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CLINICAL RESEARCH

IGFBP-7 and Outcomes in Heart Failure With Reduced Ejection Fraction

Findings From DAPA-HF

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ABSTRACT

BACKGROUND Insulin-like growth factor–binding protein-7 (IGFBP-7) has been proposed as a potential prognostic biomarker in heart failure (HF), but the association between elevation in IGFBP-7 and HF outcomes in ambulant patients with heart failure with reduced ejection fraction (HFrEF) is unknown.

OBJECTIVES The authors addressed this question in a post hoc analysis of the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial.

METHODS The primary outcome was a composite of cardiovascular death or a worsening HF event. The risk of adverse outcome was compared across tertiles of IGFBP-7 concentration by means of Cox proportional hazard models adjusted for N-terminal pro–B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin T (hsTnT). The efficacy of randomized treatment across IGFBP-7 tertiles was assessed. Change in IGFBP-7 at 12 months was compared with the use of geometric means.

RESULTS A total of 3,158 patients had IGFBP-7 measured at baseline, and 2,493 had a repeated measure at 12 months. Patients in the highest tertile of IGFBP-7 had evidence of more advanced HFrEF. The adjusted HR for the primary endpoint in tertile 3, compared with tertile 1, was 1.48 (95% CI: 1.17-1.88). There was no modification of the benefit of dapagliflozin by baseline IGFBP-7 (P interaction = 0.34). Dapagliflozin did not change IGFBP-7 levels over 1 year (P = 0.34).

CONCLUSIONS Higher IGFBP-7 in patients with HFrEF was associated with worse clinical profile and an increased risk of adverse clinical outcomes. IGFBP-7 provided prognostic information incremental to clinical variables, NT-proBNP, and hsTnT. The benefit of dapagliflozin was not modulated by IGFBP-7 level. (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) (J Am Coll Cardiol HF 2023;11:291-304) © 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 license (http://creativecommons.org/licenses/by/4.0/).

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ABBREVIATIONS AND ACRONYMS

CV = cardiovascular

eGFR = estimated glomerular filtration rate

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

hsTnT = high-sensitivity troponin T

IGFBP = insulin-like growth factor–binding protein

LVEF = left ventricular ejection fraction

NRI = net reclassification index

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

SBP = systolic blood pressure

Insulin-like growth factor-binding protein (IGFBP)-7 has been identified as a peptide hormone of interest in several cardiovascular and noncardiovascular conditions including atherosclerosis, atrial fibrillation, diabetes, various types of cancer, and chronic kidney disease.[1] Although IGFBP-7 is known to inhibit insulin binding to its receptor and to contribute to the development of insulin resistance, its role in controlling the growth, proliferation, and differentiation of cells may also be important in the development of disease.[2] As such, IGFBP-7 may be a biomarker for cell-cycle arrest and thus reflect tissue senescence.[3] The resultant failure of tissue renewal may lead to fibrosis. IGFBP-7 was proposed as a potential biomarker in heart failure (HF) after its identification through a proteomic search in animal models of this condition.[4] Subsequently, IGFBP-7 levels were found to be elevated in patients with heart failure with preserved ejection fraction (HFpEF) and associated with left atrial size and Doppler echocardiographic measures of diastolic dysfunction.[5-11] Moreover, in a large epidemiologic study of community-dwelling people aged 65-84 years, higher IGFBP-7 levels were associated with the development of similar cardiac changes, as well as left ventricular hypertrophy and atrial fibrillation.[12] It has been hypothesized that IGFBP-7 is a biomarker that reflects premature tissue ageing and myocardial fibrosis, which can lead to decreased chamber compliance. In contrast, very little is known about IGFBP-7 in heart failure with reduced ejection fraction (HFrEF).[5,8,13] Consequently, we investigated this biomarker in participants enrolled in the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial) (NCT03036124) (**Central Illustration**).[14-16] We examined the association between patient characteristics and IGFBP-7 levels and evaluated the prognostic performance of IGFBP-7, including when combined with N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin T (hsTnT). We also examined the effect of dapagliflozin on clinical outcomes according to the baseline IGFBP-7 level and the effect of dapagliflozin on the concentration of IGFBP-7.

METHODS

DAPA-HF was a randomized, double-blind, placebo-controlled trial of 10 mg dapagliflozin once daily in addition to standard care in patients with HFrEF.[14-16] The trial was approved by the ethics committees at each of the 410 participating institutions in 20 countries, and every participant provided written informed consent. Participation in the biomarker substudy was optional and required a separate informed consent. The trial was conducted in accordance with the principles of the Declaration of Helsinki.

STUDY PATIENTS. The core eligibility criteria for the study were age ≥18 years, New York Heart Association (NYHA) functional class II-IV symptoms, reduced left ventricular ejection fraction (LVEF) (≤40%) and elevated natriuretic peptide levels while on optimal HF therapies as determined by the investigator.[14,16] Patients were excluded if they had a diagnosis of type 1 diabetes mellitus, symptomatic hypotension/systolic blood pressure (SBP) <95 mm Hg, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, or a condition other than HF likely to limit expectancy to <2 years.[14,16]

MEASUREMENT OF IGFBP-7. Not all countries participated in the DAPA-HF biomarker substudy. In those that did, samples for biomarker analysis were taken at the randomization visit and the 1-year follow-up visit. Plasma IGFBP-7 was measured with the use of a commercially available research-use immunoassay (IGFBP-7 Duoset assay, R&D Systems). The IGFBP-7 assay has an intra-assay coefficient of variation of 4.7% and interassay coefficient of variation of 14.9%.

PRESPECIFIED TRIAL OUTCOMES. The primary outcome of DAPA-HF was the time to first occurrence

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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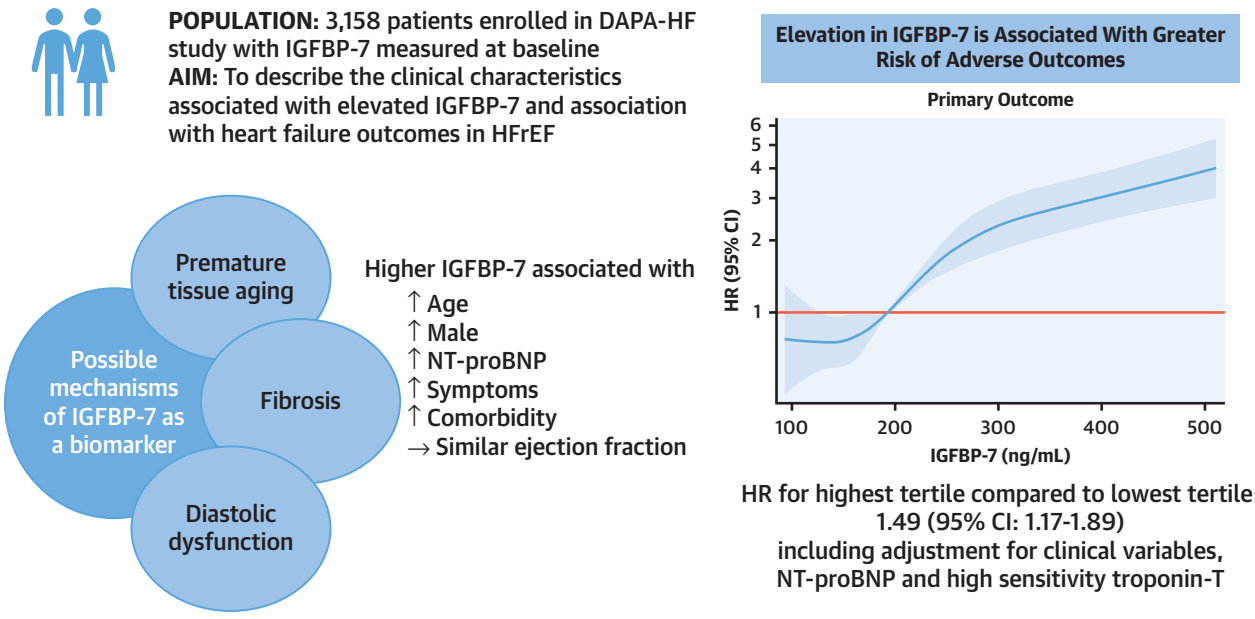
CENTRAL ILLUSTRATION **IGFBP-7 and Outcomes in HFrEF: Findings From DAPA-HF**



