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CLINICAL RESEARCH

Prevalent and Incident Anemia in PARADIGM-HF and the Effect of Sacubitril/Valsartan

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ABSTRACT

BACKGROUND Anemia is common in patients with heart failure with reduced ejection fraction and is associated with poor clinical outcomes. Renin-angiotensin system blockers lower hemoglobin and may induce anemia.

OBJECTIVES The authors investigated whether concomitant neprilysin inhibition might ameliorate this effect of renin-angiotensin system blockers in PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure).

METHODS Anemia was defined as hemoglobin <120 g/L in women and <130 g/L in men at screening. The authors investigated the effect of randomized treatment on clinical outcomes according to anemia status, change in hemoglobin from baseline, and the incidence of anemia.

RESULTS Of 8,239 participants with a baseline hemoglobin measurement, 1,677 (20.4%) were anemic. Patients with anemia had a more severe heart failure profile, worse kidney function, greater neurohormonal derangement, and worse clinical outcomes. Sacubitril/valsartan, compared with enalapril, decreased the risk of cardiovascular death or heart failure hospitalization similarly in patients with (HR: 0.84; 95% CI: 0.71-1.00) and without anemia (HR: 0.78 [95% CI: 0.71-0.87]; *P* value for interaction = 0.478). Between baseline and 12 months, hemoglobin decreased by 1.5 g/L (95% CI: 1.2-1.7 g/L) with sacubitril/valsartan compared with 2.3 g/L (95% CI: 2.0-2.6 g/L) with enalapril: mean difference 0.8 g/L (95% CI: 0.5-1.2 g/L; $P < 0.001$). Patients assigned to sacubitril/valsartan were less likely to develop anemia at 12 months (321 of 2,806 [11.4%]) compared with patients randomized to enalapril (440 of 2,824 [15.6%]) (OR: 0.70 [95% CI: 0.60-0.81]; $P < 0.001$). These findings were similar in PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) (sacubitril/valsartan vs valsartan). There was biomarker evidence of increased iron utilization with sacubitril/valsartan.

CONCLUSIONS Irrespective of anemia status, sacubitril/valsartan compared with enalapril, decreased mortality and hospitalization. Hemoglobin decreased less with sacubitril/valsartan and the incidence of new anemia was lower with sacubitril/valsartan. (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure [PARADIGM-HF] trial; NCT01035255) (J Am Coll Cardiol HF 2023;11:749–759) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ARB = angiotensin receptor blocker

BNP = B-type natriuretic peptide

eGFR = estimated glomerular filtration rate

HFrEF = heart failure with reduced ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

RAS = renin-angiotensin system

SGLT2 = sodium-glucose cotransporter-2

Anemia is common in patients with heart failure and is associated with worse symptoms and exercise tolerance, as well as an increased risk of heart failure hospitalization and death.[1-3] Although this association may be related to the correlation between anemia and more advanced disease, anemia might also contribute directly to adverse outcomes by further impairing tissue oxygen delivery. Anemia is also associated with unfavorable cardiac remodeling, and it has been proposed that the development of anemia initiates a vicious cycle in heart failure.[1-3] Based on these observations, the correction of anemia has been investigated as a therapeutic option for heart failure. However, in a large morbidity and mortality trial, treatment with the erythropoiesis-stimulating agent darbepoetin did not improve outcomes in patients with heart failure with reduced ejection fraction (HFrEF) and increased the risk of stroke.[4]

Paradoxically, renin-angiotensin system (RAS) blockers, which are clearly beneficial in HFrEF, decrease hemoglobin, probably by inhibiting erythropoietin production, and, in the case of angiotensin-converting enzyme (ACE) inhibitors, by increasing levels of the tetrapeptide N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP), which suppresses hematopoiesis.[5-8] In the SOLVD (Studies Of Left Ventricular Systolic Dysfunction) trial, enalapril increased the adjusted odds of incident anemia at 1 year by 56% (OR: 1.56; 95% CI: 1.26-1.93).[8] In the Val-HeFT (Valsartan Heart Failure Trial), treatment with an angiotensin receptor blocker (ARB) also caused a reduction in hemoglobin.[7]

Neprilysin (neutral endopeptidase) may also influence hemoglobin levels. Substance P stimulates hematopoiesis.[9] However, it is also a substrate for neprilysin and the amino-terminal cleavage product, SP(1-4), is believed to be an inhibitor of hematopoiesis. Consequently, inhibition of neprilysin should promote hematopoiesis by increasing substance P and decreasing SP(1-4).[9] In keeping with this, the neprilysin inhibitor thiorphan has been shown to stimulate hematopoiesis in human bone marrow cultures.[10] This finding suggests that the combination of a neprilysin inhibitor with a RAS blocker might decrease or prevent the decrease in hemoglobin induced by a RAS blocker alone.

We examined the prevalence, incidence, and consequences of anemia in PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure) and evaluated the hypothesis that concomitant neprilysin inhibition might attenuate the decline in hemoglobin caused by RAS blockade.[11]

METHODS

STUDY DESIGN AND PARTICIPANTS. PARADIGM-HF was a multicenter, double-blind, randomized controlled trial comparing the effect of treatment with the ARB-neprilysin inhibitor sacubitril/valsartan against treatment with an ACE inhibitor, enalapril, in patients with HFrEF.[11] Inclusion criteria included a left ventricular ejection fraction of ≤40% (subsequently changed to ≤35% by a protocol amendment) and NYHA functional class II, III, or IV. Patients were required to have a plasma B-type natriuretic peptide (BNP) level of ≤150 pg/mL (or an N-terminal pro-B-type natriuretic peptide [NT-proBNP] level ≥600 pg/mL) unless hospitalized for heart failure within the previous year, in which case a BNP of ≤100 pg/mL (or NT-proBNP of ≥400 pg/mL) was required. The main exclusion criteria included symptomatic hypotension, systolic blood pressure of <100 mm Hg at screening or 95 mm Hg at randomization, an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m^2 at screening or, at randomization, a decrease in the eGFR of >25% (subsequently amended to >35%) between screening and randomization, and serum potassium level of more than 5.2 mmol/L at screening (or >5.4 mmol/L at randomization). Hemoglobin value or a history of anemia did not determine eligibility for the trial. The trial was approved by

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an ethics committee at each study center and all patients provided written informed consent before enrollment.

