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ORIGINAL RESEARCH ARTICLE

Iron Deficiency in Heart Failure and Effect of Dapagliflozin: Findings From DAPA-HF

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BACKGROUND: Iron deficiency is common in heart failure and associated with worse outcomes. We examined the prevalence and consequences of iron deficiency in the DAPA-HF trial (Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure) and the effect of dapagliflozin on markers of iron metabolism. We also analyzed the effect of dapagliflozin on outcomes, according to iron status at baseline.

METHODS: Iron deficiency was defined as a ferritin level <100 ng/mL or a transferrin saturation <20% and a ferritin level 100 to 299 ng/mL. Additional biomarkers of iron metabolism, including soluble transferrin receptor, erythropoietin, and hepcidin were measured at baseline and 12 months after randomization. The primary outcome was a composite of worsening heart failure (hospitalization or urgent visit requiring intravenous therapy) or cardiovascular death.

RESULTS: Of the 4744 patients randomized in DAPA-HF, 3009 had ferritin and transferrin saturation measurements available at baseline, and 1314 of these participants (43.7%) were iron deficient. The rate of the primary outcome was higher in patients with iron deficiency (16.6 per 100 person-years) compared with those without (10.4 per 100 person-years; P<0.0001). The effect of dapagliflozin on the primary outcome was consistent in iron-deficient compared with iron-replete patients (hazard ratio, 0.74 [95% CI, 0.58–0.92] versus 0.81 [95% CI, 0.63–1.03]; P-interaction=0.59). Similar findings were observed for cardiovascular death, heart failure hospitalization, and all-cause mortality. Transferrin saturation, ferritin, and hepcidin were reduced and total iron-binding capacity and soluble transferrin receptor increased with dapagliflozin compared with placebo.

CONCLUSIONS: Iron deficiency was common in DAPA-HF and associated with worse outcomes. Dapagliflozin appeared to increase iron use but improved outcomes, irrespective of iron status at baseline.

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Key Words: anemia ■ erythropoiesis ■ ferritin ■ heart failure ■ hepcidin ■ iron ■ sodium-glucose cotransporter 2 inhibitor ■ transferrin

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Absolute and functional iron deficiency, the latter reflecting reduced iron mobilization and use, are common in patients with heart failure.[1–3] The causes are thought to include reduced dietary intake, reduced absorption because of gut edema and use of drugs such as proton pump inhibitors, blood loss, and

Clinical Perspective

What Is New?

- In the DAPA-HF trial (Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure), among patients with heart failure and reduced ejection fraction, the presence of iron deficiency at baseline was a risk factor for cardiovascular death and worsening heart failure events, including after adjustment for NT-proBNP (N-terminal pro-B-type natriuretic peptide) and high-sensitivity troponin T.
- In the DAPA-HF trial, the clinical benefits of dapagliflozin were consistent regardless of the presence or absence of iron deficiency at baseline.
- Dapagliflozin caused changes in biomarkers relating to iron metabolism consistent with an increase in iron mobilization and use, likely secondary to increased erythropoiesis.

What Are the Clinical Implications?

- The presence of iron deficiency should not be considered a barrier to the use of dapagliflozin in patients with heart failure and reduced ejection fraction.
- Regular monitoring of iron status should be performed in patients with heart failure and reduced ejection fraction, and guideline recommendations followed with regards to intravenous iron replacement when indicated.

Nonstandard Abbreviations and Acronyms

DAPA-HF	Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure
eGFR	estimated glomerular filtration rate
HFrEF	heart failure and reduced ejection fraction
NT-proBNP	N-terminal pro-B-type natriuretic peptide
SGLT2	sodium-glucose cotransporter 2
sTFR	soluble transferrin receptor
TSAT	transferrin saturation

inflammation, which may inhibit both iron absorption and use.[1–3] Some but not all patients with iron deficiency also have anemia.[1–3] Patients with iron deficiency have worse symptoms and quality of life, greater functional impairment, and higher rates of hospital admission and death than those without iron deficiency, irrespective of anemia status.[1–4] That iron deficiency is causally implicated in worse clinical status in patients with heart failure has been proven by the salutary effects of treatment with intravenous iron.[5–9] Several randomized trials have shown improvement in symptoms, health-related quality of life, and exercise capacity with ferric carboxymaltose.

Recently, the AFFIRM-AHF study (Study to Compare Ferric Carboxymaltose With Placebo in Patients With Acute Heart Failure and Iron Deficiency) demonstrated that intravenous iron also reduced the risk of readmission when given to patients hospitalized with worsening heart failure.[9] Avoidance, detection, and treatment of iron deficiency are therefore recommended in contemporary heart failure guidelines.[10,11]

Iron deficiency may have implications for another new development in heart failure therapeutics. SGLT2 (sodium-glucose cotransporter 2) inhibitors have been shown to increase hematocrit and hemoglobin, and correct and prevent anemia in patients with heart failure.[12–14] Although the increase in hematocrit was originally thought to reflect volume contraction caused by diuresis, it is now thought that SGLT2 inhibitors also stimulate erythropoiesis.[15–19] Erythropoiesis uses iron and may be restricted by existing iron deficiency. This may be important if an increase in hematocrit contributes to the benefits of SGLT2 inhibitors, as has been suggested.[13,14] Conversely, erythropoiesis may induce iron depletion, which is undesirable in heart failure, as discussed above, and some patients treated with an SGLT2 inhibitor might require concomitant iron replacement, analogous to the iron cotreatment required in patients with chronic kidney disease treated with an erythropoiesis-stimulating agent.[20,21] The placebo-controlled DAPA-HF trial (Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure) provided a unique opportunity to examine the effect of an SGLT2 inhibitor on iron status in patients with heart failure and reduced ejection fraction (HFrEF) and the interaction between the effect of dapagliflozin on symptoms, quality of life, hospitalization and mortality, and iron status.[22,23]

METHODS

The efficacy and safety of dapagliflozin 10 mg once daily, compared with placebo, added to standard care was tested in patients with HFrEF in the prospective, randomized, double-blind, placebo-controlled DAPA-HF trial.[22,23] Ethics committees at each participating site approved the protocol, and each patient gave written informed consent. The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Patients

Adults in New York Heart Association functional class II to IV, with a left ventricular ejection fraction (LVEF) ≤40% and an elevated NT-proBNP (N-terminal pro-B-type natriuretic peptide) level, optimally treated with pharmacological and device therapy, according to local guidelines, were eligible. The key exclusion criteria included the following: symptoms of hypotension or systolic blood pressure <95 mm Hg, estimated glomerular filtration rate (eGFR) <30 mL·min·1.73 m², and type 1 diabetes. There was no exclusion related to iron, anemia, or hemoglobin/hematocrit. A full list of exclusion criteria is provided in the design article.[22]

Measurement of Markers of Iron Metabolism and Other Biomarkers

Hematocrit was measured at baseline, as well as 14 days, 2 months and 4 months after randomization, and every 4 months thereafter. Hemoglobin was measured at baseline and at the end of the trial, but not routinely after randomization.

Biomarkers relating to iron metabolism were measured in a central laboratory (University of Glasgow) at baseline and 12 months after randomization. Not all countries participated in the DAPA-HF biomarker substudy; therefore, the results presented include only those with available measurements. Serum ferritin, unsaturated iron-binding capacity, iron, and soluble transferrin receptor (sTFR) were measured using an automated platform and the manufacturer's calibrators and quality control material (c311, Roche Diagnostics Burgess Hill, United Kingdom). Coefficient of variation over 2 levels was ≤2.6% for ferritin, ≤6.0% for unsaturated iron-binding capacity, ≤8.5% for iron, and <5.7% for sTFR. Total iron-binding capacity was calculated as the sum of serum iron and serum unsaturated iron-binding capacity. Transferrin saturation (TSAT), expressed as a percentage, was calculated by dividing the serum iron concentration by the total iron-binding capacity. Plasma hepcidin and erythropoietin were measured by immunoassay (Ella Protein Simplex, Biotechne, Abingdon, United Kingdom) with the coefficient of variation of quality control samples over 2 levels ≤7.6% and ≤6.5%, respectively.

Definition of Iron Deficiency

In keeping with clinical trials and the European Society of Cardiology 2021 guidelines on heart failure, we defined iron deficiency as a ferritin level <100 ng/mL ("absolute iron deficiency") or a TSAT <20% and a ferritin level of 100 to 299 ng/mL ("functional iron deficiency").[10] We also used an alternative definition based on sex-specific sTFR concentrations (male >4.70 mg/L and female >4.59 mg/L) based on the assay-specific upper limit of the normal reference range. Anemia was defined at baseline using sex-specific baseline hemoglobin thresholds (male <130 g/L and female <120 g/L).