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Insulin-like growth factor–binding protein (IGFBP)-7 has been proposed as a potential biomarker in heart failure, with possible links to premature tissue aging, fibrosis, and diastolic dysfunction. In 3,158 patients with measured IGFBP-7 at baseline in the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial, higher IGFBP-7 was associated with older age, greater comorbidity, and more advanced heart failure. Elevated IGFBP-7 was associated with increased risk of the primary and secondary outcomes, and this increased risk remained significant in models adjusted for baseline clinical characteristics, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and high-sensitivity troponin T. HFrEF = heart failure with reduced ejection fraction.

of either worsening HF (HF hospitalization or urgent visit for HF requiring intravenous therapy) or cardiovascular (CV) death. Prespecified secondary endpoints included HF hospitalization or CV death individually, and total (first and recurrent) HF hospitalizations and CV deaths. An additional secondary endpoint was the change from baseline to 8 months in Kansas City Cardiomyopathy Questionnaire-Total Symptom Score (KCCQ-TSS), including the proportion of patients with a clinically meaningful increase or decrease (≥5 points) at 8 months, as previously described.[14,16] There was also a prespecified renal outcome, but because of the low number (n = 36) of these events among participants in the biomarker substudy, that endpoint was not further examined.

STATISTICAL ANALYSIS. Patients were categorized into groups defined by tertile of baseline IGFBP-7 measurement. Baseline characteristics were summarized as mean ± SD or median (IQR) and percentages of categoric variables. A *P* value for trend was calculated across groups of increasing IGFBP-7.

Predictors of baseline IGFBP-7 above the population median were investigated by means of stepwise linear regression. Variables with a value of $P < 0.10$ in **Table 1** were considered as potential predictors. Continuous variables were log-transformed if they had a skewed distribution, and all were standardized to a mean of 0 and SD of 1. Backward stepwise logistic regression with a *P* value <0.05 to be retained in the model was applied.

Patients were defined as having metabolic syndrome using an adaptation of the World Health Organization classification: patients with type 2 diabetes mellitus or mildly elevated hemoglobin A_{1c} (HbA_{1c}) (>42 mmol/mol) plus body mass index >30 kg/m^2 and either history of hypertension or SBP >140 mm Hg; other components such as waist-hip ratio, dyslipidemia, and microalbuminuria were not available.[17] IGFBP-7 levels were compared in patients with and without metabolic syndrome with the use of a Wilcoxon rank-sum test and box plot.

The risk of each outcome was assessed across tertiles of IGFBP-7 using Kaplan-Meier estimates and Cox proportional hazard models with the lowest

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TABLE 1 Baseline Characteristics According to Tertile of IGFBP-7 at Baseline

	1st Tertile (n = 1,073)	2nd Tertile (n = 1,046)	3rd Tertile (n = 1,039)	*P* Value (Trend)
IGFBP-7, ng/mL	147 (43-169)	193 (170-224)	272 (225-864)	
Age, y	64.9 ± 10.6	68.0 ± 10.0	68.9 ± 10.3	<0.001
Female	282 (26.3)	225 (21.5)	195 (18.8)	<0.001
BMI, kg/m^2	28.4 ± 6.0	28.4 ± 5.8	28.9 ± 6.1	0.04
Obesity (BMI ≥30 kg/m^2)	401 (37.4)	396 (37.9)	425 (40.9)	0.10
Race				0.03
White	812 (75.7)	818 (78.2)	850 (81.8)	
Black	31 (2.9)	29 (2.8)	27 (2.6)	
Asian	227 (21.2)	193 (18.5)	159 (15.3)	
Other	3 (0.3)	6 (0.6)	3 (0.3)	
Region				0.02
North America	160 (14.9)	187 (17.9)	179 (17.2)	
South America	82 (7.6)	90 (8.6)	93 (9.0)	
Europe	607 (56.6)	586 (56.0)	610 (58.7)	
Asia/Pacific	224 (20.9)	183 (17.5)	157 (15.1)	
SBP, mm Hg	122.6 ± 15.9	122.9 ± 15.5	121.8 ± 15.8	0.23
Heart rate, beats/min	69.9 ± 10.7	70.7 ± 11.1	71.7 ± 11.7	<0.001
eGFR, mL/min/1.73 m^2	73.3 ± 17.6	64.3 ± 17.6	57.3 ± 17.6	<0.001
eGFR <60 mL/min/1.73 m^2	237 (22.1)	438 (41.9)	611 (58.9)	<0.001
NT-proBNP, pg/mL	1,071.6 (694.3-1,762.7)	1,349.1 (882.0-2,323.0)	2,078.7 (1,211.6-3,940.9)	<0.001
NT-proBNP if baseline ECG AFL, pg/mL	1,420.0 (962.0-2,368.8)	1,728.1 (1,205.1-2,708.8)	2,302.7 (1,441.6-4,068.8)	<0.001
NT-proBNP if baseline ECG not AFL, pg/mL	1,011.1 (663.4-1,689.9)	1,252.3 (792.0-2,23.0)	1,973.4 (1,081.4-3,821.7)	<0.001
hsTnT, ng/L	15.5 (10.9-23.0)	20.1 (14.2-29.1)	26.0 (18.1-39.1)	<0.001
Bilirubin, μmol/L	9.0 (7.0-13.0)	10.0 (7.0-13.7)	12.0 (8.0-17.0)	<0.001
Alkaline phosphatase, IU/L	71 (60-87)	74 (61-92)	83 (66-108)	<0.001
Alanine transaminase, IU/L	18 (14-25)	18 (13-24)	18 (13-24)	0.30
Aspartate transaminase, IU/L	20 (17-25)	21 (17-26)	22 (18-27)	<0.001
HbA_{1c}, %	5.9 (5.6-6.5)	6.1 (5.7-6.8)	6.3 (5.8-7.1)	<0.001
Baseline hemoglobin, g/L	138.0 ± 14.4	135.8 ± 15.5	133.7 ± 17.5	<0.001
Ischemic etiology	614 (57.2)	626 (59.8)	641 (61.7)	0.04
HF diagnosis duration				0.001
0-3 mo	35 (3.3)	40 (3.8)	27 (2.6)	
>3-6 mo	113 (10.5)	93 (8.9)	64 (6.2)	
>6-12 mo	139 (13.0)	106 (10.1)	103 (9.9)	
>1-2 y	152 (14.2)	130 (12.4)	150 (14.4)	
>2-5 y	235 (21.9)	256 (24.5)	237 (22.8)	
>5 y	399 (37.2)	421 (40.2)	458 (44.1)	
Time from last HF hospitalization to randomization				0.10
0-3 mo	74 (6.9)	70 (6.7)	86 (8.3)	
>3-6 mo	82 (7.6)	98 (9.4)	86 (8.3)	
>6-12 mo	105 (9.8)	94 (9.0)	104 (10.0)	
>1-2 y	71 (6.6)	68 (6.5)	82 (7.9)	
>2-5 y	83 (7.7)	86 (8.2)	62 (6.0)	
>5 y	56 (5.2)	48 (4.6)	74 (7.1)	
No prior HF hospitalization	602 (56.1)	582 (55.6)	545 (52.5)	
Ejection fraction, %	31.3 ± 6.8	31.3 ± 6.6	31.1 ± 7.0	0.57
NYHA functional class III/IV	285 (26.6)	332 (31.7)	366 (35.2)	<0.001
Total KCCQ-TSS score at baseline	80.2 (63.5-93.8)	80.2 (62.5-93.8)	72.9 (56.2-88.5)	<0.001
Hypertension	764 (71.2)	815 (77.9)	840 (80.8)	<0.001
Type 2 diabetes	384 (35.8)	475 (45.4)	563 (54.2)	<0.001
History of AF	310 (28.9)	430 (41.1)	550 (52.9)	<0.001
Baseline ECG AFL	150 (14.0)	266 (25.4)	346 (33.3)	<0.001
Hospitalization for HF	471 (43.9)	464 (44.4)	494 (47.5)	0.09
Previous myocardial infarction	504 (47.0)	504 (48.2)	497 (47.8)	0.69
Previous stroke	89 (8.3)	98 (9.4)	120 (11.5)	0.01

