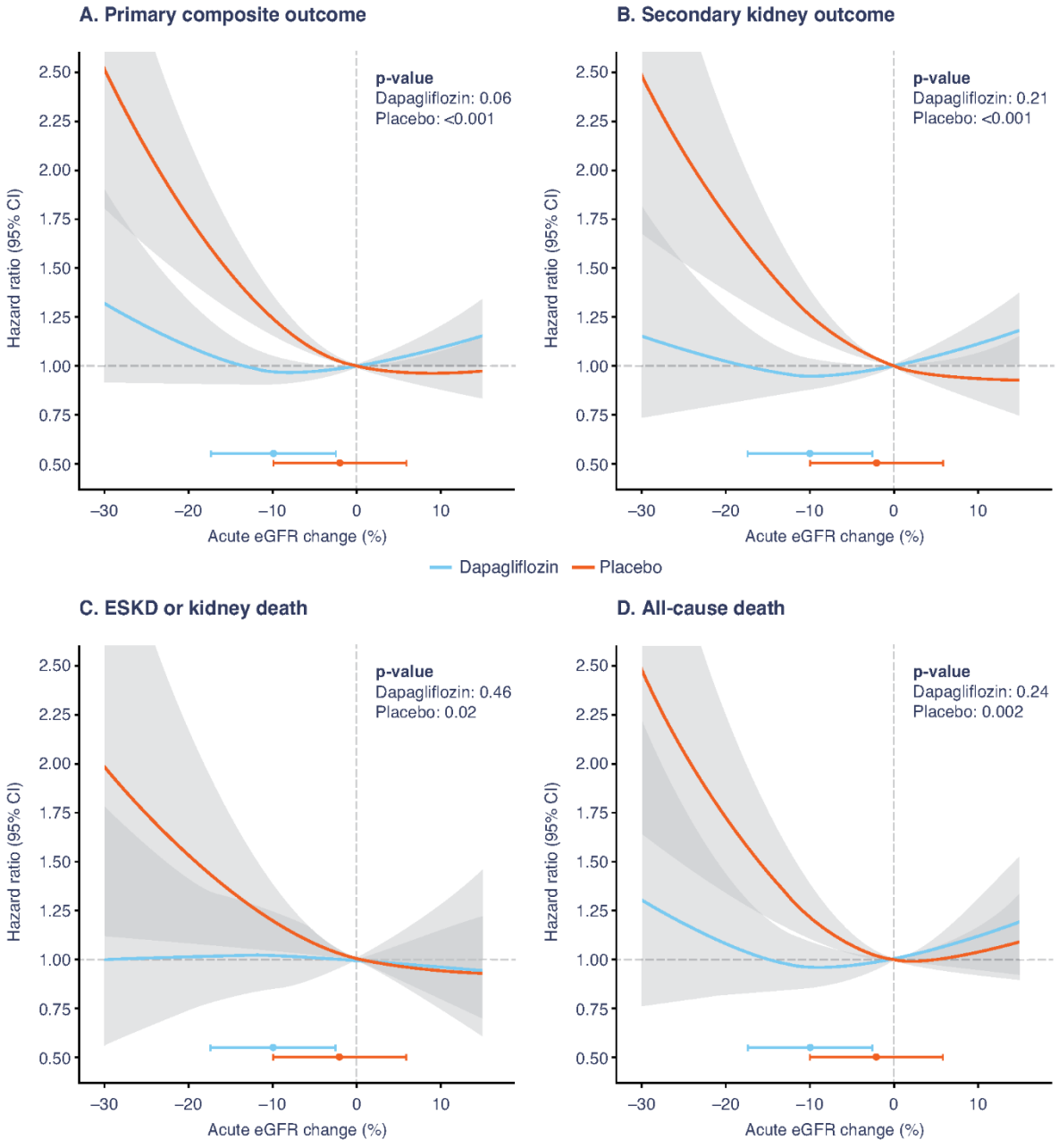


Figure 5: Hazard ratio as function of acute eGFR slope fitted as a continuous variable with a restricted cublic spline model.



P-values indicate the statistical significance of the association between the acute eGFR change (%) and clinical outcomes.

