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Effects of canagliflozin on anaemia in patients with type 2 diabetes and chronic kidney disease: a post-hoc analysis from the CREDENCE trial

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Summary

Background Sodium-glucose co-transporter 2 inhibitors might enhance erythropoiesis and increase red blood cell mass. We assessed the long-term effects of canagliflozin on anaemia-related outcomes.

Methods In a post-hoc analysis of the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, we included patients with type 2 diabetes and chronic kidney disease who were randomly assigned to treatment with canagliflozin or placebo at 690 sites in 34 countries. We assessed the effects of canagliflozin versus matched placebo on haemoglobin and haematocrit using linear mixed-effects models. The primary outcome of this post-hoc analysis was a composite outcome of investigator-reported anaemia or treatment for anaemia, which was assessed using Kaplan-Meier analysis and Cox regression models. All analyses were done by intention to treat.

Findings Between March 24, 2014, and May 5, 2017, 4401 participants were randomly assigned to receive canagliflozin (100 mg; n=2202) or placebo (n=2199). At baseline, mean haemoglobin concentration was 132.0 g/L (SD 17.7), 1599 (36%) of 4401 participants had anaemia (defined as haemoglobin <130 g/L in men or <120 g/L in women), and 33 (<1%) of 4401 participants used erythropoiesis-stimulating agents. During a median follow-up period of 2.6 years (IQR 2.1–3.1), mean haemoglobin concentration was 7.1 g/L (95% CI 6.4–7.8) higher and haematocrit was 2.4% (2.2–2.6) higher in the canagliflozin group than the placebo group. Overall, 573 of 4401 participants had either an investigator-reported anaemia event or initiation of treatment for anaemia: 358 (8%) of 4401 participants reported anaemia events, 343 (8%) initiated iron preparations, 141 (3%) initiated erythropoiesis-stimulating agents, and 114 (2%) received blood transfusion. The risk of the composite outcome of anaemia events or initiation of treatment for anaemia was lower in the canagliflozin group than the placebo group (hazard ratio 0.65, 95% CI 0.55–0.77; $p<0.0001$). Compared with the placebo group, participants in the canagliflozin group also had lower risks of anaemia events alone (0.58, 0.47–0.72; $p<0.0001$), initiation of iron preparations (0.64, 0.52–0.80; $p<0.0001$), and need for erythropoiesis-stimulating agents (0.65, 0.46–0.91; $p=0.012$).

Interpretation These data suggest that canagliflozin reduces the risk of anaemia-associated outcomes, including the need for erythropoiesis-stimulating agents, among patients with type 2 diabetes and chronic kidney disease.

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Introduction

Approximately 40% of patients with type 2 diabetes will develop chronic kidney disease, and these individuals are at high risk of progression to end-stage kidney disease.¹ Anaemia occurs frequently in people with type 2 diabetes and chronic kidney disease, and is associated with decreases in estimated glomerular filtration rate (eGFR).² Anaemia is an independent risk factor for adverse kidney and cardiovascular outcomes and is associated with cognitive impairment and poor quality of life.³ The management of anaemia in chronic kidney disease consists of iron therapy and synthetic derivatives of recombinant erythropoietin.⁴ Although correction of chronic kidney disease-related anaemia with erythropoietin reduces the need for blood transfusion,

erythropoietin does not reduce the risks of adverse kidney or cardiovascular outcomes in patients with chronic kidney disease.⁵ Novel treatments to manage anaemia in patients with type 2 diabetes and chronic kidney disease are therefore desired.

Canagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, increases urinary glucose excretion and improves glycaemic control in patients with type 2 diabetes.⁶ Because SGLT2 inhibitors simultaneously inhibit reabsorption of sodium and glucose in the proximal tubule, a mild diuretic effect has been observed that has been associated with contraction of plasma volume, improvements in blood pressure and bodyweight, and increases in haematocrit.^{7,8} The elevation in haematocrit is commonly attributed to haemoconcentration, but SGLT2

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Research in context

Evidence before this study

We searched PubMed for any publications in English published between Jan 1, 1990, and July 31, 2020, using the search terms “SGLT2”, “SGLT2 inhibitor”, “anaemia”, “blood transfusion”, “chronic kidney disease”, “nephropathy”, “erythropoietin”, “erythropoietin alpha”, and “erythropoiesis stimulating agent”. Anaemia is a frequently occurring complication of chronic kidney disease. Observational studies have shown that anaemia is a strong and independent predictor of progression of chronic kidney disease, cardiovascular morbidity, and mortality. Previous trials have shown that increasing haemoglobin concentrations with erythropoietin-stimulating agents did not reduce the risk of adverse cardiovascular or kidney outcomes in patients with chronic kidney disease with or without type 2 diabetes. Sodium-glucose co-transporter 2 (SGLT2) inhibitors have cardiovascular and kidney benefits in people with type 2 diabetes, as shown in large cardiovascular and kidney outcome trials and registries from clinical practice. Small and short-term studies have shown that SGLT2 inhibitors enhance erythropoiesis and increase red blood cell mass. Additionally, sustained increases in haematocrit and haemoglobin concentration are consistently reported in clinical trials with SGLT2 inhibitors. However, whether long-term treatment with SGLT2 inhibitors decreases the risk of anaemia remains unknown.