Continued on the next page

TABLE 1 Continued

	1st Tertile (n = 1,073)	2nd Tertile (n = 1,046)	3rd Tertile (n = 1,039)	*P* Value (Trend)
COPD, %	119 (11.1)	144 (13.8)	149 (14.3)	0.03
Smoking status				0.01
Current	181 (16.9)	176 (16.8)	125 (12.0)	
Former	465 (43.3)	464 (44.4)	480 (46.2)	
Never	427 (39.8)	406 (38.8)	434 (41.8)	
ACEI/ARB/ARNI	1,017 (94.8)	993 (94.9)	953 (91.7)	0.004
Diuretic	996 (92.8)	972 (92.9)	993 (95.6)	0.01
Digoxin	108 (10.1)	176 (16.8)	198 (19.1)	<0.001
Beta-blocker	1,035 (96.5)	1,009 (96.5)	983 (94.6)	0.03
Mineralocorticoid antagonist	820 (76.4)	751 (71.8)	681 (65.5)	<0.001
Oral anticoagulant	365 (34.0)	492 (47.0)	569 (54.8)	<0.001
Antiplatelet	624 (58.2)	569 (54.4)	522 (50.2)	<0.001
Statin	751 (70.0)	736 (70.4)	676 (65.1)	0.02
ICD/CRT-D, %	331 (30.8)	318 (30.4)	338 (32.5)	0.41
Diabetic treatments in diabetic patients only	(n = 384)	(n = 475)	(n = 563)	
Biguanide	182 (47.4)	223 (46.9)	227 (40.3)	0.02
Sulfonylurea	67 (17.4)	95 (20.0)	122 (21.7)	0.11
DPP-4 inhibitor	68 (17.7)	77 (16.2)	89 (15.8)	0.45
GLP-1 receptor agonist	2 (0.5)	3 (0.6)	6 (1.1)	0.33
Insulin	73 (19.0)	109 (22.9)	168 (29.8)	0.001

Values are median (IQR), mean ± SD, or n (%). A *P* value for trend across tertiles of IGFBP-7 is reported, using the Cochran-Armitage test for binary response variables and the Jonckheere-Terpstra test for continuous variables. Multiple-level categoric variables were compared by means of chi-square test.

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; AFL = atrial flutter; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CRT-D = cardiac resynchronization therapy with defibrillator; DPP = dipeptidyl peptidase; ECG = electrocardiographic; eGFR = estimated glomerular filtration rate; GLP = glucagon-like peptide; HbA_{1C} = glycosylated hemoglobin; HF = heart failure; hsTnT = high-sensitivity troponin T; ICD = implantable cardioverter-defibrillator; IGFBP = insulin-like growth factor–binding protein; KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire-Total Symptom Score; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure.

tertile as reference. Cox proportional hazard models were adjusted for randomized treatment history of HF hospitalization (apart from the all-cause mortality outcome) and stratified by diabetes status. The proportional hazards assumption was examined with the use of log-log plots. Additional adjustments were carried out for age, sex, race, region, SBP, heart rate, LVEF, eGFR, (log-transformed) NT-proBNP, NYHA functional class, hypertension, stroke, previous myocardial infarction, atrial fibrillation and ischemic etiology of HF. A second adjusted model included these variables with the addition of (log-transformed) hsTnT. A semiparametric proportional rates model was used to examine the recurrent HF hospitalization and CV death outcome.[18] To explore the relative contribution of each variable in a Cox model for the primary outcome, we calculated and ranked the chi-square statistic from the Wald *z*-statistic.[19] These were calculated from a model that included all the clinical variables above, IGFBP-7, NT-proBNP, and hsTnT.

The risk of each outcome over the range of continuous IGFBP-7 at baseline was explored with restricted cubic splines using 5 knots placed at default values based on Harrell's recommended percentiles, restricted to observations within the 1st to 99th centiles and the median value used as reference.[20] Log-transformed IGFBP-7 was also entered into Cox models, adjusting for the same covariates as for the analysis of tertiles. The relationship between IGFBP-7 and outcome was examined separately in patients with and without metabolic syndrome.

Patients were defined by groups in a 2-way categorization by tertiles of both IGFBP-7 and other blood results of interest (NT-proBNP, hsTnT, bilirubin, and eGFR). Rates of the primary outcome were compared between subgroups and the hazard for examined outcomes, with the lowest tertile of both blood results as reference. A test for trend of the survivor function across increasing IGFBP-7 tertiles was tested in each tertile of the other biomarker.

The predictive performance of IGFBP-7 in addition to the PREDICT-HF (Risk of Events and Death in the Contemporary Treatment of Heart Failure) pseudo-score (as described previously[21]) and the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) risk score for all-cause mortality were examined by comparing the C-statistic in models using the risk score alone (adjusted for randomized treatment only) or the risk score plus log-transformed IGFBP-7.[19,22]

Survival models were compared with the use of continuous net reclassification index (NRI) and integrated discrimination index using the R package "survIDINRI." The continuous NRI was calculated in preference to a categoric NRI because no accepted categories of risk exist and rather than creating arbitrary cut offs of risk, and to allow easier comparison in the future, we present the continuous NRI per log unit increase in IGFBP-7.[23]

The effect of randomized treatment on outcomes was assessed within each tertile of IGFBP-7, and modification of treatment between tertiles was examined by means of an interaction test. The difference in proportions of patients experiencing a ≥5 point change in KCCQ-TSS at 8 months was assessed by previously described methods with an odds ratio presented for improvement and deterioration in each IGFBP-7 tertile.[14,16]

Change in IGFBP-7 was calculated by ratio of the geometric mean at 1 year compared with the baseline value in each treatment group. Treatment effect was estimated using ratio of the ratio of the geometric means.

