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ORIGINAL RESEARCH

Interleukin-6 in Heart Failure With Reduced Ejection Fraction and the Effect of Dapagliflozin

An Exploratory Analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure Trial

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ABSTRACT

BACKGROUND Inflammation may play an important pathophysiological role in the development and progression of heart failure (HF). Interleukin (IL)-6 is a circulating cytokine and is the main regulator of the release of C-reactive protein (CRP).

OBJECTIVES The authors examined the association between IL-6 and high-sensitivity (hs)-CRP and outcomes in patients with HFrEF in the DAPA-HF trial and their relationship with the effect of dapagliflozin.

METHODS Inclusion criteria included: 1) NYHA functional class II-IV; 2) left ventricular ejection fraction ≤40%; 3) elevated N-terminal pro-B-type natriuretic peptide; and 4) estimated glomerular filtration rate ≥30 mL/min/1.73 m^2. The primary outcome was a composite of a worsening HF event or cardiovascular death. IL-6 and hs-CRP were measured at baseline and 12 months (Roche Diagnostics). The associations between IL-6 and hs-CRP and outcomes were adjusted for known prognostic variables, including NT-proBNP.

RESULTS Among 2,940 patients, median IL-6 and hs-CRP at baseline were 6.01 pg/mL (Q1-Q3: 4.18-9.28 pg/mL) and 2.05 mg/L (Q1-Q3: 0.83-4.9 mg/L), respectively. Baseline IL-6 tertiles (T) were: T1 ≤4.72 pg/mL; T2 4.73-7.89 pg/mL; and T3 ≥7.90 pg/mL. The adjusted risks of the primary outcome relative to T1 were as follows: T2 = HR 1.34 (95% CI: 1.04-1.73) and T3 = HR 1.80 (95% CI: 1.41-2.31). A rise in IL-6 between baseline and 12 months was associated with worse outcomes. The beneficial effect of dapagliflozin on the primary outcome was consistent regardless of IL-6 concentration (continuous interaction $P = 0.57$), with similar results for hs-CRP. Dapagliflozin did not reduce IL-6 or hs-CRP at 12 months.

CONCLUSIONS In DAPA-HF, elevated IL-6 and hs-CRP levels were each associated with the risk of worsening HF or cardiovascular death. Dapagliflozin reduced the risk of adverse outcomes regardless of baseline IL-6 or hs-CRP. (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure [DAPA-HF]; NCT03036124) (JACC Heart Fail. 2025;■:■–■) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ABBREVIATIONS AND ACRONYMS

CKD = chronic kidney disease

CRP = C-reactive protein

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

hs-CRP = high-sensitivity C-reactive protein

hs-TnT = high-sensitivity troponin T

IL = interleukin

LVEF = left ventricular ejection fraction

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

SGLT2i = sodium-glucose cotransporter 2 inhibitor

TNF = tumor necrosis factor

Interleukin (IL)-6 is a circulating cytokine and is the main regulator of the release of C-reactive protein (CRP) along with other acute-phase proteins.[1] In patients with atherosclerosis, inhibition of IL-1β (ie, the upstream mediator of IL-6) reduced fatal and nonfatal cardiovascular events, including heart failure (HF) hospitalization.[2,3] Recently, a large outcome trial with anti-IL-6 therapy was initiated in patients with heart failure with preserved ejection fraction (HFpEF) because inflammation is believed to play an important pathophysiological role in the development and progression of this type of HF.[4] Similar trials are under way in patients with chronic kidney disease (CKD) and atherosclerotic cardiovascular disease, and after acute myocardial infarction (eg, ARTEMIS [Effects of ziltivekimab versus placebo on cardiovascular outcomes in patients with acute myocardial infarction; NCT06118281]).[5]

The role of inflammation in heart failure with reduced ejection fraction (HFrEF) is less certain. Previous attempts to suppress proinflammatory signaling had neutral or negative effects (eg, targeting tumor necrosis factor [TNF]-α).[6,7] However, the IL-6 pathway may be more pathophysiologically relevant, as is thought to be the case in HFpEF. In a cohort of patients recently hospitalized for HFpEF, IL-6, and CRP concentrations were associated with the risk of mortality and rehospitalization for HF. whereas TNF-α was associated with the risk of rehospitalization only.[8] But whether IL-6 is a predictor of outcomes in chronic ambulatory HFrEF after adjustment for other prognostic markers, including NT-proBNP and hs-cTn, and potentially a therapeutic target, is unknown. Therefore, in this post hoc analysis of the DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure; NCT03036124) trial, we examined the associations between IL-6 and CRP concentrations and outcomes in patients with HFrEF.[9,10] Given the postulated role of IL-6 signaling in the progression of kidney disease and the development of iron deficiency, we also examined those outcomes.[11-14] Finally, because one of the potential mechanisms of action of sodium-glucose cotransporter 2 inhibitors (SGLT2is) is to reduce inflammation, we also evaluated the effect of dapagliflozin, compared with placebo, on IL-6 and CRP concentrations (and the effectiveness of dapagliflozin according to baseline IL-6 and CRP levels).

METHODS

DAPA-HF was a prospective, randomized, double-blind, placebo-controlled, event-driven trial, which examined the efficacy and safety of dapagliflozin 10 mg once daily, compared with placebo, in patients with HFrEF. The design, baseline characteristics, and primary results are published.[9,10] Ethics committees for the 410 participating institutions in 20 countries approved the protocol, including the biomarker substudy, and all patients gave written consent. Participation in the biomarker study was optional and required a separate consent form. Participation was offered to all enrolled patients in countries where local restrictions approved prospective biomarker sample collection.

STUDY PATIENTS AND TREATMENT. Patients in NYHA functional class II-IV, with a left ventricular ejection fraction (LVEF) ≤40%, and elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration, were eligible if receiving standard pharmacological and device therapy. The key exclusion criteria included type 1 diabetes mellitus, symptomatic

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hypotension or systolic blood pressure <95 mm Hg, and an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2. Patients were excluded if they had evidence of current acute decompensated HF or were hospitalized because of decompensated HF <4 weeks before enrollment.

MEASUREMENT OF IL-6 AND hs-CRP. IL-6 and high-sensitivity (hs)-CRP were measured at baseline and 12 months after randomization. Venous blood samples were collected and stored at −20 °C or colder until shipped on dry ice to a central repository, where they were stored at −80 °C or colder until thawed for analysis. Serum IL-6 (cobas e411, Roche Diagnostics) and hs-CRP (cobas c311, Roche Diagnostics) were measured at the University of Glasgow on automated platforms using the manufacturer's calibrators and quality control material. The IL-6 assay has been standardized against the NIBSC (National Institute for Biological Standards and Control) first international standard 89/548. Low- and high-quality controls ran with a coefficient of variation of 7.3% and 6.8%, respectively, for IL-6 and 5.0% and 4.9%, respectively, for hs-CRP.

OUTCOMES. The primary trial outcome was the composite of worsening HF event (HF hospitalization or urgent visit for HF requiring intravenous therapy) or cardiovascular death, whichever occurred first. In this study, we investigated the association between baseline IL-6 and hs-CRP levels and the risk of the primary outcome, its components, all-cause mortality, myocardial infarction, and stroke. All cardiovascular endpoints and deaths were adjudicated by an independent blinded committee. The change in kidney function over time was assessed by the annualized slope of change in eGFR. We investigated the development of iron deficiency at 12 months (defined as a ferritin level <100 ng/mL or a transferrin saturation <20% with a ferritin level of 100-299 ng/mL) among those patients who were iron replete at baseline. This analysis included adjustment for randomized treatment because of the established effect of dapagliflozin on iron indices.[15]

STATISTICAL ANALYSIS. The IL-6 levels at baseline were categorized into tertiles according to the baseline distribution and additionally into 2 groups according to the assay-specific 95th percentile of the normal range (≤ or >7.0 pg/mL).[16] The hs-CRP was dichotomized at a value of ≥2 mg/L (the value commonly used to indicate the presence of systemic inflammation).[4,5] Baseline characteristics according to IL-6 tertiles and hs-CRP groups are presented as frequencies and percentages for categorical variables, means ± SD, or medians (Q1-Q3) for continuous variables. A nonparametric test for trend across groups, an extension of the Wilcoxon rank sum test, was used to examine for variation in continuous baseline characteristics across IL-6 tertiles, and Fisher exact test was used to compare race and NYHA functional class across IL-6 tertiles due to the low frequency of some values.

