ORIGINAL ARTICLE

Dapagliflozin and Anemia in Patients with Chronic Kidney Disease

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Abstract

BACKGROUND In the DAPA-CKD (Dapagliflozin in Patients with Chronic Kidney Disease) 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 an estimated glomerular filtration rate of 25 to 75 ml/min/1.73 m^2 and a urinary albumin-to-creatinine ratio of 200 to 5000 mg/g to receive dapagliflozin 10 mg or placebo daily. Hematocrit was measured at baseline, 2 weeks, 2 and 4 months, and every 4 months thereafter. Anemia was defined as hematocrit less than 39% in men and less than 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 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 the 2.4-year median follow-up, patients assigned to dapagliflozin had an increase in hematocrit of 2.3 percentage points (95% confidence interval [CI], 2.1 to 2.5) greater than those assigned to placebo. Among patients with anemia at baseline, anemia was corrected in 443 (53.3%) patients randomized to receive dapagliflozin and 247 (29.4%) patients randomized to receive placebo (hazard ratio, 2.29; 95% CI, 1.96 to 2.68). Among patients without anemia at baseline, 10.4% of patients assigned to dapagliflozin developed incident anemia compared with 23.7% in the placebo group (hazard ratio, 0.39; 95% CI, 0.31 to 0.48). Anemia-related adverse events occurred in 2.2% of patients assigned to dapagliflozin compared with 3.8% assigned to placebo. Effects of dapagliflozin on the correction and prevention of anemia were consistent in patients with and without T2D. The adverse event profile was similar to that known for dapagliflozin.

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CONCLUSIONS This exploratory analysis suggests that dapagliflozin is associated with the prevention or correction of anemia in patients with CKD with and without T2D. (Funded by AstraZeneca; ClinicalTrials.gov number, NCT03036150.)

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 stage G5, 50% to 80% of patients experience anemia, despite the availability of oral and intravenous iron supplementation and erythropoietin-stimulating agents (ESAs).[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 concentrations and hematocrit levels relative to placebo.[8-12] However, clinical relevance (as assessed by incidence of investigator-reported anemia or treatment for anemia) was shown only in patients with T2D and CKD treated with canagliflozin.[8] The effects of dapagliflozin on the correction or prevention of anemia in patients with CKD with and without T2D are unknown.

In this post hoc analysis of the DAPA-CKD (Dapagliflozin in Patients with Chronic Kidney Disease) 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-blind, randomized, placebo-controlled trial that assessed the effects of dapagliflozin on kidney, cardiovascular, mortality, and safety outcomes in patients with CKD.[5] In brief, eligible patients were 18 years or older 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 receive dapagliflozin 10 mg once daily or matching placebo in a 1:1 ratio (Fig. S1 in the Supplementary Appendix). We stratified randomization by presence of T2D and by UACR (≤1000 or >1000 mg/g). The full trial protocol has been described previously.[13] The DAPA-CKD trial was conducted in accordance with the Declaration of Helsinki principles (ClinicalTrials.gov number, NCT03036150). The trial protocol was approved by local ethics committees at each participating institution. All trial participants provided written informed consent.

HEMATOCRIT AND HEMOGLOBIN MEASUREMENTS

Hematocrit was measured at baseline, 2 weeks, 2 and 4 months, and every 4 months thereafter. Hemoglobin concentrations were measured 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 prespecified primary outcome of the DAPA-CKD trial was the composite of a sustained 50% or higher eGFR decline, end-stage kidney disease, 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. All outcomes were adjudicated by a masked independent committee. The trial gathered information on prespecified adverse events according to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. Predefined adverse events of interest were volume depletion, kidney events, major hypoglycemia, fractures, amputations, and potential ketoacidosis.

Anemia-Related Outcomes

Anemia was defined as hematocrit less than 39% in men and less than 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, incident anemia was defined as two consecutive measurements below these thresholds in patients without anemia at baseline. In a sensitivity analysis, baseline anemia was defined by using hemoglobin thresholds (<130 g/l in men and <120 g/l in women).[14] Adverse events leading to drug discontinuation or serious adverse events were considered to be anemia related when MedDRA preferred terms contained the word "anemia."[8] We used an absolute 3.0% or higher hematocrit increase from baseline in companion analyses. A 3.0% or higher increase in hematocrit is considered clinically relevant; the corresponding 1.0 g/dl or higher increase in hemoglobin has been used as a surrogate outcome in clinical trials designed to correct anemia.