The association between change in IGFBP-7 at 1 year and subsequent risk of clinical outcomes was assessed by means of a landmark Cox regression analysis. Analysis time started 1 year after randomization, and the following outcomes were examined: HF hospitalization or CV death, CV death, and all-cause death. Tertiles of change in IGFBP-7 approximated a 30-ng/mL decrease or increase, so those cutoff points were used to define change categories. We also examined change in IGFBP-7 as a continuous variable with the use of restricted cubic splines. All models were adjusted for baseline IGFBP-7 level and randomized treatment, and stratified by diabetes status.

Change in eGFR in placebo-treated patients from baseline in groups defined by IGFBP-7 above and below the median value was evaluated with the use of a repeated-measures mixed-effects model. The models were adjusted for IGFBP-7 group at baseline, follow-up time, and interaction between time and IGFBP-7 group, with intercepts and slopes allowed to vary randomly between patients and with patient and time as random effects.

Safety analyses were performed in randomized patients who had received at least 1 dose of dapagliflozin or placebo. The interaction between baseline IGFBP-7 tertile and randomized treatment on the occurrence of the prespecified safety outcomes was tested in a logistic regression model.

Analyses were conducted with the use of Stata version 17.0 (StataCorp), SAS version 9.4 (SAS Institute), and R version 3.6.1 (R Foundation for Statistical Computing). A value of $P < 0.05$ was considered to be statistically significant.

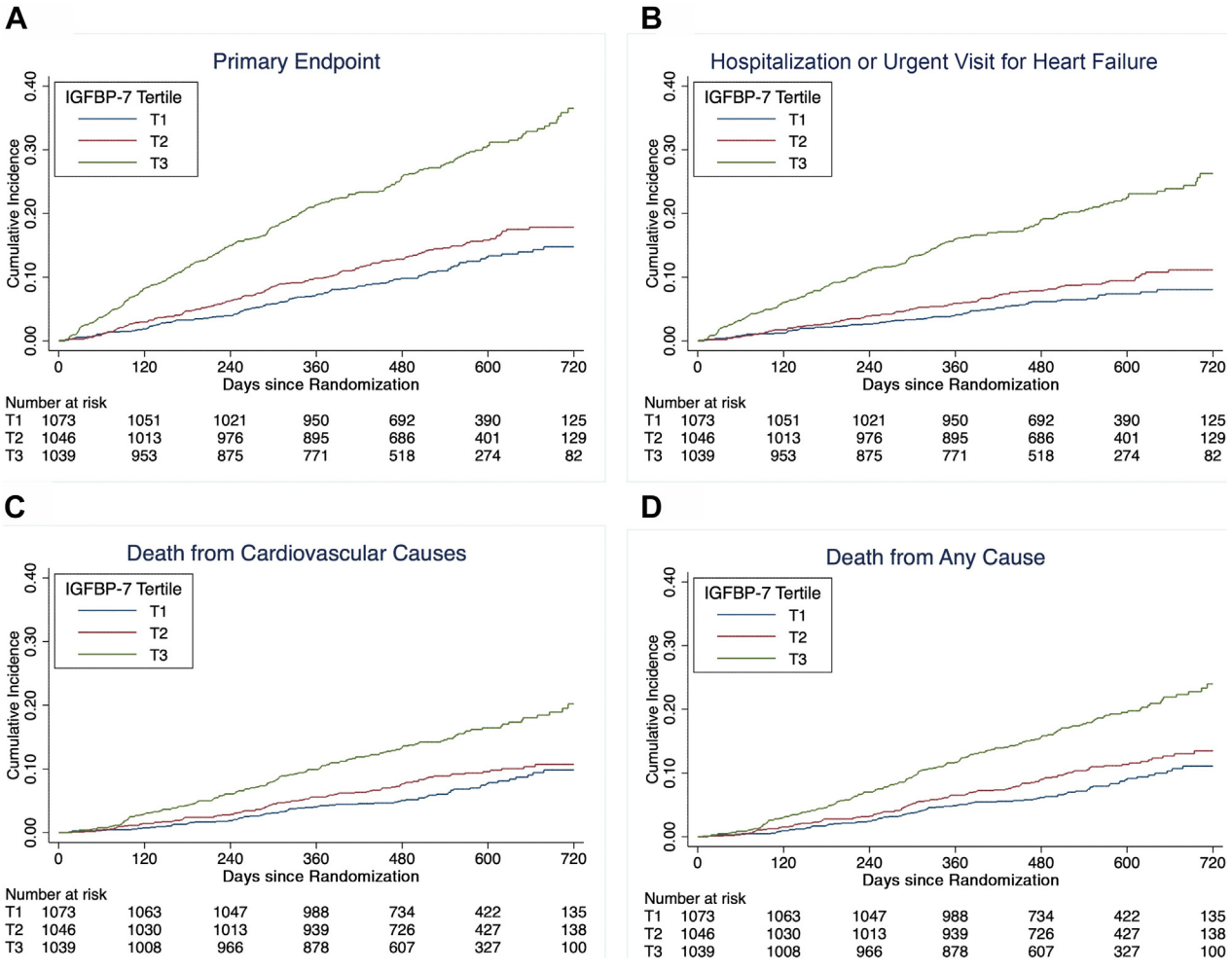
RESULTS

Of the 4,744 patients randomized in DAPA-HF, 3,158 had IGFBP-7 measured at baseline and 2,493 a repeated measurement at 12 months. The distribution at baseline was right-skewed, and the median value was 192 (IQR: 158-246) ng/mL (Supplemental Figure 1). Median follow-up time in the cohort was 18.4 (IQR: 14.5-21.7) months.

BASELINE CHARACTERISTICS. There were many differences in baseline characteristics across tertiles of IGFBP-7 (**Table 1, Central Illustration**). Compared with those in the lowest tertile of IGFBP-7 levels, patients in the highest tertile were older (68.9 ± 10.3 years vs 64.9 ± 10.6 years) and more likely to be male (81.2% vs 73.7%). Patients with the highest levels of IGFBP-7 had evidence of more advanced HF, including higher NT-proBNP concentrations (2,078.7 [IQR: 1,211.6-3,940.9] pg/mL vs 1,071.6 [IQR: 694.3-1,762.7] pg/mL), worse NYHA functional class symptoms (35.2% class III/IV vs 26.6% class III/IV) and lower (worse) KCCQ-TSS. However, LVEF did not differ across IGFBP-7 tertiles. Levels of hsTnT and bilirubin were higher in those with higher IGFBP-7 concentrations. Renal function was worse in participants in the highest third of IGFBP-7 levels, with a mean eGFR of 57.3 ± 17.6 mL/min/1.73 m^2 in the highest tertile vs 73.3 ± 17.6 mL/min/1.73 m^2 in the lowest tertile of IGFBP-7 levels. Patients in the highest tertile of IGFBP-7 concentrations also had a greater burden of comorbidity including more hypertension, type 2 diabetes, and atrial fibrillation. Fewer patients in the highest tertile of IGFBP-7 levels were treated with an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, angiotensin receptor-neprilysin inhibitor, beta-blocker, or mineralocorticoid receptor antagonist, but more were treated with diuretic and digoxin. A larger proportion of participants within the highest tertile of IGFBP-7 concentrations were treated with insulin for diabetes, and fewer were treated with a biguanide.

