Dapagliflozin and anemia in patients with chronic kidney disease

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ABSTRACT (Current word count: 304)

Background: In the DAPA-CKD trial, dapagliflozin improved kidney and cardiovascular outcomes in patients with chronic kidney disease (CKD) with or without type 2 diabetes (T2D). In this post-hoc analysis of DAPA-CKD, we assessed the effects of dapagliflozin on the correction and prevention of anemia.

Methods: The DAPA-CKD trial randomized patients (1:1) with estimated glomerular filtration rate 25-75 mL/min/1.73m^2 and urinary albumin-to-creatinine ratio 200-5000 mg/g to dapagliflozin 10 mg or placebo. Hematocrit was measured at baseline, 2 weeks, 2 and 4 months, and every 4 months thereafter. Anemia was defined as hematocrit <39% in men or <36% in women. Correction and incidence of anemia were defined as two consecutive measurements above or below these thresholds relative to baseline, respectively, during follow-up. We classified anemia-related adverse events using data from site investigator reports.

Results: The mean age of the 4304 participants was 61.8 years and 67.5% had T2D. Among the 4292 (99.7%) participants with baseline hematocrit data, 1716 (40.0%) had anemia. Over 2.4-years median follow-up, patients assigned to dapagliflozin had an increase in hematocrit of 2.3 percentage points (95%CI 2.1-2.5) greater than those assigned to placebo. Among patients with anemia at baseline, anemia was corrected in 443 (53.3%) patients randomized to dapagliflozin and 247 (29.4%) patients randomized to placebo (HR 2.29 [95%CI 1.96-2.68]). Among patients without anemia at baseline, dapagliflozin 10.4% developed incident anemia compared to 23.7% in the placebo group (HR 0.39 [95%CI 0.31-0.48]). Anemia-related adverse events occurred in 2.2% of patients assigned to dapagliflozin compared to 3.8% in the control group. The effects of dapagliflozin on correction and prevention of anemia were consistent in patients with and without T2D. The adverse event profile was similar to that known for dapagliflozin.

Conclusion: This exploratory analysis suggests that dapagliflozin is associated with the prevention or correction of anemia in patients with CKD with and without T2D.

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INTRODUCTION

Anemia is common in patients with chronic kidney disease (CKD), a phenomenon attributed to decreased erythropoietin synthesis, absolute and functional iron deficiency, and other known and as yet unknown mechanisms.[1] As CKD advances, anemia often becomes more prominent. In CKD-G5, 50-80% of patients experience anemia, despite the availability of oral and intravenous iron supplementation and erythropoietin stimulating agents (ESA).[1,2] Altogether, the presence of anemia in patients with CKD is associated with worse clinical outcomes.[3]

Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of adverse cardiovascular and kidney outcomes in patients with type 2 diabetes (T2D), heart failure, and/or CKD.[4-7] In some of these clinical trials, SGLT2 inhibitors increased hemoglobin concentration and hematocrit relative to placebo.[8-12] However, the clinical relevance (as assessed by incidence of investigator-reported anemia or treatment for anemia) was only shown in patients with T2D and CKD treated with canagliflozin.[8] The effects of dapagliflozin on correction or prevention of anemia in patients with CKD with and without T2D are unknown.

In this post-hoc analysis of the DAPA-CKD trial, we evaluated the effects of dapagliflozin on hematocrit, correction of anemia in patients with anemia at baseline, incidence of anemia in patients without anemia at baseline, and anemia-related adverse events in patients with CKD with or without T2D.

METHODS

Participants and trial design

The DAPA-CKD trial was a multicenter, double-blinded, randomized, placebo-controlled trial, which assessed the effects of dapagliflozin on kidney, cardiovascular, mortality, and safety outcomes in patients with CKD.[5] In brief, eligible patients were ≥18 years old with or without T2D and had an estimated glomerular filtration rate (eGFR) of 25 to 75 mL/min/1.73 m^2 and a urinary albumin-to-creatinine ratio (UACR) of 200 to 5000 mg/g. Patients were also required to receive a stable dose of angiotensin converting enzyme inhibitor or angiotensin receptor blocker, if not medically contradicted. We excluded patients with type 1 diabetes, polycystic kidney disease, lupus nephritis, or antineutrophil cytoplasmic antibody–associated vasculitis. Participants were recruited at 386 centers in 21 countries between February 2, 2017, and June 12, 2020, and randomly assigned to dapagliflozin 10 mg once daily or matching placebo in a 1:1 ratio (**Figure S1**). We stratified randomization by presence of T2D and by UACR (≤1000 or >1000 mg/g). The full trial protocol has been previously described.[13] The DAPA-CKD trial was conducted in accordance with the Declaration of Helsinki principles (clinicaltrials.gov identifier: NCT03036150). The trial protocol was approved by local ethics committees at each participating institution. All trial participants provided written informed consent.

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Hematocrit and hemoglobin measurements

We measured hematocrit at baseline, 2 weeks, 2 and 4 months, and every 4 months thereafter. We measured hemoglobin concentration only at baseline and last study visits. All measurements were performed in a central laboratory.