Added value of this study

In this post-hoc analysis of the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial of participants with type 2 diabetes and chronic kidney disease, we found that the proportion of patients with anaemia events or initiation of treatment for anaemia was significantly lower in the canagliflozin group than in the placebo group during a median follow-up of 2.6 years. These effects were consistent across various participant subgroups. Furthermore, patients in the canagliflozin group had increases in haemoglobin, haematocrit, and erythrocyte count compared with participants in the placebo group. Proportional effects of canagliflozin on haemoglobin were greater than effects on serum albumin suggesting that direct effects on erythropoiesis contributed to the observed increases in haemoglobin concentrations.

Implications of all the available evidence

In addition to the benefits for kidney and cardiovascular outcomes, the available evidence suggests that canagliflozin might reduce the risk of anaemia and minimise the need for erythropoiesis-stimulating agents and other treatments for anaemia in patients with type 2 diabetes and chronic kidney disease.

inhibitors also cause a transient rise in erythropoietin and increase in reticulocyte count, which together also increase haematocrit and haemoglobin in a volume-independent manner.^{7,9} These effects on erythropoiesis suggest that SGLT2 inhibitors might reduce the incidence of anaemia.

The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial⁶ assessed the effects of canagliflozin on kidney outcomes in patients with type 2 diabetes and chronic kidney disease. In this post-hoc analysis of the CREDENCE trial, we aimed to assess the effects of canagliflozin on haematological parameters and anaemia-related outcomes in patients with type 2 diabetes and chronic kidney disease.

Methods

Study design and participants

We did a post-hoc analysis of the CREDENCE trial, a multicentre, double-blind, randomised controlled trial. Full details of the trial design, protocol, and statistical analysis plan, and main results have been published previously.⁶ Briefly, eligible patients were aged 30 years or older and had type 2 diabetes with HbA_{1c} levels of 6.5–12.0% (48–108 mmol/mol). Patients were also required to have chronic kidney disease, defined as an eGFR of 30 mL/min to less than 90 mL/min per 1.73 m² and a urinary albumin-to-creatinine ratio higher than 33.9 up to 565.6 mg/mmol (>300 to 5000 mg/g). These criteria led to a study population of 4401 individuals who were randomly assigned to canagliflozin or placebo at

690 clinical sites in 34 countries between March 24, 2014, and May 5, 2017. The trial protocol was approved by the local institutional ethics committees at each site. All participants provided written informed consent. The trial was done in accordance with the Declaration of Helsinki.

Randomisation and masking

All participants received a stable dose of renin-angiotensin-aldosterone system inhibitors for at least 4 weeks before randomisation. Participants were randomly assigned (1:1) to receive oral canagliflozin (100 mg daily) or matching placebo using randomly permuted blocks, stratified by eGFR at screening (30 to <45 mL/min per 1.73 m², 45 to <60 mL/min per 1.73 m², or 60 to <90 mL/min per 1.73 m²). The use of other background therapy for glycaemic management and control of cardiovascular risk factors were recommended in accordance with local guidelines.

Procedures

MO extracted data from the CREDENCE trial database held by The George Institute in Sydney (NSW, Australia). Haemoglobin concentration, haematocrit, erythrocyte count, and total protein and serum albumin as surrogates for blood plasma volume status, were measured during the study at a central laboratory. We used two approaches to identify anaemia outcomes. First, we searched the adverse events database for records including permutations of the words anaemia or cytopenia. Anaemia

adverse events were spontaneously reported by the investigator. The definition of anaemia included the preferred terms of anaemia in the Medical Dictionary for Regulatory Activities. Second, we searched the concomitant medications database for recorded post-randomisation treatments used for the management of anaemia, including iron preparations, erythropoiesis-stimulating agents, and red blood cell transfusion. The initiation of iron preparations or erythropoiesis-stimulating agents was defined as use of either treatment after randomisation if patients had no documented use at baseline.

Outcomes

The primary outcome of this post-hoc analysis was a composite of investigator-reported anaemia events or the initiation of treatments for anaemia (including anaemia events alone, initiation of iron preparations, initiation of erythropoiesis-stimulating agents, or red blood cell transfusion) by the end of the trial (May 5, 2017). The secondary outcomes were new-onset anaemia, defined as a post-randomisation haemoglobin concentration of less than 130 g/L in men or less than 120 g/L in women, according to WHO guidelines,¹⁰ in individuals without anaemia or those not receiving treatment for anaemia at baseline; severe anaemia, defined as a post-randomisation haemoglobin concentration of less than 100 g/L in individuals with baseline haemoglobin concentrations of 100 g/L or higher who were not receiving treatment for anaemia; and correction of anaemia, defined as post-randomisation haemoglobin concentration of 130 g/L or higher in men or 120 g/L or higher in women, in individuals with anaemia (haemoglobin concentration of <130 g/L in men or <120 g/L in women) at baseline. These outcomes were not prespecified in the original study. The primary endpoint was defined in accordance with previous trials for anaemia management.^{11,12}

Statistical analysis

Since this analysis was post hoc, no power calculation was done a priori. However, a study of 4401 individuals with equal randomisation that records 573 events provides more than 90% power (two-sided $\alpha=0.05$) to detect a 12% or greater reduction in the relative risk ratio of anaemia outcomes. All analyses were done by intention to treat.

Baseline characteristics were summarised in the canagliflozin and placebo groups. Continuous variables were presented as mean (SD) for variables with approximately symmetrical distributions. Results for variables with skewed distributions were presented as median (IQR).