VARIABLES ASSOCIATED WITH ELEVATED BASELINE IGFBP-7. Variables associated with an IGFBP-7 greater than the median value at baseline included atrial fibrillation; higher creatinine, NT-proBNP, hsTnT, HbA_{1c}, and body mass index (BMI); elevated liver function tests (aspartate transaminase, bilirubin, alkaline phosphatase); and lower hemoglobin (Supplemental Table 1). In patients meeting the modified criteria for metabolic syndrome, baseline

FIGURE 1 Kaplan-Meier Curves



Unadjusted estimates for the cumulative incidence of **(A)** the primary composite endpoint, **(B)** hospitalization or urgent visit for heart failure, **(C)** death from cardiovascular causes, or **(D)** death from any cause in patients grouped by baseline insulin-like growth factor–binding protein-7 (IGFBP-7) tertile.

IGFBP-7 was higher than in other patients (Supplemental Figure 2).

CARDIOVASCULAR OUTCOMES ACCORDING TO BASELINE IGFBP-7. Rates of the primary endpoint were highest in those with the highest IGFBP-7 levels (**Figure 1**). For the primary endpoint, the adjusted HR for tertile 3 of IGFBP-7 concentration, compared with tertile 1, was 1.49 (95% CI: 1.17-1.89) with adjustment for (log-transformed) NT-proBNP, (log-transformed) hsTnT, previous hospitalization for HF, treatment allocation, age, sex, race, region, SBP, heart rate, LVEF, eGFR, NYHA functional class, hypertension, previous stroke, previous myocardial infarction, atrial fibrillation, and HF etiology, and stratified by diabetic status. NT-proBNP and hsTnT had the highest chi-square values (42.1 and 39.3, respectively), followed by IGFBP-7 20.7) and then clinical variables (Supplemental Table 2).

For a worsening HF event, the corresponding adjusted HR was 1.84 (95% CI: 1.35-2.50), for CV death it was 1.13 (95% CI: 0.82-1.56), and for all-cause mortality it was 1.27 (95% CI: 0.95-1.71). The corresponding rate ratio for the recurrent outcome of HF hospitalizations and CV death was 1.48 (95% CI: 1.22-1.81) (**Table 2**).

When IGFBP-7 was considered as a continuous variable, the HR for each unit (log-transformed) increase in IGFBP-7, with the same adjustment described above, was 1.91 (95% CI: 1.46-2.51). The

TABLE 2 Event Frequencies, Event Rates, HRs for Key Study Outcomes According to Tertile of IGFBP-7

	1st Tertile (n = 1,073)	2nd Tertile (n = 1,046)	*P* Value	3rd Tertile (n = 1,039)	*P* Value
Primary endpoint, %	125 (11.7)	158 (15.1)		297 (28.6)	
Event rate, number of cases per 100 patient-years	7.9 (6.7-9.5)	10.3 (8.8-12.1)		22.3 (19.9-25.0)	
HR, unadjusted	1.00 (Ref.)	1.26 (0.99-1.59)	0.06	2.67 (2.16-3.29)	<0.001
HR, adjusted model 1	1.00 (Ref.)	0.99 (0.77-1.26)	0.92	1.63 (1.29-2.07)	<0.001
HR, adjusted model 2	1.00 (Ref.)	0.94 (0.74-1.20)	0.62	1.49 (1.17-1.89)	0.001
HF urgent visit or hospitalization, %	70 (6.5)	94 (9.0)		207 (19.9)	
Event rate, number of cases per 100 patient-years	4.4 (3.5-5.6)	6.1 (5.0-7.5)		15.6 (13.6-17.8)	
HR, unadjusted	1.00 (Ref.)	1.34 (0.98-1.82)	0.07	3.30 (2.51-4.34)	<0.001
HR, adjusted model 1	1.00 (Ref.)	1.04 (0.75-1.42)	0.83	2.01 (1.48-2.73)	<0.001
HR, adjusted model 2	1.00 (Ref.)	0.99 (0.72-1.36)	0.94	1.84 (1.35-2.50)	<0.001
Death from cardiovascular causes, %	75 (7.0)	93 (8.9)		159 (15.3)	
Event rate, number of cases per 100 patient-years	4.6 (3.7-5.8)	5.9 (4.8-7.2)		10.9 (9.3-12.7)	
HR, unadjusted	1.00 (Ref.)	1.22 (0.90-1.66)	0.20	2.24 (1.70-2.96)	<0.001
HR, adjusted model 1	1.00 (Ref.)	0.94 (0.69-1.29)	0.72	1.22 (0.89-1.68)	0.21
HR, adjusted model 2	1.00 (Ref.)	0.90 (0.66-1.24)	0.52	1.13 (0.82-1.56)	0.45
Death from any cause, %	88 (8.2)	114 (10.9)		192 (18.5)	
Event rate, number of cases per 100 patient-years	5.4 (4.4-6.6)	7.2 (6.0-8.6)		13.1 (11.4-15.1)	
HR, unadjusted	1.00 (Ref.)	1.28 (0.97-1.69)	0.08	2.32 (1.80-2.99)	<0.001
HR, adjusted model 1	1.00 (Ref.)	1.01 (0.76-1.34)	0.96	1.35 (1.01-1.80)	0.04
HR, adjusted model 2	1.00 (Ref.)	0.98 (0.73-1.31)	0.88	1.27 (0.95-1.71)	0.10
Total number of hospitalizations for HF and cardiovascular deaths, n	183	208		480	
Event rate, number of cases per 100 patient-years	11.3 (9.8-13.0)	13.1 (11.4-15.0)		32.9 (30.1-36.0)	
HR, unadjusted	1.00 (Ref.)	1.12 (0.92-1.36)	0.27	2.76 (2.33-3.28)	<0.001
HR, adjusted model 1	1.00 (Ref.)	0.87 (0.71-1.07)	0.18	1.61 (1.33-1.96)	<0.001
HR, adjusted model 2	1.00 (Ref.)	0.83 (0.68-1.02)	0.08	1.48 (1.22-1.81)	<0.001

Values are n (%) or HR (95% CI). Crude models have been adjusted for previous hospitalization for HF and treatment allocation and stratified according to diabetic status. Models for all-cause mortality are not adjusted for previous HF hospitalization. Adjusted model 1 has additional adjustment for age, sex, race, region, SBP, heart rate, left ventricular ejection fraction, eGFR, NT-proBNP (log-transformed), NYHA functional class, hypertension, previous stroke, previous myocardial infarction, AF, and HF etiology. Adjusted model 2 has the same variables as model 1 with the addition of (log-transformed) hsTnT.

Ref. = reference; other abbreviations as in Table 1.

corresponding HR was 2.51 (95% CI: 1.80-3.49) for a worsening HF event, 1.34 (95% CI: 0.93-1.93) for CV death, and 1.44 (95% CI: 1.03-2.01) for all-cause death (Supplemental Table 3). Findings were consistent in patients with and without metabolic syndrome (Supplemental Table 3).