Outcomes:

Primary and secondary trial outcomes and safety outcomes

The pre-specified primary outcome of the DAPA-CKD trial was the composite of sustained >50% eGFR decline, end-stage kidney disease (ESKD), or death from a kidney or cardiovascular cause.[5] Key secondary outcomes were a composite kidney outcome (the primary outcome excluding cardiovascular death), a cardiovascular composite outcome of heart failure hospitalization or cardiovascular death; and all-cause mortality.[5] All outcomes were adjudicated by a masked independent committee. The trial gathered information on pre-specified adverse events according to Medical Dictionary for Regulatory Activities [MedDRA] preferred terms. Predefined adverse events of interest were volume depletion, kidney event, major hypoglycemia, fractures, amputations, and potential ketoacidosis.[5]

Anemia-related outcomes

Anemia was defined as hematocrit <39% in men or <36% in women.[10,11] We defined correction of anemia as two consecutive hematocrit values above these thresholds among patients with anemia at baseline. Conversely, we defined incident anemia as two consecutive measurements below these thresholds in patients without anemia at baseline. In a sensitivity analysis, we defined baseline anemia using hemoglobin thresholds (<130g/L in men or <120g/L in women).[14] We considered adverse events leading to drug discontinuation or serious adverse events to be anemia-related when MedDRA preferred terms contained the word “anaemia”.[8] We used an absolute ≥3.0% hematocrit increase from baseline in companion analyses. A ≥3.0% increase in hematocrit is considered clinically relevant; the corresponding ≥1.0 g/dL increase

in hemoglobin has been employed as a surrogate outcome in clinical trials designed to correct anemia.

Statistical analysis

We described baseline continuous variables with approximately normal distribution by mean (SD), and those with skewed distribution by median (25%, 75% range). Baseline categorical variables were described with proportions.

We described the proportion of patients with correction (among patients with anemia at baseline) and incidence of anemia (among patients without anemia at baseline). We performed Cox proportional hazards regression models accounting for the two stratification factors (T2D and UACR) and adjusted for baseline eGFR.[5] Companion analyses were conducted using the Fine-Gray modification of the Cox model to account for the competing risk of death. We also determined the effects of dapagliflozin on anemia-related outcomes by pre-specified subgroups defined by baseline age (<65 or ≥65 years), sex, presence of T2D, eGFR (≥45 or <45 mL/min/1.73 m^2), and UACR (≤1000 or >1000 mg/g).

The effect of dapagliflozin relative to placebo on hematocrit over time was determined using a linear mixed effects model using a restricted maximum likelihood estimator. This model contained treatment allocation, visit, and treatment-by-visit interaction as fixed effects, and baseline hematocrit and the interaction of hematocrit-by-visit as covariates. We tested for effect modification according to pre-specified patient subgroups by adding the main effect for the subgroup and separate three-way interaction terms between the subgroup, treatment allocation, and visit.

To estimate the association between presence of anemia at baseline and the risk of kidney, cardiovascular, and mortality outcomes, we applied stepwise adjusted Cox proportional hazards regression. Model 1 was unadjusted. Model 2 was adjusted for age, sex, race and treatment allocation. Model 3 was additionally adjusted for Quételet (body mass) index (BMI), smoking, history of heart failure, systolic blood pressure, glycated hemoglobin (HbA1c), eGFR, and log-transformed UACR.
We assessed the effects of dapagliflozin on the trial primary and secondary endpoints by baseline anemia status using Cox models with the same stratification and adjustment approach applied to the analysis on anemia-related outcomes. Safety outcomes were presented by baseline anemia as the proportion of patients with an event.

We considered p-values <0.05 statistically significant without adjustment for multiplicity. Since no multiplicity adjustments for the secondary and exploratory end points were defined, only point estimates and 95% confidence intervals are provided. The confidence intervals have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects.

All analyses were done using STATA, version 17.1 (StataCorp College Station, TX, USA) except for the mixed effects models where we used R Statistical Software version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Contributions

This study was designed by XX.

YY gathered the data.

PV and NJ analyzed the data; HJLH and AK vouch for the data and the analysis.

HJLH, AK and GMC wrote the first draft of the paper. All authors reviewed the manuscript drafts, provided approval for the final version for submission, and take responsibility for the accuracy and integrity of the data.

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RESULTS

Patient characteristics

The mean age at baseline of the 4304 participants was 61.8 years. Of these, 1425 (33.1%) were women, and 2906 (67.5%) had T2D. Hematocrit was available at baseline for 4292 (99.7%) participants. Mean hematocrit was 38.9% (5.4) and 1716 (40.0%) participants had hematocrit-defined anemia (**Table1**). Compared to patients without anemia, those with anemia were more likely to have T2D, lower eGFR, and higher UACR. Within the anemia subgroups, baseline characteristics were well balanced between dapagliflozin and placebo groups (**Table1**). Similar results were obtained when baseline anemia was defined using hemoglobin thresholds (**Table S1**). The representativeness of the trial population is shown in **Table S2**.