STATISTICAL ANALYSIS

Baseline continuous variables with approximately normal distribution are described by using means (±SD) and those with skewed distribution by median (25%, 75% range). Baseline categorical variables are 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). Cox proportional-hazards regression models were performed accounting for the two stratification factors (T2D and UACR) and were adjusted for baseline eGFR.[5] Companion analyses were conducted by using the Fine and 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 according to prespecified 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).

Table 1. Baseline Characteristics of the Participants According to Hematocrit-Defined Anemia Status and Randomized Treatment Assignment.*

Characteristic	No Anemia			Anemia		
	Whole Group (N=2576)	Dapagliflozin (n=1289)	Placebo (n=1287)	Whole Group (N=1716)	Dapagliflozin (n=858)	Placebo (n=858)
Age — yr	61.1±12.3	61.4±12.1	60.9±12.4	63.0±11.8	62.5±11.9	63.4±11.7
Female sex — no. (%)	843 (32.7)	415 (32.2)	428 (33.3)	576 (33.6)	292 (34.0)	284 (33.1)
Body mass index — kg/m^2	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
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 ml/min/1.73 m^2 — 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
HbA$_{1c}$ — %	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 mg/g — 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 inhibitors/ARBs	2532 (98.3)	1268 (98.4)	1264 (98.2)	1666 (97.1)	839 (97.8)	827 (96.4)
Diuretics	1038 (40.3)	511 (39.6)	527 (40.9)	843 (49.1)	416 (48.5)	427 (49.8)
ESAs	25 (1.0)	16 (1.2)	9 (0.7)	64 (3.7)	29 (3.4)	35 (4.1)
Iron supplements	115 (4.4)	63 (4.9)	52 (4.0)	287 (16.7)	138 (16.1)	149 (17.4)

* Values are presented as the mean (±SD) unless indicated otherwise. ACE denotes angiotensin-converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration ratio; ESAs, erythropoietin-stimulating agents; HbA$_{1c}$, glycated hemoglobin; and UACR, urinary albumin-to-creatinine ratio.

The effect of dapagliflozin relative to placebo on hematocrit over time was determined by using a linear mixed-effects model with 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 prespecified 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 the 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 Quetelet (body mass) index, smoking, history of heart failure, systolic blood pressure, glycated hemoglobin, eGFR, and log-transformed UACR.

We assessed the effects of dapagliflozin on the trial's primary and secondary end points by baseline anemia status using Cox models with the same stratification and adjustment approach applied to the analysis on anemia-related outcomes. Safety outcomes are presented by baseline anemia as the proportion of patients with an event.

Because no multiplicity adjustments for the secondary and exploratory end points were defined, only point estimates
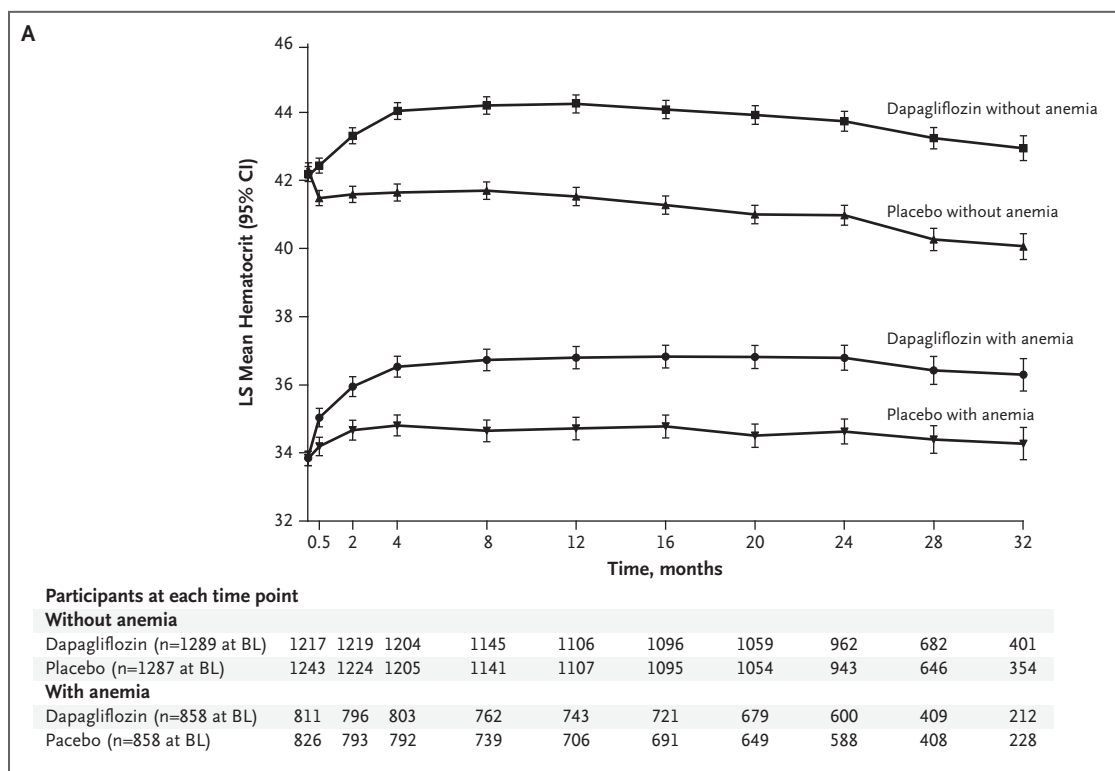