Baseline plasma volume was estimated using the Kaplan-Hakim formula:¹³ plasma volume $(1-\text{haematocrit}) \times (a + [b \times \text{weight}(\text{kg})])$, where haematocrit is a fraction, and $a=1530$ in males and 864 in females, and $b=41$ in males and 47.9 in females. This formula was

	Canagliflozin (n=2202)	Placebo (n=2199)
Age, years	62.9 (9.2)	63.2 (9.2)
Sex		
Male	1440 (65%)	1467 (67%)
Female	762 (35%)	732 (33%)
Race or ethnicity*		
White	1487 (68%)	1444 (66%)
Black	112 (5%)	112 (5%)
Asian	425 (19%)	452 (21%)
Other	178 (8%)	191 (9%)
Current smoker	341 (16%)	298 (14%)
History of hypertension	2131 (97%)	2129 (97%)
Duration of diabetes, years	15.5 (8.7)	16.0 (8.6)
History of cardiovascular disease	1113 (51%)	1107 (50%)
Haemoglobin		
Concentration, g/L†	132.6 (17.7)	131.1 (17.7)
<100 g/L	59 (3%)	58 (3%)
100 to <120 g/L	462 (21%)	513 (23%)
120 to <130 g/L	438 (20%)	449 (20%)
≥130 g/L	1240 (56%)	1176 (54%)
Anaemia‡	769 (35%)	830 (38%)
Severe anaemia	59 (3%)	58 (3%)
Haematocrit, %§	40.6 (5.3)	40.2 (5.3)
Erythrocyte count, $\times 10^{12}/\text{L} \ddagger$	4.49 (0.58)	4.45 (0.59)
Estimated plasma volume, mL	2992.1 (623.7)	2996.7 (619.8)
BMI, kg/m^2	31.4 (6.2)	31.3 (6.2)
Systolic blood pressure, mm Hg	139.8 (15.6)	140.2 (15.6)
Diastolic blood pressure, mm Hg	78.2 (9.4)	78.4 (9.4)
HbA _{1c} , %	8.3 (1.3)	8.3 (1.4)
HbA _{1c} , mmol/mol	67 (14)	67 (15)
Total protein, g/L¶	70.7 (5.4)	70.8 (5.5)
Serum albumin, g/L¶	39.5 (3.8)	39.5 (3.8)
Estimated glomerular filtration rate, mL/min per 1.73 m ²	56.3 (18.2)	56.0 (18.3)
Urinary albumin to creatinine ratio, mg/mmol	104.3 (52–203)	105.2 (53–211)
Medication		
Iron preparation	123 (6%)	110 (5%)
Erythropoiesis-stimulating agent	18 (<1%)	15 (<1%)
Vitamin B12 or folic acid	93 (4%)	96 (4%)
Diuretic	1026 (47%)	1031 (47%)

Data are mean (SD), n (%), or median (IQR). Percentages might not sum to 100% because of rounding. *Self-reported; other includes American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported. †Six patients (three patients in the canagliflozin group; three patients in the placebo group) did not have baseline haemoglobin and erythrocyte measurements. ‡Anaemia was defined as a haemoglobin concentration of <130 g/L in men and <120 g/L in women, according to the WHO guideline.¹⁰ §25 patients (17 patients in the canagliflozin group and eight patients in the placebo group) did not have baseline haematocrit measurements. ¶One patient in the canagliflozin group did not have baseline total protein measurements and two patients did not have albumin measurements. ||923.0 mg/g (459–1794) for the canagliflozin group and 931.0 mg/g (473–1868) for the placebo group.

Table 1: Baseline characteristics

	Patients, n		Haemoglobin concentration, g/L		Mean difference during follow-up (95% CI)*	P _{interaction}
	Canagliflozin	Placebo	Mean at baseline (SD)			
			Canagliflozin	Placebo		
All participants	2043	2005	132.9 (17.6)	131.5 (17.4)	7.1 (6.4–7.8)	..
Age, years						
<65	1108	1055	132.4 (17.8)	130.8 (18.5)	7.3 (6.3–8.2)	0.61
≥65	935	950	133.6 (17.4)	132.3 (16.3)	6.9 (6.0–7.8)	..
Sex						
Male	1334	1336	137.7 (16.9)	135.6 (17.3)	8.0 (7.1–8.8)	0.0004
Female	709	669	124.0 (15.2)	123.4 (14.8)	5.5 (4.5–6.6)	..
Anaemia						
No	1347	1254	142.3 (12.8)	141.6 (12.7)	7.3 (6.5–8.1)	0.54
Yes	696	751	114.8 (9.8)	114.7 (9.7)	6.8 (5.7–8.0)	..
Haemoglobin, g/L						
<100	53	47	92.8 (4.8)	92.5 (6.5)	7.4 (0.8–14.1)	0.26
100 to <120	418	465	112.1 (5.3)	111.7 (5.5)	5.9 (4.4–7.3)	..
120 to <130	404	413	124.7 (2.9)	124.7 (2.9)	7.0 (5.6–8.5)	..
≥130	1168	1080	145.1 (11.4)	144.4 (11.5)	7.6 (6.7–8.4)	..
Haematocrit†						
Below median	844	918	118.6 (11.9)	118.4 (11.6)	7.5 (6.4–8.5)	0.45
Median or higher	1185	1082	143.0 (13.4)	142.7 (13.4)	7.0 (6.1–7.8)	..
Estimated plasma volume†						
Below median	986	944	136.8 (18.0)	135.7 (18.5)	6.7 (5.7–7.6)	0.16
Median or higher	1043	1056	129.2 (16.3)	127.9 (15.6)	7.7 (6.7–8.6)	..
Iron preparation						
No	1930	1907	133.8 (17.3)	132.3 (17.3)	7.2 (6.5–7.9)	0.41
Yes	113	98	118.8 (16.2)	116.4 (14.6)	6.2 (3.3–9.1)	..
Erythropoiesis-stimulating agent						
No	2028	1990	133.1 (17.6)	131.7 (17.4)	7.1 (6.5–7.8)	0.70
Yes	15	15	115.9 (12.3)	110.3 (15.6)	7.7 (–1.5–17.0)	..
Race or ethnicity						
White	1383	1313	134.6 (17.1)	133.8 (16.6)	6.9 (6.1–7.7)	0.54
Black	102	98	124.9 (17.0)	126.9 (17.9)	5.6 (2.9–8.3)	..
Asian	395	422	129.1 (17.7)	123.9 (17.4)	7.9 (6.5–9.3)	..
Other	163	172	132.8 (19.3)	130.2 (19.7)	7.4 (4.9–9.9)	..
Smoker						
No	1725	1741	131.9 (17.5)	130.9 (17.2)	6.8 (6.0–7.5)	0.016
Yes	318	264	138.4 (17.1)	135.8 (8.7)	8.9 (7.2–10.5)	..
History of hypertension						
No	65	65	126.6 (17.9)	129.2 (19.7)	8.9 (5.6–12.1)	0.35
Yes	1978	1940	133.2 (17.6)	131.6 (17.4)	7.0 (6.4–7.7)	..
History of cardiovascular disease						
No	1013	990	132.1 (18.0)	130.5 (17.3)	6.9 (6.0–7.8)	0.57
Yes	1030	1015	133.8 (17.2)	132.5 (17.7)	7.3 (6.5–8.2)	..
Duration of diabetes, years						
<15	988	925	135.2 (18.1)	133.4 (18.2)	7.7 (6.7–8.7)	0.078
≥15	1055	1080	130.8 (16.9)	129.9 (16.7)	6.5 (5.6–7.4)	..