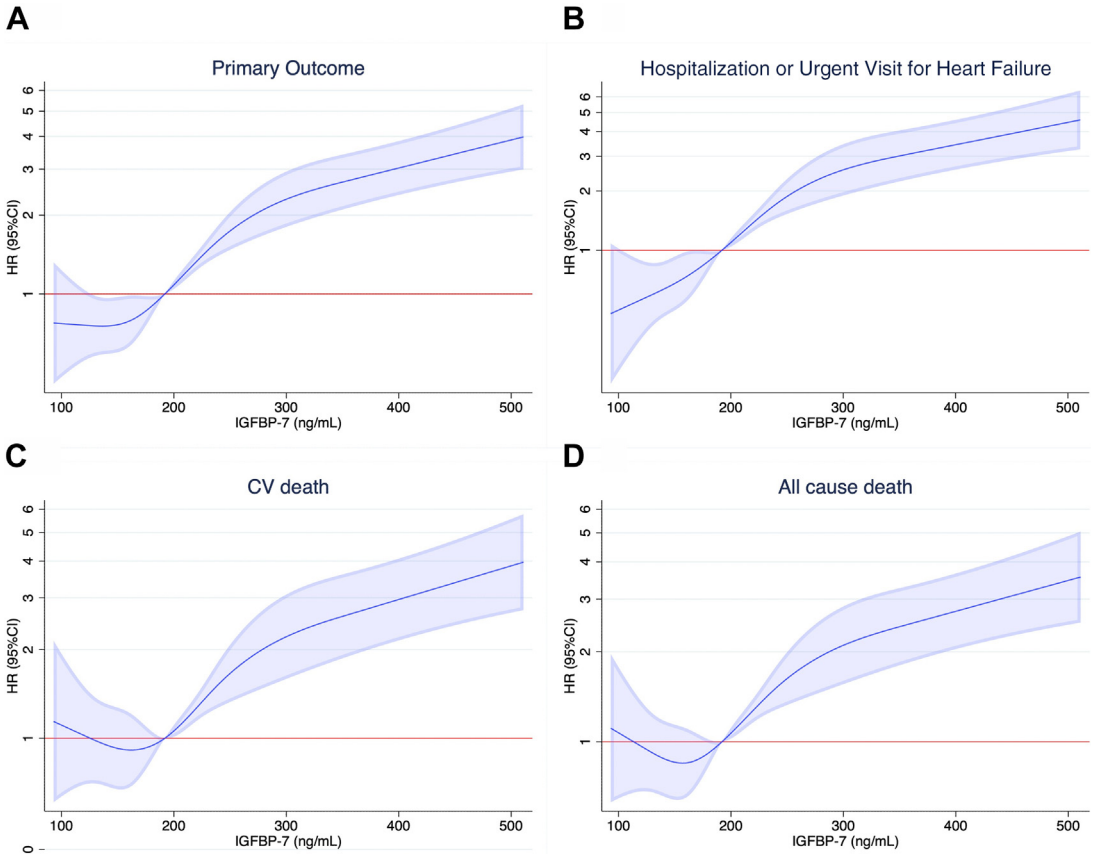
Using restricted cubic splines to flexibly model the HR for each outcome, considering IGFBP-7 as a continuous variable, we found an approximately linear relationship between increasing level of IGFBP-7 and increasing risk for each outcome at values greater than the median population value of IGFBP-7 (**Figure 2**). At levels below the median value, there was a flatter relationship between IGFBP-7 levels and the risk of each outcome, most clearly for mortality outcomes, while the risk of worsening HF event remained approximately linear.

Rates of the primary outcome in groups of patients defined by tertile of both IGFBP-7 and each of hsTnT, NT-proBNP, bilirubin, and eGFR showed the highest rates of the primary outcome in patients in the highest tertile of IGFBP-7 levels and the upper tertile for each of the other markers (**Figure 3**).

PREDICTIVE PERFORMANCE OF IGFBP-7 IN ADDITION TO PREDICT-HF AND MAGGIC RISK SCORES. The addition of IGFBP-7 to previously established risk scores for all-cause mortality showed a small, but statistically significant improvement in the model fit for both PREDICT-HF (continuous NRI: 0.09 [95% CI: 0.008-0.189]; $P = 0.03$) and MAGGIC (Supplemental Table 4).

EFFECT OF DAPAGLIFLOZIN ON PRIMARY AND SECONDARY TRIAL OUTCOMES ACCORDING TO BASELINE IGFBP-7 CONCENTRATION. The benefit of dapagliflozin was consistent across tertiles of

FIGURE 2 **Restricted Cubic Splines**



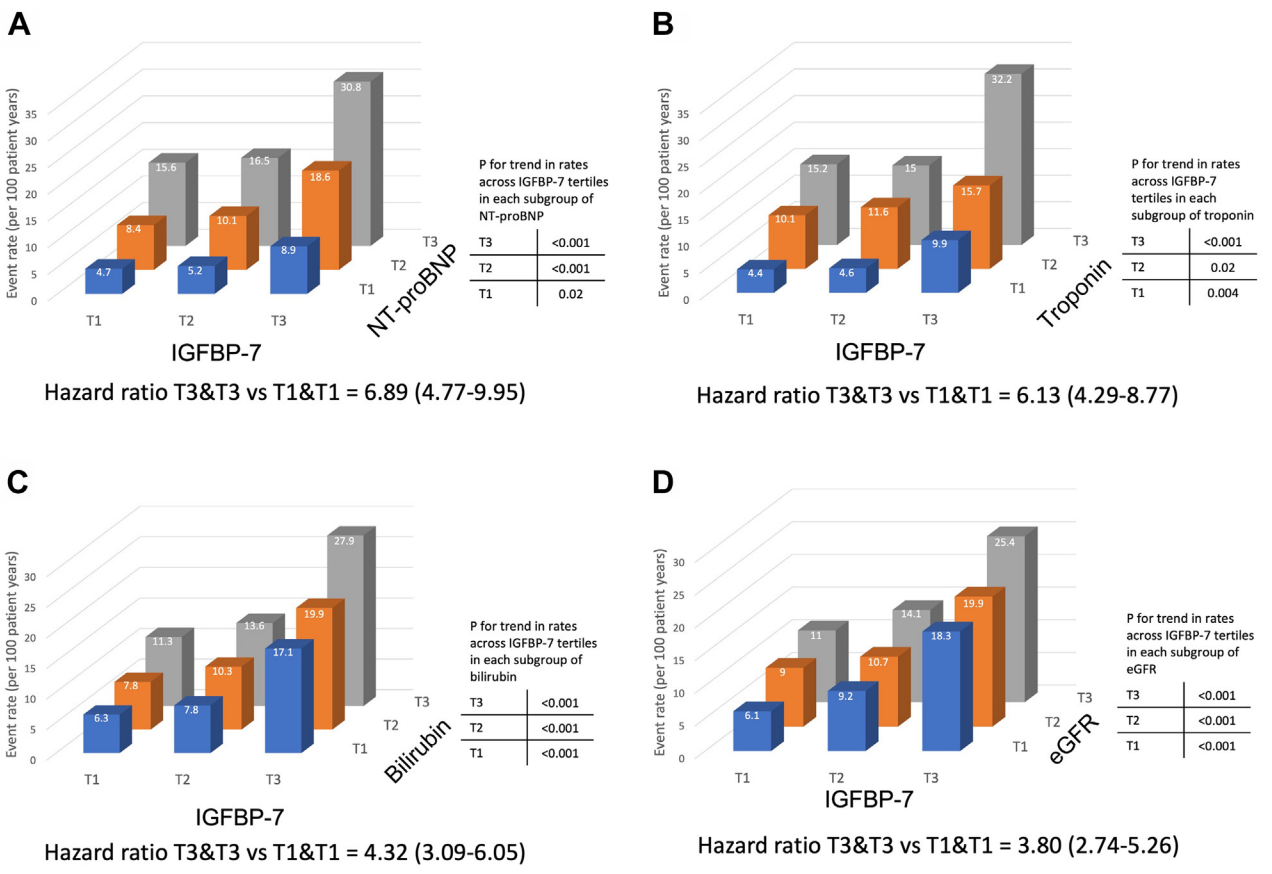
Association between total IGFBP-7 as a continuous variable with modeling using restricted cubic splines and the risk of **(A)** the primary composite endpoint, **(B)** hospitalization or urgent visit for heart failures, **(C)** death from cardiovascular (CV) cause, or **(D)** death from any cause. The reference point is the median value of baseline IGFBP-7. There is an approximately linear relationship between increasing level of IGFBP-7 and increasing risk for each outcome at values greater than the median. Below the median value, the relationship remains approximately linear for worsening heart failure event but is flatter for mortality outcomes. Abbreviation as in Figure 1.