Dapagliflozin associated outcomes for hematocrit and hemoglobin

Relative to patients randomized to placebo, patients randomized to dapagliflozin had higher mean hematocrit at the first post-randomization visit (week 2; **Figure 1A**). The between-group difference gradually increased reaching a plateau around 4 months from randomization and remained at about that level throughout the trial (absolute

between-group least-square mean difference over time 2.3 percentage points [95%CI 2.1, 2.5 percentage points]). The outcomes associated with dapagliflozin treatment on hematocrit was consistent across pre-specified subgroups (**Figure 2**) and was similar in an on-treatment analysis (**Figure S3**). The mean (SD) hemoglobin level at the last study visit was 132.8 [20.7] g/L in the dapagliflozin group compared to 125.1 [19.4] g/L in the placebo group; **Figure 1B**)

Dapagliflozin associated outcomes on other anemia-related measures

Among patients with anemia at baseline (**Figure S1**), 443 (53.3%) patients in the dapagliflozin group and 247 (29.4%) patients in the placebo group (HR 2.29 [95%CI 1.96-2.68]; **Figure 3A**) reached hematocrit levels consistent with our case-definition of correction of anemia. In patients without anemia at baseline, dapagliflozin treatment was associated with a reduced risk of incident anemia relative to placebo (131 [10.4%] versus 300 [23.7%]; HR 0.39 [95%CI 0.31-0.48]; **Figure 3B**); similar associations with anemia-related outcomes were noted across baseline subgroups (**Figure 4),** for the competing risk of death (**Figure 3**) or when defining anemia at baseline by the hemoglobin concentration **Figures S2A and S2B**). The proportion of patients with anemia-related adverse events was 47 [2.2%] versus 82 [3.8%] **Figure 3C** in patients assigned to dapagliflozin compared to placebo respectively. An increase in hematocrit ≥3.0% was observed in 1429 (69%) patients assigned to dapagliflozin and 772 (37%) patients assigned to placebo (HR 2.57 [95%CI 2.35-2.81]; **Figure 3D**)

Figure 4 shows anemia-related serious adverse events for active and control treatments across baseline subgroups**.** Further information on anemia-related serious adverse events as per MedDRA is provided in **Table S3**.

Association of baseline anemia with the trial primary and secondary endpoints and safety outcomes

During a median follow-up of 2.4 years, the primary composite endpoint occurred in 293 (17.1%) and 215 (8.3%) patients with and without anemia at baseline, respectively (**Table S4**). Similar findings in patients with anemia at baseline were observed also for the secondary endpoints and safety outcomes (**Tables S4 and S5**). After adjusting for baseline risk factors (model 3), comparing with patients without anemia to patients with anemia, the hazard ratio for the primary composite endpoint was 1.74 (95%CI 1.45-2.09), the secondary kidney composite endpoint was 1.95(95% CI1.57-2.42), the secondary cardiovascular composite endpoint 1.47 (95%CI 1.13-1.93), and the secondary all-cause mortality endpoint 1.47 (95%CI 1.13-1.91) (**Table S4)**.

Effect of dapagliflozin on the trial primary and secondary endpoints and safety outcomes by baseline anemia status

The effects of dapagliflozin on the primary and secondary endpoints were consistent by baseline anemia subgroups when anemia was considered on a relative scale. **Figure 5** shows the data when considering anemia on an absolute scale. For the primary composite endpoint and the secondary composite kidney endpoint some heterogeneity was noted; no heterogeneity was noted on the composite cardiovascular and all-cause mortality endpoints (**Figure 5**). Repeating these analyses with anemia defined using hemoglobin thresholds yielded similar results (**Table S6**).

Adverse Events

As noted previously, the incidence of adverse events was similar in the dapafliglozinand control groups.[5]

DISCUSSION

This post-hoc analysis of the DAPA-CKD trial showed that treatment with dapagliflozin, an SGLT2 inhibitor, was associated with an increase in hematocrit, the correction of anemia, and a reduced risk of incident anemia in patients with CKD with or without T2D. Previous randomized controlled trials showed that SGLT2 inhibitors increase hematocrit and hemoglobin concentration in patients with T2D with or without CKD [7,9,12,15], as well as in patients with heart failure with or without T2D.[10,11] In most of these studies, the clinical relevance of these findings was not assessed[9-12] , except for a post-hoc analysis of the CREDENCE trial,[8] demonstrating that canagliflozin reduced the risk for anemia-related adverse events and the need for initiation of iron repletion and/or ESA therapy in patients with CKD and T2D. The current post-hoc analysis from the DAPA-CKD trial extends these associations to a broader CKD population of patients with and without T2D, of whom 15% had stage 4 CKD, patients excluded from previous SGLT2 outcome trials and in whom anemia is commonly present.