Trial Outcomes

The primary outcome was the composite of worsening heart failure or cardiovascular death, whichever occurred first. An episode of worsening heart failure was either an urgent visit resulting in intravenous therapy for heart failure, not leading to hospital admission, or unplanned hospitalization for heart failure. The secondary outcomes were the composite of heart failure hospitalization or cardiovascular death; the total number of recurrent heart failure hospitalizations (including repeat admissions) and cardiovascular deaths; change from baseline to 8 months in the total symptom score of the Kansas City Cardiomyopathy Questionnaire Total Symptom Score using a scale from 0 to 100, with a higher score indicating fewer symptoms and a 5 or greater point change considered clinically meaningful; the incidence of a composite worsening renal function outcome (not included in the present analysis as there were few of these events); and death from any cause. All cardiovascular end points and deaths were adjudicated by an independent blinded committee.

In the present analyses, we compared the effect of dapagliflozin with placebo on the primary composite outcome, the individual components of cardiovascular death and worsening heart failure events, total heart failure hospitalizations and cardiovascular death, and death from any cause.

Statistical Analysis

Baseline characteristics were compared between iron status groups by using the Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables. The cumulative incidence of the primary end point by treatment assignment in the iron status subgroups was analyzed and plotted graphically using the Kaplan-Meier method. The effect of dapagliflozin compared with placebo on each outcome was calculated as hazard ratio and 95% CI derived from Cox proportional hazards models adjusted for a history of hospitalization for heart failure (not included in the model for all-cause mortality) and treatment assignment and stratified by baseline diabetes status, as prespecified in the statistical analysis plan for the main trial. The effect of dapagliflozin compared with placebo according to change in iron status between baseline and 12 months was examined using a landmark analysis from 12 months using the same model including patients who were alive at 12 months. For the iron deficiency yes/no subgroup analyses, an interaction test was performed to assess for any modification of treatment effect by iron status. The effect of dapagliflozin on the primary outcome according to the level of several iron metabolism biomarkers (analyzed as continuous variables) was examined using a fractional polynomial analysis using the Stata mfpi command.[24] The relationship between iron status at baseline and subsequent outcomes was shown by hazard ratio and 95% CI derived from Cox proportional hazards models adjusted for a history of hospitalization for heart failure and treatment assignment. For the end point of all-cause mortality, no adjustment for a history of hospitalization for heart failure was performed. The effect of treatment on the composite end point of recurrent (first and total) heart failure hospitalizations and cardiovascular death (ie, total events) was examined using a semiparametric proportional rates model.[25] Further analyses were performed with additional adjustment for age, sex, heart rate, systolic blood pressure, body mass index, ischemic cause, left ventricular ejection fraction, New York Heart Association class, NT-proBNP level (log-transformed), atrial fibrillation, and eGFR. This model was repeated with additional adjustment for high-sensitivity troponin T concentrations (log-transformed). The effects of dapagliflozin on biomarkers relating to iron metabolism between baseline and 12 months are presented as a ratio of geometric means derived from linear regression models including adjustment for log-transformed baseline values. Because hemoglobin was not measured routinely at the 12-month visit but was measured at the end-of-trial visit, the last recorded measurement was used to calculate the effect of dapagliflozin on hemoglobin using the same method as the iron biomarkers. Changes in hematocrit were analyzed using a mixed model for repeated measurements (adjusted for baseline values, visit, randomized treatment and interaction of treatment, and visit with a random intercept and slope per patient) and the between treatment group difference at 12 months after randomization are presented by subgroup as least square means difference and 95% CI. The slope of change in eGFR from day

14 to day 720 of follow-up according to randomized treatment was analyzed using a mixed model for repeated measurements with the same adjustment factors as described above. The effect of dapagliflozin on the development of iron deficiency during follow-up was examined with a logistic regression model with randomized treatment as the only independent variable. The proportion of patients with a clinically meaningful improvement (≥5 point increase) or deterioration (≥5 point decrease) in Kansas City Cardiomyopathy Questionnaire Total Symptom Score was compared between treatments using an odds ratio with a 95% CI calculated using methods previously described.[23] All analyses were performed using Stata version 16 (College Station, TX) and SAS version 9.4 (SAS Institute). A *P* value <0.05 was considered statistically significant. No adjustment for multiple comparisons was made, and as such, all results should be considered exploratory.

RESULTS

Of the 4744 patients randomized in DAPA-HF, 3009 had ferritin and TSAT measurements available at baseline, and 1314 of these participants (43.7%) were iron deficient, as defined by ferritin and TSAT criteria. Of the 1314 patients with iron deficiency, 926 (70.5%) had absolute iron deficiency (ferritin <100 ng/mL), and 388 (29.5%) had functional iron deficiency (TSAT <20% and ferritin 100−300 ng/mL). Using the alternative definition based on sTFR, 412 of 2888 participants (14.3%) with a baseline sTFR measurement had iron deficiency. The distributions of baseline ferritin, TSAT, and sTFR by sex are shown in Figure S1. The proportion of patients with iron deficiency at baseline in the dapagliflozin and placebo groups was identical (666/1525 [43.7%] versus 648/1484 [43.7%]).

Patient Characteristics According to Iron Status at Baseline

The baseline characteristics of patients according to their iron status are shown in Table 1. Compared with those who did not have iron deficiency, patients who had iron deficiency were more likely to be female (27.9% versus 17.6% male) but were not older and had a similar heart rate and systolic blood pressure compared with those without iron deficiency. People with iron deficiency were more likely to have an eGFR <60 mL·min·1.73 m^2 (45.7% versus 36.7%, respectively) and to have anemia (35.5% versus 20.7%), coronary heart disease, hypertension, and diabetes. Patients with iron deficiency had worse New York Heart Association functional class (New York Heart Association class III/IV, 36.3% versus 26.3%) and markedly lower (worse) Kansas City Cardiomyopathy Questionnaire scores than those without, although previous heart failure hospitalization was not more common among those with iron deficiency. Baseline NT-proBNP level was higher in participants with iron deficiency, although atrial fibrilla-

tion was no more common and left ventricular ejection fraction was slightly higher than in patients without iron deficiency. High-sensitivity troponin T levels were higher in patients with iron deficiency compared with those who were iron replete at baseline. The prescription of key treatments was similar in the 2 groups, except for use of diuretics (more common) and mineralocorticoid receptor antagonists (less frequent) in individuals with iron deficiency. The use of anticoagulants did not differ between the 2 groups, but antiplatelet therapy was used more often in patients with iron deficiency. Proton pump inhibitor use was more common in patients with iron deficiency (36.5%) than in those without (28.7%). A greater number of patients with baseline iron deficiency, compared with those without, received treatments for iron deficiency or anemia during follow-up (including patients taking these at the time of randomization): intravenous iron in 16 (1.2%) versus 4 (0.2%), oral iron in 97 (7.4%) versus 67 (4.0%), vitamin B$_{12}$ in 37 (2.8%) versus 31 (1.8%), and folic acid in 55 (4.2%) versus 49 (2.9%). The baseline characteristics for patients in whom iron deficiency was not determinable, compared with those with an assessment of iron status, are displayed in Table S1.

Cardiovascular Outcomes According to Iron Status at Baseline

The cumulative incidence of the primary and secondary morbidity/mortality end points are shown in Figure 1 and Table 2. For each end point, the risk was higher in participants with iron deficiency compared with those without in both unadjusted and adjusted analyses. A sensitivity analysis using the alternative definition of iron deficiency based on sTFR showed similar findings (Table S2).

eGFR Slopes According to Iron Status at Baseline

The rate of decline in kidney function over time was similar in patients with iron deficiency at baseline (−1.74 [95% CI, −2.16 to −1.32] mL·min·1.73 m^2 per year) and in those without (−2.01 [95% CI, −2.38 to −1.66] mL/min/1.73 m^2 per year; interaction *P*=0.32).

Effects of Dapagliflozin on Cardiovascular Outcomes According to Baseline Iron Status

The effects of dapagliflozin, compared with placebo, in patients with and without iron deficiency are shown in Figure 2 and Table 3.

The beneficial effect of dapagliflozin, compared with placebo, on the primary end point (hazard ratio, 0.74 [95% CI, 0.65−0.85] in the trial overall) was consistent in patients with (hazard ratio, 0.74 [95% CI, 0.58−0.92]) and