Figure 6: Safety events according acute eGFR change in the dapagliflozin and placebo groups separately

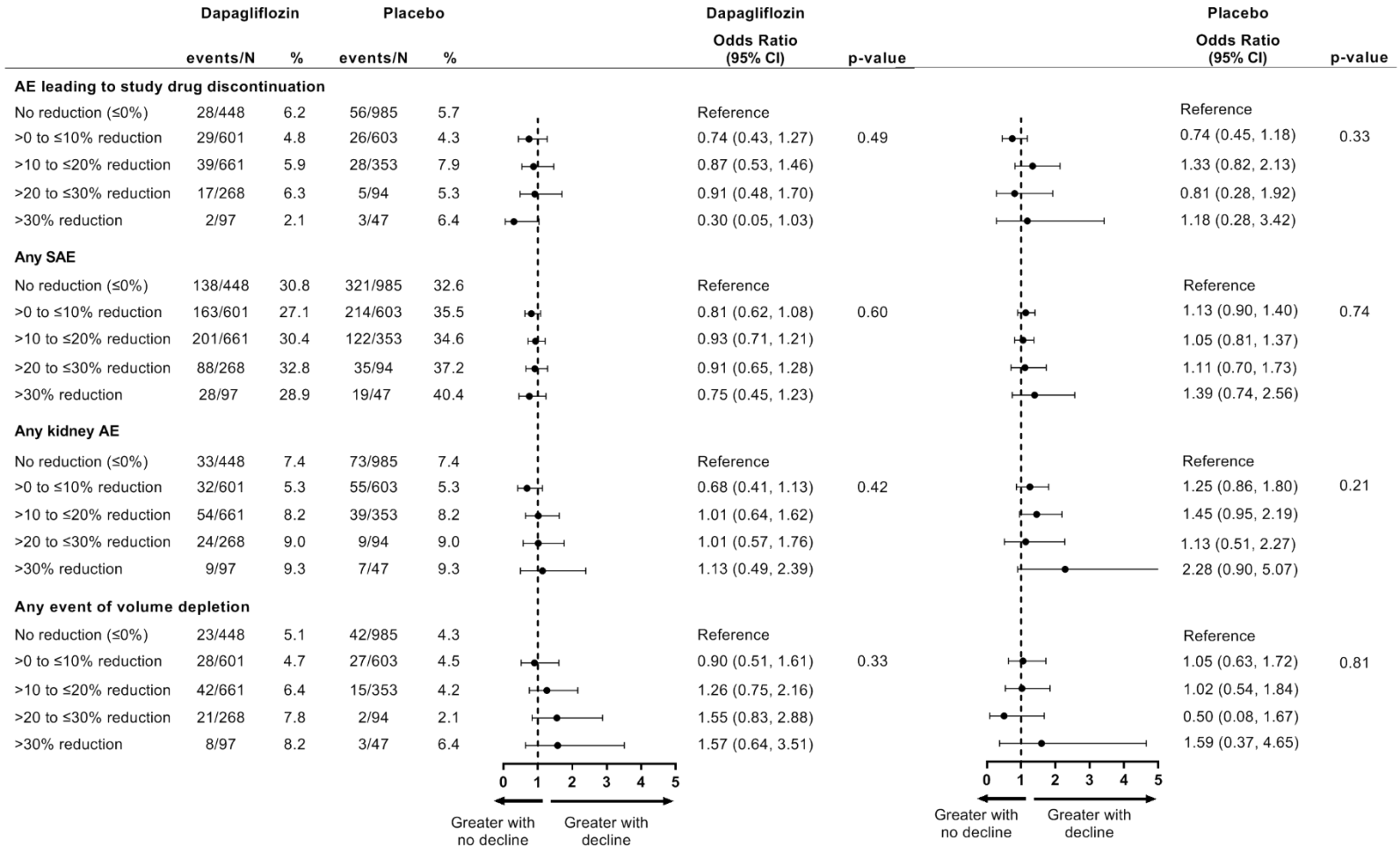
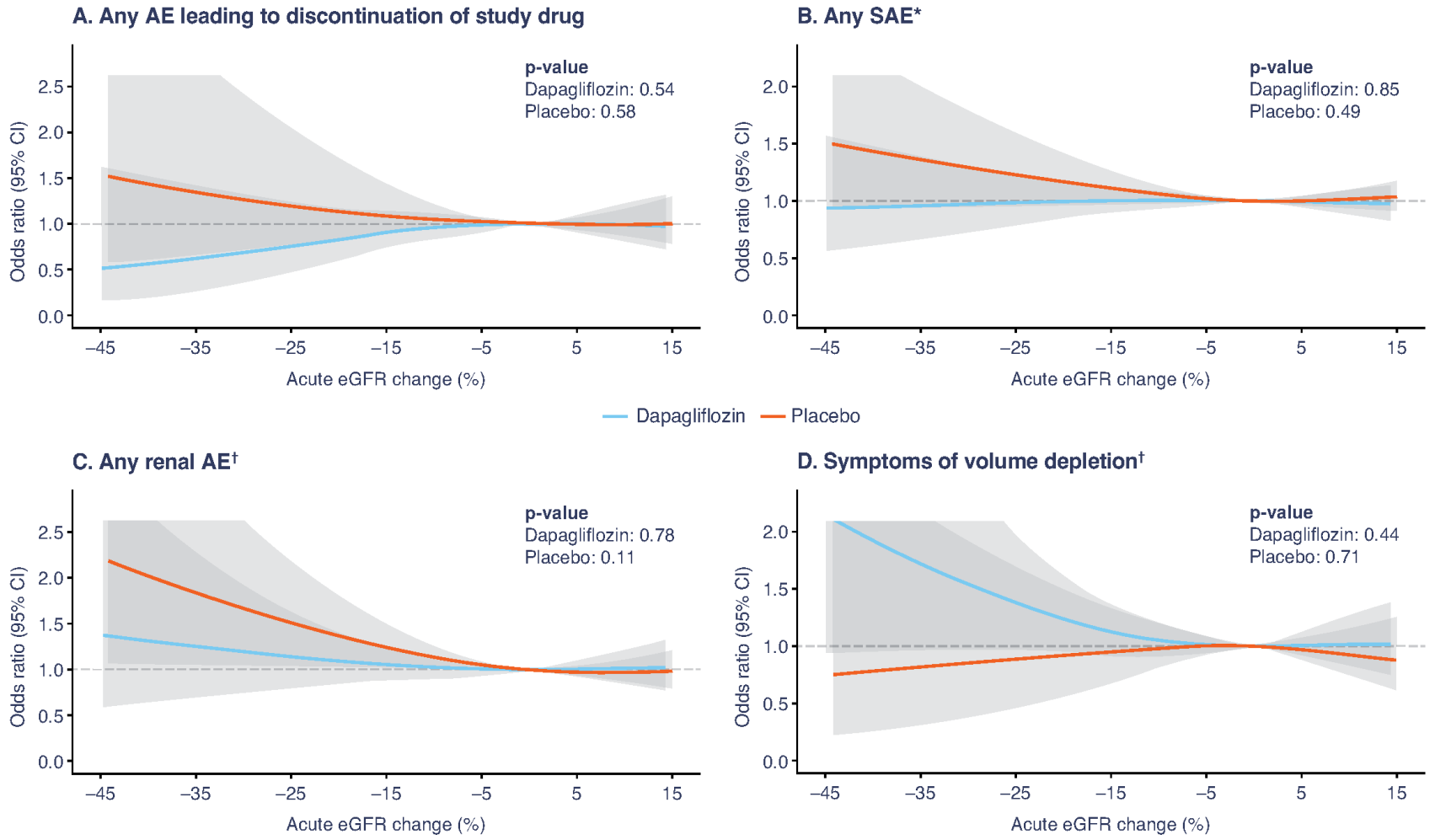