Incidence rates for each outcome of interest according to IL-6 and hs-CRP are presented per 100 person-years of follow-up and are presented graphically using Kaplan-Meier survival curves.

The relationships between IL-6 levels and hs-CRP levels at baseline and subsequent outcomes were analyzed separately for each biomarker using Cox proportional hazards regression models stratified by diabetes status and adjusted for a history of HF hospitalization (not included in the model for all-cause mortality). Further adjustment was performed for age, sex, heart rate, blood pressure, body mass index, ischemic cause of HF, left ventricular ejection fraction, atrial fibrillation, log-NT-proBNP, log-hs-TnT, and eGFR. The proportional hazards assumption was evaluated visually using log-minus-log plots and quantitatively using Schoenfeld residuals and was found to be valid. No imputation for missing data was performed.

The relationships between IL-6 and hs-CRP as continuous variables and outcomes were analyzed using restricted cubic splines with 4 knots at the 5th, 35th, 65th, and 95th percentiles using the median log-transformed value as the reference. The annualized slope of change in eGFR over time from baseline to day 720 of follow-up according to IL-6 tertiles was analyzed using a mixed model for repeated measurements (adjusted for baseline values, visit, randomized treatment and interaction of treatment and visit, and interaction between IL-6 tertile and time with a random intercept and slope per patient). The association between change in IL-6 from baseline to 12 months and risk of subsequent outcomes was analyzed in a landmark analysis of patients who were alive at 12-month follow-up with available IL-6 data.

The effect of dapagliflozin compared with placebo on each outcome was calculated as HR and 95% CI derived from Cox proportional hazards models adjusted for a history of hospitalization for HF (not included in models for all-cause mortality) and treatment assignment with stratification by baseline diabetes status, as prespecified in the statistical analysis plan of the trial. The effect of dapagliflozin on outcomes according to the levels of IL-6 and hs-CRP (analyzed as a continuous variable) was examined using a fractional polynomial analysis using the Stata *mfpi* command.

TABLE 1 Demographics According to Tertile of IL-6 at Baseline

	Tertile 1 (n = 987)	Tertile 2 (n = 973)	Tertile 3 (n = 980)	*P* Value
IL-6, pg/mL	3.6 (2.8-4.2)	6.0 (5.3-6.8)	11.8 (9.3-17.2)	<0.001
Randomized to dapagliflozin	488 (49.4)	512 (52.6)	488 (49.8)	0.31
Age, y	65.9 ± 11.2	67.5 ± 9.8	68.4 ± 10.0	<0.001
Male	749 (75.9)	759 (78.0)	788 (80.4)	0.02
Race				<0.001
White	696 (70.5)	773 (79.4)	824 (84.1)	
Asian	255 (25.8)	168 (17.3)	129 (13.2)	
Black	33 (3.3)	25 (2.6)	25 (2.6)	
Other	3 (0.3)	7 (0.7)	2 (0.2)	
Region				<0.001
Asia/Pacific	250 (25.3)	163 (16.8)	124 (12.7)	
Europe	517 (52.4)	569 (58.5)	576 (58.8)	
North America	147 (14.9)	161 (16.5)	183 (18.7)	
South America	73 (7.4)	80 (8.2)	97 (9.9)	
NYHA functional class				<0.001
II	774 (78.4)	669 (68.8)	598 (61.0)	
III	210 (21.3)	302 (31.0)	377 (38.5)	
IV	3 (0.3)	2 (0.2)	5 (0.5)	
Pulse, beats/min	69.3 ± 10.8	70.7 ± 10.8	72.6 ± 11.8	<0.001
Systolic blood pressure, mm Hg	122.1 ± 15.8	123.3 ± 15.6	121.5 ± 15.8	0.31
LVEF, %	31.1 ± 6.6	31.3 ± 6.9	31.1 ± 6.8	0.97
Median NT-proBNP, pg/mL	1,105.1 (721.6-1,857.7)	1,357.1 (862.8-2,429.8)	2,017.3 (1,171.2-3,946.8)	<0.001
Median hs-TnT, ng/L	16.6 (11.8-24.9)	19.9 (13.8-29.1)	24.8 (16.8-38.1)	<0.001
Median hs-CRP, mg/L	0.9 (0.5-2.0)	2.0 (0.9-3.7)	5.3 (2.3-11.4)	<0.001
eGFR, mL/min/1.73 m^2	69.1 ± 18.8	65.0 ± 18.7	61.3 ± 18.2	<0.001
eGFR, <60 mL/min/1.73 m^2	328 (33.3)	379 (39.0)	485 (49.5)	<0.001
Median bilirubin, μmol/L	10.0 (7.0-14.0)	10.0 (7.0-14.0)	10.3 (8.0-15.7)	<0.001
Median AST, IU/L	22.0 (18.0-26.0)	21.0 (17.0-26.0)	20.0 (16.0-26.0)	0.0004
Median ALT, IU/L	19.0 (14.0-25.5)	18.0 (13.0-24.0)	17.0 (13.0-23.0)	<0.001
Median alkaline phosphatase, IU/L	69.0 (58.0-83.0)	75.5 (61.0-95.0)	82.0 (68.0-106.0)	<0.001
Hemoglobin, g/L	136.7 ± 14.9	136.5 ± 15.5	133.8 ± 16.9	<0.001
Anemia[a]	232 (23.7)	242 (25.0)	318 (32.7)	<0.001
Iron deficiency[b]	314 (32.8)	422 (44.6)	492 (52.0)	<0.001
Median iron, μmol/L	15.8 (12.6-19.6)	13.9 (10.8-17.8)	11.8 (8.8-15.2)	<0.001
Median ferritin, ng/mL	181.9 (96.2-322.9)	159.8 (83.2-281.2)	151.7 (84.7-273.5)	<0.001
Median TSAT, %	28.1 (21.7-35.9)	24.3 (18.0-31.6)	20.5 (14.9-27.0)	<0.01
Median hepcidin, ng/mL	32.3 (16.1-55.8)	27.6 (12.5-51.5)	30.0 (11.3-59.1)	0.012
Baseline KCCQ-TSS	83.3 (66.7-95.8)	80.2 (62.5-92.7)	72.9 (52.1-87.5)	<0.001
Baseline body mass index, kg/m^2	27.3 ± 5.2	28.9 ± 6.0	29.2 ± 6.2	<0.001
Investigator-reported cause of HF				<0.001
Ischemic	542 (54.9)	603 (62.0)	592 (60.4)	
Nonischemic	386 (39.1)	291 (29.9)	311 (31.7)	
Unknown	59 (6.0)	79 (8.1)	77 (7.9)	
Medical history				
Prior HF hospitalization	457 (46.3)	434 (44.6)	452 (46.1)	0.94
Time from last HF hospitalization to randomization				0.28
0-3 mo	60 (13.1)	59 (13.6)	88 (19.5)	
>3-6 mo	84 (18.4)	87 (20.0)	80 (17.7)	
>6-12 mo	97 (21.2)	89 (20.5)	102 (22.6)	
>1-2 y	75 (16.4)	67 (15.4)	62 (13.7)	
>2-5 y	81 (17.7)	79 (18.2)	65 (14.4)	
>5 y	60 (13.1)	53 (12.2)	55 (12.2)	
Atrial fibrillation	325 (32.9)	396 (40.7)	465 (47.4)	<0.001
Type 2 diabetes	362 (36.7)	419 (43.1)	452 (46.1)	<0.001
Gout	75 (7.6)	104 (10.7)	144 (14.7)	<0.001
Cancer	45 (4.6)	49 (5.0)	49 (5.0)	0.65

Continued on the next page

TABLE 1 Continued

	Tertile 1 (n = 987)	Tertile 2 (n = 973)	Tertile 3 (n = 980)	*P* Value
Device therapy				
ICD or CRT-D	295 (29.9)	315 (32.4)	311 (31.7)	0.38
Cardiac resynchronization therapy[c]	80 (8.1)	84 (8.6)	86 (8.8)	0.59
HF medication				
Diuretic	788 (79.8)	820 (84.3)	875 (89.3)	0.001
ACEI	561 (56.8)	545 (56.0)	560 (57.1)	0.89
ARB	274 (27.8)	253 (26.0)	233 (23.8)	0.04
Sacubitril/valsartan	117 (11.9)	117 (12.0)	121 (12.3)	0.74
Beta-blocker	944 (95.6)	937 (96.3)	938 (95.7)	0.94
MRA	729 (73.9)	670 (68.9)	690 (70.4)	0.09
Digoxin	126 (12.8)	144 (14.8)	185 (18.9)	0.0002
Glucocorticoid	19 (1.9)	16 (1.6)	18 (1.8)	0.89

Values are median (Q1-Q3), n (%), or mean ± SD, unless otherwise indicated. [a]Anemia defined as baseline hemoglobin <130 g/L and <120 g/L for men and women, respectively. [b]Iron deficiency defined as a serum ferritin <100 ng/mL or 100-299 ng/mL if transferrin saturation <20%. [c]Cardiac resynchronization therapy with or without a defibrillator.