Table 1. Baseline Characteristics According to the Presence of Iron Deficiency

	Iron deficient (n=1314)	Not iron deficient (n=1695)	P value
Age, y	67.5±10.3	67.0±10.5	0.18
Sex, n (%)			<0.001
Female	367 (27.9)	299 (17.6)	
Male	947 (72.1)	1396 (82.4)	
Race/ethnicity, n (%)			<0.001
White	1058 (80.5)	1281 (75.6)	
Black	45 (3.4)	40 (2.4)	
Asian	207 (15.8)	366 (21.6)	
Other	4 (0.3)	8 (0.5)	
NYHA functional classification, n (%)			<0.001
II	836 (63.6)	1,249 (73.7)	
III	475 (36.1)	439 (25.9)	
IV	3 (0.2)	7 (0.4)	
Heart rate, beats/min	71.2±11.1	70.6±11.3	0.13
Systolic blood pressure, mm Hg	122.5±15.5	122.3±16.2	0.63
Left ventricular ejection fraction, %	31.6±6.7	30.9±6.8	0.004
≤30%, n (%)	547 (41.6)	787 (46.4)	0.009
Median NT-proBNP (IQR), pg/mL	1526 (918–2936)	1333 (809–2340)	<0.001
AF on baseline ECG	1941 (1309–3350)	1830 (1200–2913)	0.058
No AF on baseline ECG	1414 (848–2772)	1192 (743–2137)	<0.001
Median hsTnT, ng/L	21.3 (14.5–32.3)	19.3 (13.1–28.6)	<0.001
Median KCCQ-TSS (IQR)	74.0 (56.2–89.6)	81.2 (63.5–93.8)	<0.001
Median KCCQ-OSS (IQR)	67.9 (52.5–82.5)	75.0 (57.6–88.1)	<0.001
Median KCCQ-CSS (IQR)	70.1 (54.9–85.3)	77.8 (61.1–90.6)	<0.001
Body mass index, kg/m²	28.9±6.2	28.1±5.7	<0.001
Principal cause of heart failure, n (%)			<0.001
Ischemic	867 (66.0)	913 (53.9)	
Nonischemic	366 (27.9)	642 (37.9)	
Unknown	81 (6.2)	140 (8.3)	
Medical history, n (%)			
Hospitalization for heart failure	577 (43.9)	794 (46.8)	0.11
Atrial fibrillation	535 (40.7)	688 (40.6)	0.94
Type 2 diabetes	635 (48.3)	620 (36.6)	<0.001
Hypertension	1,042 (79.3)	1,249 (73.7)	<0.001
PCI	561 (42.7)	555 (32.7)	<0.001
CABG	302 (23.0)	271 (16.0)	<0.001
Estimated GFR, mL·min·1.73 m² of body surface area	63.2±18.6	66.7±18.8	<0.001
Estimated GFR rate <60 mL·min·1.73 m², n (%)	600 (45.7)	621 (36.7)	<0.001
Hemoglobin, g/L	131.8±16.0	138.6±15.1	<0.001
Anemia, n (%)*	463 (35.5)	349 (20.7)	<0.001
Device therapy, n (%)			0.086
Implantable cardioverter defibrillator†	446 (33.9)	493 (29.1)	0.004
Cardiac resynchronization therapy‡	123 (9.4)	129 (7.6)	<0.001
Heart failure medication at randomization visit, n (%)			
Diuretic	1139 (86.7)	1405 (82.9)	0.004

(*Continued*)

Table 1. Continued

	Iron deficient (n=1314)	Not iron deficient (n=1695)	P value
ACE inhibitor/ARB	1083 (82.4)	1377 (81.2)	0.41
Sacubitril-valsartan	153 (11.6)	214 (12.6)	0.41
β-Blocker	1270 (96.7)	1612 (95.1)	0.036
Mineralocorticoid receptor antagonist	877 (66.7)	1255 (74.0)	<0.001
Digitalis	186 (14.2)	283 (16.7)	0.057
Anticoagulant	603 (45.9)	760 (44.8)	0.57
History of AF	457/535 (85.4)	601/688 (87.4)	0.33
No history of AF	146/779 (18.7)	159/1007 (15.8)	0.10
Antiplatelet	781 (59.4)	845 (49.9)	<0.001
Proton pump inhibitor	479 (36.5)	486 (28.7)	<0.001

Data presented as mean±SD unless otherwise indicated. Percentages may not total 100 because of rounding. Iron deficiency defined as a serum ferritin <100 ng/mL or 100 to 299 ng/mL if transferrin saturation <20%. The KCCQ-TSS ranges from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. A score of 75 or higher is considered to reflect satisfactory health status. ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin-receptor blocker; CABG, coronary artery bypass graft; GFR, glomerular filtration rate; hsTnT, high-sensitivity troponin T; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association. KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; and PCI, percutaneous coronary intervention.

*Anemia defined as baseline hemoglobin <130 g/L and <120 g/L for men and women, respectively.

†Either implantable cardioverter defibrillator or cardiac resynchronization therapy with a defibrillator.

‡Cardiac-resynchronization therapy with or without a defibrillator.

without (hazard ratio, 0.81 [95% CI, 0.63−1.03]) iron deficiency (interaction P=0.59). A sensitivity analysis using the alternative definition of iron deficiency on the basis of sTFR gave similar findings (Table S3). The beneficial effect was also generally consistent across the range of ferritin, iron, TSAT, and sTFR levels at baseline when examined as a continuous variable (Figure 3), although there was a nominally significant interaction between baseline ferritin level and the effect of dapagliflozin, with a larger reduction in the primary outcome among patients with lower ferritin concentrations (Figure 3).

The effect of dapagliflozin on each of the components of the primary outcome and the secondary outcomes was generally similar for individuals with and without iron deficiency (Figure 2 and Table 3).

Because of the much higher event rate in patients with iron deficiency, the absolute risk reductions with dapagliflozin compared with placebo were larger than in iron-replete patients, ie, 5.0 versus 3.0 per 100 person-years for the primary composite outcome, 1.7 versus 1.1 per 100 person-years for cardiovascular death, and 4.0 versus 2.1 per 100 person-years for worsening heart failure.

Effects of Dapagliflozin on Kansas City Cardiomyopathy Questionnaire Total Symptom Score According to Baseline Iron Status

Eight months after randomization, the mean increase (improvement) in Kansas City Cardiomyopathy Questionnaire Total Symptom Score with dapagliflozin compared with placebo, was +2.37 (95% CI, 0.11−4.63) in patients with iron deficiency and was similar to those without (+1.82 [95% CI, 0.03−3.61]; interaction P=0.62; Table 3).

Effects of Dapagliflozin on Hematocrit, Hemoglobin, and Anemia According to Iron Status

The effects of dapagliflozin compared with placebo on hematocrit and markers of iron metabolism are shown in Figure 4 and Table 4. Between baseline and 12 months, there was a significant increase in hematocrit in the dapagliflozin group compared with the placebo group. The mean placebo-corrected increase in hematocrit at 12 months was 2.62% (95% CI, 2.40−2.85) and was not different between participants with iron deficiency (2.27% [95% CI, 1.82−2.71]) and those without iron deficiency (3.00% [95% CI, 2.65−3.35]; interaction P=0.10; Figure 4). The placebo-corrected increase in hemoglobin was 7.0 (95% CI, 6.2−7.9) g/L using the last available measurement during trial follow-up. This increase tended to be higher in iron-replete patients (7.34 [95% CI, 6.11−8.58] g/L) compared with those with iron deficiency at baseline (5.42 [95% CI, 3.77−7.08] g/L; interaction P=0.06). The effect of dapagliflozin on increasing hemoglobin was consistent whether patients had absolute or functional iron deficiency (interaction P=0.56). Using hematocrit-based definitions of anemia,[14] dapagliflozin more
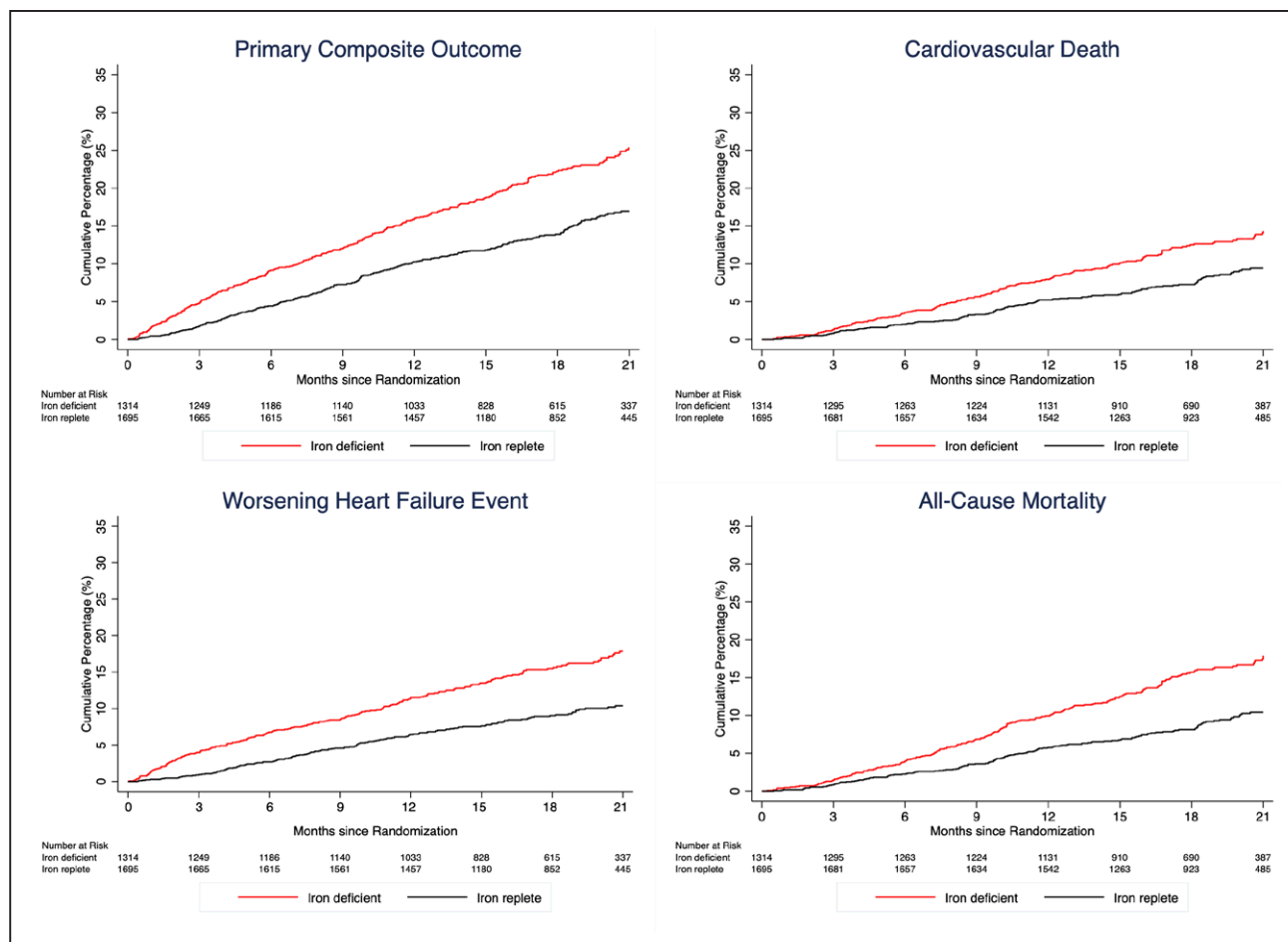
ORIGINAL RESEARCH ARTICLE