(Table 2 continues on next page)

(Table 2 continues on next page)

derived from curve-fitting analytics in comparison to direct plasma volume measurement and was validated in a historic cohort of patients with chronic kidney disease.^{14,15}

Least-squares mean changes from baseline in haemoglobin concentration, haematocrit, erythrocyte count, total protein, and serum albumin over time were analysed using linear mixed-effects models with a restricted maximum likelihood-based repeated measures up to week 182. The models included the fixed, categorical effects of treatment, trial visit, eGFR at screening, and treatment-by-visit interaction, and continuous, fixed covariates of baseline value and baseline value-by-visit interaction. An unstructured covariance structure was used to model the within-patient errors. We also calculated mean percentage change from baseline in these values using the same linear mixed-effects models. Effects of canagliflozin versus placebo on mean change in haemoglobin concentration were determined for baseline patient subgroups defined by age (<65 years vs ≥65 years), sex, anaemia (haemoglobin concentration <130 g/L in men or <120 g/L in women), haemoglobin concentration (<100 g/L, 100 to <120 g/L, 120 to <130 g/L, or ≥130 g/L), haematocrit (below median vs median or higher; 0.41 for men and 0.38 for women), estimated plasma volume (below median vs median or higher; 2952 mL for men and 2791 mL for women), baseline treatment of anaemia (iron preparations or erythropoiesis-stimulating agents), race, smoking status, history of hypertension and cardiovascular disease, duration of diabetes (<15 years vs ≥15 years), BMI (<30 kg/m² or ≥30 kg/m²), systolic blood pressure (<140 mm Hg or ≥140 mm Hg), HbA_{1c} (<8% [64 mmol/mol] or ≥8% [64 mmol/mol]), total protein (<60 g/L or ≥60 g/L), serum albumin (<35 g/L or ≥35 g/L), eGFR (30 to <45 mL/min per 1.73 m², 45 to <60 mL/min per 1.73 m², or 60 to <90 mL/min per 1.73 m²), urinary albumin-to-creatinine ratio (<113 mg/mmol or ≥113 mg/mmol [<1000 mg/g or ≥1000 mg/g]), and diuretic use. The interaction was assessed by adding treatment by subgroup interaction terms to the relevant models without correcting for multiplicity.

We estimated the effects of canagliflozin versus placebo on anaemia from a Kaplan-Meier analysis with Cox proportional hazards models to determine hazard ratios (HR) and 95% CIs. Analyses were stratified by eGFR at screening as prespecified for the main analysis.⁶ We investigated the consistency of treatment effects across baseline participant subgroups.

To assess the associations between an anaemia event and subsequent risks of adverse kidney, cardiovascular, and safety events, we used multivariable Cox proportional hazards models to estimate HR and 95% CIs for kidney, cardiovascular, and safety events in participants who met the primary anaemia outcome versus those who did not meet the anaemia outcome.

All analyses were done using SAS (version 9.4) and Stata (version 15). A two-sided p value of less than 0.05 was

considered significant; no adjustment was made for multiplicity.

Role of funding source

The CREDENCE trial was sponsored by Janssen Research and Development and was overseen by an independent steering committee, which involved non-voting members from the sponsor. The steering committee oversaw the design of the trial, the conduct of the study, and the management and analysis of the data. The funder was involved in the study design, data collection, data analysis, data interpretation, and the writing of the report. All authors had full access to the data. MO and HJLH had the final responsibility for the decision to submit for publication.