ACEI = angiotensin-converting enzyme inhibitor; ALT = alanine transaminase; ARB = angiotensin receptor blocker; AST = aspartate transaminase; CRT-D = cardiac resynchronization therapy defibrillator; eGFR = estimated glomerular filtration rate; HF = heart failure; hs-CRP = high-sensitivity C-reactive protein; hs-TnT = high-sensitivity troponin T; ICD = implantable cardioverter-defibrillator; IL = interleukin; KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire-Total Symptom Score; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; TSAT = transferrin saturation.

The predictive value of IL-6 and hs-CRP and their additional predictive value to the PREDICT-HF risk model were examined using the area under the curve (AUC) from receiver-operating characteristic curves following logistic regression models using log-transformed IL-6 and hs-CRP. The additional predictive value was expressed using a continuous net reclassification index and integrated discrimination improvement metric with 95% CIs (1,000× bootstrapping). Missing data for variables in the PREDICT-HF model that were not measured in DAPA-HF were imputed with the median value from the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) derivation cohort as described earlier.[17]

The treatment effect of dapagliflozin on the changes in IL-6 and hs-CRP from baseline at 1 year was estimated using a linear regression model using log-transformed values including baseline value, and is presented as a ratio of the ratio of geometric means.

All analyses were performed using Stata version 17 (College Station) A value of $P < 0.05$ was considered statistically significant.

RESULTS

Of the 4,744 patients randomized in DAPA-HF, 2,940 (62%) had IL-6 and hs-CRP measured at baseline (Supplemental Table 1). At 12 months, 2,219 patients had an IL-6 measurement and 2,263 had an hs-CRP measurement. Both IL-6 and hs-CRP distributions were right-skewed (Supplemental Figure 1). The median value of IL-6 was 6.01 pg/mL (Q1-Q3: 4.18-9.28 pg/mL), and 1,172 (39.9%) had a value >7.0 pg/mL, the 95th percentile of the normal range for the assay used. The tertiles and the corresponding ranges of IL-6 values were as follows: tertile 1 = ≤4.72 pg/mL; tertile 2 = 4.73-7.89 pg/mL; and tertile 3 = ≥7.90 pg/mL. The median hs-CRP was 2.05 mg/L (Q1-Q3: 0.83-4.9 mg/L), and 1,491 (50.7%) had a value ≥2 mg/L.

PATIENT CHARACTERISTICS. Baseline characteristics according to tertiles of IL-6 and hs-CRP <2 mg/L or ≥2 mg/L are displayed in **Table 1** and Supplemental Table 2, respectively. Patients with higher concentrations of IL-6 were older, were more often in worse NYHA functional class; had higher heart rate, body mass index, NT-proBNP, hs-TnT, and hs-CRP concentrations; and had lower eGFR and Kansas City Cardiomyopathy Questionnaire Total Symptom Scores (KCCQ-TSS) (ie, worse health status). Patients with higher IL-6 levels more frequently had an ischemic cause of HF; had a history of diabetes, atrial fibrillation, and gout; and were more likely to be treated with a diuretic and digoxin.

Those with higher IL-6 levels also had higher levels of bilirubin and alkaline phosphatase and were more likely to have iron deficiency and anemia.

The findings were generally similar for those with hs-CRP ≥2 mg/L vs those with levels below this cutoff.

CORRELATIONS. Baseline log-transformed IL-6 and log-transformed hs-CRP were strongly correlated: Pearson's $r = 0.59$; $P < 0.001$ (Supplemental Figure 2).

TABLE 2 Risk of Outcomes According to Tertile of IL-6 at Baseline

	n	Crude Rate per 100-Persons/Year	Unadjusted HR (95% CI)	*P* Value	Adjusted[a] HR (95% CI)	*P* Value
CV death or worsening HF event[b]						
IL-6 tertile						
T1: ≤4.72	99	6.8 (5.6-8.3)	1.00 (Ref.)		1.00 (Ref.)	
T2: 4.73-7.89	162	11.6 (9.9-13.5)	1.67 (1.30-2.14)	0.0001	1.34 (1.04-1.73)	0.025
T3: ≥7.90	273	21.4 (19.0-24.1)	3.04 (2.41-3.83)	<0.001	1.80 (1.41-2.31)	<0.001
IL-6 per 1 U increase (log)			1.68 (1.53-1.84)	<0.001	1.32 (1.18-1.48)	<0.001
CV death						
IL-6 tertile						
T1: ≤4.72	56	3.8 (2.9-4.9)	1.00 (Ref.)		1.00 (Ref.)	
T2: 4.73-7.89	83	5.6 (4.5-7.0)	1.46 (1.04-2.05)	0.029	1.20 (0.85-1.69)	0.31
T3: ≥7.90	157	11.3 (9.6-13.2)	2.88 (2.12-3.91)	<0.001	1.67 (1.20-2.33)	0.002
IL-6 per 1 U increase (log)			1.69 (1.50-1.91)	<0.001	1.29 (1.11-1.51)	0.001
Worsening HF event[b]						
IL-6 tertile						
T1: ≤4.72	50	3.5 (2.6-4.6)	1.00 (Ref.)		1.00 (Ref.)	
T2: 4.73-7.89	110	7.9 (6.5-9.5)	2.25 (1.61-3.14)	<0.001	1.76 (1.25-2.47)	0.001
T3: ≥7.90	185	14.5 (12.6-16.8)	4.07 (2.98-5.57)	<0.001	2.32 (1.67-3.24)	<0.001
IL-6 per 1 U increase (log)			1.79 (1.61-1.99)	<0.001	1.42 (1.24-1.63)	<0.001
All-cause death						
IL-6 tertile						
T1: ≤4.72	68	4.6 (3.6-5.8)	1.00 (Ref.)		1.00 (Ref.)	
T2: 4.73-7.89	95	6.5 (5.3-7.9)	1.38 (1.01-1.88)	0.044	1.16 (0.85-1.59)	0.36
T3: ≥7.90	192	13.8 (11.9-15.9)	2.91 (2.20-3.84)	<0.001	1.78 (1.32-2.40)	<0.001
IL-6 per 1 U increase (log)			1.73 (1.55-1.93)	<0.001	1.37 (1.20-1.58)	<0.001
CV death and total number of hospitalizations for HF						
IL-6 tertile						
T1: ≤4.72	142	8.8 (7.5-10.4)	1.00 (Ref.)		1.00 (Ref.)	
T2: 4.73-7.89	248	16.7 (14.8-18.9)	1.87 (1.52-2.30)[c]	<0.001	1.50 (1.21-1.84)[c]	0.0002
T3: ≥7.90	410	32.9 (29.8-36.2)	3.64 (3.00-4.40)[c]	<0.001	2.07 (1.68-2.54)[c]	<0.001
Myocardial infarction (fatal or not fatal)						
IL-6 tertile						
T1: ≤4.72	15	1.0 (0.6-1.7)	1.00 (Ref.)		1.00 (Ref.)	
T2: 4.73-7.89	21	1.5 (0.9-2.2)	1.40 (0.72-2.71)	0.32	1.24 (0.63-2.44)	0.53
T3: ≥7.90	22	1.6 (1.0-2.4)	1.53 (0.79-2.95)	0.21	1.26 (0.62-2.57)	0.52
IL-6 per 1 U increase (log)			1.28 (0.91-1.80)	0.16	1.17 (0.79-1.72)	0.43
Stroke (fatal or nonfatal)						
IL-6 tertile						
T1: ≤4.72	11	0.7 (0.4-1.3)	1.00 (Ref.)		1.00 (Ref.)	
T2: 4.73-7.89	20	1.4 (0.9-2.1)	1.86 (0.89-3.89)	0.044	1.62 (0.77-3.43)	0.20
T3: ≥7.90	13	0.9 (0.5-1.6)	1.22 (0.55-2.74)	0.62	0.89 (0.38-2.10)	0.79
IL-6 per 1 U increase (log)			0.99 (0.64-1.54)	0.96	0.80 (0.48-1.31)	0.37