Figure 1. Cardiovascular outcomes according to the presence of iron deficiency.
The primary outcome was a composite of death from cardiovascular causes, hospitalization for heart failure, or an urgent visit resulting in intravenous therapy for heart failure. The cumulative incidences of the primary outcome, worsening heart failure event, death from cardiovascular causes, and death from any cause were estimated with the use of the Kaplan-Meier method.

frequently led to a reversal of anemia both in patients with iron deficiency at baseline (odds ratio, 2.43 [95% CI, 1.57–3.75]) and those iron-replete (odds ratio, 2.17 [95% CI, 1.40–3.37]; interaction P=0.72).

Effects of Dapagliflozin on Markers of Iron Metabolism

There were reductions in TSAT, ferritin, and hepcidin, along with an increase in total iron-binding capacity and sTFR, in the dapagliflozin group compared with placebo, and a trend to an increase in erythropoietin (Table 4). There was no significant difference in serum iron concentrations between the groups. These changes were largely consistent in patients with and without iron deficiency, and with and without anemia, at baseline (Tables S4 and S5).

In those without iron deficiency at baseline (n=1334), 196 (28.4%) and 120 (18.6%) in the dapagliflozin and placebo groups, respectively, had new iron deficiency at 12 months defined using ferritin and TSAT criteria; the odds ratio (dapagliflozin versus placebo) for the development of

iron deficiency by 12 months was 1.74 (95% CI, 1.34–2.25), P<0.001. The corresponding odds ratio using the sTFR-based definition was 2.26 (95% CI, 1.57–3.26), P<0.001.

Outcomes Associated With the Development of Iron Depletion During Follow-Up

In a landmark analysis at 1 year after randomization, the rate of the primary outcome in patients without iron deficiency at baseline (defined using ferritin and TSAT criteria) who developed iron deficiency (n=315 [23.7%]), irrespective of treatment allocation, was higher than in those who remained iron-replete during follow-up (n=1016 [76.3%]): 17.0 (95% CI, 12.0–24.2) per 100 person-years versus 9.0 (95% CI, 6.9–11.8) per 100 person-years, giving an adjusted hazard ratio of this outcome for the development of iron deficiency versus not developing iron deficiency of 1.92 (95% CI, 1.21–3.04). Of the patients who had iron deficiency at baseline, the event rate in those who still had iron deficiency (n=716 [76.3%]) was 17.8 (95% CI, 14.2–22.2) per 100

Table 2. Cardiovascular Outcomes According to the Presence of Iron Deficiency

	Iron deficient (n=1314)	Not iron deficient (n=1695)
Primary composite end point*		
n (%)	297 (22.6)	254 (15.0)
Event rate per 100 person-years (95% CI)	16.6 (14.8–18.6)	10.4 (9.2–11.8)
Unadjusted HR (95% CI)	1.53 (1.30–1.82); *P*<0.0001	1.00 (referent)
Adjusted HR (95% CI), model 1	1.37 (1.15–1.63); *P*=0.0003	1.00 (referent)
Adjusted HR (95% CI), model 2	1.36 (1.14–1.62); *P*=0.0005	1.00 (referent)
Cardiovascular death		
n (%)	166 (12.6)	140 (8.3)
Event rate per 100 person-years (95% CI)	8.6 (7.4–10.0)	5.5 (4.7–6.5)
Unadjusted HR (95% CI)	1.49 (1.19–1.87); *P*=0.0006	1.00 (referent)
Adjusted HR (95% CI), model 1	1.30 (1.03–1.64); *P*=0.026	1.00 (referent)
Adjusted HR (95% CI), model 2	1.30 (1.03–1.64); *P*=0.026	1.00 (referent)
Worsening HF event		
n (%)	202 (15.4)	153 (9.0)
Event rate per 100 person-years (95% CI)	11.3 (9.8–12.9)	6.3 (5.4–7.4)
Unadjusted HR (95% CI)	1.75 (1.41–2.16); *P*<0.0001	1.00 (referent)
Adjusted HR (95% CI), model 1	1.57 (1.26–1.95); *P*=0.0001	1.00 (referent)
Adjusted HR (95% CI), model 2	1.54 (1.24–1.91); *P*=0.0001	1.00 (referent)
All-cause mortality		
n (%)	211 (16.1)	158 (9.3)
Event rate per 100 person-years (95% CI)	10.9 (9.6–12.5)	6.2 (5.3–7.3)
Unadjusted HR (95% CI)	1.68 (1.37–2.07); *P*<0.0001	1.00 (referent)
Adjusted HR (95% CI), model 1	1.50 (1.21–1.85); *P*=0.0002	1.00 (referent)
Adjusted HR (95% CI), model 2	1.51 (1.22–1.87); *P*=0.0002	1.00 (referent)
Total HF hospitalizations and cardiovascular death†		
Number of events	457	369
Event rate per 100 person-years (95% CI)	23.8 (21.7–26.1)	14.5 (13.1–16.1)
Unadjusted RR (95% CI)	1.57 (1.30–1.91); *P*<0.0001	1.00 (referent)
Adjusted RR (95% CI), model 1	1.40 (1.14–1.71); *P*=0.0011	1.00 (referent)
Adjusted RR (95% CI), model 2	1.39 (1.14–1.71); *P*=0.0013	1.00 (referent)

Iron deficiency was defined as a serum ferritin <100 ng/mL or a transferrin saturation <20% and a ferritin of 100 to 299 ng/mL. Unadjusted analysis includes factors for iron deficiency, randomized treatment, and history of HF hospitalization and is stratified by diabetes status. Adjusted analysis includes factors for iron deficiency, randomized treatment, history of HF hospitalization, age, sex, heart rate, systolic blood pressure, body mass index, ischemic cause of HF, left ventricular ejection fraction, New York Heart Association functional classification, NT-proBNP (N-terminal pro-B-type natriuretic peptide), atrial fibrillation, and estimated glomerular filtration rate (model 1). Model 2 includes the same factors as model 1 with the addition of hsTnT. HF indicates heart failure; HR, hazard ratio; hsTnT, high-sensitivity troponin T; and RR, rate ratio.

*The primary outcome was a composite of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or death from cardiovascular causes.

†Risk estimate presented is a RR.

person-years and 16.6 (95% CI, 11.0–24.9) per 100 person-years in those who had resolution of iron deficiency at 12 months (n=222 [23.7%]).

Adverse Events According to Baseline Iron Status

Regardless of randomized treatment group, patients with iron deficiency were more likely to discontinue treatment overall, and to discontinue treatment because of an adverse event (Table S6). Prespecified adverse events of interest were generally similar for dapagliflozin and placebo, regardless of the presence of iron deficiency at baseline.