PRESPECIFIED TRIAL OUTCOMES. The primary composite outcome in PARADIGM-HF was time to the first occurrence of cardiovascular death or heart failure hospitalization. All-cause death was one of several prespecified secondary outcomes.

HEMOGLOBIN COLLECTION AND REPORTING. Hemoglobin was measured at screening (baseline in this analysis), randomization, at 12 months, 20 months, 24 months, and 36 months after randomization. Only trial time points with >1,000 hemoglobin values available were included in this analysis. Anemia was defined according to the World Health Organization definition as <120 g/L in females and <130 g/L in males.[12]

STATISTICAL ANALYSES. The baseline characteristics of patients with and without anemia were examined. Categorical variables are reported as whole numbers with percentages. Continuous variables are reported as mean ± SD for normally distributed variables or median (IQR) for non-normally distributed variables. Associations between anemia at baseline and clinical endpoints were examined in time-to-first event analyses using Cox proportional hazards models. Primary analyses were adjusted for randomized treatment assignment, geographical region, with further adjustment made for factors known to influence heart failure prognosis, including log-transformed NT-proBNP, left ventricular ejection fraction, age, Kansas City Cardiomyopathy Questionnaire (KCCQ)-Clinical Summary Score, NYHA functional class, eGFR, prior heart failure hospitalization, diabetes, heart rate, systolic blood pressure, body mass index, atrial fibrillation, myocardial infarction, stroke, and for additional factors that can modify hemoglobin levels (chronic obstructive pulmonary disease, diuretic agents, and volume status as evidenced by the presence of rales, jugular venous distension, or edema). The effects of sacubitril/valsartan, compared with enalapril, on the primary endpoint, its components, and mortality were examined in patients with and without anemia in Cox proportional hazards models. The Cox proportional hazards assumption was examined with log(-log [survival]) curves and scaled Schoenfeld residuals, and the assumption was not violated for any of the models. The interaction between anemia and randomized treatment was tested with anemia status (defined by the World Health Organization criteria for anemia and calculated from the baseline hemoglobin value) modeled categorically in a postestimation test and with baseline hemoglobin modeled continuously in fractional polynomial models. Event rates per 100 person-years were calculated and are presented with 95% CIs. The cumulative incidences of outcomes are presented graphically using the Kaplan-Meier method. Because different modes of death precluded the occurrence of dying from another cause, we examined the effect of sacubitril/valsartan compared with enalapril on cardiovascular death, sudden death, and heart failure death with other causes of mortality analyzed as a competing risk.

Change from baseline (screening) in hemoglobin was analyzed using a linear mixed-effects model of repeated measures with adjustment for randomized treatment, region, sex, baseline hemoglobin, study visit, and interaction between study visit and

TABLE 1 Baseline Characteristics According to Anemia[a] Status at Screening

	No Anemia (n = 6,562, 79.6%)	Anemia (n = 1,677, 20.4%)	*P* Value
Hemoglobin, g/L			
Male	≥130	<130	
Female	≥120	<120	
Age, y	63 ± 11	66 ± 11	<0.001
Ethnicity			<0.001
White	4,448 (67.8)	971 (57.9)	
Black	309 (4.7)	113 (6.7)	
Asian	1,073 (16.4)	423 (25.2)	
Other	732 (11.2)	170 (10.1)	
Region			<0.001
North America	428 (6.5)	163 (9.7)	
Latin America	1,165 (17.8)	250 (14.9)	
Western Europe	1,574 (24.0)	436 (26.0)	
Central Europe	2,341 (35.7)	408 (24.3)	
Asia-Pacific	1,054 (16.1)	420 (25.0)	
Male	5,082 (77.4)	1,354 (80.7)	0.004
SBP, mm Hg	129 ± 17	127 ± 16	<0.001
Heart rate, beats/min	74 ± 13	73 ± 12	0.045
BMI, kg/m^2	28 ± 6	27 ± 5	<0.001
LVEF, %	30 (25-34)	30 (25-34)	0.083
NYHA functional class			0.007
I	23 (0.4)	5 (0.3)	
II	4,316 (65.9)	1,029 (61.4)	
III	2,121 (32.4)	617 (36.8)	
IV	94 (1.4)	25 (1.5)	
KCCQ score	80 (64-93)	78 (61-91)	<0.001
Medical history			
Ischemic etiology	3,836 (58.5)	1,107 (66.0)	<0.001
Hypertension	4,659 (71.0)	1,159 (69.1)	0.130
Diabetes	2,130 (42.5)	704 (42.0)	<0.001
AF on history	2,425 (37.0)	558 (33.3)	0.005
AF/AFL on ECG	1,692 (25.8)	339 (20.2)	<0.001
Prior HF hospitalization	4,096 (62.4)	1,072 (63.9)	0.260
MI	2,786 (42.5)	781 (46.6)	0.002
Stroke	576 (8.8)	127 (7.6)	0.120
COPD	806 (12.3)	247 (14.7)	0.007