A fraction of the increase in hematocrit observed in patients treated with SGLT2 inhibitors can be attributed to modest diuretic effects. However, our findings suggest that our observations cannot be attributed to hemoconcentration alone. First, whilst the diuretic effects of dapagliflozin are evident very early in the course of treatment [8,16], we found that the increase in hematocrit was gradual and reached a maximum

only around 4 months following treatment initiation. Second, previous studies have demonstrated that SGLT2 inhibitors including dapagliflozin increase plasma erythropoietin concentration and exert anti-inflammatory effects,[17-20] suggesting that they may directly influence the pathophysiology of anemia in CKD. If there is a direct causal impact of dapagliflozin on anemia, our data cannot establish a mechanism for it.

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Our study has several limitations. Anemia-related adverse events were not adjudicated and were defined based on investigator reporting. We used hematocrit thresholds to define anemia because of the lack of serial hemoglobin concentrations, although repeating the analyses with anemia defined by the baseline and end-of-study hemoglobin concentration yielded qualitatively similar results. We were unable to assess the relationship between dapagliflozin treatment and the provision of oral or intravenous iron, ESAs treatment, or transfusion over time. Finally, we did not obtain transferrin saturation, ferritin, serum concentrations of erythropoietin or hepcidin, or other metrics of inflammation that might confound interpreting our data on hematocrit and the discrete outcomes we captured.

In conclusion, in this post-hoc analysis of data from the DAPA-CKD trial, we demonstrate that dapagliflozin treatment was associated with an increase in hematocrit, with correction of anemia in patients with anemia at baseline, and with a lower risk of anemia in patients without anemia at baseline.

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Statement of support:

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The DAPA-CKD trial was sponsored by AstraZeneca as a collaboration between the sponsor and academic-led steering committees. The steering committees consisted of academic experts and included members who were employees of the sponsor. The steering committee was responsible for the design and scientific integrity of the trial, supervised the study and was responsible for reporting the results. The sponsor (AstraZeneca) had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and review, or approval of the manuscript prior to submission for technical and scientific accuracy. The lead and corresponding author vouch for the accuracy of the reported results. The decision to submit the manuscript for publication was made jointly by all authors.

Data sharing statement

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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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JLG has been an advisor on scientific boards for AstraZeneca, Bayer, and Novo Nordisk; has lectured for AstraZeneca, Boehringer Ingelheim, Esteve, Bayer, Eli Lilly, Mundipharma, Novartis, Bayer, Astellas, and Novo Nordisk; and has done research activities for AstraZeneca.

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Table1. Baseline characteristics of the participants according to hematocrit-defined anemia status and randomized treatment assignment

	No anemia				Anemia		
	Whole group	**Dapagliflozin**	**Placebo**		**Whole group**	**Dapagliflozin**	**Placebo**
	N=2,576	**N=1,289**	**N=1,287**		**N=1,716**	**N= 858**	**N= 858**
Age – year	61.1 (12.3)	61.4 (12.1)	60.9 (12.4)		63.0 (11.8)	62.5 (11.9)	63.4 (11.7)
Women– no. (%)	843 (32.7)	415 (32.2)	428 (33.3)		576 (33.6)	292 (34.0)	284 (33.1)
Body mass index	29.9 (6.1)	29.8 (6.0)	30.0 (6.2)		28.9 (6.2)	28.8 (6.1)	29.1 (6.3)
Systolic blood pressure – mm Hg	136.5 (17.0)	136.4 (17.0)	136.5 (16.9)		138.0 (18.0)	137.2 (18.1)	138.9 (17.9)
Diastolic blood pressure – mm Hg	79.1 (10.3)	79.0 (10.2)	79.2 (10.3)		75.1 (10.4)	75.2 (10.9)	75.0 (9.8)
Mean eGFR – mL/min/1.73 m^2	45.4 (12.5)	45.6 (12.5)	45.2 (12.5)		39.7 (11.4)	39.7 (11.2)	39.6 (11.5)
eGFR <45 – no. (%)	1313 (51.0)	656 (50.9)	657 (51.0)		1202 (70.0)	613 (71.4)	589 (68.6)
Hemoglobin – g/L	137.8 (14.2)	138.2 (14.0)	137.4 (14.5)		113.9 (12.9)	114.2 (13.0)	113.7 (12.7)
Hematocrit – %	42.2 (3.9)	42.2 (3.9)	42.2 (3.8)		33.8 (3.0)	33.8 (3.1)	33.8 (3.0)
HbA1c - %	7.0 (1.8)	7.1 (1.8)	7.0 (1.8)		7.1 (1.6)	7.1 (1.6)	7.1 (1.6)
Median UACR -mg/g (IQR)	865 (445, 1693)	885 (428, 1715)	841 (458, 1673)		1111 (526, 2179)	1081 (528, 2183)	1130 (523, 2174)
UACR >1000 – no. (%)	1149 (44.6)	589 (45.7)	560 (43.5)		921 (53.7)	454 (52.9)	467 (54.4)
Type 2 diabetes – no. (%)	1594 (61.9)	818 (63.5)	776 (60.3)		1305 (76.0)	634 (73.9)	671 (78.2)
–							
Cardiovascular disease – no. (%)	971 (37.7)	504 (39.1)	467 (36.3)		635 (37.0)	306 (35.7)	329 (38.3)
Heart failure – no. (%)	303 (11.8)	155 (12.0)	148 (11.5)		162 (9.4)	78 (9.1)	84 (9.8)
Prior Medication – no. (%)							
ACE inhibitor/ARB	2532 (98.3)	1268 (98.4)	1264 (98.2)		1666 (97.1)	839 (97.8)	827 (96.4)
Diuretic	1038 (40.3)	511 (39.6)	527 (40.9)		843 (49.1)	416 (48.5)	427 (49.8)
Erythropoietin Stimulating Agents	25 (1.0)	16 (1.2)	9 (0.7)		64 (3.7)	29 (3.4)	35 (4.1)