Figure 7: Safety events according acute eGFR change fitted as a continuous variable in the dapagliflozin and placebo groups separately



*Includes death

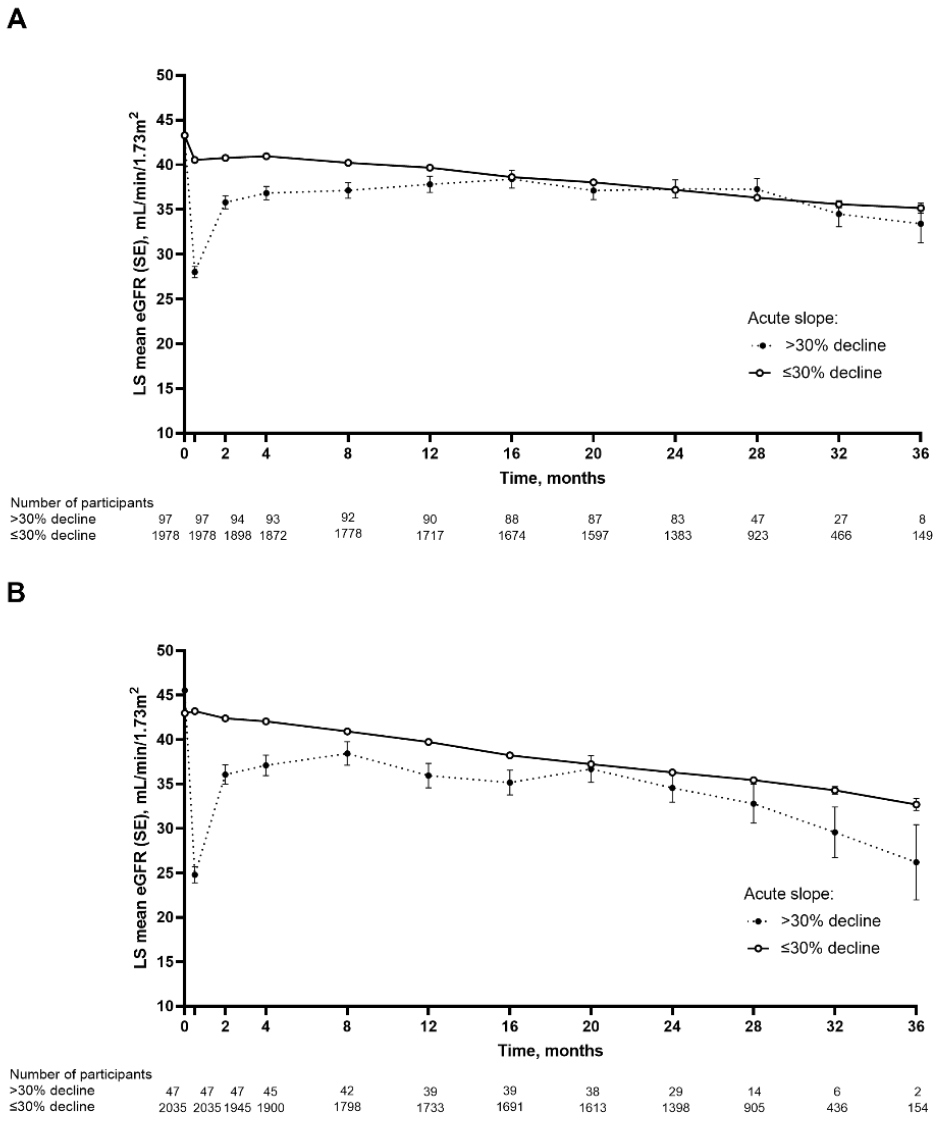
P-values indicate the statistical significance of the association between the acute eGFR change (%) and safety outcomes.