Continued on the next page

TABLE 1 Continued

	No Anemia (n = 6,562, 79.6%)	Anemia (n = 1,677, 20.4%)	*P* Value
Medical therapy			
ACE inhibitor/ARB (pretrial)	6,549 (99.8)	1,670 (99.6)	0.100
Diuretic	5,215 (79.5)	1,400 (83.5)	<0.001
Beta-blocker	6,140 (93.6)	1,524 (90.9)	<0.001
MRA	3,683 (56.1)	893 (53.2)	0.034
Digoxin	2,016 (30.7)	482 (28.7)	0.120
Anticoagulant	2,159 (32.9)	472 (28.1)	<0.001
Antiplatelet	3,624 (55.2)	1,021 (60.9)	<0.001
ICD (including CRT-D)	947 (14.4)	276 (16.5)	0.037
CRT	429 (6.5)	136 (8.1)	0.023
Physical signs			
Rales	521 (7.9)	144 (8.6)	0.390
Jugular distension	630 (9.6)	172 (10.3)	0.420
Edema	1,341 (20.4)	380 (22.7)	0.046
Blood biomarkers[b]			
Hematocrit	44 ± 3	36 ± 2	<0.001
eGFR, mL/min/1.73 m^2	69 ± 19	65 ± 21	<0.001
Albumin, g/L	44 ± 3	42 ± 4	<0.001
NT-proBNP, pg/mL	1,516 (852-2,929)	2,155 (1,064-4,728)	<0.001
Troponin T, μg/L	0.014 (0.001-0.021)	0.020 (0.013-0.030)	<0.001

Values are mean ± SD, n (%), or median (IQR), unless otherwise indicated. Percentages may not total 100 because of rounding. [a]Anemia defined as a hemoglobin of <120 g/L in women and <130 g/L in men. [b]Numbers of patients with biomarker values: NT-proBNP = 8,348; troponin = 1,907.

ACE = angiotensin converting enzyme; AF = atrial fibrillation; AFL = atrial flutter; ARB = angiotensin receptor blocker; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy-defibrillator; ECG = electrocardiograph; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implanted cardioverter defibrillator; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure.

treatment with a random intercept and slope per patient. A sensitivity analysis was also performed comparing the change in hemoglobin in patients randomly assigned to sacubitril/valsartan, compared with valsartan, in the PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) trial.[13] The assumptions of the mixed models were checked by plotting the residuals. Plots are presented in Supplemental Figure 2, Supplemental Figure 3B, and Supplemental Figure 4B. Proportions of patients developing new-onset anemia were calculated between baseline and 12 and 24 months of follow-up. The probability of developing anemia at 12 and 24 months in nonanemic patients was examined according to randomized treatment in logistic regression models. The incidence rate ratios for new-onset anemia were calculated from the number of events and person-time and according to randomized treatment. Adverse events in patients with or without anemia were examined according to randomized treatment.

Because indices of iron metabolism were not measured in PARADIGM-HF or PARAGON-HF, we analyzed these in plasma samples available from a small mechanistic randomized controlled trial, RECOVER-LV (Effects of Sacubitril/Valsartan Compared to Valsartan on LV Remodelling in Asymptomatic LV Systolic Dysfunction After MI), which compared the effect of sacubitril/valsartan with valsartan on left ventricular remodeling in patients with asymptomatic left ventricular systolic dysfunction.[14] The effect of sacubitril/valsartan compared with valsartan on biomarkers relating to iron metabolism from baseline to 6 and 12 months was analyzed using an analysis of covariance model using log-transformed values and adjusted for log-transformed baseline values. Regression coefficients from these models were back-transformed and the relative between-group differences with 95% CIs are presented as ratios of geometric means.

A value of $P < 0.05$ was considered statistically significant. Statistical analyses were performed using STATA/SE 17.

RESULTS

Among the 8,399 patients randomized, hemoglobin was recorded at screening (baseline) in 8,239 participants (98.1%) and 6,977 patients (83.1%) at 12 months after randomization. The mean hemoglobin was 140 ± 16 g/L (Supplemental Figure 1).

BASELINE CHARACTERISTICS. The baseline characteristics of patients with or without anemia are shown in **Table 1**. Overall, 1,677 patients (20.4%) were anemic by the World Health Organization definition. Patients with anemia were older, more likely to be male, reside in Asia, have poorer kidney function and lower systolic blood pressure, body mass index and heart rate. They had a greater symptom burden, evidenced by lower KCCQ scores and greater proportions in NYHA functional class III or IV. Patients with anemia were more likely to have diabetes, chronic obstructive pulmonary disease, and a history of ischemic heart disease with higher use of antiplatelet agents. Patients with anemia were less likely to have atrial fibrillation and were less likely to be on an oral anticoagulant but had higher rates of diuretic use and implanted devices at baseline. Fewer patients with anemia were taking mineralocorticoid receptor antagonists and beta-blockers at baseline, although rates of beta-blocker use were high (>90%) in both groups. Patients with anemia had evidence of greater neurohormonal derangement, with higher levels of natriuretic peptides and troponin T.

TABLE 2 Cox Proportional Hazard Models of Clinical Outcomes According to Anemia Status

	Anemia (n = 1,677)		No Anemia (n = 6,562)		Primary Analysis[a]	Adjusted Analysis[b]
	n (%)	Event Rate per 100 Person-Years	n (%)	Event Rate per 100 Person-Years	HR (95% CI)	HR (95% CI)
Primary endpoint	510 (30.4)	16.0 (14.7-17.5)	1,484 (22.6)	10.8 (10.3-11.4)	1.49 (1.34-1.64); $P < 0.001$	1.25 (1.12-1.40); $P < 0.001$
HF hospitalization	310 (18.4)	9.8 (8.7-10.9)	867 (13.2)	6.3 (5.9-6.8)	1.53 (1.34-1.74); $P < 0.001$	1.29 (1.12-1.48); $P < 0.001$
All-cause death	397 (23.7)	11.4 (10.3-12.6)	1,116 (17.0)	7.6 (7.2-8.1)	1.52 (1.36-1.71); $P < 0.001$	1.26 (1.11-1.42); $P < 0.001$
Cardiovascular death	330 (19.7)	9.4 (8.5-10.5)	894 (13.6)	6.1 (5.7-6.5)	1.57 (1.38-1.79); $P < 0.001$	1.30 (1.13-1.49); $P < 0.001$
HF death	99 (5.9)	2.8 (2.3-3.4)	224 (3.4)	1.5 (1.3-1.7)	1.85 (1.46-2.35); $P < 0.001$	1.48 (1.14-1.92); $P = 0.003$
Sudden death	133 (7.9)	3.8 (3.2-4.5)	415 (6.3)	2.8 (2.6-3.1)	1.32 (1.08-1.61); $P = 0.006$	1.08 (0.86-1.34); $P = 0.508$