DISCUSSION

In this post hoc analysis of DAPA-HF, 43.7% of participants had iron deficiency at baseline, as defined using
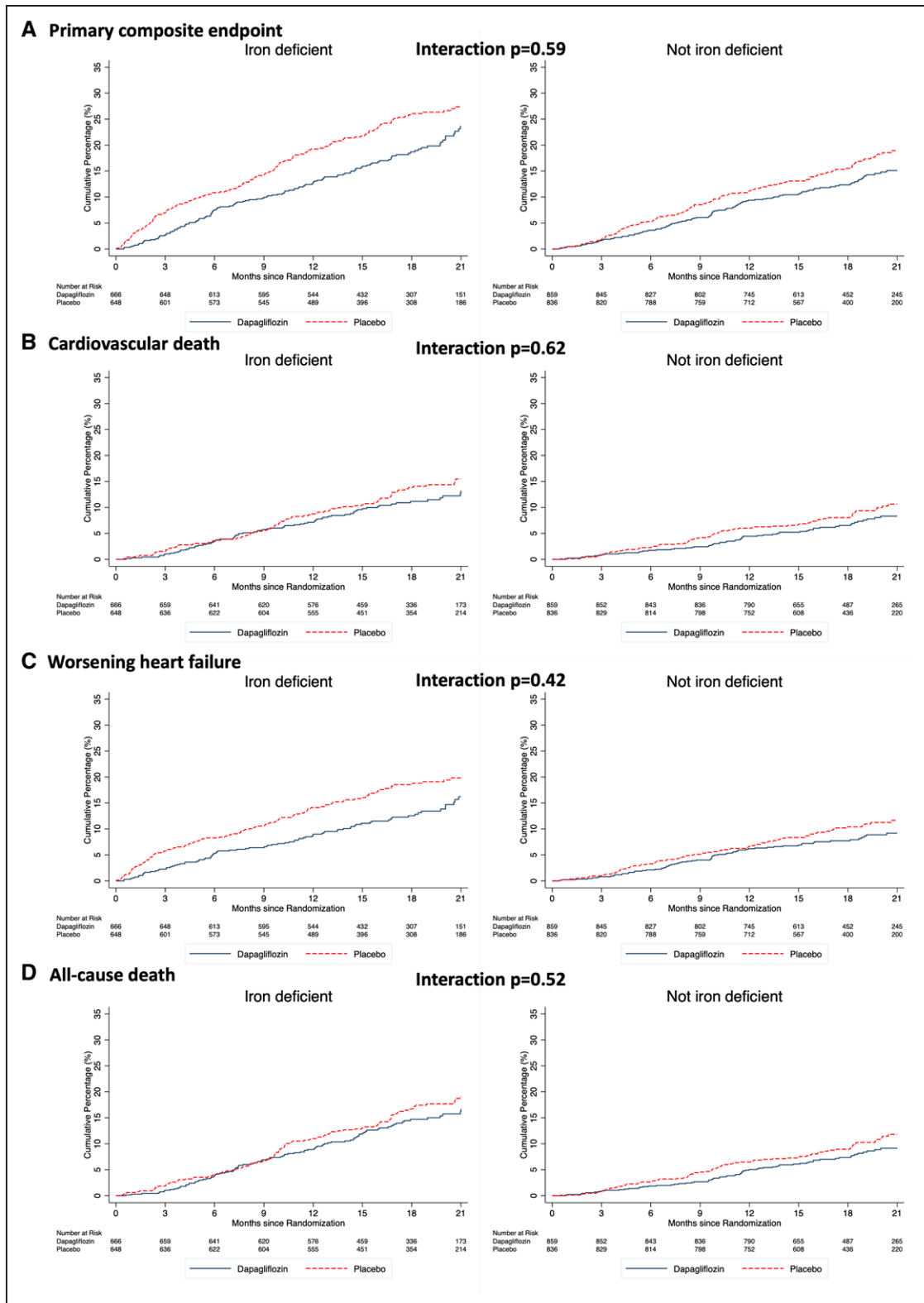
Figure 2. Effect of dapagliflozin, compared with placebo, on cardiovascular outcomes according to the presence of iron deficiency.

A, Primary composite outcome. **B**, Cardiovascular death. **C**, Worsening heart failure event. **D**, All-cause death. The primary outcome was a composite of death from cardiovascular causes, hospitalization for heart failure, or an urgent visit resulting in intravenous therapy for heart failure. The cumulative incidences of the primary outcome, worsening heart failure event, death from cardiovascular causes, and death from any cause were estimated with the use of the Kaplan-Meier method. The interaction *P* value presented represents a treatment–by–iron deficiency interaction term.

Table 3. Effect of Dapagliflozin, Compared With Placebo, on Clinical Outcomes According to the Presence of Iron Deficiency at Baseline

	Iron deficient (n=1314)		Not iron deficient (n=1695)		Interaction P value
	Dapagliflozin	Placebo	Dapagliflozin	Placebo	
Primary composite outcome*					
Number of events (n/N) (%)	131/666 (19.7)	166/648 (25.6)	117/859 (13.6)	137 (16.4)	
Rate (95% CI)	14.2 (12.0–16.9)	19.1 (16.4–22.2)	9.3 (7.7–11.1)	11.6 (9.8–13.7)	
HR (95% CI)	0.74 (0.58–0.92)		0.81 (0.63–1.03)		0.59
Cardiovascular death					
Number of events (n/N)	78/666 (11.7)	88/648 (13.6)	63/859 (7.3)	77/836 (9.2)	
Rate (95% CI)	8.1 (6.5–10.1)	9.2 (7.4–11.3)	4.8 (3.8–6.2)	6.2 (5.0–7.8)	
HR (95% CI)	0.87 (0.64–1.18)		0.77 (0.56–1.08)		0.62
Worsening heart failure event*					
Number of events (n/N)	86/666 (12.9)	116/648 (17.9)	71/859 (8.3)	82/836 (9.8)	
Rate (95% CI)	9.3 (7.6–11.5)	13.3 (11.1–16.0)	5.6 (4.5–71)	7.0 (5.6–8.6)	
HR (95% CI)	0.69 (0.52–0.91)		0.82 (0.59–1.12)		0.42
All-cause death					
Number of events (n/N)	100/666 (15.0)	111/648 (17.1)	71/859 (8.3)	87/836 (10.4)	
Rate (95% CI)	10.3 (8.5–12.6)	11.5 (9.6–13.9)	5.4 (4.3–6.8)	7.1 (5.7–8.7)	
HR (95% CI)	0.88 (0.67–1.16)		0.77 (0.56–1.05)		0.52
First and recurrent heart failure hospitalization and cardiovascular death					
Number of events	204	253	159	210	
Rate (95% CI)	21.2 (18.5–24.3)	26.5 (23.4–30.0)	12.2 (10.4–14.2)	17.1 (14.9–19.6)	
Rate ratio (95% CI)	0.79 (0.62–1.01)		0.72 (0.54–0.96)		0.62
Kansas City Cardiomyopathy Questionnaire Total Symptom Score					
Mean Change in score at 8 mo (95% CI)	5.49 (3.88–7.10)	3.11 (1.53–4.70)	4.44 (3.25–5.63)	2.62 (1.28–3.96)	0.62
Patients with >5- point improvement at 8 mo (%)	55.2 (51.2–59.2)	48.2 (44.2–52.3)	58.3 (54.7–61.8)	52.3 (48.8–55.8)	
Odds ratio (95% CI)	1.14 (1.01–1.28)		1.12 (1.01–1.24)		0.84
Patients with >5-point deterioration at 8 mo (%)	28.2 (24.7–31.7)	34.6 (30.8–38.5)	23.2 (20.3–26.2)	30.9 (27.6–34.1)	
Odds ratio (95% CI)	0.87 (0.77–0.98)		0.83 (0.74–0.93)		0.59

Event rates presented per 100 patient-years. Hazard ratios (HRs) and 95% CIs were estimated with the use of Cox regression models, stratified according to diabetes status, with a history of hospitalization for heart failure and treatment-group assignment as explanatory variables (for all-cause mortality, history of hospitalization for heart failure was not included in the model).

*The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or death from cardiovascular causes.

the ferritin and TSAT criteria recommended in contemporary heart failure guidelines.[10,11] This prevalence is consistent with other recent reports using the same diagnostic criteria. For example, in a recent study from Sweden, iron deficiency was present in 46.3% of ambulatory patients with HFrEF.[26] In a large Australian primary care study of patients with heart failure, the prevalence of iron deficiency, defined in the same way, was 39.7%, and among people with self-reported heart failure in NHANES (National Health and Nutrition Examination Survey 2017–2018), the prevalence of iron deficiency was 48.2% (95% CI, 36.8%–59.7%).[27,28] A recent study from the United Kingdom reported an even higher prevalence, with 61% in patients with HFrEF iron-deficient.[29] Conversely, using an alternative definition based on

sTFR, we found a much lower prevalence of iron deficiency. However, there are few studies of sTFR levels in heart failure and variability between assays, resulting in uncertainty about the cut point to define iron deficiency using this approach.[30,31]