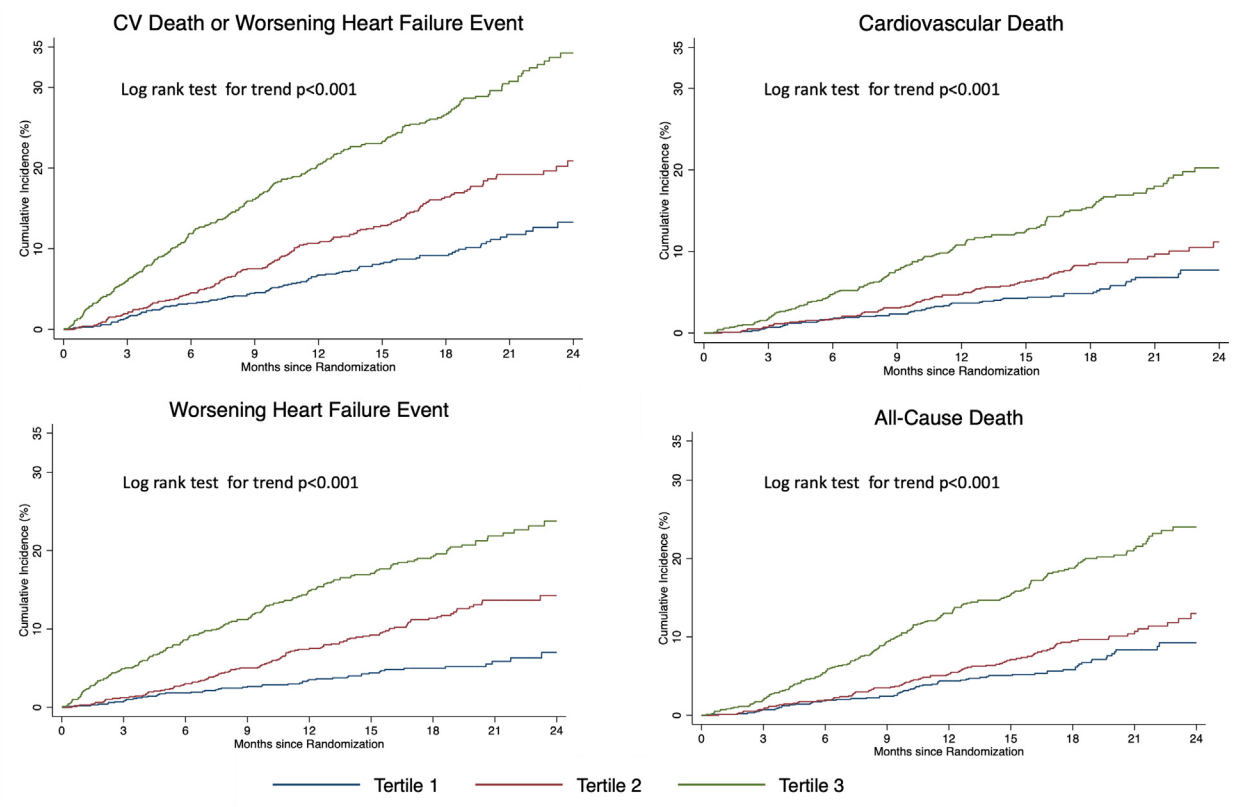
[a]Adjusted for the following baseline variables: age, sex, systolic blood pressure, heart rate, ejection fraction, previous HF hospitalization, diabetes status, atrial fibrillation, ischemic etiology, eGFR, randomized treatment (dapagliflozin), log hs-TnT, and log NT-proBNP. [b]Worsening HF event includes unplanned HF hospitalization or urgent visit for worsening HF requiring intravenous diuretic therapy. [c]Rate ratio estimated from a semiparametric proportional-rates model.

PY = person years; Ref. = Reference; T = tertile; other abbreviations as in Table 1.

Each log unit increase in IL-6 was associated with a 1.08 log unit increase in hs-CRP. Log-transformed IL-6 was more strongly correlated with NT-proBNP and hs-TnT (both log-transformed) and eGFR than was hs-CRP with these biomarkers (Supplemental Figure 3).

OUTCOMES ACCORDING TO BASELINE IL-6 LEVEL. The cumulative incidence of the primary composite outcome, its components, and all-cause mortality, according to tertiles of IL-6, are shown in Table 2 and Figure 1. The rate of events increased across tertiles of IL-6. The risk of the composite outcome and a worsening HF event was higher across tertiles 2 and 3 relative to tertile 1. The risk of death (cardiovascular and all-cause) was higher across all tertiles in unadjusted models; however, in the adjusted

FIGURE 1 Cumulative Incidence of Outcomes of Interest According to Tertile of IL-6 at Baseline



Kaplan-Meier estimates of the cumulative incidence of outcomes of interest according to tertile of baseline IL-6. CV = cardiovascular; IL = interleukin.

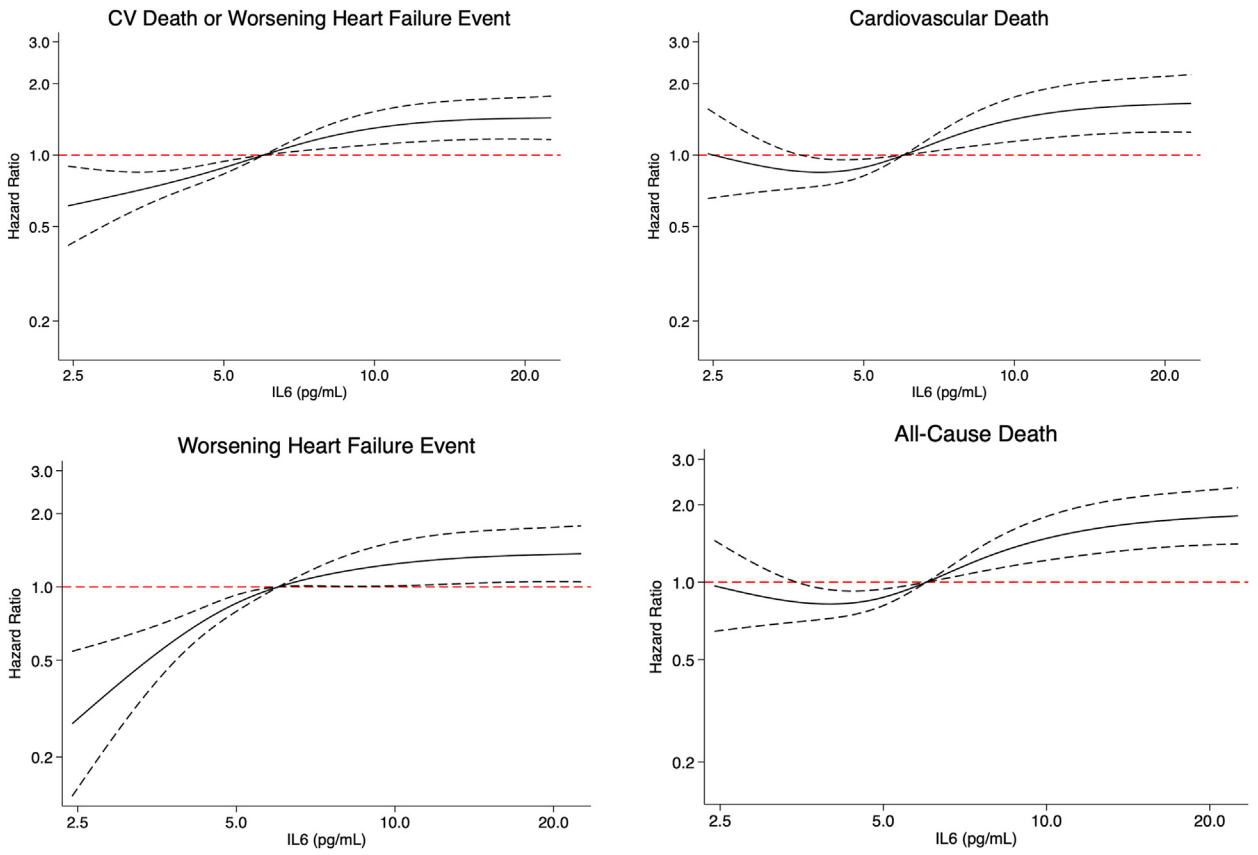
model the risk was higher in tertile 3, but not tertile 2, relative to tertile 1. The risk of myocardial infarction or stroke did not differ significantly according to baseline IL-6 levels. The associations between IL-6 analyzed as a continuous variable and outcomes are displayed in **Table 2** and **Figure 2**. Each log unit increase in IL-6 was associated with an approximately 29% to 42% higher adjusted risk of the outcomes of interest. Similar results were seen when IL-6 was analyzed by concentrations ≤ or >7.0 pg/mL (Supplemental Table 3).