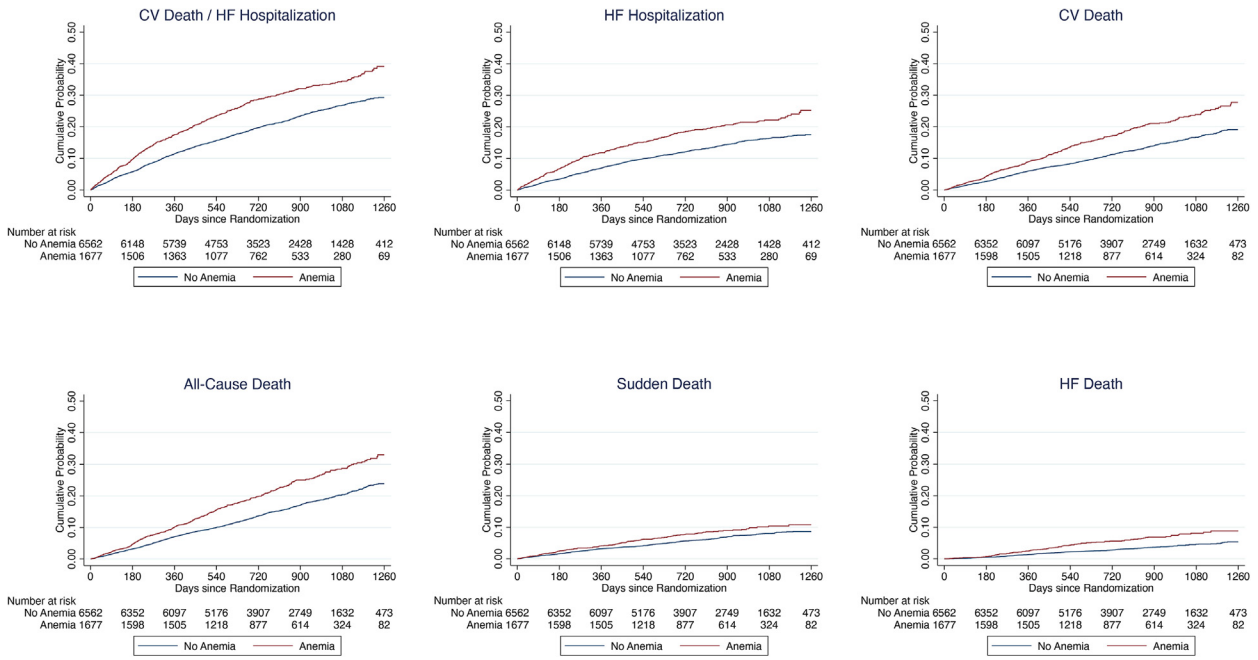
[a]Primary analysis included factors for randomized treatment assignment and geographical region. [b]Adjusted analysis included factors for randomized treatment assignment, geographical region, age, KCCQ-CSS, LVEF, NYHA class, log-transformed NT-proBNP, eGFR, prior HF hospitalization, diabetes, heart rate, SBP, BMI, atrial fibrillation, MI, stroke, COPD, diuretic agents, rales, jugular venous distension, and edema.

KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; MI = myocardial infarction; other abbreviations as in Table 1.

CLINICAL OUTCOMES IN PATIENTS WITH OR WITHOUT ANEMIA. Patients with anemia, compared with those without, had a higher rate of the primary composite endpoint (adjusted HR: 1.25 [95% CI: 1.12-1.40]; $P < 0.001$) and of its components, all-cause mortality, and heart ("pump") failure death in primary and adjusted analyses. Most deaths were from cardiovascular causes. The rate of noncardiovascular death and sudden death was higher in anemic patients in the primary analysis, but not after multivariable adjustment (Table 2, Figure 1).

CLINICAL OUTCOMES ACCORDING TO RANDOMIZED TREATMENT. The primary outcome occurred in 245 of 857 patients with anemia assigned to sacubitril/valsartan compared with 265 of 820 patients with anemia assigned to enalapril, giving event rates of 14.7 (95% CI: 13.0-16.7) and 17.5 (95% CI: 15.6-19.8) per 100 patient-years, respectively, and a HR of 0.84 (95% CI: 0.71-1.00). In patients without anemia, 654 of the 3,252 patients taking sacubitril/valsartan and 830 of the 3,310 patients taking enalapril experienced the primary outcome. Compared with patients taking

FIGURE 1 Kaplan-Meier Curves of Clinical Outcomes in Cox Proportional Hazard Models in Patients With and Without Anemia at Baseline



CV = cardiovascular; HF = heart failure.

TABLE 3 Cox Proportional Hazard Models of Clinical Outcomes According to Randomized Treatment Assignment in Patients With and Without Anemia