Much less is known about the incidence of new iron deficiency, which occurred in 18.6% of our patients assigned to placebo during 1 year, although the best criteria to diagnose true iron deficiency are under debate.[32] Using a different definition of iron deficiency (serum iron ≤13 μmol/L), Graham and colleagues reported that 30.5% of patients with heart failure developed iron deficiency during 1 year.[33] The proportion of patients in the placebo group in DAPA-HF with new iron deficiency at 12 months using this definition was 34.7%. Using a
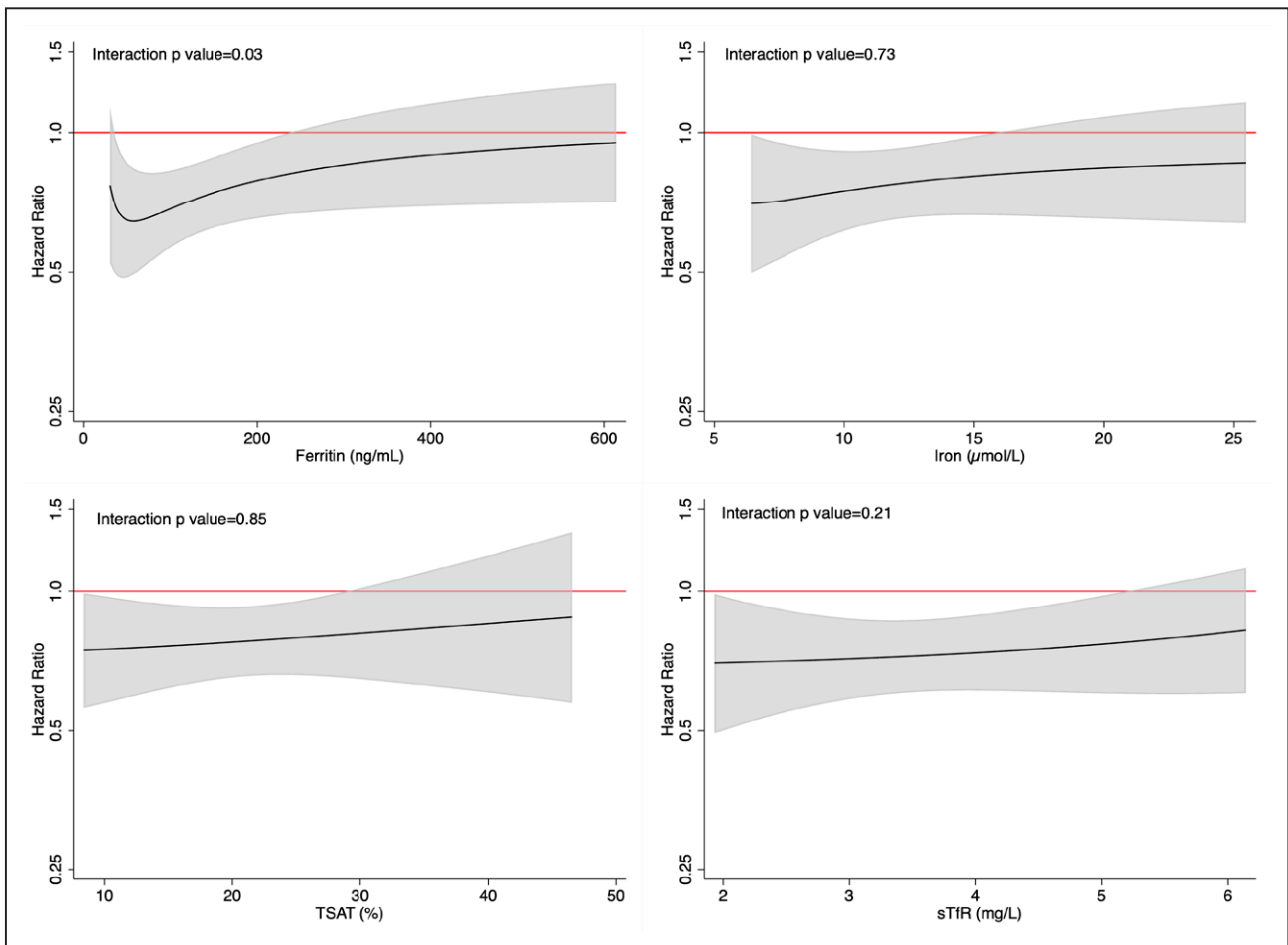
Figure 3. Effect of dapagliflozin on the primary outcome according to baseline levels of iron metabolism biomarkers.
The solid black line represents a continuous hazard ratio, and the solid red line represents a hazard ratio of 1 (ie, no difference between treatments). The shaded area represents the 95% CI around the hazard ratio. The hazard ratio represents the treatment effect of dapagliflozin compared with placebo for the primary composite outcome.
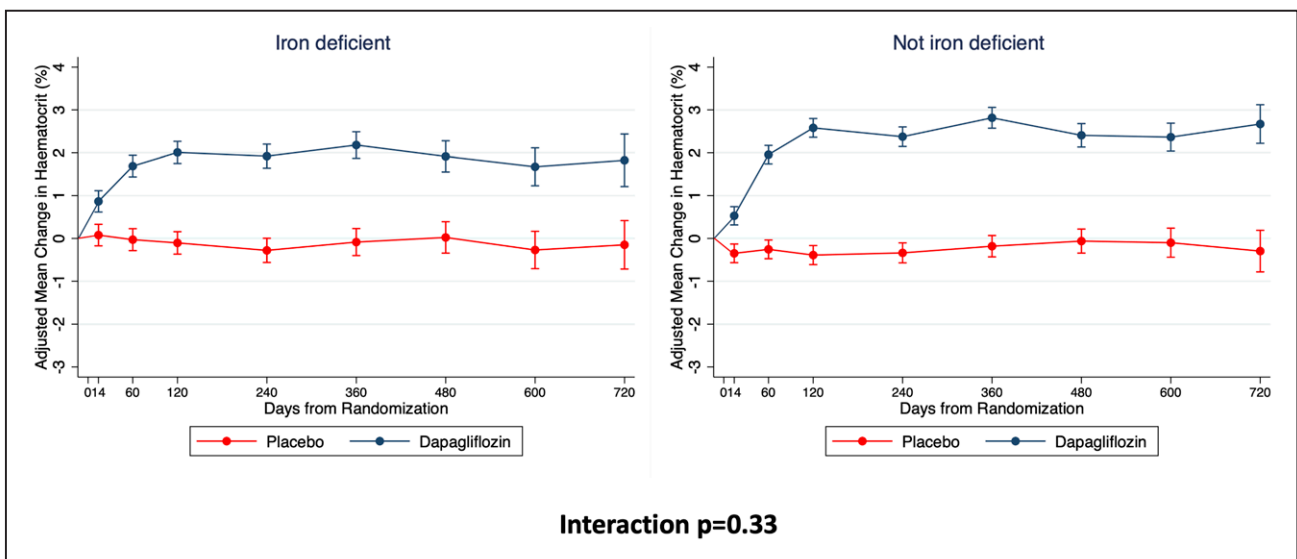

Figure 4. Effect of dapagliflozin, compared with placebo, on hematocrit according to the presence of iron deficiency.
Means and 95% CIs were derived from a mixed-effect model adjusted for baseline values, visit, randomized treatment, and interaction of treatment and visit with a random intercept and slope per patient. Least-square mean changes along with 95% CI are shown.

Table 4. Effect on Dapagliflozin, Compared With Placebo, on Biomarkers Relating to Iron Metabolism

	Dapagliflozin			Placebo			
	N	Baseline	12 mo	N	Baseline	12 mo	Ratio of geometric means (95% CIs)
Iron (µmol/L)	1148	13.9 (13.6–14.3)	13.5 (13.1–13.8)	1116	13.7 (13.4–14.1)	13.5 (13.2–13.8)	0.99 (0.96–1.02); P=0.60
UIBC (µmol/L)	1151	42.2 (41.3–43.1)	43.5 (42.5–44.6)	1121	43.1 (42.2–44.1)	42.2 (41.3–43.1)	1.04 (1.01–1.07); P=0.004
TIBC (µmol/L)	1147	58.6 (57.8–59.4)	59.8 (58.9–60.7)	1116	59.2 (58.4–60.1)	58.1 (57.3–58.9)	1.03 (1.02–1.05); P=0.0002
Transferrin saturation (%)	1147	23.8 (23.1–24.6)	22.5 (21.8–23.3)	1116	23.2 (22.5–23.9)	23.3 (22.6–24.0)	0.96 (0.92–1.00); P=0.029
Ferritin (ng/mL)	1240	158.2 (150.3–166.5)	130.4 (123.6–137.6)	1183	159.4 (151.3–167.9)	155.1 (147.1–163.5)	0.85 (0.81–0.88); P<0.0001
Hepcidin (ng/mL)	1270	24.3 (22.5–26.2)	17.2 (15.8–18.8)	1211	22.8 (21.1–24.7)	21.9 (20.2–23.7)	0.75 (0.69–0.83); P<0.0001
Erythropoietin (mIU/mL)	1265	23.2 (22.4–24.0)	24.9 (24.0–25.8)	1209	22.5 (21.7–23.3)	23.6 (22.7–24.5)	1.04 (0.99–1.08); P=0.08
Soluble transferrin receptor (mg/L)	1085	3.20 (3.13–3.26)	3.53 (3.46–3.61)	1034	3.13 (3.06–3.20)	3.20 (3.13–3.27)	1.09 (1.07–1.11); P<0.0001

Data presented as geometric means (95% CIs) for those with paired baseline and 12-mo data. TIBC indicates total iron binding capacity; and UIBC, unsaturated iron binding capacity.

TSAT <20% to define iron deficiency, Fitzsimons and colleagues observed that 20% of patients developed incident iron deficiency during 6 months; the corresponding proportion in the present study using the same definition was 20.4% among patients assigned to placebo.[34,35] These findings suggest that irrespective of definition, the short-term incidence, as well as prevalence, of iron deficiency is high in patients with heart failure.