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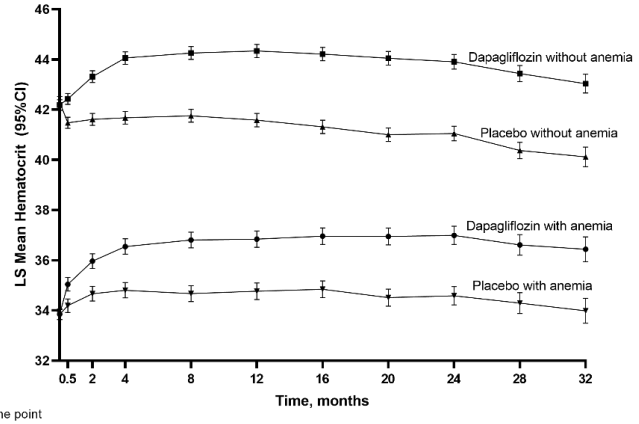
Iron supplementation	115 (4.4)	63 (4.9)	52 (4.0)		287 (16.7)	138 (16.1)	149 (17.4)

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidylpeptidase-4; eGFR, estimated glomerular filtration ratio; UACR, urine albumin-creatinine ratio

Figure 1A. Hematocrit levels over time in the treatment groups and baseline anemia status



Participants at each time point

Without anemia										
Dapagliflozin (n=1289 at BL)	1211	1210	1178	1117	1076	1064	1023	893	585	301
Placebo (n=1287 at BL)	1235	1205	1174	1118	1077	1057	1015	869	567	262
With anemia										
Dapagliflozin (n=858 at BL)	802	782	776	735	707	684	633	543	343	158
Placebo (n=858 at BL)	815	780	762	710	671	651	602	528	327	161

Hematocrit levels were determined at baseline, 14 days, 2 and 4 months, and every 4 months thereafter. The mean hematocrit values and 95% confidential intervals at each visit were calculated using mixed effect model for repeated measures. The model was adjusted for baseline hematocrit value, treatment arm, visit, interaction of treatment and visit, and interaction of baseline value and visit. BL, baseline

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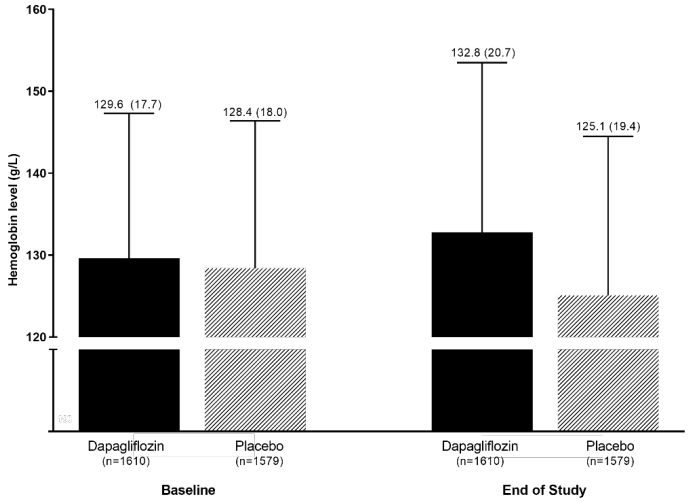
Figure 1B. Hemoglobin levels in patients with hemoglobin defined anemia at baseline and end of study by treatment group*



*The mean (SD) hemoglobin levels at baseline were 129.6 (17.7), 128.4 (18.0) g/L in the dapagliflozin group and placebo group, respectively. At the last study visit, the mean Hb level was higher in the dapagliflozin group compared to placebo group (132.8 [20.7] g/L vs 125.1 [19.4] g/L,

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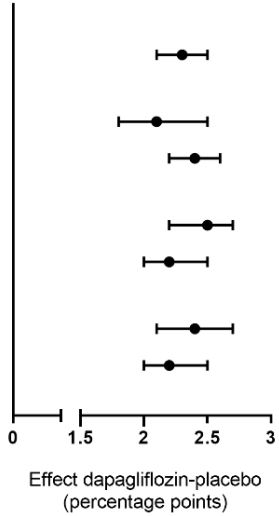
Figure 2. Median treatment differences, dapagliflozin minus placebo, averaged over the time in trial, in hematocrit by baseline subgroup