Figure 1. Hematocrit and Hemoglobin Changes over Time in the Dapagliflozin and Placebo Groups.
Hematocrit levels over time in the treatment groups and BL anemia status (Panel A). Hematocrit levels were determined at BL, 14 days, 2 and 4 months, and every 4 months thereafter. The mean hematocrit values and 95% CIs at each visit were calculated by using a mixed-effects model for repeated measures. The model was adjusted for BL hematocrit value, treatment arm, visit, interaction of treatment and visit, and interaction of BL value and visit. Hemoglobin levels in patients with hemoglobin-defined anemia at BL and end-of-study according to treatment group (Panel B). The mean (±SD) hemoglobin levels at BL were 129.6±17.7 g/l and 128.4±18.0 g/l in the dapagliflozin group and placebo group, respectively. At the last study visit, the mean hemoglobin level was higher in the dapagliflozin group compared with the placebo group (132.8±20.7 g/l vs. 125.1±19.4 g/l). BL denotes baseline; CI, confidence interval; and LS, least squares.
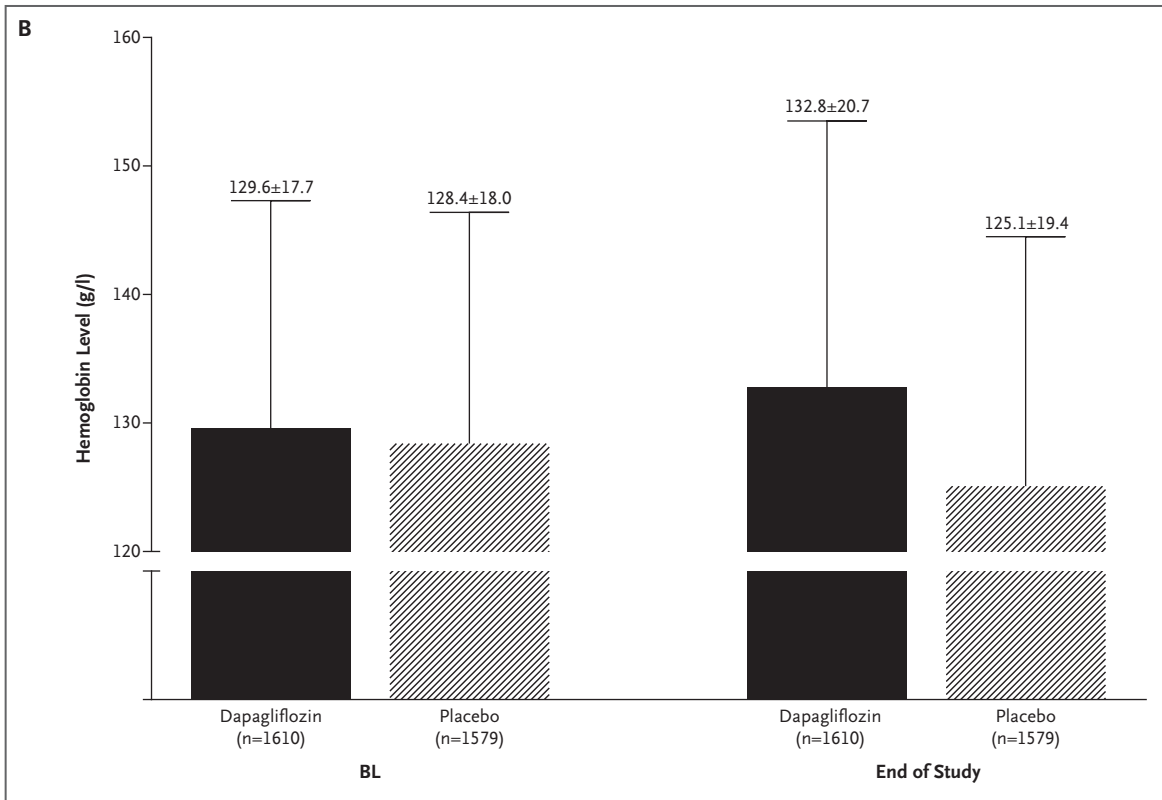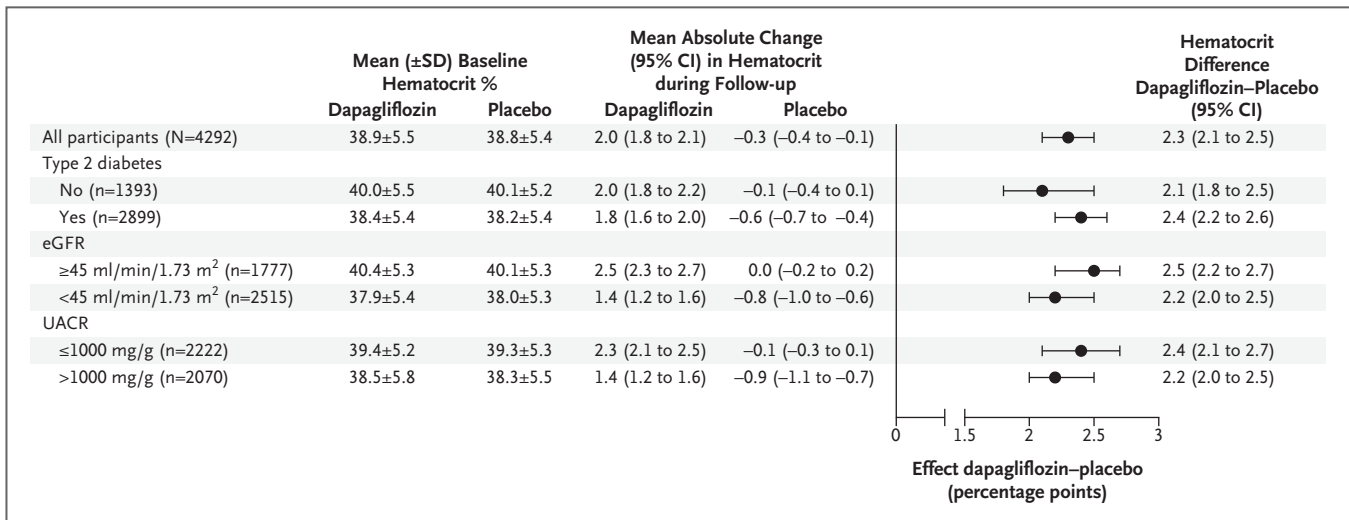
Figure 1. Continued