Although iron deficiency is known to be associated with worse outcomes, the association with all-cause death, particularly after adjustment for other prognostic variables, has been an inconsistent finding, and recently there has been controversy about whether all biomarker definitions of iron deficiency carry the same prognostic import.[29,35–37] Indeed, the predictive value of the combined ferritin and TSAT criteria used in this report has been challenged.[29,35–37] However, we found iron deficiency, defined using ferritin and TSAT criteria, to be a statistically significant independent predictor of death (and other outcomes) even in models with extensive adjustment for other known prognostic variables including NT-proBNP and, we believe for the first time, high-sensitivity troponin T as well.

However, the most novel findings in the present study relate to the effect of dapagliflozin on indices of iron metabolism, given the evidence that agents of this type may stimulate erythropoiesis.[15–19,38] Several studies have shown an early and transient rise in circulating erythropoietin levels after starting treatment with an SGLT2 inhibitor, and this seems to precede an increase in reticulocyte count and subsequently hematocrit and hemoglobin.[15–19,38] If this is correct, SGLT2 inhibitor treatment should also increase the use of iron for erythropoiesis. Our findings are consistent with this. Although there was only a borderline significant increase in erythropoietin, other studies suggest that an earlier peak may

have been missed because this measurement was only repeated 12 months after starting treatment in DAPA-HF.[16,17] However, erythropoiesis, leading to increased mobilization and use of iron, would be expected to cause an increase in soluble transferrin receptor levels and iron-binding capacity, coupled with a decrease in ferritin, TSAT, and hepcidin, all of which were observed in DAPA-HF. Consistent with this hypothesis of greater use of iron after SGLT2 inhibition, treatment with dapagliflozin led to a higher incidence of iron deficiency during 12 months, defined using ferritin and TSAT criteria, compared with treatment with placebo. These observations raise the following question: What, if any, is the clinical significance of these biomarker changes, and our hypothesis to explain them? We believe there are 3 key considerations. First, does the increase in hematocrit/hemoglobin contribute to the benefit of SGLT2 inhibitors? Second, does iron deficiency as defined in this study attenuate the rise in hematocrit/hemoglobin in response to SGLT2 inhibition? Third, are the biomarker changes suggestive of iron deficiency induced by dapagliflozin clinically relevant? Although it has been suggested that the increase in hematocrit contributes to the benefits of SGLT2 inhibitors, this possibility is based on the results of mediation analysis and remains hypothetical.[39,40] Although erythropoiesis may be restricted by iron deficiency, as recognized in the treatment of patients with chronic kidney disease, we did not find clear evidence of this in the patients in DAPA-HF.[20,21] The mean placebo-corrected increase in hematocrit at 12 months did not differ significantly between iron-replete participants and those who were iron deficient (3.00% versus 2.27%; P-interaction=0.10), although there was a trend to a greater increase in hemoglobin (7.34 versus 5.42 g/L; P-interaction=0.06). Last, incident iron deficiency, as defined by changes in ferritin and TSAT, was associated with worse

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outcomes irrespective of treatment allocation. Although confounded, these findings are consistent with those of another recent study and with the randomized controlled trials using intravenous ferric carboxymaltose to treat iron deficiency.[34,36] It is important to note, however, that the relative risk reductions in the primary and secondary morbidity and mortality end points with dapagliflozin, compared with placebo, were consistent in patients with and without iron deficiency at baseline (and the absolute risk reductions with dapagliflozin in individuals with iron deficiency were substantial, as a result of the high rates of death and hospitalization in these patients). Furthermore, the finding of a consistent benefit of dapagliflozin by iron status at baseline means that preexisting iron deficiency should not be considered as a barrier to the initiation of dapagliflozin or the development of iron deficiency during treatment as a reason to discontinue.

International guidelines already recommend testing for and treating iron deficiency in patients with HFrEF.[10,11] Although none of our individual findings are definitive, collectively they do raise the question whether testing for and treating iron deficiency after the initiation of SGLT2 inhibition might also be desirable. As we have reported previously, dapagliflozin leads to the correction of anemia in many but not all patients with HFrEF, and the beneficial effect of dapagliflozin was consistent in those with and without anemia at baseline.[14] In the present study, the effect of dapagliflozin on reversing anemia was consistent regardless of the presence or not of iron deficiency at baseline. Our new observations raise the potential for a therapeutic synergy between iron replenishment and SGLT2 inhibition in some patients with HFrEF not just to avoid iron deficiency but perhaps also to treat anemia.

Limitations

As with all studies of this type, there are inherent limitations. Analysis of iron deficiency was not prespecified. Reticulocyte count, mean corpuscular hemoglobin concentration, and other indices that might have helped confirm an erythropoietic response to dapagliflozin were not measured in DAPA-HF. Ferritin levels can also reflect metabolic liver disease, which may be improved by SGLT2 inhibitors.[41,42] We did not have serial measurements of iron indices and hemoglobin over time and may have missed earlier changes in some of these before the 1-year time point. Dapagliflozin improved survival compared with placebo, resulting in some survivor bias in our analyses.

Conclusions

In conclusion, the prevalence and incidence of iron deficiency were high among patients with HFrEF in DAPA-HF, and participants with iron deficiency had worse outcomes than those who were iron-replete. Dapagliflozin appeared to increase iron use but improved outcomes, irrespective of iron status at baseline.

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Supplemental Material

Tables S1–S6

Figure S1

REFERENCES

1. Alnuwaysir RIS, Hoes MF, van Veldhuisen DJ, van der Meer P, Beverborg NG. Iron deficiency in heart failure: mechanisms and pathophysiology. *J Clin Med.* 2021;11:125. doi: 10.3390/jcm11010125

2. Sawicki KT, Ardehali H. Intravenous iron therapy in heart failure with reduced ejection fraction: tackling the deficiency. *Circulation.* 2021;144:253–255. doi: 10.1161/CIRCULATIONAHA.121.054271

3. von Haehling S, Ebner N, Evertz R, Ponikowski P, Anker SD. Iron deficiency in heart failure: an overview. *JACC Heart Fail.* 2019;7:36–46. doi: 10.1016/j.jchf.2018.07.015

4. Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, Borodulin-Nadzieja L, Banasiak W, Polonski L, Filippatos G, et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. *Eur Heart J.* 2010;31:1872–1880. doi: 10.1093/eurheartj/ehq158

5. Khan MS, Usman MS, von Haehling S, Doehner W, Stewart Coats AJ. Ferric carboxymaltose for the treatment of iron-deficient heart failure patients: a systematic review and meta-analysis. *ESC Heart Fail.* 2020;7:3392–3400. doi: 10.1002/ehf2.13146

6. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Lüscher TF, Bart B, Banasiak W, Niegowska J, et al. FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med.* 2009;361:2436–2448. doi: 10.1056/NEJMoa0908355

7. van Veldhuisen DJ, Ponikowski P, van der Meer P, Metra M, Böhm M, Doletsky A, Voors AA, Macdougall IC, Anker SD, Roubert B, et al. EFFECT-HF Investigators. Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency. *Circulation.* 2017;136:1374–1383. doi: 10.1161/CIRCULATIONAHA.117.027497

8. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, McDonagh T, Parkhomenko A, Tavazzi L, Levesque V, et al; CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J.* 2015;36:657–668. doi: 10.1093/eurheartj/ehu385

9. Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozdz J, Fabien V, Filippatos G, Göhring UM, Keren A, et al. AFFIRM-AHF investigators. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet.* 2020;396:1895–1904. doi: 10.1016/S0140-6736(20)32339-4

10. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, et al. ESC Scientific Document Group. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail.* 2022;24:4–131. doi: 10.1002/ejhf.2333

11. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al; Writing Committee Members. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2022;79:e263–e421. doi: 10.1016/j.jacc.2021.12.012

12. Oshima M, Neuen BL, Jardine MJ, Bakris G, Edwards R, Levin A, Mahaffey KW, Neal B, Pollock C, Rosenthal N, et al. Effects of canagliflozin on anaemia in patients with type 2 diabetes and chronic kidney disease: a post-hoc analysis from the CREDENCE trial. *Lancet Diabetes Endocrinol.* 2020;8:903–914. doi: 110.1016/S2213-8587(20)30300-4

13. Ferreira JP, Anker SD, Butler J, Filippatos G, Iwata T, Salsali A, Zeller C, Pocock SJ, Zannad F, Packer M. Impact of anaemia and the effect of empagliflozin in heart failure with reduced ejection fraction: findings from EMPEROR-Reduced. *Eur J Heart Fail.* 2022;24:708–715. doi: 10.1002/ejhf.2409

14. Docherty KF, Curtain JP, Anand IS, Bengtsson O, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, Martinez FA, Ponikowski P, et al; DAPA-HF Investigators and Committees. Effect of dapagliflozin on anaemia in DAPA-HF. *Eur J Heart Fail.* 2021;23:617–628. doi: 10.1002/ejhf.2132