	Mean (SD) baseline hematocrit, %		Mean absolute change (95% CI) in hematocrit during follow-up		Hematocrit Difference dapagliflozin-placebo (95% CI)
	Dapagliflozin	Placebo	Dapagliflozin	Placebo	
All participants (N=4292)	38.9 (5.5)	38.8 (5.4)	2.0 (1.8, 2.1)	-0.3 (-0.4, -0.1)	2.3 (2.1, 2.5)
Type 2 diabetes					
No (n=1393)	40.0 (5.5)	40.1 (5.2)	2.0 (1.8, 2.2)	-0.1 (-0.4, 0.1)	2.1 (1.8, 2.5)
Yes (n=2899)	38.4 (5.4)	38.2 (5.4)	1.8 (1.6, 2.0)	-0.6 (-0.7, -0.4)	2.4 (2.2, 2.6)
eGFR					
≥45mL/min/1.73m^2 (n=1777)	40.4 (5.3)	40.1 (5.3)	2.5 (2.3, 2.7)	0.0 (-0.2, 0.2)	2.5 (2.2, 2.7)
<45mL/min/1.73m^2 (n=2515)	37.9 (5.4)	38.0 (5.3)	1.4 (1.2, 1.6)	-0.8 (-1.0, -0.6)	2.2 (2.0, 2.5)
UACR					
<1000 mg/g (n=2222)	39.4 (5.2)	39.3 (5.3)	2.3 (2.1, 2.5)	-0.1 (-0.3, 0.1)	2.4 (2.1, 2.7)
≥1000 mg/g (n=2070)	38.5 (5.8)	38.3 (5.5)	1.4 (1.2, 1.6)	-0.9 (-1.1, -0.7)	2.2 (2.0, 2.5)



Hematocrit levels were determined at baseline, 14 days, 2 and 4 months, and every four months thereafter. The least square mean differences of hematocrit between dapagliflozin group and placebo group were calculated using mixed effect model for repeated measures. The model was adjusted for baseline hematocrit value,

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Commented [A19]: Delete the P-value column

Commented [A20]: The abscissa on the graph should be labeled
Hematocrit Difference (dapagliflozin-placebo)

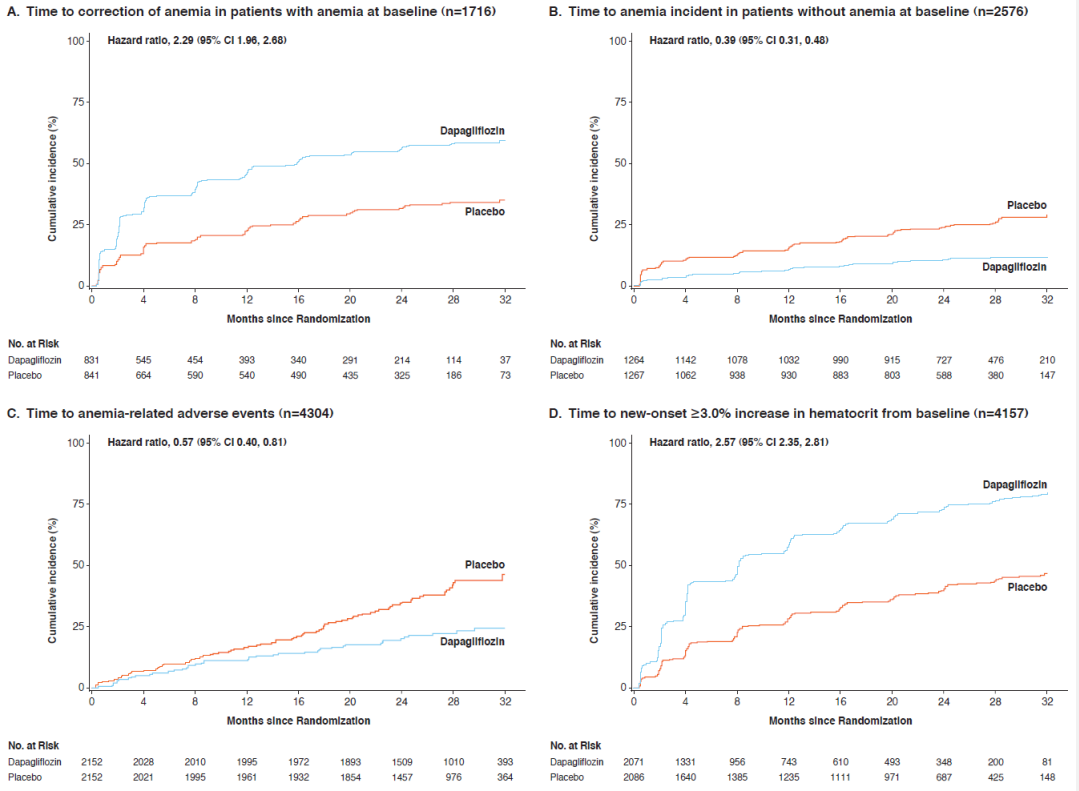
The column label "Effect dapagliflozin-placebo" should be changed to "Hematocrit Difference dapagliflozin-placebo"

The abscissa label should be changed to ""Effect dapagliflozin-placebo (percentage points)"s

treatment arm, visit, interaction of treatment and visit, and interaction of baseline value and visit. Treatment effect was also tested by pre-specified patient subgroups adding the main effect for the subgroup and separate three-way interaction terms between the subgroup, treatment allocation, and visit.