Figure 2. Effect of Dapagliflozin on Hematocrit by Baseline Subgroups.

Hematocrit levels were determined at baseline, 14 days, 2 and 4 months, and every 4 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, treatment arm, visit, interaction of treatment and visit, and interaction of baseline value and visit. Treatment effect was also tested by prespecified patient subgroups adding the main effect for the subgroup and separate three-way interaction terms between the subgroup, treatment allocation, and visit. CI denotes confidential interval; eGFR, estimated glomerular filtration ratio; and UACR, urinary albumin-to-creatinine ratio.

and 95% confidence intervals (CIs) are provided. The CIs have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects.

All analyses were performed by using STATA version 17.1 (StataCorp, College Station, Texas) except for the mixed-effects models, for which we used R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

PATIENT CHARACTERISTICS

The mean age at baseline of the 4304 participants was 61.8 years; 1425 (33.1%) were female, and 2906 (67.5%) had T2D. Hematocrit data were available at baseline for 4292 (99.7%) participants. Mean hematocrit was
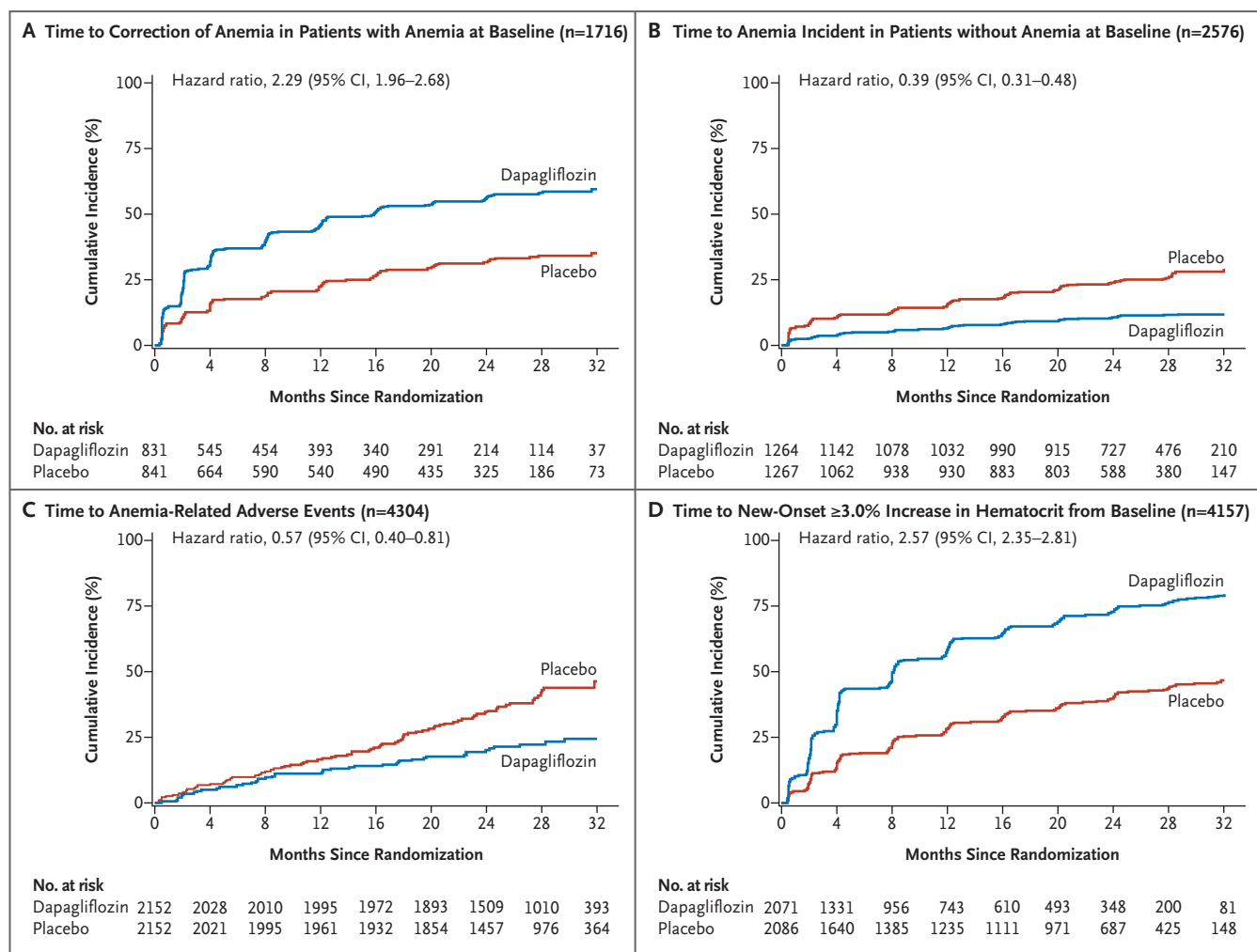

Figure 3. Time-Based Results of Dapagliflozin or Placebo on Various Anemia Outcomes.
Anemia was defined as hematocrit measurements less than 39% for men and less than 36% for women. An event was defined as two consecutive measurements above the threshold (anemia correction; Panel A) or below the threshold (anemia onset; Panel B). Anemia-related adverse events were defined as adverse events with a Preferred Term (within the Medical Dictionary for Regulatory Activities