	Sacubitril/Valsartan		Enalapril			
	Anemia (n = 857) No Anemia (n = 3,252)		Anemia (n = 820) No Anemia (n = 3,310)			
	n (%)	Rate per 100 Person-Years (95% CI)	n (%)	Rate per 100 Person-Years (95% CI)	HR[a] (95% CI)	Interaction *P* Value[b]
CV death/HF hospitalization						0.478
Anemia	245 (28.6)	14.7 (13.0-16.7)	265 (32.3)	17.5 (15.6-19.8)	0.84 (0.71-1.00)	
No anemia	654 (20.1)	9.5 (8.8-10.3)	830 (25.1)	12.2 (11.4-13.0)	0.78 (0.71-0.87)	
HF hospitalization						0.455
Anemia	150 (17.5)	9.0 (7.7-10.6)	160 (19.5)	10.6 (9.1-12.4)	0.86 (0.69-1.07)	
No anemia	381 (11.7)	5.5 (5.0-6.1)	486 (14.7)	7.1 (6.5-7.8)	0.78 (0.68-0.89)	
All-cause death						0.352
Anemia	198 (23.1)	10.9 (9.5-12.5)	199 (24.3)	11.9 (10.3-13.6)	0.91 (0.75-1.11)	
No anemia	500 (15.4)	6.8 (6.3-7.5)	616 (18.6)	8.3 (7.7-9.0)	0.82 (0.73-0.92)	
Cardiovascular death						0.494
Anemia	158 (18.4)	8.7 (7.4-10.2)	172 (21.0)	10.2 (8.8-11.9)	0.85 (0.68-1.05)	
No anemia	388 (11.9)	5.3 (4.8-5.9)	506 (15.3)	6.9 (6.3-7.5)	0.77 (0.68-0.88)	
Sudden death						0.606
Anemia	59 (6.9)	3.2 (2.5-4.2)	74 (9.0)	4.4 (3.5-5.5)	0.74 (0.53-1.04)	
No anemia	186 (5.7)	2.5 (2.2-2.9)	229 (6.9)	3.1 (2.7-3.5)	0.82 (0.68-0.99)	
HF death						0.899
Anemia	46 (5.4)	2.5 (1.9-3.4)	53 (6.5)	3.2 (2.4-4.1)	0.80 (0.54-1.19)	
No anemia	97 (3.0)	1.3 (1.1-1.6)	127 (3.8)	1.7 (1.4-2.0)	0.77 (0.59-1.01)	

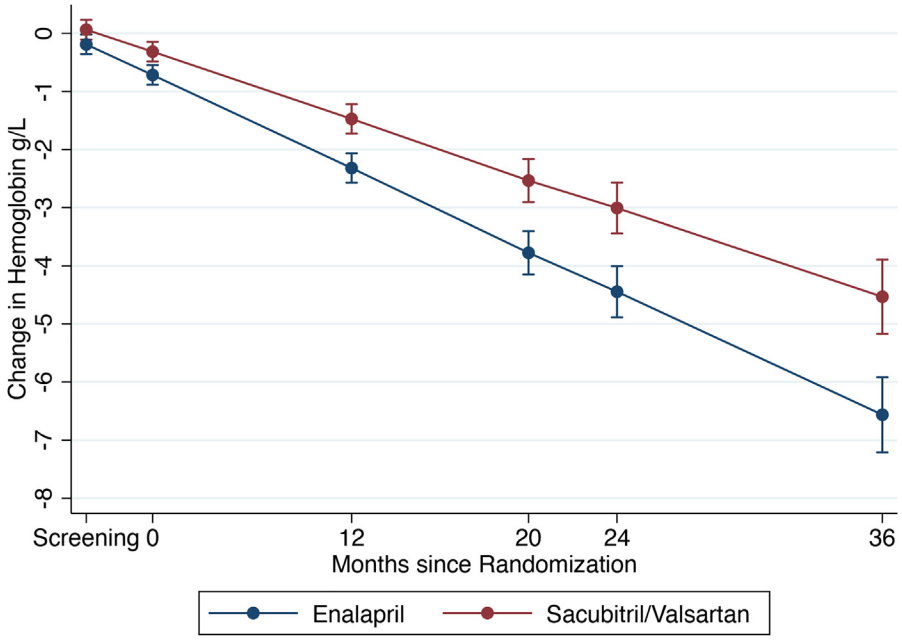
[a]Model included factors for randomized treatment assignment and geographical region. [b]Interaction between randomized treatment effect and anemia status.
CV = cardiovascular; other abbreviation as in Table 1.

enalapril, patients without anemia assigned to sacubitril/valsartan had a lower incidence of the primary outcome with event rates of 9.5 (95% CI: 8.8-10.3) compared with 12.2 (95% CI: 11.4-13.0) per 100 patient-years, giving an HR of 0.78 (95% CI: 0.71-0.87; *P* value for interaction between anemia status at baseline and randomized treatment = 0.478). Decreases in the components of the primary outcome with sacubitril/valsartan were also consistent in patients with or without anemia (Table 3). The associations with cardiovascular death, sudden death, and heart failure deaths did not change when competing causes of death were accounted for. There was no interaction between hemoglobin and the effect of randomized treatment on the primary outcome, its components, or other causes of mortality when anemia status was modeled categorically or when hemoglobin was analyzed as a continuous variable (Table 3, Figure 3).

CHANGE IN HEMOGLOBIN ACCORDING TO RANDOMIZED TREATMENT. Hemoglobin decreased over time in both treatment groups but the decrease was less in patients randomly assigned to sacubitril/valsartan. Between baseline and 12 months, the decrease in hemoglobin was 1.5 g/L (95% CI: 1.2-1.7 g/L) in the sacubitril/valsartan group compared with 2.3 g/L (95% CI: 2.1-2.6 g/L) in the enalapril group (mean difference: 0.8 g/L [95% CI: 0.5-1.2 g/L]; $P < 0.001$). This between-treatment difference persisted up to 36 months after randomization: decrease of 4.4 g/L (95% CI: 3.8-5.1 g/L) vs 6.5 g/L (95% CI: 5.8-7.1 g/L) in the sacubitril/valsartan and enalapril groups, respectively; mean difference of 2.0 g/L (95% CI: 1.1-2.9 g/L; $P < 0.001$) (Figure 2).

In a sensitivity analysis, we also examined hemoglobin change in PARAGON-HF, where hemoglobin decreased less in the sacubitril/valsartan arm compared with the valsartan arm at 12 months and this difference persisted for ≤36 months after randomization: decrease at 36 months of 1.7 g/L (95% CI: 1.0-2.4 g/L) vs 3.6 g/L (95% CI: 2.9-4.3 g/L), respectively; difference of 1.9 g/L (95% CI: 1.0-2.9 g/L; $P < 0.001$) (Supplemental Figure 2A). In both PARADIGM-HF and PARAGON-HF combined, the decrease in hemoglobin at 36 months was 3.3 g/L (95% CI: 2.8-3.7 g/L) in patients who received sacubitril/valsartan vs 5.3 g/L (95% CI: 4.9-5.8 g/L) in patients treated with either enalapril or valsartan; mean difference of 2.1 g/L (95% CI: 1.4-2.8 g/L) (Supplemental Figure 2B).