OUTCOMES ACCORDING TO BASELINE hs-CRP LEVEL. The cumulative incidence of the outcomes of interest according to baseline hs-CRP (<2 mg/L or ≥2 mg/L) are shown in Supplemental Figure 4 and Supplemental Table 4. When using the cutoff value of ≥2 mg/L, the risks of the primary outcome, its components, and all-cause mortality were higher in patients with elevated hs-CRP levels in both unadjusted and adjusted analyses. The association between hs-CRP analyzed as a continuous variable and outcomes are displayed in Supplemental Figure 5 and Supplemental Table 4.

CHANGE IN KIDNEY FUNCTION ACCORDING TO BASELINE IL-6. The change in kidney function over time according to IL-6 tertiles is displayed in Supplemental Figure 6. The annual slope of change in tertile 1 was −2.2 mL/min/1.73 m^2 per year (95% CI: −2.6 to −1.7 mL/min/1.73 m^2 per year), in tertile 2 was −2.4 mL/min/1.73 m^2 per year (95% CI: −2.8 to −1.9 mL/min/1.73 m^2 per year), and tertile 3 was −3.0 mL/min/1.73 m^2 per year (95% CI: −3.5 to −2.6 mL/min/1.73 m^2 per year); in tertile 2 vs tertile 1 ($P = 0.51$), in tertile 3 vs tertile 1 ($P = 0.011$), and joint test for interaction ($P = 0.032$).

DEVELOPMENT OF IRON DEFICIENCY DURING FOLLOW-UP ACCORDING TO BASELINE IL-6. Of the 1,622 patients who were iron replete at baseline and had available IL-6 concentrations, iron status was measurable in 1,276 (79%) at 12 months. Of those, new iron deficiency developed in 105 of the 528 (19.9%) in the lowest IL-6 tertile at baseline and in 197 of the 748

FIGURE 2 Association Between Baseline IL-6 Level and Risk of Primary Composite Outcome (Worsening HF or CV Death), Worsening HF, CV Death, and All-Cause Death



The models were adjusted for age, sex, systolic blood pressure, heart rate, ejection fraction, previous HF hospitalization, atrial fibrillation, ischemic etiology, eGFR, log hs-TnT, and log NT-proBNP randomized treatment (dapagliflozin), and stratified by diabetes status. The reference is the median log value of IL-6. eGFR = estimated glomerular filtration rate; HF = heart failure; hs-TnT = high-sensitivity troponin T; NT-proBNP = N-terminal pro-B-type natriuretic peptide; other abbreviations as in Figure 1.

(26.3%) in IL-6 tertiles 2 and 3 (OR: 1.42 [95% CI: 1.08-1.85]; $P = 0.012$). The OR for the development of iron deficiency per log unit increase in IL-6 was OR: 26 (95% CI: 1.04-1.54); $P = 0.021$.

OUTCOMES ACCORDING TO CHANGE IN IL-6 FROM BASELINE TO 12 MONTHS. Figure 3 displays the association between the change in IL-6 from baseline at 12 months and the subsequent risk of the primary composite outcome. A doubling of IL-6 was associated with HR: 1.34 (95% CI: 1.19-1.50) and a halving of IL-6 with HR: 0.75 (95% CI: 0.67-0.84).

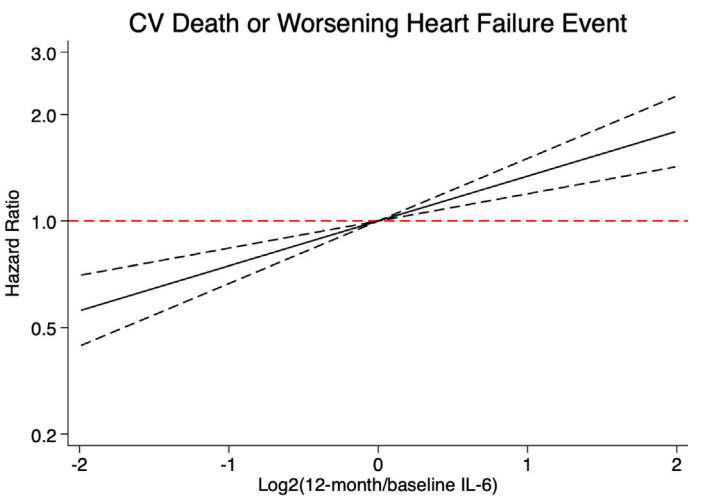
PREDICTIVE VALUE OF IL-6 AND hs-CRP. The IL-6 levels at baseline had a relatively higher predictive value than hs-CRP levels at baseline (AUC for the primary outcome: 0.653 vs 0.608; $P = 0.003$) (Supplemental Figure 7). When individually added to the PREDICT-HF risk model (AUC: 0.714) for the composite outcome, baseline levels of both biomarkers added additional prognostic information. Adding IL-6 resulted in a continuous net reclassification index of 45.7 (95% CI: 33.7-55.6) and an integrated discrimination index of 1.3 (95% CI: 0.2-2.4; P for comparison of AUC = 0.005). Adding hs-CRP resulted in a continuous net reclassification index of 55.9 (95% CI: 42.8-68.7) and an integrated discrimination index of 1.3 (95% CI: 0.1-2.6; P for comparison of AUC = 0.04). The association of continuous IL-6 with outcomes of interest was generally stronger than for hs-CRP; eg, the adjusted HR for the primary composite outcome for 1 SD increase in logIL-6 was aHR: 1.32 (95% CI: 1.18-1.48) as compared with aHR: 1.14 (95% CI 1.06-1.22) for 1 SD increase in hs-CRP.

EFFECT OF DAPAGLIFLOZIN ACCORDING TO BASELINE IL-6 AND hs-CRP. The effect of dapagliflozin compared with placebo on the primary outcome and the secondary morbidity/mortality outcomes is presented by IL-6 tertiles in **Table 3** and as a continuous variable in **Figure 4** and the **Central Illustration**. The benefits of dapagliflozin in reducing the risk of outcomes were consistent across all levels of IL-6. This benefit was also consistent across the range of hs-CRP levels at baseline when examined as a dichotomized value (<2 mg/L vs ≥2 mg/L) or as a continuous variable (Supplemental Table 5, Supplemental Figure 8)

EFFECT OF DAPAGLIFLOZIN ON IL-6 AND hs-CRP LEVELS AT 12 MONTHS. A comparison of values at baseline and 1 year showed a slight increase in IL-6 in both randomized treatment arms but no significant difference between dapagliflozin and placebo. The ratio of geometric means between follow-up and baseline was 1.03 (95% CI: 0.99-1.08) in the dapagliflozin group and 1.09 (95% CI: 1.04-1.38) in the placebo group; the ratio of these was 0.96 (95% CI: 0.91-1.01; $P = 0.14$).

The ratio of geometric mean between follow-up and baseline hs-CRP was 1.08 (95% CI: 1.02-1.16) in the dapagliflozin group and 1.14 (95% CI: 1.06-1.22) in the placebo group; the ratio of these was 0.98 (95% CI: 0.90-1.07; $P = 0.73$).