classification hierarchy) that contain the word "anemia." Curves were plotted by using Kaplan–Meier models. Hazard ratios and CIs were estimated by using Cox proportional-hazards regression models, stratified according to randomization factors (diabetes diagnosis and urinary albumin-to-creatinine ratio [>1000 or ≤1000 mg/g]) and adjusted for baseline estimated glomerular filtration ratio as a continuous variable. The analyses were repeated by using the Fine and Gray model accounting for competing risk of death. Using these models, the subdistribution hazard ratios were 2.28 (95% CI, 1.95 to 2.66), 0.39 (95% CI, 0.32 to 0.48), and 0.55 (95% CI, 0.37 to 0.82), for correction of anemia, incidence of anemia, and anemia-related adverse events, respectively. CI denotes confidence interval.

38.9%±5.4%, and 1716 (40.0%) participants had hematocrit-defined anemia (Table 1). Compared with 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 the dapagliflozin and placebo groups. Similar results were obtained when baseline anemia was defined according to 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 receive placebo, patients randomized to receive dapagliflozin had higher mean hematocrit at the first postrandomization visit (week 2) (Fig. 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 squares mean difference over time, 2.3 percentage points; 95% CI, 2.1 to 2.5). The outcomes associated with dapagliflozin treatment on hematocrit were consistent across prespecified subgroups (Fig. 2) and were similar in an on-treatment analysis (Fig. S3). The mean hemoglobin level at the last study visit was 132.8±20.7 g/l in the dapagliflozin group compared with 125.1±19.4 g/l in the placebo group (Fig. 1B).