Supplemental Table of Contents

1. Supplementary Figure 1
2. Supplementray Figure 2

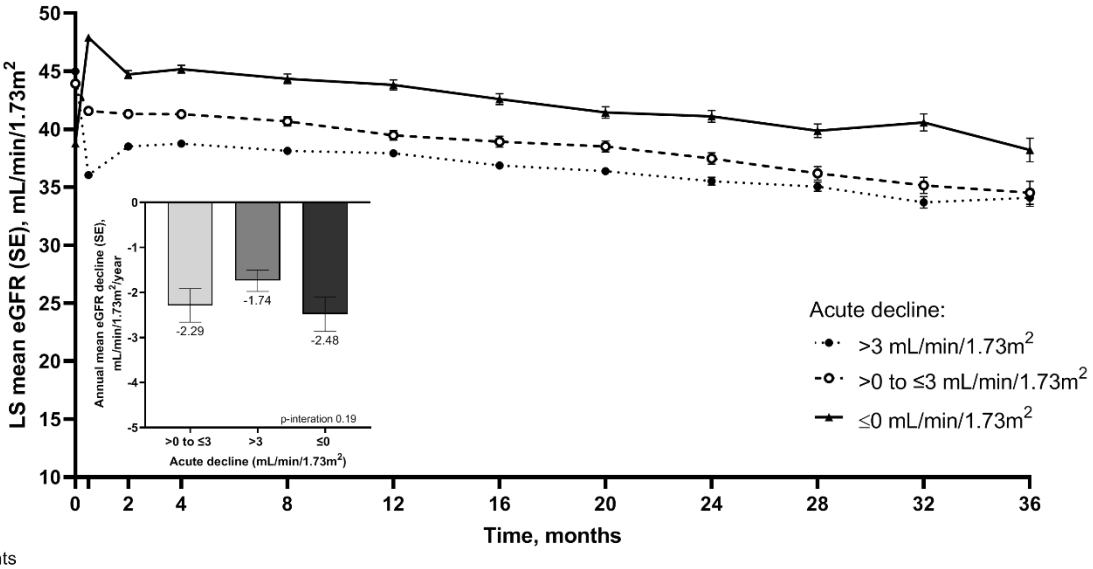
Supplementary figures

Supplementary figure 1 Acute decline in eGFR >30% or ≤ 30% in the dapagliflozin group (panel A) and placebo group (panel B)



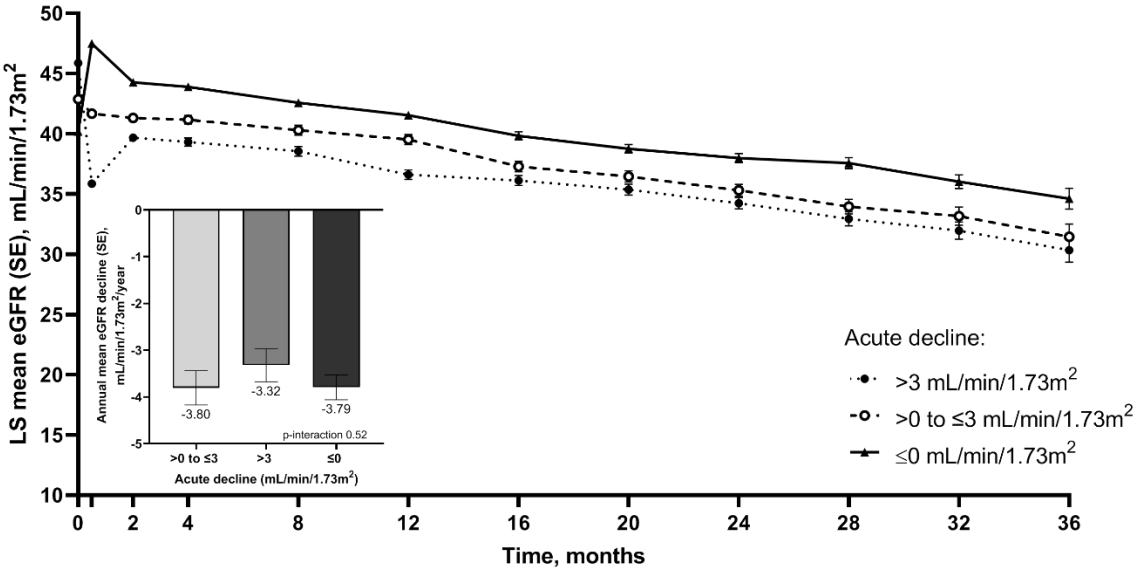
Supplementary figure 2 eGFR by acute absolute decline categories for dapagliflozin and placebo. Panel A shows the dapagliflozin group; panel B the placebo group and panel C the annual eGFR decline from Week 2 to end of treatment decline as a function of acute changes in eGFR in the placebo and dapagliflozin group.