Results

The CREDENCE trial population consisted of 4401 participants randomly assigned to canagliflozin (n=2202) or placebo (n=2199). The median follow-up period was 2.6 years (IQR 2.1–3.1), until the last trial visits (clinic or telephone), which were done on Oct 30, 2018. At baseline, mean haemoglobin concentration was 132.0 g/L (SD 17.7), mean haematocrit was 40.4% (5.3), and mean erythrocyte count was $4.47 \times 10^{12}/L$ (0.58). 1599 (36%) of 4401 participants had anaemia (haemoglobin <130 g/L in men or <120 g/L in women) and 117 (3%) of participants had severe anaemia (haemoglobin <100 g/L) at baseline (table 1). At baseline, 233 (5%) of 4401 participants reported use of iron preparations and 33 (<1%) participants reported use of erythropoiesis-stimulating agents. Mean haemoglobin concentration and haematocrit were lower in women than men (136.4 g/L [SD 17.3] and 38.2% [4.6] vs 136.4 g/L [17.3] and 41.5% [5.3], respectively), and the proportion of participants who had anaemia was higher in women than men (612 [41%] of 1494 women vs 987 [34%] of 2907 men).

4395 participants had a haemoglobin measurement at baseline and 4048 participants had at least one measurement during follow-up. In both the canagliflozin and placebo groups, mean baseline haemoglobin concentration was lower in women, Black or African American individuals, Asian individuals, non-smokers, those with lower BMI, lower eGFR, lower serum albumin, lower total protein, and higher estimated plasma volumes, and albuminuria, no history of cardiovascular disease, and longer duration of diabetes (table 2).

Mean haemoglobin concentration, haematocrit, and erythrocyte count increased after randomisation and remained higher in those treated with canagliflozin than those treated with placebo during follow-up. Haemoglobin concentration, haematocrit, and erythrocyte count declined in both groups after month 12 (figure 1A–C). Compared with placebo, mean haemoglobin was 7.1 g/L (95% CI 6.4–7.8) higher in the canagliflozin

	Patients, n		Haemoglobin concentration, g/L		Mean difference during follow-up (95% CI)*	P _{interaction}
	Canagliflozin	Placebo	Mean at baseline (SD)			
			Canagliflozin	Placebo		
(Continued from previous page)						
BMI, kg/m ² ‡						
<30	920	947	131.7 (17.8)	129.7 (17.9)	6.5 (5.5–7.5)	0.12
≥30	1119	1056	134.0 (17.4)	133.2 (16.9)	7.6 (6.7–8.5)	..
Systolic blood pressure, mm Hg						
≤140	1117	1076	133.6 (17.4)	132.5 (17.9)	6.9 (6.0–7.8)	0.47
>140	926	929	132.1 (17.9)	130.5 (17.0)	7.3 (6.4–8.3)	..
HbA _{1c} §		[A5]				
<8% (<64 mmol/mol)	953	948	132.1 (17.5)	130.8 (17.7)	6.8 (5.9–7.8)	0.39
≥8% (≥64 mmol/mol)	1090	1056	133.7 (17.7)	132.2 (17.3)	7.3 (6.4–8.2)	..
Total protein, g/L						
<60	47	40	124.2 (22.1)	116.5 (16.3)	7.5 (1.6–13.3)	0.80
≥60	1996	1965	133.1 (17.4)	131.8 (17.4)	7.1 (6.4–7.8)	..
Serum albumin, g/L						
<35	166	190	125.0 (21.3)	120.7 (17.2)	6.9 (6.0–7.8)	0.47
≥35	1877	1815	133.6 (17.1)	132.7 (17.1)	7.1 (6.4–7.8)	..
Estimated glomerular filtration rate, mL/min per 1.73 m ²						
30 to <45	601	589	128.7 (18.1)	127.4 (17.6)	7.6 (6.3–8.9)	0.61
45 to <60	594	580	131.7 (17.9)	130.5 (18.0)	7.2 (6.0–8.4)	..
60 to <90	848	836	136.8 (16.2)	135.2 (16.3)	6.7 (5.7–7.8)	..
Urinary albumin-to-creatinine ratio						
<113 mg/mmol (<1000 mg/g)	1112	1069	134.4 (16.8)	132.9 (17.2)	6.8 (6.0–7.6)	0.33
≥113 mg/mmol (≥1000 mg/g)	931	936	131.2 (18.4)	129.9 (17.7)	7.5 (6.4–8.5)	..
Diuretic						
No	1088	1066	133.9 (17.6)	131.8 (17.8)	6.8 (5.9–7.6)	0.26
Yes	955	939	131.9 (17.6)	131.2 (17.1)	7.5 (6.5–8.5)	..

*Canagliflozin group minus placebo group. †14 patients in the canagliflozin group and five patients in the placebo group did not have baseline haematocrit or plasma volume measurements. ‡Four patients in the canagliflozin group and two patients in the placebo group did not have baseline BMI measurements. §One patient in the placebo group did not have baseline HbA_{1c} measurement.