DAPAGLIFLOZIN-ASSOCIATED OUTCOMES ON OTHER ANEMIA-RELATED MEASURES

Among patients with anemia at baseline (Fig. S1), 443 (53.3%) patients in the dapagliflozin group and 247 (29.4%) patients in the placebo group (hazard ratio, 2.29; 95% CI, 1.96 to 2.68) (Fig. 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%] vs. 300 [23.7%]; hazard ratio, 0.39; 95% CI, 0.31 to 0.48) (Fig. 3B). Similar associations with anemia-related outcomes were noted across baseline subgroups (Fig. 4), for the competing risk of death (Fig. 3), or when defining anemia at baseline according to the hemoglobin concentration (Fig. S2). The proportion of
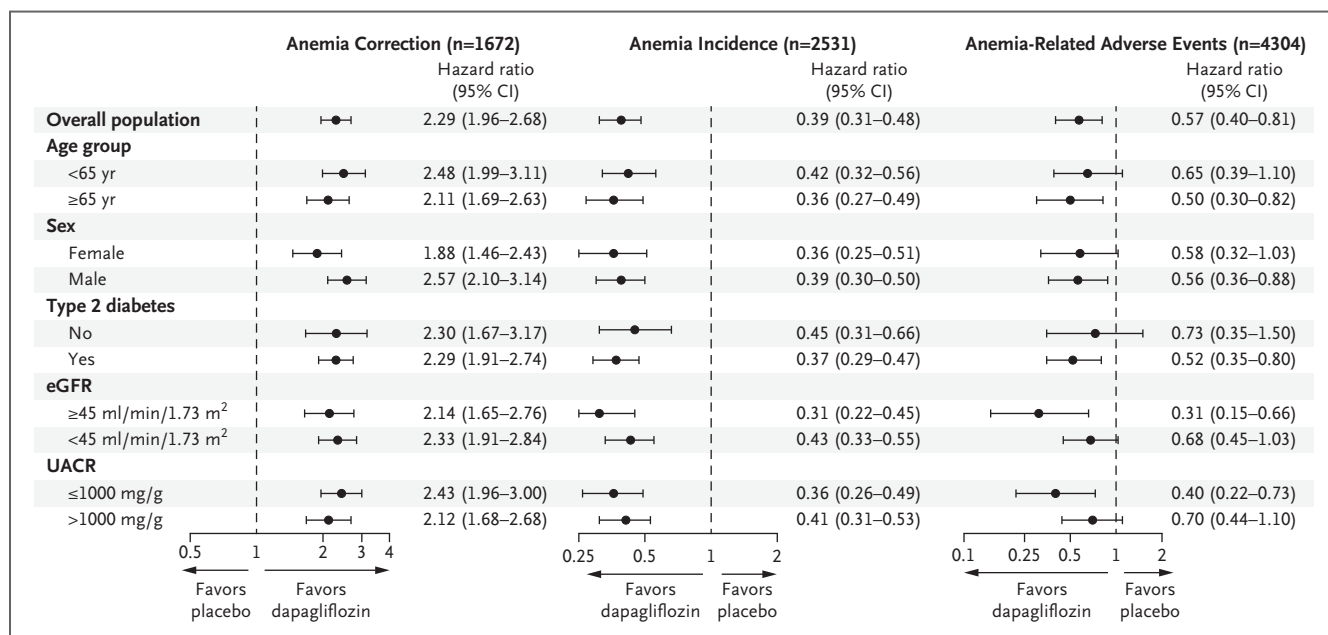
	Anemia Correction (n=1672) Hazard ratio (95% CI)	Anemia Incidence (n=2531) Hazard ratio (95% CI)	Anemia-Related Adverse Events (n=4304) Hazard ratio (95% CI)
Overall population	2.29 (1.96–2.68)	0.39 (0.31–0.48)	0.57 (0.40–0.81)
Age group			
<65 yr	2.48 (1.99–3.11)	0.42 (0.32–0.56)	0.65 (0.39–1.10)
≥65 yr	2.11 (1.69–2.63)	0.36 (0.27–0.49)	0.50 (0.30–0.82)
Sex			
Female	1.88 (1.46–2.43)	0.36 (0.25–0.51)	0.58 (0.32–1.03)
Male	2.57 (2.10–3.14)	0.39 (0.30–0.50)	0.56 (0.36–0.88)
Type 2 diabetes			
No	2.30 (1.67–3.17)	0.45 (0.31–0.66)	0.73 (0.35–1.50)
Yes	2.29 (1.91–2.74)	0.37 (0.29–0.47)	0.52 (0.35–0.80)
eGFR			
≥45 ml/min/1.73 m²	2.14 (1.65–2.76)	0.31 (0.22–0.45)	0.31 (0.15–0.66)
<45 ml/min/1.73 m²	2.33 (1.91–2.84)	0.43 (0.33–0.55)	0.68 (0.45–1.03)
UACR			
≤1000 mg/g	2.43 (1.96–3.00)	0.36 (0.26–0.49)	0.40 (0.22–0.73)
>1000 mg/g	2.12 (1.68–2.68)	0.41 (0.31–0.53)	0.70 (0.44–1.10)