FIGURE 3 Change in IL-6 From Baseline to 12 Months and Risk of Subsequent Outcomes



This figure displays the subsequent risk of the primary composite outcome according to the change in IL-6 concentration from baseline to 12 months. HR for the primary outcome according to the log2-transformed ratio of 12 months to baseline IL-6 were modeled using a Cox model with adjustment for baseline value. The referent point is patients with no change in IL-6. Dotted lines represent 95% CIs of the HR estimates. A value of 1.0 on the X-axis represents a doubling in IL-6 and a value of 0.5 a halving of IL-6 from baseline to 12 months. Abbreviations as in **Figure 1**.

DISCUSSION. In this post hoc exploratory analysis of DAPA-HF, we found that inflammation, as evidenced by elevated IL-6 and hs-CRP concentrations, was common in patients with chronic ambulatory HFrEF, with 40% having an IL-6 concentration above the assay-specific 95th percentile of normal (>7 pg/mL) and 51% a hs-CRP ≥2 mg/L. Direct comparisons between absolute IL-6 concentrations between trials are challenging because of interassay differences; however, the proportion of patients in DAPA-HF with a value above the assay-specific 95th percentile of normal (40%) was similar to that reported in BIOSTAT-CHF, wherein 89% of patients had HFrEF and 57% had an IL-6 level above the 95th percentile of normal.[18] Even accounting for interassay differences, IL-6 concentrations in DAPA-HF were substantially higher than in a pooled analysis of 4 trials in patients with ambulatory HFpEF (median IL-6 = 1.6 pg/mL) but comparable with levels reported in a cohort of patients recently hospitalized with HFpEF.[8,19] The proportion of patients in DAPA-HF with a hs-CRP ≥2 mg/L (51%) was similar to that in patients with HFrEF in the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trial (68%) and in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial in patients with ambulatory HFpEF (62%).[20,21] Taken together, these data suggest that a substantial proportion of patients with ambulatory HFrEF have activation of the IL-1β/IL-6 signaling pathway.

Several features suggest that patients with higher levels of IL-6 and hs-CRP had more severe HF, including higher NT-proBNP and hs-TnT concentrations, higher heart rate and lower blood pressure, a greater degree of kidney dysfunction, and lower (ie, worse) KCCQ-TSS. Interestingly, LVEF did not differ significantly across tertiles of IL-6 concentrations or by CRP < or ≥2 mg/L, which suggests that the presence of inflammation is independent of the degree of left ventricular systolic dysfunction. Concordant with the features of more severe HF, the risk of the primary composite outcome, its components, and all-cause mortality was higher with increasing IL-6 levels (**Central Illustration**). In the highest IL-6 tertile (≥7.9 pg/mL), the association with an elevated risk of adverse outcomes remained significant after adjustment for other prognostic variables, including NT-proBNP and hs-TnT, with the greatest relative risk seen with worsening HF events (42% higher per 1 U increase in log-transformed IL-6). There were no

TABLE 3 Effect of Randomized Treatment on Outcomes According to Tertile of IL-6 at Baseline

	Tertile 1 (n = 987)		Tertile 2 (n = 973)		Tertile 3 (n = 980)		
	Placebo (n = 499)	Dapagliflozin (n = 488)	Placebo (n = 461)	Dapagliflozin (n = 512)	Placebo (n = 492)	Dapagliflozin (n = 488)	*P* Value for Interaction
CV death or worsening HF[a]							
n (%)	55 (11.0)	44 (9.02)	83 (18.0)	79 (15.4)	153 (31.1)	120 (24.6)	
Rate (95% CI)	7.6 (5.8-9.9)	6.1 (4.5-8.1)	12.6 (10.1-15.6)	10.6 (8.5-13.2)	24.9 (21.2-29.2)	18.1 (15.2-21.8)	
HR (95% CI)	0.80 (0.54-1.18)		0.83 (0.61-1.13)		0.74 (0.58-0.94)		0.80
CV death							
n (%)	29 (5.8)	27 (5.5)	45 (9.8)	38 (7.4)	84 (17.1)	73 (15.0)	
Rate (95% CI)	3.8 (2.7-5.5)	3.7 (2.5-5.4)	6.5 (4.8-8.7)	4.9 (3.6-6.7)	12.2 (9.8-15.1)	10.4 (8.2-13.0)	
HR (95% CI)	0.95 (0.57-1.61)		0.73 (0.47-1.13)		0.86 (0.63-1.17)		0.76
Worsening HF event[a]							
n (%)	31 (6.2)	19 (3.9)	54 (11.7)	56 (10.9)	106 (21.5)	79 (16.2)	
Rate (95% CI)	4.3 (3.0-6.1)	2.6 (1.7-4.1)	8.2 (6.3-10.7)	7.5 (5.8-9.8)	17.2 (14.3-20.9)	12.0 (9.6-14.9)	
HR (95% CI)	0.61 (0.34-1.08)		0.91 (0.62-1.32)		0.71 (0.53-0.95)		0.39
All-cause death							
n (%)	35 (7.0)	33 (6.6)	49 (10.6)	46 (8.9)	105 (21.3)	87 (17.8)	
Rate (95% CI)	4.6 (3.3-6.5)	4.5 (3.2-6.3)	7.1 (5.3-9.3)	5.9 (4.4-7.9)	15.2 (12.6-18.4)	12.3 (10.0-15.2)	
HR (95% CI)	0.97 (0.60-1.56)		0.81 (0.54-1.22)		0.82 (0.61-1.08)		0.83
CV death and total number of HF hospitalizations							
n	79	63	132	116	229	181	
Rate (95% CI)	9.8 (7.9-12.2)	7.9 (6.1-10.1)	18.5 (15.6-21.9)	15.1 (12.6-18.1)	37.7 (33.1-42.9)	28.3 (24.5-32.7)	
RR (95% CI)[b]	0.80 (0.67-1.11)		0.81 (0.63-1.04)		0.76 (0.62-0.92)		0.88

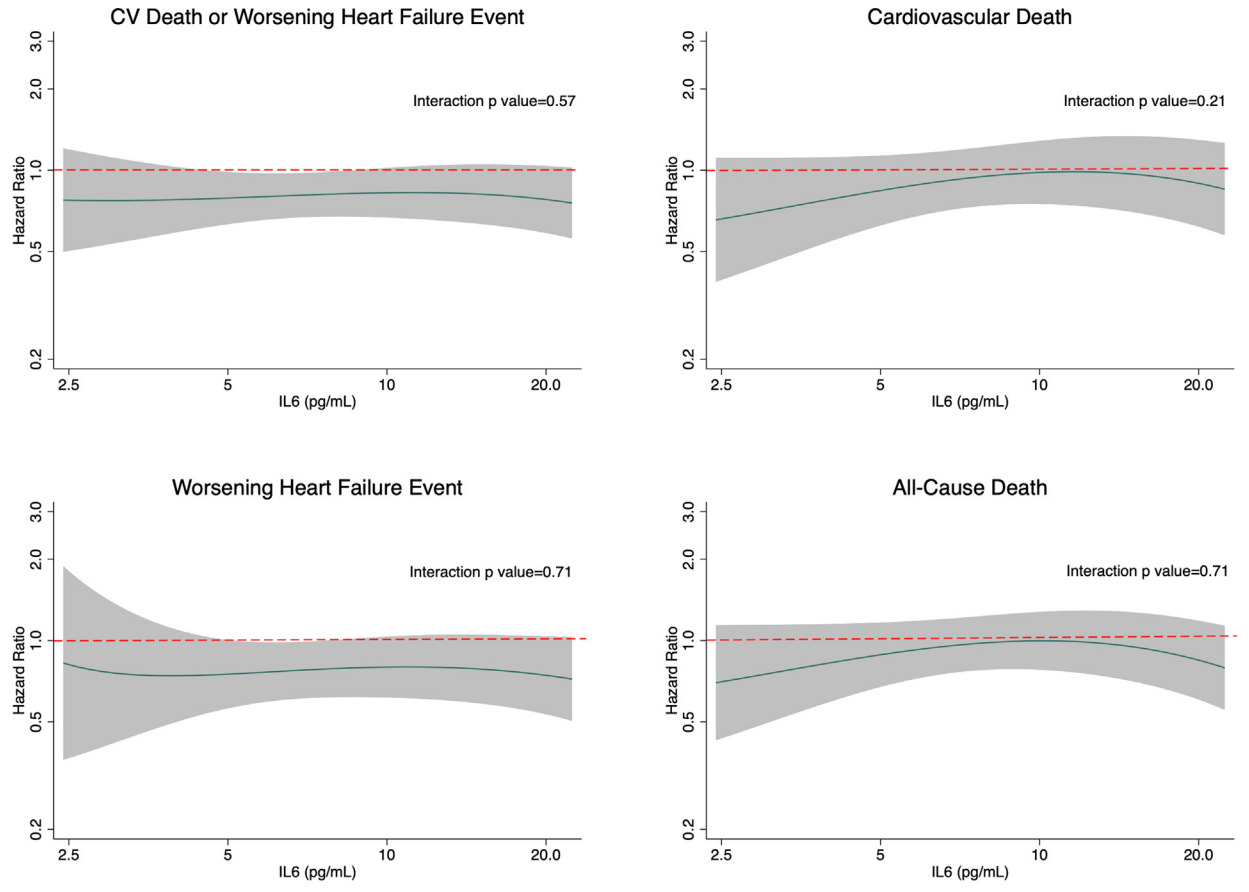
Event rates presented per 100 patient-years. For time-to-first event models, HRs and 95% CIs were estimated with the use of Cox regression models, stratified according to diabetes status, with a history of hospitalization for HF and treatment-group assignment as explanatory variables (for all-cause mortality, history of hospitalization for HF was not included in the model). For total (first and recurrent) event outcomes, rate ratios and 95% CIs were estimated from a semiparametric proportional-rates model. [a]Worsening HF event includes unplanned HF hospitalization or urgent visit for worsening HF requiring intravenous diuretic therapy. [b]Rate ratio estimated from a semiparametric proportional-rates model.