Table 2: Effects of canagliflozin on haemoglobin concentration in participant subgroups defined by baseline characteristics

group, haematocrit was 2.4% (2.2–2.6) higher, and erythrocyte counts were $0.25 \times 10^{12}/L$ (0.23–0.27) higher. Increases in haemoglobin concentration between baseline and week 182 were greater in men ($p_{\text{interaction}}=0.0004$) and smokers ($p_{\text{interaction}}=0.016$; table 2). The effect of canagliflozin on haemoglobin was consistent regardless of baseline haemoglobin and haematocrit levels or estimated plasma volume status and independent of the presence or absence of anaemia (all p values for interaction >0.05; table 2). Participants in the canagliflozin group also had increased serum albumin and total protein concentrations compared

Figure 1: Effects of canagliflozin on haematological parameters

(A) Mean change in haemoglobin concentration; mean baseline haemoglobin levels were 132.9 g/L for the canagliflozin and 131.5 g/L for the placebo group. (B) Mean change in haematocrit; mean baseline haematocrit was 40.6% in the canagliflozin group and 40.2% in the placebo group. (C) Mean change in erythrocyte count; mean baseline erythrocyte count was $4.50 \times 10^{12}/L$ in the canagliflozin group and $4.45 \times 10^{12}/L$ in the placebo group. (D) Mean change in total protein; mean baseline total protein was 70.7 g/L in the canagliflozin group and 70.8 g/L in the placebo group. (E) Mean change in serum albumin; mean baseline serum albumin was 39.5 g/L in the canagliflozin group and 39.5 g/L in the placebo group. (F) Mean between-group difference in percentage change in haematological parameters from baseline to week 182. Error bars show 95% CIs.

with those in the placebo group (figure 1D, E). The proportional effect of canagliflozin on haemoglobin (percentage change in least-squares mean 5.40%),

haematocrit (6.00%), and erythrocyte count (5.58%) were larger than the effects on total protein (1.87%) or serum albumin (2.60%; figure 1F).

Figure 2: Kaplan-Meier curves of effects of canagliflozin versus placebo on anaemia or initiation of treatment for anaemia (A), anaemia events alone (B), initiation of iron preparations (C), initiation of erythropoiesis-stimulating agents (D), and blood transfusion (E)
HR=hazard ratio.

During a median follow-up of 2.6 years (IQR 2.1–3.1), 573 of 4401 participants had an investigator-reported anaemia event or initiation of treatment for anaemia (the composite outcome); 358 (8%) had an investigator-reported anaemia event (of whom 38 [11%] required or

prolonged hospitalisation; appendix p 2), 343 (8%) initiated iron preparations, 141 (3%) commenced treatment with an erythropoiesis-stimulating agent, and 114 (2%) received a red blood cell transfusion. Among 573 participants who had anaemia events, the types of

See Online for appendix

Figure 3: Forest plot of effects of canagliflozin versus placebo on anaemia or initiation of treatment for anaemia

anaemia and drug action were similar between the canagliflozin and placebo groups (appendix p 2). There was no documented record of anaemia due to malignant disease.

The risk of anaemia events or initiation of treatment for anaemia was lower in the canagliflozin group than the placebo group (41.2 patients vs 63.0 patients with an event per 1000 patient-years; HR 0.65, 95% CI 0.55–0.77; $p<0.0001$; figures 2, 3). The effect on the anaemia composite outcome was greater in participants not receiving a diuretic than those receiving a diuretic at baseline ($p_{\text{interaction}}=0.018$) and in smokers ($p_{\text{interaction}}=0.029$; figure 4). The effect of canagliflozin was generally consistent in all subgroups defined by baseline demographic or clinical characteristics (all $p_{\text{interaction}}$ values >0.13 with the exception of smoking and diuretic use; figure 4). Similar effect estimates were observed when the components of the composite anaemia endpoint were analysed. Compared with patients in the placebo group, patients in the canagliflozin group had fewer anaemia events alone (23.9 patients vs 41.1 patients with an event per 1000 patient-years; HR 0.58, 95% CI 0.47–0.72; $p<0.0001$); fewer patients initiated iron preparations (24.4 patients vs 37.9 patients with an event per 1000 patient-years; 0.64, 0.52–0.80; $p<0.0001$); and fewer patients initiated treatment with erythropoiesis-stimulating agents (9.8 patients vs 15.1 patients with an event per 1000 patient-years; 0.65, 0.46–0.91; $p=0.012$; figures 2, 3). Numerically, the need for blood transfusion was consistent with the other components of the anaemia outcomes, however, few patients required a blood transfusion in either treatment group (9.5 patients vs 10.6 patients with an event per 1000 patient-years; 0.89, 0.62–1.29; $p=0.55$; figure 2, 3).

The risk of new-onset anaemia was lower with canagliflozin than placebo in participants without anaemia who were not receiving treatment for anaemia at baseline (84.2 patients vs 165.6 patients with an event per 1000 patient-years; HR 0.48, 95% CI 0.41–0.55; $p<0.0001$; appendix p 5). Patients in the canagliflozin group also had a lower risk of severe anaemia than did

those in the placebo group (19.2 patients vs 37.8 patients with an event per 1000 patient-years, HR 0.50, 95% CI 0.39–0.64; $p<0.0001$; appendix p 5). In contrast, among participants with anaemia at baseline, correction of anaemia occurred more frequently in participants assigned to canagliflozin than placebo (275.6 patients vs 109.8 patients with an event per 1000 patient-years; HR 2.59, 95% CI 2.18–3.08; $p<0.0001$; appendix p 5).

In the assessment of the associations between anaemia and adverse outcomes, kidney, cardiovascular, and safety events occurred more frequently in participants who met the primary composite anaemia outcome than in those who did not (appendix pp 3–4).