Anemia Correction scale: 0.5 1 2 3 4 — Favors placebo / Favors dapagliflozin
Anemia Incidence scale: 0.25 0.5 1 2 — Favors dapagliflozin / Favors placebo
Anemia-Related Adverse Events scale: 0.1 0.25 0.5 1 2 — Favors dapagliflozin / Favors placebo

Figure 4. Hazard Ratio, Dapagliflozin versus Control, for Anemia Outcomes According to Baseline Subgroup.

Anemia was defined as hematocrit measurements less than 39% for men and less than 36% for women. Correction of anemia was defined as two consecutive measurements above the threshold in patients with anemia at baseline. Conversely, incident anemia was defined as two 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 Medical Dictionary for Regulatory Activities classification hierarchy) that contains the word "anemia" and assessed in the DAPA-CKD (Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease) participants. Hazard ratios and CIs were estimated by using Cox proportional-hazards regression models, stratified according to randomization factors (diabetes diagnosis and UACR) and adjusted for baseline eGFR. CI denotes confidence interval; eGFR, estimated glomerular filtration ratio; and UACR, urinary albumin-to-creatinine ratio.

patients with anemia-related adverse events was 47 (2.2%) versus 82 (3.8%) (Fig. 3C) in patients assigned to dapagliflozin compared with placebo, respectively. An increase in hematocrit 3.0% or higher was observed in 1429 (69%) patients assigned to dapagliflozin and 772 (37%) patients assigned to placebo (hazard ratio, 2.57; 95% CI, 2.35 to 2.81) (Fig. 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 END POINTS AND SAFETY OUTCOMES

During a median follow-up of 2.4 years, the primary composite end point 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 also observed for the secondary end points and safety outcomes (Tables S4 and S5). After adjusting for baseline risk

factors (model 3), comparing patients without anemia versus patients with anemia, the hazard ratio for the primary composite end point was 1.71 (95% CI, 1.42 to 2.05), the secondary kidney composite end point was 1.91 (95% CI, 1.54 to 2.37), the secondary cardiovascular composite end point was 1.39 (95% CI, 1.07 to 1.82), and the secondary all-cause mortality end point was 1.46 (95% CI, 1.13 to 1.87) (Table S4).