A

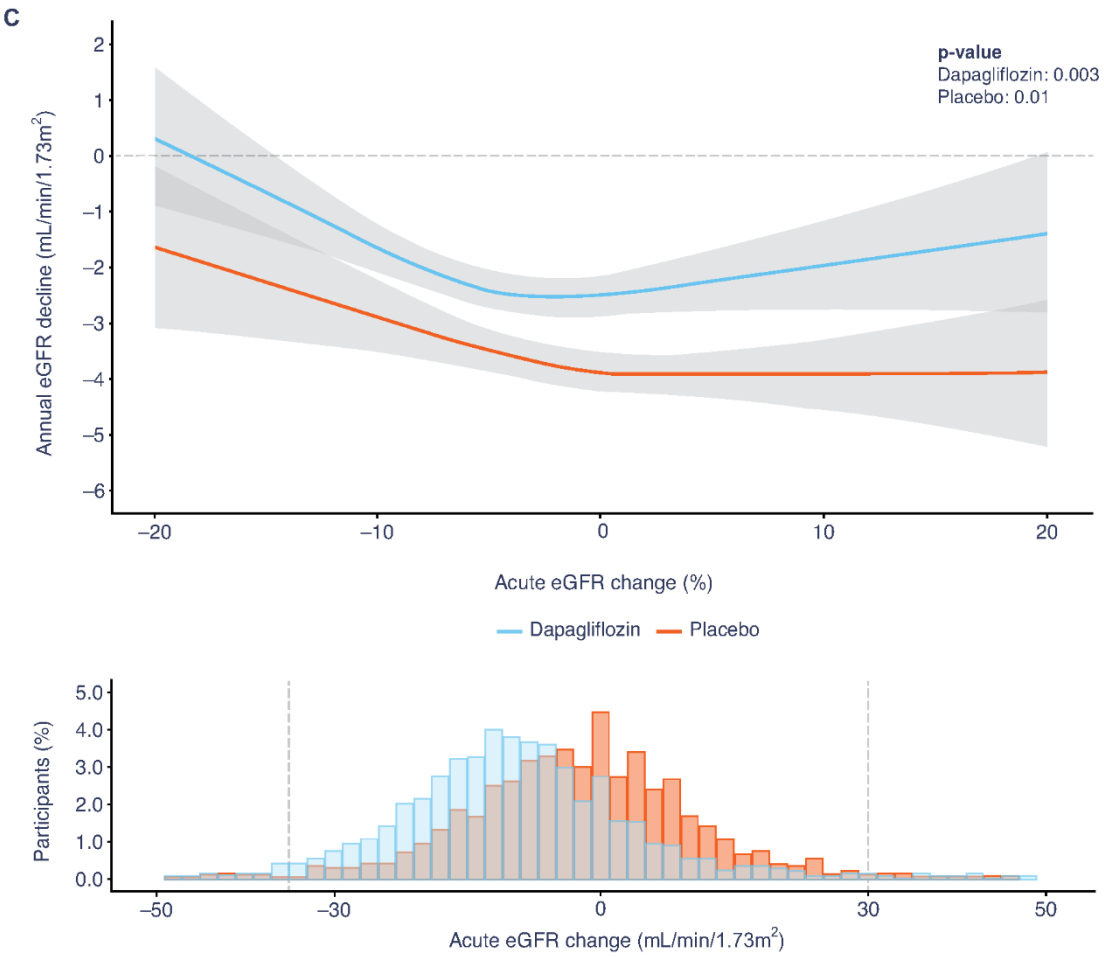


Number of participants												
>3 mL/min/1.73m^2	1137	1137	1096	1083	1037	1003	973	937	814	550	284	79
>0 to ≤3 mL/min/1.73m^2	490	490	468	460	437	423	412	397	343	220	116	41
≤0 mL/min/1.73m^2	448	448	428	422	396	381	377	350	309	200	93	37

B



Number of participants												
>3 mL/min/1.73m^2	576	576	550	538	510	494	487	474	401	254	123	47
>0 to ≤3 mL/min/1.73m^2	521	521	501	491	458	439	426	408	353	229	108	42
≤0 mL/min/1.73m^2	985	985	941	916	872	839	817	769	673	436	211	67



Chronic slope shown

P-values indicate the statistical significance of the association between the acute eGFR change (%) and long-term eGFR decline (mL/min/1.73m^2/year)