Discussion

Previous short-term and small studies have shown that SGLT2 inhibitors increase haemoglobin concentrations and haematocrit in patients with type 2 diabetes and relatively normal kidney function.^{7–9,16} Whether these effects persist during long-term treatment and reduce the risk of anaemia in patients with type 2 diabetes and chronic kidney disease remains unknown. In this post-hoc analysis of the CREDENCE trial, we found that the effects of canagliflozin on haemoglobin and haematocrit persist over a median of 2.6 years and that canagliflozin reduces the risk of anaemia-associated outcomes in patients with type 2 diabetes and chronic kidney disease, including initiation of erythrocyte-stimulating agents.

The main finding in this study was that the risk of anaemia or initiation of treatment for anaemia was significantly lower in the canagliflozin group than the placebo group. To date, no studies have assessed the effect of SGLT2 inhibitors on anaemia-related clinical events. The CREDENCE trial, the largest and only kidney outcome study of an SGLT2 inhibitor to date, enrolled participants with established chronic kidney disease who were therefore at high risk of developing anaemia. These criteria enabled robust assessment of the effect of canagliflozin on a range of anaemia-related outcomes. Although this study is a post-hoc analysis, the strength and consistency of the observed effects on a range of

Figure 4: Forest plot of effects of canagliflozin versus placebo on anaemia or initiation of treatment for anaemia in participant subgroups defined by baseline characteristics n=number of events. N=total number of patients with available data.

anaemia-related outcomes and the comparability of findings across participants with different baseline characteristics suggest a genuine and long-term protective effect of canagliflozin on anaemia in people with type 2 diabetes, including minimising the need for erythrocyte-stimulating agents. These findings suggest that a drug originally developed as a glucose lowering agent might have additional value as an adjunct therapy for anaemia in patients with chronic kidney disease. To provide the evidence required to support clinical practice, these data require confirmation in a prospective clinical trial.

SGLT2 inhibition leads to a contraction in plasma volume as a result of mild diuretic effects.^{7,17} The increase in haemoglobin concentration and haematocrit can thus be partly attributed to plasma volume contraction. Only a small increase in serum albumin and total protein was observed in the canagliflozin group. The proportional larger effects of canagliflozin on haemoglobin and haematocrit compared with serum albumin and total protein were observed in a pooled analysis of clinical trials with the SGLT2 inhibitor dapagliflozin (unpublished).¹⁸ These data suggest that the increases in haemoglobin concentration and haematocrit are not attributable to plasma volume contraction alone and support a possible direct effect of canagliflozin on erythropoiesis. This is further supported by the consistent effects of canagliflozin on haemoglobin regardless of baseline haemoglobin levels or estimated plasma volume.

SGLT2 inhibitors have been reported to cause a transient increase in erythropoietin 2–4 weeks after treatment initiation in patients with type 2 diabetes, which is accompanied by an increase in red blood cell mass and reticulocyte count,^{7,9,19} although erythropoietin and reticulocyte count were not measured in the CREDENCE trial. Increased erythropoietin release has been hypothesised to result from improvements in the hypoxic microenvironment in the proximal tubule.²⁰ SGLT2 inhibitors decrease ATP-dependent workload of the proximal tubule cells thereby alleviating metabolic stress and tubulointerstitial hypoxia.²⁰ This reduction in ATP-dependent workload of the proximal tubule cells has been hypothesised to reverse the conversion of myofibroblasts to erythropoietin-producing fibroblasts, thereby enhancing erythropoiesis and haematocrit. SGLT2 inhibitors also suppress hepcidin, which might lead to an increase in bioavailability and utilisation of iron and increased erythropoiesis.²¹ Additionally, SGLT2 inhibition causes a shift in sodium reabsorption to the medullary thick ascending limb, which increases oxygen demands in distal parts of the tubule. A decrease in oxygen tension in the medulla stimulates hypoxia inducible factor-1 α (HIF-1 α), which can increase erythropoietin production in a volume-independent manner.²² HIF-1 α stabilisers have proven effective in treating anaemia in patients with chronic kidney disease.²³ Stimulation of erythropoiesis might be vasopressin-dependent. As a result of mild diuretic effects, SGLT2 inhibitors increase copeptin, a surrogate marker of

vasopressin.²⁴ In experimental models of anaemia, vasopressin stimulates erythropoietin release and the mass production of red blood cells, providing another explanation for the observed increase in haemoglobin and haematocrit in our study.²⁵ Furthermore, SGLT2 inhibitors restore impaired tubuloglomerular feedback and reduce hyperfiltration in diabetes, which could preserve long-term kidney function and reduce hypoxia.^{26,27}

Previous long-term and large clinical trials of SGLT2 inhibitors have reported similar increases in haemoglobin concentrations and haematocrit during follow-up in patients with type 2 diabetes and relatively normal kidney function.^{8,28–30} These studies also showed that changes in haemoglobin concentrations and haematocrit from baseline explained nearly half of the effects of SGLT2 inhibitors versus placebo on the risk of cardiovascular death, heart failure, and kidney failure.^{28–30} These data suggest a strong association between erythropoiesis parameters with cardiovascular and kidney outcomes, which is supported by the findings from the current analysis demonstrating that development of anaemia was significantly associated with subsequent risk of adverse kidney and cardiovascular outcomes.