EFFECT OF DAPAGLIFLOZIN ON THE TRIAL PRIMARY AND SECONDARY END POINTS AND SAFETY OUTCOMES BY BASELINE ANEMIA STATUS

The effects of dapagliflozin on the primary and secondary end points were consistent according to baseline anemia subgroups when anemia was considered on a relative scale. Figure 5 displays the data when considering anemia on an absolute scale. For the primary composite end point and the secondary composite kidney end point, some heterogeneity was noted; no heterogeneity was noted on the composite cardiovascular and all-cause mortality end points. Repeating these analyses with anemia defined by using hemoglobin thresholds yielded similar results (Table S6).
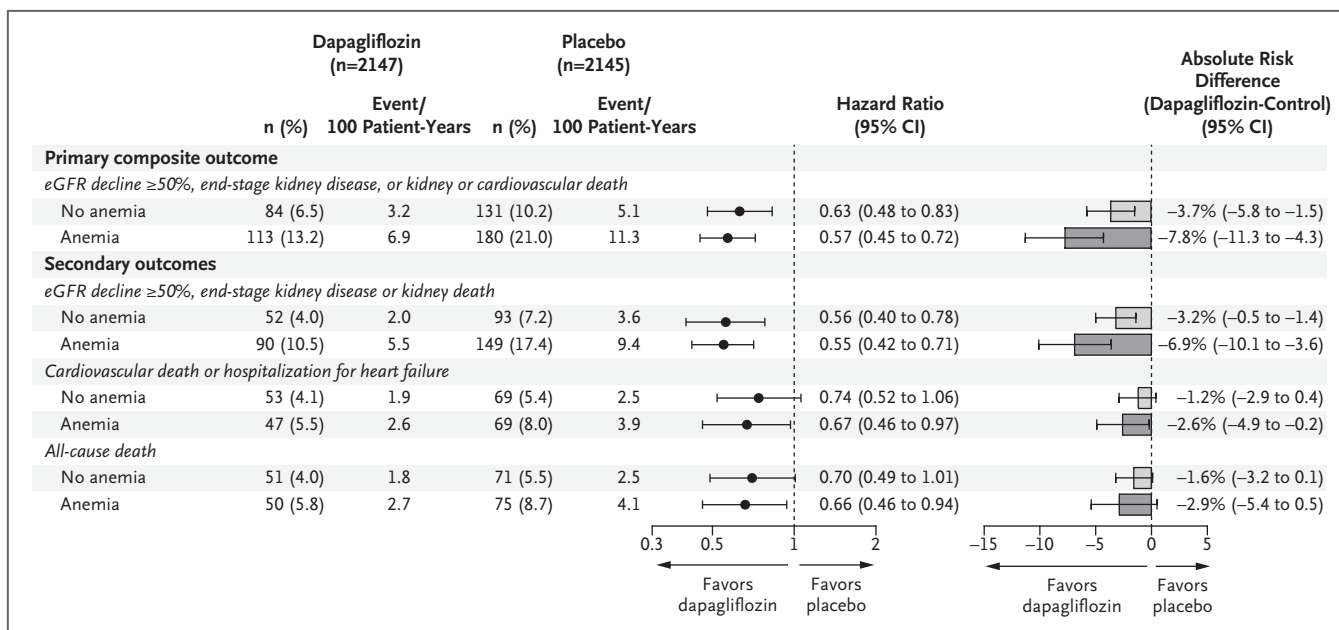
	Dapagliflozin (n=2147)		Placebo (n=2145)		Hazard Ratio (95% CI)		Absolute Risk Difference (Dapagliflozin-Control) (95% CI)
	n (%)	Event/ 100 Patient-Years	n (%)	Event/ 100 Patient-Years			
Primary composite outcome							
eGFR decline ≥50%, end-stage kidney disease, or kidney or cardiovascular death							
No anemia	84 (6.5)	3.2	131 (10.2)	5.1		0.63 (0.48 to 0.83)	−3.7% (−5.8 to −1.5)
Anemia	113 (13.2)	6.9	180 (21.0)	11.3		0.57 (0.45 to 0.72)	−7.8% (−11.3 to −4.3)
Secondary outcomes							
eGFR decline ≥50%, end-stage kidney disease or kidney death							
No anemia	52 (4.0)	2.0	93 (7.2)	3.6		0.56 (0.40 to 0.78)	−3.2% (−0.5 to −1.4)
Anemia	90 (10.5)	5.5	149 (17.4)	9.4		0.55 (0.42 to 0.71)	−6.9% (−10.1 to −3.6)
Cardiovascular death or hospitalization for heart failure							
No anemia	53 (4.1)	1.9	69 (5.4)	2.5		0.74 (0.52 to 1.06)	−1.2% (−2.9 to 0.4)
Anemia	47 (5.5)	2.6	69 (8.0)	3.9		0.67 (0.46 to 0.97)	−2.6% (−4.9 to −0.2)
All-cause death							
No anemia	51 (4.0)	1.8	71 (5.5)	2.5		0.70 (0.49 to 1.01)	−1.6% (−3.2 to 0.1)
Anemia	50 (5.8)	2.7	75 (8.7)	4.1		0.66 (0.46 to 0.94)	−2.9% (−5.4 to 0.5)

Hazard Ratio scale: 0.3 0.5 1 2 — Favors dapagliflozin / Favors placebo

Absolute Risk Difference scale: −15 −10 −5 0 5 — Favors dapagliflozin / Favors placebo

Figure 5. Primary and Key Secondary Study Outcomes According to Treatment Assignment and Anemia Status at Baseline.

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

As noted previously, the incidence of adverse events was similar in the dapagliflozin and 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 concentrations 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 trials, the clinical relevance of these findings was not assessed,[9-12] except for a post hoc analysis of the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial,[8] which showed 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, although 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 after treatment initiation. Second, previous studies have shown that SGLT2 inhibitors, including dapagliflozin, increase plasma erythropoietin concentrations 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 effect of dapagliflozin on anemia, our data cannot establish a mechanism for it.

The current 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 using 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, ESA treatment, or transfusion over time. Finally, we did not obtain transferrin saturation, ferritin levels, 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 found 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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