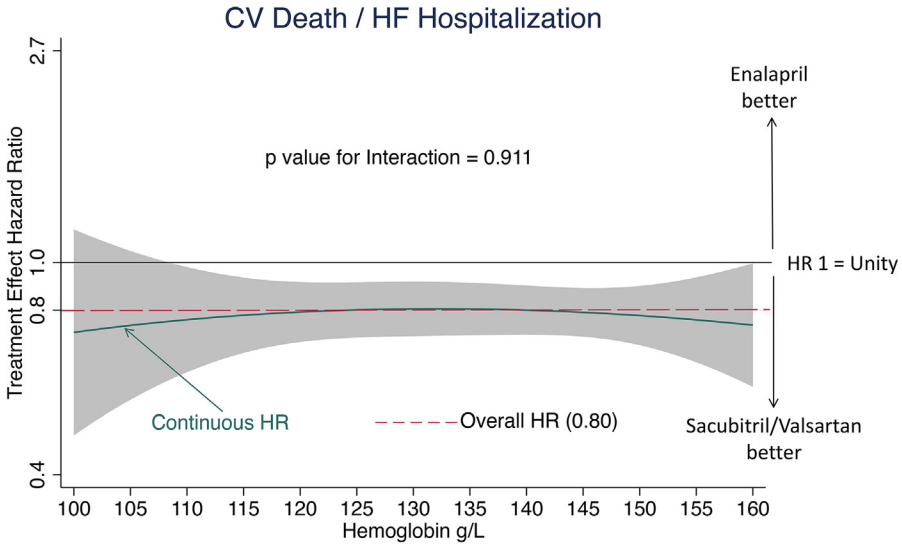
FIGURE 2 Change in Hemoglobin (per g/L) With 95% CIs According to Randomized Treatment Assignment in PARADIGM-HF



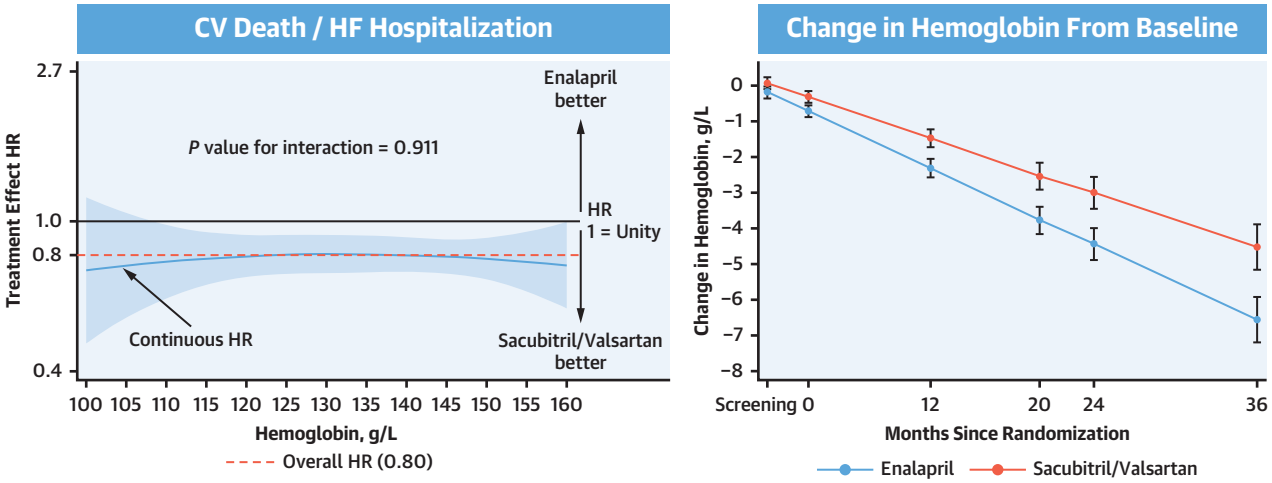
PARADIGM-HF = Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure.

NEW-ONSET ANEMIA ACCORDING TO RANDOMIZED TREATMENT. Among patients who were not anemic at baseline, those assigned to sacubitril/valsartan were less likely to develop anemia at 12 months (321/2,806 [11.4%]) compared with patients randomized to enalapril (440/2,824 [15.6%]), giving an OR of 0.70 (95% CI: 0.60-0.81; $P < 0.001$). This was also the case at 24 months (OR: 0.80 [95% CI: 0.68-0.95];

FIGURE 3 Effect of Randomized Treatment on the Primary Outcome and Interaction With Hemoglobin Modeled as a Continuous Variable



CENTRAL ILLUSTRATION **Prevalent and Incident Anemia in PARADIGM-HF and the Effect of Sacubitril/Valsartan**



New-Onset Anemia During Follow-Up According to Randomized Treatment Assignment

Follow-Up Month	Sacubitril/Valsartan	Enalapril	OR (95% CI)
12 months	321/2,806 (11.4%)	440/2,824 (15.6%)	0.70 (0.60-0.81)
24 months	286/2,017 (14.2%)	340/1,992 (17.1%)	0.80 (0.68-0.95)

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CV = cardiovascular; HF = heart failure; PARADIGM-HF = Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure.

$P = 0.012$) (Central Illustration). The incidence rate ratios of new-onset anemia at 12 months (incident rate ratio: 0.74 [95% CI: 0.64-0.85]; $P < 0.001$) and 24 months (incident rate ratio: 0.84 [95% CI: 0.71-0.98]; $P = 0.028$) were lower when treated with sacubitril/valsartan compared with enalapril. Similar findings were seen when sacubitril/valsartan was compared with valsartan in the PARAGON-HF trial (Supplemental Table 1A, Supplemental Table 1B).