The strengths of our study include the large number of participants, long duration of follow-up, sequential measurements of haemoglobin, and high number of anaemia-associated events. However, our study has several limitations. First, this study was post hoc, which increases the risk of chance findings due to multiple analyses. All conclusions can thus only be considered hypothesis generating; as such, reported p values were nominal and no adjustment for multiplicity was applied. Second, the primary outcome consists of a composite of anaemia thresholds as surrogate events and initiation of treatment for anaemia, which is clinically meaningful to patients and clinicians. Third, we did not measure erythropoietin, reticulocyte count, or iron status, and therefore, could not more directly assess erythropoiesis. However, several studies have already reported on the erythropoiesis-stimulating effects of SGLT2 inhibitors. Additionally, the effects of canagliflozin on anaemia outcomes could be partly explained by slowing progressive loss of kidney function rather than direct effects on erythropoiesis. However, the effects of canagliflozin on haematopoietic parameters persisted until the end of the trial, despite an approximately 3 mL/min per 1.73 m² per year decrease in eGFR during canagliflozin treatment,⁶ suggesting that improvements in anaemia outcomes were not solely achieved through preservation of kidney function. Fourth, anaemia was not an adjudicated endpoint and was captured as part of routine adverse event reporting during the trial. Some anaemia events might have been missed, but such errors would be expected to have occurred non-differentially across active and placebo groups and relative effect estimates should therefore be unbiased.

In conclusion, canagliflozin reduced the risk of anaemia-related outcomes, including the need for

erythropoiesis-stimulating agents, and increased haemoglobin concentrations in patients with type 2 diabetes and chronic kidney disease. These findings suggest that canagliflozin could be a novel adjunct therapy for anaemia management in this population. Further prospective studies are required to confirm these observations.

Contributors

MO, MJJ, and HJLH designed the study. MO analysed the data. MO and HJLH wrote the first draft of the manuscript. All authors contributed to the design and conduct of the study and the interpretation of the data. All authors provided input into subsequent drafts and approved the final version for submission. All authors reviewed and approved the manuscript.

Declaration of interests

BLN has received travel expenses from Janssen. MJJ is responsible for research projects that have received unrestricted funding from Baxter, Amgen, Eli Lilly, and Merck Sharp and Dohme; serves on a steering committee sponsored by CSL; has served on advisory boards sponsored by Akebia, Baxter, Boehringer Ingelheim, Merck Sharp and Dohme, and Vifor; and has spoken at scientific meetings sponsored by Janssen and Amgen, with any consultancy, honoraria, or travel expenses paid to her institution. GB has received research funding paid to the University of Chicago for serving as principal investigator on national clinical trials for Bayer, Janssen, and Novo Nordisk; has served as a consultant for Merck, Relypsa, Novo Nordisk, and AstraZeneca; has served on a steering committee for Vascular Dynamics; has served as Editor of the *American Journal of Nephrology*, Editor-in-Chief of *UpToDate*, and the *Nephrology and Hypertension* Section Editor of *UpToDate*; and has served as Associate Editor of *Diabetes Care*, *Hypertension Research*, and *Nephrology Dialysis Transplantation*. RE is an employee of Janssen Research and Development. AL serves as a scientific advisor to Boehringer Ingelheim, AstraZeneca, and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); is on the data safety and monitoring board for NIDDK, Kidney Precision Medicine, and University of Washington Kidney Research Institute Scientific Advisory Committee; is funded by Canadian Institute of Health Research, and Kidney Foundation of Canada; and has received fees for time as CREDENCE National Coordinator from Janssen, directed to her academic team. KWM has received grants from Afferent, Amgen, Apple, AstraZeneca, Cardiva Medical, Daiichi, Ferring, Google (Verily), Johnson and Johnson, Luitpold, Medtronic, Merck, National Institutes of Health (NIH), Novartis, Sanofi, St Jude, and Tenax; and has served as a consultant (speaker fees for continuing medical education events only) for Abbott, Ablynx, AstraZeneca, Baim Institute, Boehringer Ingelheim, Bristol Myers Squibb, Elsevier, GlaxoSmithKline, Johnson and Johnson, MedErgy, Medscape, Mitsubishi Tanabe, Myokardia, NIH, Novartis, Novo Nordisk, Portola, Radiometer, Regeneron, Springer Publishing, and University of California, San Francisco. BN holds a research grant for this study from Janssen; has held research grants for other large-scale cardiovascular outcome trials from Roche, Servier, and Merck Schering-Plough; and his institution has received consultancy, honoraria, or travel expenses for contributions he has made to advisory boards or the continuing medical education programs of Abbott, Janssen, Novartis, Pfizer, Roche, and Servier. CP has received honoraria for serving on advisory boards and as a speaker for Merck Sharpe and Dohme, AstraZeneca, and Boehringer Ingelheim/Eli Lilly. NR is an employee of Janssen Research and Development. TW has received grants from Shiseido Company and honoraria for speaking from Kirin and Mitsubishi Tanabe Pharma. DCW has received fees and travel expenses from Janssen for his role as a member of the CREDENCE steering committee; and has received fees for advisory boards, steering committee roles, or scientific presentations from Amgen, AstraZeneca, Astellas, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Mitsubishi, Mundipharma, Merck Sharpe and Dohme, Napp, Ono Pharma, Tricida, and Vifor Fresenius. VP has received fees for advisory boards, steering committee roles, or scientific presentations from AbbVie, Astellas, AstraZeneca, Bayer, Baxter, Bristol Myers Squibb, Boehringer Ingelheim, Dimerix, Durect, Eli Lilly, Gilead, GlaxoSmithKline, Janssen,

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Data sharing

Data from this study will be made available in the public domain via the Yale University Open Data Access Project once the product and relevant indication studied have been approved by regulators in the USA and European Union and the study has been completed for 18 months.

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