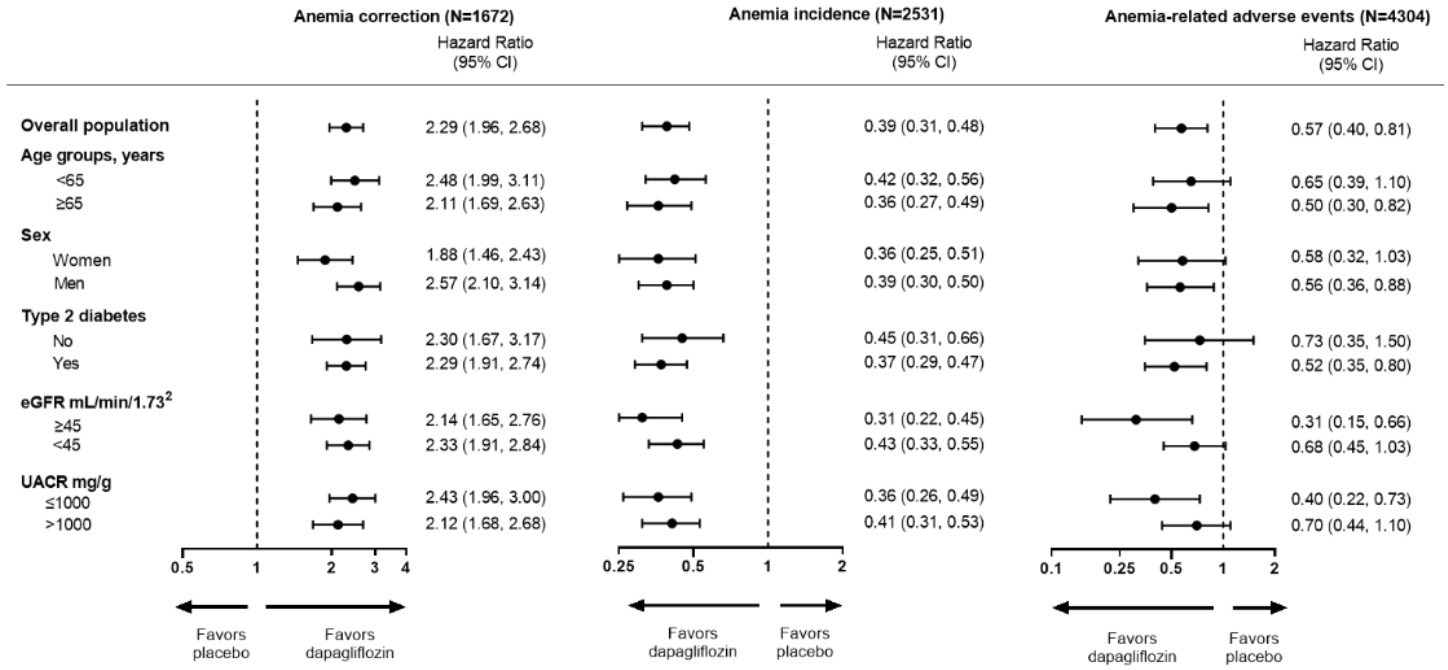
CI, confidential interval; eGFR, estimated glomerular filtration ratio; UACR, urine albumin-to-creatinine ratio

Figure 3. Time based results of dapagliflozin or placebo on various anemia outcomes



Anemia was defined as hematocrit measurements <39% for men <36% for women. For panel A and B, an event was defined as 2 consecutive measurements below the threshold (anemia onset) or above the thresholds (anemia correction). Anemia-related adverse events were defined as adverse events with a Preferred Term (within the MedDRA classification hierarchy) that contain the word “anemia”. Curves were plotted using Kaplan - Meier models. Hazard ratios, confidence intervals, were estimated using Cox proportional-hazards regression models, stratified according to randomization factors (diabetes diagnosis and urine albumin-to-creatinine ratio [>1000 mg/g or ≤1000 mg/g]) and adjusted for baseline eGFR as a continuous variable.
The analyses were repeated using the Fine-Gray model accounting for competing risk of death. Using these models the sub-distribution HR were 2.28 (95% CI 1.95, 2.66;), 0.39 (0.32, 0.48), and 0.55 (95% CI 0.37, 0.82;), for correction of anemia, incidence of anemia, and anemia-related adverse events respectively.
CI, confidential interval; eGFR, estimated glomerular filtration ratio; MedDRA, Medical Dictionary for Regulatory Activities; UACR, urine albumin-to-creatinine ratio