IGFBP-7, with no significant interaction between IGFBP-7 and the effect of randomized treatment on the occurrence of any outcome examined; the *P* value for interaction for the primary outcome was 0.34, for urgent HF visit 0.36, for CV death 0.79, and for all-cause mortality 0.81 (Table 3).

EFFECT OF DAPAGLIFLOZIN ON IGFBP-7 CONCENTRATION. Comparison of values at baseline and 1 year showed a slight increase in IGFBP-7 in both randomized treatment arms, but no difference between dapagliflozin and placebo. The ratio of geometric mean between the follow-up and baseline levels was 1.03 (95% CI: 1.01-1.05) in the dapagliflozin group and 1.04 (95% CI: 1.02-1.06) in the placebo group; the ratio of these was 0.99 (95% CI: 0.97-1.01; $P = 0.34$) (Supplemental Table 5).

EFFECT OF CHANGE IN IGFBP-7 CONCENTRATION AT 1 YEAR AND SUBSEQUENT CLINICAL OUTCOMES. Patients with an increase in IGFBP-7 of more than 30 ng/mL at 1 year had a higher risk of HF hospitalization, CV death, and all-cause death compared with patients with a relatively stable IGFBP-7 level (within ±30 ng/mL of baseline value) (Supplemental Table 6). Participants with a decrease in IGFBP-7 concentration of more than 30 ng/mL had a lower point estimate of hazard, compared with the stable group, but with CIs crossing 1, except for all-cause death (HR: 0.48; 95% CI: 0.27-0.86). Analysis of change in IGFBP-7 as a continuous variable showed an approximately linear relationship between change in IGFBP-7 and risk of each outcome, with some flattening of the relationship in patients with

FIGURE 3 Rates of the Primary Outcome in 2-Way Categorization of IGFBP-7 and Other Blood Tests



Event rates of the primary outcome per 100 patient years from a Cox regression model for patients grouped by two-way categorization of IGFBP-7 and **(A)** NT-proBNP tertile, **(B)** troponin tertile, **(C)** bilirubin tertile, and **(D)** eGFR tertile (eGFR tertile 1 has the highest eGFR, ie, better renal function). A test for trend for event rates across increasing IGFBP-7 tertile is given within each tertile of the other marker of interest. eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide; other abbreviation as in Figure 1.

a very large increase in IGFBP-7 concentration (Supplemental Figure 3).

CHANGE IN eGFR IN GROUPS DEFINED BY HIGH OR LOW IGFBP-7 AT BASELINE. Overall, in the placebo group, eGFR declined during follow-up. Patients with an IGFBP-7 level greater than the median at baseline had a lower baseline eGFR. The rate of decline (slope) in eGFR did not vary according to median IGFBP-7 at baseline (*P* for difference in slopes = 0.72) (Supplemental Figure 4).

SAFETY AND ADVERSE EVENTS. In patients randomized to placebo, any discontinuation, discontinuation caused by adverse event, volume depletion, and renal adverse events were more common in the highest tertile of IGFBP-7; however, there was no difference in the occurrence of any adverse outcome between randomized treatment groups across the tertiles of IGFBP-7 (Supplemental Table 7).

DISCUSSION

Among 3,158 ambulant patients with HFrEF enrolled in DAPA-HF, higher levels of IGFBP-7 were associated with worse cardiovascular outcomes, particularly HF hospitalization. The elevated risk associated with higher IGFBP-7 persisted after adjustment for NT-proBNP and hsTnT. Moreover, IGFBP-7 improved the performance of 2 prognostic models previously validated in patients with HFrEF. Dapagliflozin did not reduce IGFBP-7 after 1 year of treatment.

DISTRIBUTION OF IGFBP-7 CONCENTRATION IN HF. Little is known about the normal range for IGFBP-7, and no standard assay was used in previous studies. In one study of 55 controls with an average age of 54 years, the median level was 50 ng/mL (IQR: 43-55 ng/mL), but in a study of 1,913 older community-dwelling Italians (mean age: 73 years),

TABLE 3 Effect of Dapagliflozin Compared With Placebo According to Tertile of Total IGFBP-7 at Baseline