15. Marathias KP, Lambadiari VA, Markakis KP, Vlahakos VD, Bacharaki D, Raptis AE, Dimitriadis GD, Vlahakos DV. Competing effects of renin angiotensin system blockade and sodium-glucose cotransporter-2 inhibitors on erythropoietin secretion in diabetes. *Am J Nephrol.* 2020;51:349–356. doi: 10.1159/000507272

16. Lambers Heerspink HJ, de Zeeuw D, Wie L, Leslie B, List J. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. *Diabetes Obes Metab.* 2013;15:853–862. doi: 10.1111/dom.12127

17. Mazer CD, Hare GMT, Connelly PW, Gilbert RE, Shehata N, Quan A, Teoh H, Leiter LA, Zinman B, Jüni P, et al. Effect of empagliflozin on erythropoietin levels, iron stores, and red blood cell morphology in patients with type 2 diabetes mellitus and coronary artery disease. *Circulation.* 2020;141:704–707. doi: 10.1161/CIRCULATIONAHA.119.044235

18. Maruyama T, Takashima H, Oguma H, Nakamura Y, Ohno M, Utsunomiya K, Furukawa T, Tei R, Abe M. Canagliflozin improves erythropoiesis in diabetes patients with anaemia of chronic kidney disease. *Diabetes Technol Ther.* 2019;21:713–720. doi: 10.1089/dia.2019.0212

19. Ghanim H, Abuaysheh S, Hejna J, Green K, Batra M, Makdissi A, Chaudhuri A, Dandona P. Dapagliflozin suppresses hepcidin and increases erythropoiesis. *J Clin Endocrinol Metab.* 2020;105:dgaa057. doi: 10.1210/clinem/dgaa057

20. Tkaczyszyn M, Comín-Colet J, Voors AA, van Veldhuisen DJ, Enjuanes C, Moliner P, Drozd M, Sierpiński R, Rozentryt P, Nowak J, et al. Iron deficiency contributes to resistance to endogenous erythropoietin in anaemic heart failure patients. *Eur J Heart Fail.* 2021;23:1677–1686. doi: 10.1002/ejhf.2253

21. Macdougall IC, White C, Anker SD, Bhandari S, Farrington K, Kalra PA, McMurray JJV, Murray H, Tomson CRV, Wheeler DC, et al. PIVOTAL Investigators and Committees. Intravenous iron in patients undergoing maintenance hemodialysis. *N Engl J Med.* 2019;380:447–458. doi: 10.1056/NEJMoa1810742

22. McMurray JJV, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, Martinez FA, Bengtsson O, Ponikowski P, Sabatine MS, et al. DAPA-HF Committees and Investigators. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). *Eur J Heart Fail.* 2019;21:665–675. doi: 10.1002/ejhf.1432

23. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2019;381:1995–2008. doi: 10.1056/NEJMoa1911303

24. Royston P, Sauerbrei W. A new approach to modelling interactions between treatment and continuous covariates in clinical trials by using fractional polynomials. *Stat Med.* 2004;23:2509–2525. doi: 10.1002/sim.1815

25. Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. *J R Stat Soc Series B Stat Methodol.* 2000;62:711–730. doi: 10.1093/biostatistics/kxv050

26. Becher PM, Schrage B, Benson L, Fudim M, Corovic Cabrera C, Dahlström U, Rosano GMC, Jankowska EA, Anker SD, Lund LH, et al. Phenotyping heart failure patients for iron deficiency and use of intravenous iron therapy: data from the Swedish Heart Failure Registry. *Eur J Heart Fail.* 2021;23:1844–1854. doi: 10.1002/ejhf.2338

27. Sindone AP, Haikerwal D, Audehm RG, Neville AM, Lim K, Parsons RW, Piazza P, Liew D. Clinical characteristics of people with heart failure in

Australian general practice: results from a retrospective cohort study. *ESC Heart Fail.* 2021;8:4497–4505. doi: 10.1002/ehf2.13661

28. Chobufo MD, Rahman E, Gayam V, Bei Foryoung J, Agbor VN, Farah F, Dufresne A, Nfor T, El-Hamdani M. Prevalence and association of iron deficiency with anemia among patients with heart failure in the USA: NHANES 2017-2018. *J Commun Hosp Intern Med Perspect.* 2021;11:124–127. doi: 10.1080/20009666.2020.1854927

29. Masini G, Graham FJ, Pellicori P, Cleland JGF, Cuthbert JJ, Kazmi S, Inciardi RM, Clark AL. Criteria for iron deficiency in patients with heart failure. *J Am Coll Cardiol.* 2022;79:341–351. doi: 10.1016/j.jacc.2021.11.039

30. Anand IS, Gupta P. Anemia and iron deficiency in heart failure: current concepts and emerging therapies. *Circulation.* 2018;138:80–98. doi: 10.1161/CIRCULATIONAHA.118.030099

31. Sierpinski R, Josiak K, Suchocki T, Wojtas-Polc K, Mazur G, Butrym A, Rozentryt P, van der Meer P, Comin-Colet J, von Haehling S, et al. High soluble transferrin receptor in patients with heart failure: a measure of iron deficiency and a strong predictor of mortality. *Eur J Heart Fail.* 2021;23:919–932. doi: 10.1002/ejhf.2036

32. Grote Beverborg N, Klip IT, Meijers WC, Voors AA, Vegter EL, van der Wal HH, Swinkels DW, van Pelt J, Mulder AB, Bulstra SK, et al. Definition of iron deficiency based on the gold standard of bone marrow iron staining in heart failure patients. *Circ Heart Fail.* 2018;11:e004519. doi: 10.1161/CIRCHEARTFAILURE.117.004519

33. Graham FJ, Masini G, Pellicori P, Cleland JGF, Greenlaw N, Friday J, Kazmi S, Clark AL. Natural history and prognostic significance of iron deficiency and anaemia in ambulatory patients with chronic heart failure. *Eur J Heart Fail.* 2022;24:807–817. doi: 10.1002/ejhf.2251

34. Fitzsimons S, Yeo TJ, Ling LH, Sim D, Leong KTG, Yeo PSD, Ong HY, Jauferally F, Ng TP, Poppe K, et al. Impact of change in iron status over time on clinical outcomes in heart failure according to ejection fraction phenotype. *ESC Heart Fail.* 2021;8:4572–4583. doi: 10.1002/ehf2.13617

35. Fitzsimons S, Poppe KK, Choi Y, Devlin G, Lund M, Lam CS, Troughton R, Richards AM, Doughty RN. Relationship between soluble transferrin receptor and clinical outcomes in patients with heart failure according to ejection fraction phenotype: the New Zealand PEOPLE study. *J Card Fail.* 2022;S1071–9164(22)00003-3. doi: 10.1016/j.cardfail.2021.12.018

36. Klip IT, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W, Lok DJ, Rosentryt P, Torrens A, Polonski L, et al. Iron deficiency in chronic heart failure: an international pooled analysis. *Am Heart J.* 2013;165:575–582.e3. doi: 10.1016/j.ahj.2013.01.017

37. Nakano H, Nagai T, Sundaram V, Nakai M, Nishimura K, Honda Y, Honda S, Iwakami N, Sugano Y, Asaumi Y, et al. NaDEF investigators. Impact of iron deficiency on long-term clinical outcomes of hospitalized patients with heart failure. *Int J Cardiol.* 2018;261:114–118. doi: 10.1016/j.ijcard.2018.03.039

38. Thiele K, Rau M, Hartmann NK, Möllmann J, Jankowski J, Böhm M, Keszei AP, Marx N, Lehrke M. Effects of empagliflozin on erythropoiesis in patients with type 2 diabetes: data from a randomized, placebo-controlled study. *Diabetes Obes Metab.* 2021;23:2814–2818. doi: 10.1111/dom.14517

39. Li J, Neal B, Perkovic V, de Zeeuw D, Neuen BL, Arnott C, Simpson R, Oh R, Mahaffey KW, Heerspink HJL. Mediators of the effects of canagliflozin on kidney protection in patients with type 2 diabetes. *Kidney Int.* 2020;98:769–777. doi: 10.1016/j.kint.2020.04.051

40. Fitchett D, Inzucchi SE, Zinman B, Wanner C, Schumacher M, Schmoor C, Ohneberg K, Ofstad AP, Salsali A, George JT, et al. Mediators of the improvement in heart failure outcomes with empagliflozin in the EMPA-REG OUTCOME trial. *ESC Heart Fail.* 2021;8:4517–4527. doi: 110.1002/ehf2.13615

41. Itani T, Ishihara T. Efficacy of canagliflozin against nonalcoholic fatty liver disease: a prospective cohort study. *Obes Sci Pract.* 2018;4:477–482. doi: 10.1002/osp4.294

42. Phrueksotsai S, Pinyopornpanish K, Euathrongchit J, Leerapun A, Phrommintikul A, Buranapin S, Chattipakorn N, Thongsawat S. The effects of dapagliflozin on hepatic and visceral fat in type 2 diabetes patients with non-alcoholic fatty liver disease. *J Gastroenterol Hepatol.* 2021;36:2952–2959. doi: 10.1111/jgh.15580