EFFECT OF NEPRILYSIN INHIBITION COMPARED WITH RAS BLOCKADE ALONE ON IRON METABOLISM. At 6 months after randomization in RECOVER-LV, patients assigned to sacubitril/valsartan had lower levels of iron (ratio of geometric means: 0.88 [95% CI: 0.78-0.99]; $P = 0.04$) and hepcidin (0.73 [95% CI: 0.56-0.95]; $P = 0.02$) than patients taking valsartan, with a strong trend to a lower ferritin concentration (0.85 [95% CI: 0.71-1.01]; $P = 0.07$); these differences were not significant at 12 months. There was no significant difference in other indices of iron metabolism between the 2 treatment arms (Supplemental Table 2).

ADVERSE EVENTS. Patients with anemia were more likely than patients without anemia to have study drug withdrawal caused by an adverse event, or to have symptomatic hypotension, worsening renal function, or hyperkalemia (Supplemental Table 3A, Supplemental Table 3B). There was no interaction between randomized treatment and anemia status for the occurrence of adverse events. Patients taking sacubitril/valsartan, with or without anemia, were more likely to experience hypotension and less likely to have hyperkalemia or withdraw from study treatment than patients taking enalapril.

DISCUSSION

In a contemporary cohort of patients with HFrEF well-treated with guideline-recommended medical therapy, we found that anemia remains common and

is associated with worse outcomes.[1-3] Specifically, we found that 20% of patients had anemia, a very similar prevalence to the 22% found in another recent trial, DAPA-HF.[14] In addition to demonstrating elevated rates of hospitalization for heart failure and death in patients with anemia, we showed that the excess mortality was primarily driven by a higher rate of death from pump failure rather than sudden death. The benefits of sacubitril/valsartan over enalapril were consistent in patients with and without anemia for all outcomes examined.

The most novel finding in the present study was the attenuated decrease in hemoglobin over time in the sacubitril/valsartan group, compared with the enalapril group. As a result, the incidence of new anemia was decreased by 30% in the sacubitril/valsartan group. There are several potential explanations for this observation. Because anemia is associated with a worse clinical status, any treatment that slows the progression of heart failure might decrease the risk of developing anemia in a nonspecific way. However, this is not the case with ACE inhibitors and, as mentioned earlier, enalapril has even been shown to increase the incidence of anemia.[8] Similarly, carvedilol increased the risk of developing anemia, compared with metoprolol, in COMET (Carvedilol Or Metoprolol European Trial) despite reducing mortality compared with metoprolol.[15]

Another possibility is the difference in background RAS blocker in the 2 treatment arms in PARADIGM-HF (ie, enalapril vs valsartan). Theoretically, ACE inhibitors might suppress erythropoiesis to a greater extent than ARBs because they increase levels of N-acetyl-seryl-aspartyl-lysyl-proline.[16,17] However, in a sensitivity analysis, we found that the rate of decrease in hemoglobin after randomization was slower in the sacubitril/valsartan group, compared with the valsartan group, in PARAGON-HF, suggesting that neprilysin inhibition, rather than the comparator RAS blocker, explains the difference in hemoglobin; and previously, valsartan has been shown to decrease hemoglobin in patients with HFrEF.[7] To explore other potential explanations we examined indices of iron metabolism in the RECOVER-LV trial. After 6 months, sacubitril/valsartan decreased serum iron compared with valsartan alone, and there was a strong trend toward a decrease in ferritin as well. Hepcidin levels were also decreased by sacubitril/valsartan, with these findings, collectively, suggestive of increased iron utilization, potentially reflecting erythropoiesis induced by neprilysin inhibition.[18,19] As mentioned earlier, neprilysin inhibition might have this effect by increasing substance P and reducing SP(1-4).[9,10] Some support for this possibility is provided by 2 clinical studies. In patients with heart failure, lower circulating neprilysin activity has been reported to be associated with a higher plasma concentration of substance P.[20] In another study of 73 patients with HFrEF who were switched from an ACE inhibitor or ARB to sacubitril/valsartan, serum neprilysin activity decreased and substance P increased (along with other substrates for neprilysin).[21] A further possibility is that neprilysin inhibition, shown in preclinical and human studies to have anti-inflammatory properties,[22-24] may decrease levels of the acute phase protein hepcidin facilitating greater systemic iron absorption and use. The findings of this report provide a direction for more studies to examine the extent that neprilysin inhibition influences iron metabolism. Finally, although it is unclear to what extent sacubitril/valsartan acts as a diuretic, potential decreases in plasma volume with neprilysin inhibition and consequent hemoconcentration may have contributed to the attenuation in the decrease in hemoglobin observed in this study.

Two recent therapeutic developments have reawakened interest in the prevention or reversal of anemia in patients with heart failure. First, intravenous iron has been shown to improve symptoms, quality of life, and exercise tolerance in patients with HFrEF and decrease the risk of readmission in patients hospitalized with decompensated heart failure.[25] Although these benefits have been seen in iron-deficient patients with and without anemia, intravenous iron increases hemoglobin. Similarly, sodium-glucose cotransporter 2 (SGLT2) inhibitors increase hematocrit and hemoglobin by mechanisms that have yet to be fully elucidated, but include hemoconcentration and an increase in erythropoietin.[26,27] However, mediation analysis has suggested the increase in hematocrit and hemoglobin contributes significantly to the benefit of SGLT2 inhibition, including the decrease in heart failure hospitalization.[28,29] Of course, SGLT2 inhibitors almost certainly have other mechanisms of action.

STUDY LIMITATIONS. This study was not a prospectively planned analysis. The patients included were carefully selected for a clinical trial that had an active run-in period, and >75% of patients enrolled in PARADIGM-HF were male. We did not measure substance P, which might have supported the proposed mechanism for the effect of neprilysin inhibition on hemoglobin.

CONCLUSIONS

Compared with enalapril, sacubitril/valsartan decreased mortality and hospitalization in HFrEF patients with and without anemia. Hemoglobin decreased less with sacubitril/valsartan and the incidence of new anemia was lower in the sacubitril/valsartan group compared with the enalapril group.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Anemia is common in patients with heart failure and is associated with poor clinical outcomes. ACE inhibitors and ARBs decrease hemoglobin and may cause anemia. Experimental findings suggest that neprilysin inhibition promotes hematopoiesis. We found that concomitant neprilysin inhibition attenuated the hemoglobin-reducing effect of RAS blockers.