Figure 4. Hazard ratio, dapagliflozin over control, for anemia outcomes by baseline subgroup



Anemia was defined as hematocrit measurements <39% for men <36% for women. Correction of anemia was defined as 2 consecutive measurements above the threshold in patients with anemia at baseline. Conversely, incident anemia was defined as 2 consecutive measurements below the threshold in patients without anemia at baseline. Anemia-related adverse events were defined as adverse events with a Preferred Term (within the MedDRA classification hierarchy) that contains

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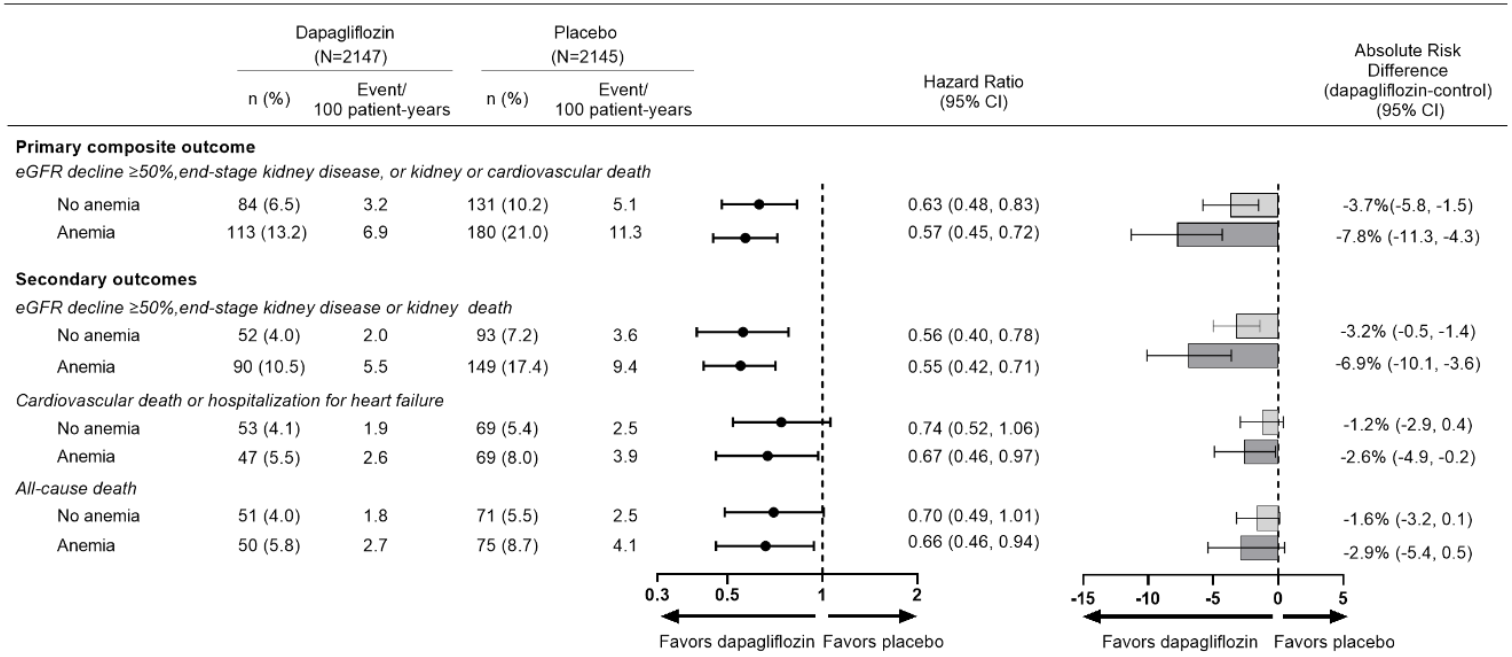
the word “anemia” and assessed in the DAPA-CKD participants. Hazard ratios and confidence intervals were estimated using Cox proportional-hazards regression models, stratified according to randomization factors (diabetes diagnosis and UACR) and adjusted for baseline eGFR.
CI, confidential interval; eGFR, estimated glomerular filtration ratio; MedDRA, Medical Dictionary for Regulatory Activities; UACR, urine albumin-to-creatinine ratio

Figure 5. Primary and key secondary study outcomes by treatment assignment and anemia status at baseline



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Anemia was defined as hematocrit measurements <39% for men <36% for women. At baseline, 1549 patients had anemia (750 in dapagliflozin and 799 in placebo group), and 2743 did not have anemia (1397 in dapagliflozin and 1346 in placebo group). The Cox proportional hazard model was stratified by type 2 diabetes and urine albumin-to-creatinine ratio (>1000 mg/g or ≤1000 mg/g) categories and was adjusted for the baseline continuous eGFR.
CI, confidential interval; eGFR, estimated glomerular filtration ratio