Abbreviations as in Table 1.

significant differences in the risk of atherothrombotic events across IL-6 tertiles; however, these analyses were limited by a small number of events. It remains unknown whether the observed associations between elevated IL-6 concentrations and the risk of clinical outcomes are reflective of a causal link between IL-6 activity and worsening HF, or whether IL-6 concentrations are simply a surrogate marker of HF severity. This question cannot be answered by the present analysis and would require a randomized trial of an anti-IL-6 therapy to address, or causal inference approaches such as Mendelian randomization or regression-discontinuity as examples.

As well as morbidity and mortality outcomes, we also found that baseline IL-6 concentrations had significant associations with other important outcomes in HFrEF. First, the decline in kidney function over time was greater in patients with higher baseline IL-6 concentrations. The relationship between elevated IL-6 concentrations and a decline in kidney function has previously been described in patients with CKD and diabetes, but to our knowledge, this is the first report of this finding in patients with HFrEF.[11,22] Interestingly, in patients with CKD in the CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study) trial, upstream modulation of IL-6 signaling through inhibition of IL-1β led to small but statistically significant reductions in eGFR in comparison with placebo; however, the magnitude of the difference was not believed to be of clinical significance.[23] In a Mendelian randomization study of the United Kingdom BioBank, there was no association between a genetic proxy of IL-6 signaling inhibition and kidney function measurements.[24] It therefore remains to be seen whether treatments targeted at IL-6 signaling will have a direct beneficial benefit on kidney function or whether elevated IL-6 concentrations are a surrogate biomarker for the severity of CKD, rather than a direct causal effector of worsening kidney function over time. Ziltivekimab, an IL-6 ligand monoclonal antibody, is currently being studied in patients with CKD and elevated hs-CRP levels in ZEUS (A Research Study to Look at How Ziltivekimab Works Compared to Placebo in People With Cardiovascular Disease, Chronic Kidney Disease and Inflammation; NCT05021835), and a range of prespecified kidney-specific secondary outcomes will help address these questions.

FIGURE 4 Effect of Dapagliflozin Compared With Placebo on Primary Composite Outcome, Its Components, and All-Cause Mortality According to Baseline IL-6 Concentration

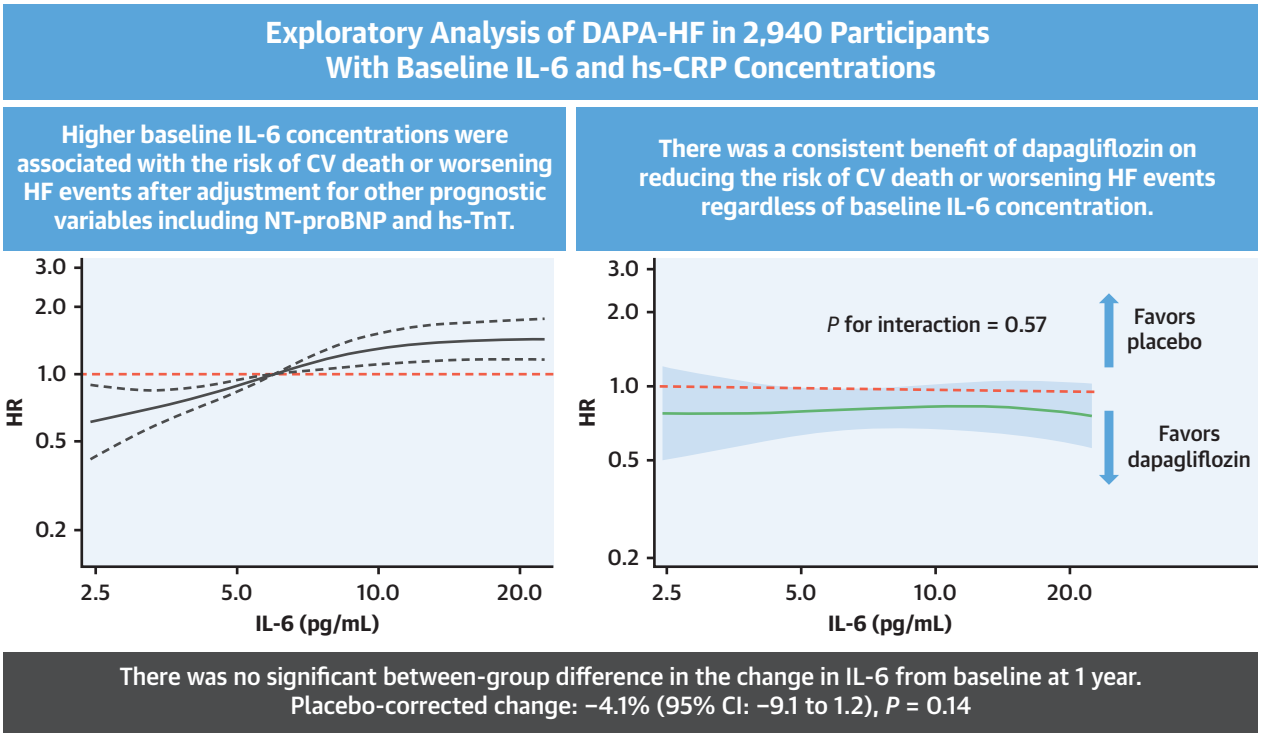


The solid line represents a continuous HR. The dashed red line represents a HR of 1 (ie, no difference between treatments). The shaded area represents the 95% CI around the HR. The HR represents the treatment effect of dapagliflozin compared with placebo for the outcome of interest. Abbreviation as in Figure 1.

Iron deficiency, with or without anemia, is a common comorbidity among patients with HF and is both an independent predictor of worse outcomes and a modifiable treatment target.[15,25] One of the suggested pathophysiological mechanisms of iron deficiency and anemia in HF is the effect of pro-inflammatory cytokines, including IL-6, on increasing hepcidin, the main regulator of ferroportin expression and iron transport, and inhibiting erythropoiesis.[26] In DAPA-HF, iron deficiency (and the biochemical hallmarks of this) and anemia were more common in patients with higher IL-6 and hs-CRP concentrations. Furthermore, iron-replete patients in the placebo group with IL-6 concentrations >4.45 pg/mL were 42% more likely to experience iron deficiency 12 months after randomization than were those with lower IL-6 levels. These data highlight the potential importance of IL-6 signaling in the development of iron deficiency and anemia in patients with HF. In patients with CKD, another condition commonly associated with iron deficiency and anemia secondary to systemic inflammation, IL-6 inhibition increased hemoglobin levels and improved circulating biomarkers of iron status.[27] This raises the question whether a similar effect would be seen in patients with HF and iron deficiency, and result in similar benefits on symptoms, functional capacity, and outcomes to those seen with parenteral iron supplementation.[25]

The relationship with elevated hs-CRP concentrations and a higher risk of outcomes was directionally similar to that seen with IL-6, but somewhat weaker. Both IL-6 and hs-CRP provided similarly additive prognostic value to the multivariable PREDICT-HF

CENTRAL ILLUSTRATION **IL-6 and hs-CRP in HFrEF and Effect of Dapagliflozin: An Exploratory Analysis of DAPA-HF**



Docherty KF, et al. JACC Heart Fail. 2025;■(■):■–■.