TRANSLATIONAL OUTLOOK: Further studies examining the effect of neprilysin inhibition on mediators of erythropoiesis such as substance P would develop a greater understanding of the mechanisms by which sacubitril/valsartan decreases the development of anemia compared with RAS blockers.

REFERENCES

1. Anand IS. Pathophysiology of anemia in heart failure. *Heart Fail Clin*. 2010;6:279–288.

2. Xia H, Shen H, Cha W, Lu Q. The prognostic significance of anemia in patients with heart failure: a meta-analysis of studies from the last decade. *Front Cardiovasc Med*. 2021;8:632318.

3. Beladan C, Botezatu S. Anemia and management of heart failure patients. *Heart Fail Clin*. 2021;17:195–206.

4. Swedberg K, Young JB, Anand IS, et al. Treatment of anemia with darbepoetin alfa in systolic heart failure. *N Engl J Med*. 2013;368:1210–1219.

5. Cheungpasitporn W, Thongprayoon C, Chiasakul T, Korpaisarn S, Erickson SB. Renin-angiotensin system inhibitors linked to anemia: a systematic review and meta-analysis. *QJM*. 2015;108:879–884.

6. Pratt MC, Lewis-Barned NJ, Walker RJ, Bailey RR, Shand BI, Livesey J. Effect of angiotensin converting enzyme inhibitors on erythropoietin concentrations in healthy volunteers. *Br J Clin Pharmacol*. 1992;34:363–365.

7. Anand IS, Kuskowski MA, Rector TS, et al. Anemia and change in hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: results from Val-HeFT. *Circulation*. 2005;112:1121–1127.

8. Ishani A, Weinhandl E, Zhao Z, et al. Angiotensin-converting enzyme inhibitor as a risk factor for the development of anemia, and the impact of incident anemia on mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol*. 2005;45:391–399.

9. Joshi DD, Dang A, Yadav P, et al. Negative feedback on the effects of stem cell factor on hematopoiesis is partly mediated through neutral endopeptidase activity on substance P: a combined functional and proteomic study. *Blood*. 2001;98:2697–2706.

10. Stanović Janda S, Boranić M, Sucić M, et al. Effects of a membrane-metallopeptidase blocking agent thiorphan in long-term cultures of human bone marrow. *Haematologia (Budap)*. 2000;30:289–302.

11. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004.

12. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. World Health Organization. Accessed September 21, 2021. https://apps.who.int/iris/bitstream/handle/10665/85839/WHO_NMH_NHD_MNM_11.1_eng.pdf

13. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381:1609–1620.

14. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008.

15. Komajda M, Anker SD, Charlesworth A, et al. The impact of new onset anaemia on morbidity and mortality in chronic heart failure: results from COMET. *Eur Heart J*. 2006;27:1440–1446.

16. van der Meer P, Lipsic E, Westenbrink BD, et al. Levels of hematopoiesis inhibitor N-acetyl-seryl-aspartyl-lysyl-proline partially explain the occurrence of anemia in heart failure. *Circulation*. 2005;112:1743–1747.

17. Azizi M, Junot C, Ezan E, Ménard J. Angiotensin I-converting enzyme and metabolism of the haematological peptide N-acetyl-seryl-aspartyl-lysyl-proline. *Clin Exp Pharmacol Physiol*. 2001;28:1066–1069.

18. Docherty KF, Campbell RT, Brooksbank KJM, et al. Effect of neprilysin inhibition on left ventricular remodeling in patients with asymptomatic left ventricular systolic dysfunction late after myocardial infarction. *Circulation*. 2021;144:199–209.

19. Anand IS, Gupta P. Anemia and iron deficiency in heart failure: current concepts and emerging therapies. *Circulation*. 2018;138:80–98.

20. Vodovar N, Seronde MF, Laribi S, et al. Elevated plasma B-type natriuretic peptide concentrations directly inhibit circulating neprilysin activity in heart failure. *J Am Coll Cardiol HF*. 2015;3:629–636.

21. Nougué H, Pezel T, Picard F, et al. Effects of sacubitril/valsartan on neprilysin targets and the metabolism of natriuretic peptides in chronic heart failure: a mechanistic clinical study. *Eur J Heart Fail*. 2000;21:598–605.

22. Bolla GB, Fedele A, Faggiano A, Sala C, Santangelo G, Carugo S. Effects of sacubitril/valsartan on biomarkers of fibrosis and inflammation in patients with heart failure with reduced ejection fraction. *BMC Cardiovasc Disord*. 2022;22:217.

23. Yu C, Li D, Li Z, Yu D, Zhai G. Effect of sacubitril/valsartan on inflammation and oxidative stress in doxorubicin-induced heart failure model in rabbits. *Acta Pharmaceutica*. 2021;71:473–484.

24. Goncalves AV, Pereira-da-Silva T, Galrinho A, et al. C-reactive protein reduction with sacubitril-valsartan treatment in heart failure patients. *Am J Cardiovasc Dis*. 2020;10:174–181.

25. Ponikowski P, Kirwan B-A, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet*. 2020;396:1895–1904.

26. Docherty KF, Curtain JP, Anand IS, et al. Effect of dapagliflozin on anaemia in DAPA-HF. *Eur J Heart Fail*. 2021;23:617–628.

27. Oshima M, Neuen BL, Jardine MJ, 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.

28. Fitchett D, Inzucchi SE, Zinman B, 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.

29. Inzucchi SE, Zinman B, Fitchett D, et al. How does empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA-REG OUTCOME trial. *Diabetes Care*. 2018;41:356–363.

KEY WORDS anemia, heart failure, PARADIGM-HF, sacubitril/valsartan

APPENDIX For supplemental tables and figures, please see the online version of this paper.