In DAPA-HF, elevated IL-6 and hs-CRP levels were each associated with the risk of worsening HF or CV death. Dapagliflozin reduced the risk of adverse outcomes regardless of baseline IL-6 or hs-CRP. CV = cardiovascular; DAPA-HF = Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure; HFrEF = heart failure with reduced ejection fraction; hs-CRP = high-sensitivity C-reactive protein; IL = interleukin.

model, which includes NT-proBNP. Given this, along with the widespread availability of hs-CRP in routine clinical practice and the strong positive correlation between hs-CRP and IL-6, these data highlight that the measurement of hs-CRP has a potentially useful role in identifying patients with activation of the IL-6 signaling pathway who may benefit from targeted anti-IL-6 therapies. This strategy is currently being used in the HERMES (A Research Study to Look at How Ziltivekimab Works Compared to Placebo in People With Heart Failure and Inflammation; NCT05636176) placebo-controlled trial in patients with HFmrEF or HFpEF who have elevated hs-CRP concentrations ≥2 mg/L.[4] Currently, we are unaware of any data on the effect of IL-6 inhibition in patients with HFrEF, although preclinical data suggest potential benefits.[28,29] Moreover, the current data from DAPA-HF show that a change in IL-6 over time is associated with a risk of subsequent outcomes in HFrEF; a doubling of IL-6 at 12 months from baseline was associated with a 34% higher risk and a halving of IL-6 was associated with a 25% lower risk of cardiovascular death or a worsening HF event. Taken together with the reduced risk of HF observed in CANTOS, these data suggest that further investigation into the potential benefits of anti-IL-6 targeted therapies in HFrEF is warranted.[3]

In DAPA-HF the benefit of dapagliflozin in reducing the risk of cardiovascular death and worsening HF events was independent of the degree of inflammation at baseline when measured by both IL-6 and hs-CRP. Preclinical studies have suggested that SGLT2is have an anti-inflammatory mechanism of action.[30] Data from patients with HF supporting this hypothesis are less convincing, with no effect of empagliflozin on hs-CRP in the placebo-controlled EMPIRE HF (Empagliflozin in Heart Failure Patients With Reduced Ejection Fraction) trial.[31] In DAPA-HF,

there were no significant between-group differences in the change from baseline at 12 months in either IL-6 or hs-CRP. These findings suggest that a direct anti-inflammatory effect mediated via the IL-1/IL-6 pathway is not among the predominant mechanisms of action of the benefit of SGLT2i in patients with HFrEF.

STUDY LIMITATIONS. The data presented in this paper should be interpreted in the context of several limitations. All analyses presented were performed post hoc and should be considered exploratory. Biomarker collection was not performed in all participating sites in DAPA-HF. This, along with the inclusion and exclusion criteria of the trial, means that the results may not be entirely representative of all patients with HFrEF and therefore limits the generalizability of the data presented. Moreover, the results in this analysis should not be extrapolated to patients with HFmrEF or HFpEF. Data on the prevalence of autoimmune disease or other inflammatory conditions was not routinely collected at baseline in DAPA-HF. The measuring of IL-6 once at 12 months after randomization means that we are not able to comment on the short- to medium-term effect of dapagliflozin on biomarkers of inflammation and the relationship between any changes and subsequent outcomes. The data presented are unable to infer causality between baseline IL-6 concentrations or changes in IL-6 and outcomes. The measurement of biomarkers of other pathways relating to inflammation (eg, TNF-α) was not performed in DAPA-HF, therefore we are unable to comment on the relationships between these pathways and outcomes, and the effect of dapagliflozin in patients with HFrEF. Several variables in the PREDICT-HF model were not measured in DAPA-HF (eg, percentage monocytes, absolute neutrophils, low-density lipoprotein cholesterol, and triglycerides). Therefore, external imputation was performed using the mean or median values from the model derivation cohort (PARADIGM-HF), as per the published methods of this risk model.[32] The analyses relating to the treatment effect of dapagliflozin according to baseline IL-6 and hs-CRP concentrations were not prespecified and were performed in a subset of the whole DAPA-HF population (ie, those with biomarker samples collected). These analyses should therefore be considered exploratory and hypothesis generating.

CONCLUSIONS

In DAPA-HF, biochemical evidence of enhanced IL-6 pathway signaling was common in patients with chronic ambulatory HFrEF. Elevated IL-6 and hs-CRP concentrations were associated with worse outcomes, including after adjustment for other variables associated with prognosis such as NT-proBNP and hs-TnT. The residual risk associated with activation of the IL-6 pathway may represent a potential therapeutic target in patients with HFrEF. The beneficial effect of dapagliflozin on reducing the risk of cardiovascular death or worsening HF was not modified by baseline levels of IL-6 or hs-CRP. Dapagliflozin had no significant effect on IL-6 or hs-CRP concentrations.

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Dr O'Meara has received research funds (paid to her institution) for clinical trials from American Regent, Amgen, AstraZeneca, Bayer, Cardurion, Cytokinetics, Novartis, and Pfizer; has received consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Eli Lilly, and Janssen; and has received speaker fees from AstraZeneca, Bayer, and Boehringer Ingelheim. Dr Morrow is a member of the TIMI Study Group, which receives institutional research grant support through Brigham and Women's Hospital from Abbott, Abiomed, Amgen, Anthos Therapeutics, AstraZeneca, Daiichi-Sankyo, Intarcia, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals Inc, Roche Diagnostics, Siemens Healthcare Diagnostics Inc, and Zora Biosciences; and has received consulting fees from Abbott Laboratories, ARCA Biopharma, Inflammatix, Merck and Co, Novartis, Regeneron, and Roche Diagnostics. 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Dr Sattar has consulted for Affimune, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, and Sanofi; and has received grant support from Boehringer Ingelheim. Dr Sattar was supported by a British Heart Foundation Centre of Research Excellence grant RE/18/6/34217. Dr Schou has received speaker fees from AstraZeneca, Boehringer Ingelheim, Novartis, and Novo Nordisk. Drs Hammarstedt, Sjöstrand, and Langkilde are employees of AstraZeneca. Dr Jhund has received speaker fees from AstraZeneca, Novartis, Alkem Metabolics, ProAdWise Communications, Sun Pharmaceuticals, Intas Pharmaceuticals; has received advisory board fees from AstraZeneca, Boehringer Ingelheim, Novartis; has received research funding from AstraZeneca, Boehringer Ingelheim, Analog Devices Inc; and is a director of Global Clinical Trial Partners. Dr Jhund's employer, the University of Glasgow, has been remunerated for clinical trial work from AstraZeneca, Bayer AG, Novartis, and NovoNordisk. Dr Solomon has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GlaxoSmithKline, Ionis, Lilly, Mesoblast, MyoKardia, National Institutes of Health/NHLBI, Neurotronik, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, US2.AI; and has consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GlaxoSmithKline, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellPro-Thera, Moderna, American Regent, and Sarepta. 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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In a biomarker substudy of the DAPA-HF trial in patients with HFrEF, a proinflammatory state, as indicated by elevated IL-6 and hs-CRP concentrations, was present in 40% and 51%, respectively. Elevated IL-6 and hs-CRP concentrations were associated with the risk of adverse outcomes after adjustment for other established prognostic markers. The effect of dapagliflozin on reducing the risk of worsening HF or cardiovascular death was consistent regardless of baseline IL-6 or hs-CRP concentrations.

TRANSLATIONAL OUTLOOK: Activation of the IL-6 signaling pathway may represent a potential treatment target to modify the residual risk of adverse outcomes in patients with HFrEF despite contemporary medical and device-based therapy.

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