	1st Tertile (n = 1,073)		2nd Tertile (n = 1,046)		3rd Tertile (n = 1,039)		
	Placebo (n = 530)	Dapagliflozin (n = 543)	Placebo (n = 518)	Dapagliflozin (n = 528)	Placebo (n = 511)	Dapagliflozin (n = 528)	*P* Value for Interaction
Primary endpoint							
Total number of events, %	68 (12.8)	57 (10.5)	95 (18.3)	63 (11.9)	154 (30.1)	143 (27.1)	
Rate per 100 patient-years	8.9 (7.0-11.2)	7.1 (5.4-9.1)	12.7 (10.4-15.5)	8.1 (6.3-10.3)	24.2 (20.7-28.4)	20.6 (17.5-24.3)	
Unadjusted HR	0.78 (0.55-1.12)		0.64 (0.47-0.89)		0.86 (0.69-1.08)		0.34
Adjusted HR[a]	0.80 (0.56-1.14)		0.66 (0.48-0.91)		0.87 (0.69-1.10)		
Hospitalization for HF or urgent HF visit							
Total number of events, %	39 (7.4)	31 (5.7)	59 (11.4)	35 (6.6)	109 (21.3)	98 (18.6)	
Rate per 100 patient-years	5.1 (3.7-7.0)	3.8 (2.7-5.5)	7.9 (6.1-10.2)	4.5 (3.2-6.2)	17.1 (14.2-20.7)	14.1 (11.6-17.2)	
Unadjusted HR	0.74 (0.46-1.19)		0.58 (0.38-0.88)		0.83 (0.63-1.09)		0.36
Adjusted HR[a]	0.70 (0.43-1.13)		0.58 (0.38-0.88)		0.83 (0.63-1.09)		
Cardiovascular death							
n (%)	39 (7.4)	36 (6.6)	53 (10.2)	40 (7.6)	83 (16.2)	76 (14.4)	
Rate per 100 patient-years	4.9 (3.6-6.7)	4.3 (3.1-6.0)	6.7 (5.2-8.8)	5.0 (3.7-6.8)	11.6 (9.4-14.4)	10.1 (8.1-12.7)	
Unadjusted HR	0.89 (0.57-1.41)		0.74 (0.49-1.12)		0.88 (0.64-1.20)		0.79
Adjusted HR[a]	0.97 (0.61-1.54)		0.77 (0.51-1.17)		0.92 (0.67-1.26)		
All-cause death							
n (%)	47 (8.9)	41 (7.6)	64 (12.4)	50 (9.5)	99 (19.4)	93 (17.6)	
Rate per 100 patient-years	5.9 (4.4-7.8)	4.9 (3.6-6.7)	8.1 (6.4-10.4)	6.2 (4.7-8.2)	13.9 (11.4-16.9)	12.4 (10.1-15.2)	
Unadjusted HR	0.84 (0.55-1.28)		0.77 (0.53-1.11)		0.90 (0.68-1.19)		0.81
Adjusted HR[a]	0.91 (0.59-1.38)		0.80 (0.55-1.17)		0.94 (0.71-1.25)		
Recurrent HF hospitalizations or cardiovascular death							
Number of events	106	77	117	91	259	221	
Rate per 100 patient-years	13.3 (11.0-16.1)	9.3 (7.5-11.7)	14.9 (12.5-17.9)	11.3 (9.2-13.9)	36.5 (32.3-41.3)	29.5 (25.8-33.6)	
Rate ratio	0.70 (0.47-1.04)		0.77 (0.54-1.10)		0.81 (0.63-1.05)		0.80
Adjusted rate ratio[a]	0.71 (0.48-1.06)		0.79 (0.55-1.14)		0.85 (0.66-1.09)		
Significant worsening in KCCQ-TSS (≥5) at 8 mo							
Proportion ± SE, %	31.2 ± 2.1	26.1 ± 2.0	34.6 ± 2.2	24.4 ± 1.9	32.6 ± 2.1	26.3 ± 2.0	
Odds ratio	0.90 (0.77-1.03)		0.79 (0.69-0.91)		0.86 (0.75-0.98)		0.95
Significant improvement in KCCQ-TSS (≥5) at 8 mo							
Proportion ± SE, %	52.5 ± 2.3	57.8 ± 2.3	48.5 ± 2.3	58.1 ± 2.2	49.6 ± 2.3	55.1 ± 2.3	
Odds ratio	1.10 (0.96-1.26)		1.20 (1.06-1.36)		1.12 (0.98-1.28)		0.92

Ranges in parentheses are 95% CIs. Unadjusted models are adjusted for previous HF hospitalization (apart from the all-cause mortality outcome) and stratified by diabetes status. [a]Adjustment for age, sex, race, region, SBP, heart rate, left ventricular ejection fraction, eGFR, NT-proBNP (log-transformed), NYHA functional class, hypertension, stroke, previous myocardial infarction, AF, and ischemic etiology.

Abbreviations as in Table 1.

the median concentration was 166 (IQR: 151-184) ng/mL.[12,24]

In a few small studies using the same assay, the median IGFBP-7 concentration ranged from 74 to 141 ng/mL in patients with HFrEF and from 52 to 261 in patients with HFpEF (these cohorts varied widely in terms of patient age, severity, and comorbidity).[5-7,9,24,25] In one study using a different assay, levels were higher in HFrEF than in HFpEF.[8] In another study of acute HF, the median level was 146 ng/mL (vs 86 ng/mL in dyspneic patients without acute heart failure; $P < 0.001$).[10] Consistent with these studies, the median IGFBP-7 level in DAPA-HF was 192 (IQR: 158-246) ng/mL. These values compare with a median concentration of 182 ng/mL in patients with atrial fibrillation (with and without HF).[1] Recently, a geometric mean concentration of 96.9 ng/mL was reported in patients with type 2 diabetes, and 49% of participants had a level >96.5 ng/mL; the geometric mean in DAPA-HF was 199 ng/mL, and 99% of participants had a concentration >96.5 ng/mL.[26]

IGFBP-7, HF CHARACTERISTICS, AND OUTCOMES.

Motiwala et al[25] and Hage et al[8] reported associations between higher IGFBP-7 levels and older age, worse NYHA functional class, higher NT-proBNP, and lower eGFR. We confirmed these, found an association

between higher IGFBP-7 levels and lower KCCQ-TSS score (supporting the finding related to NYHA functional class), and showed further strong associations between IGFBP-7 and atrial fibrillation and diabetes mellitus (and HbA_{1c}).[27] The latter associations have also been shown in patients with HFpEF and other populations, with the association between IGFBP-7 and diabetes potentially reflecting the role of this peptide in promoting insulin resistance. We also identified a smaller proportion of women among participants with the highest IGFBP-7 levels; a similar finding was made in a large community-based survey of elderly Italians, although it was not shown in previous HF studies, probably because of their small size.[12] Two other notable additional associations in DAPA-HF were between IGFBP-7 level and hsTnT concentration (a marker of myocyte necrosis) and bilirubin (probably a marker of congestion), although, notably, there was no association between IGFBP-7 and LVEF in our trial. Collectively, these findings suggest that higher IGFBP-7 concentrations are associated with an overall profile of more advanced HF and greater comorbidity, and are consistent with the proposal that IGFBP-7 is a marker of tissue ageing and metabolic dysfunction.

The key question was whether this novel biomarker, potentially reflecting different pathophysiologic pathways, would add useful predictive information to that obtained from established prognostic variables and the proven biomarkers NT-proBNP and hsTnT. IGFBP-7 was an independent predictor of outcomes even in comprehensive multivariable models including NT-proBNP and hsTnT, although more so for worsening HF events than for mortality. When ranked by chi-square value, IGFBP-7 was the third largest contributor to a Cox regression model for the primary outcome, after NT-proBNP and hsTnT. Adding IGFBP-7 to 2 validated risk models, MAGGIC and PREDICT-HF, led to an improvement in model fit with modest but statistically significant improvements in the c-statistic and reclassification indices. These findings suggest that IGFBP-7 may reflect pathophysiologic pathways distinct from those represented by conventional cardiac biomarkers and not only may provide incremental prognostic information, but also may point to additional disease mechanisms and potential therapeutic targets.

Dapagliflozin did not alter IGFBP-7 levels after 1 year, which contrasts with its effect on NT-proBNP.[28] Another sodium glucose cotransporter 2 (SGLT2) inhibitor did not reduce IGFBP-7 levels in patients with type 2 diabetes.[26] The lack of effect of SGLT2 inhibition on IGFBP-7 in HF also contrasts with the finding that sacubitril/valsartan reduced IGFBP-7 in patients with HFpEF and 2 reports that heart transplantation and implantation of a left ventricular assist device reduced IGFBP-7 level in patients with HFrEF.[8,9,29] The reasons for these differences between treatments and the factors increasing IGFBP-7 in HF are not known. Elevation of cardiac filling pressures has been suggested as one possibility, and sacubitril/valsartan probably has a larger effect on those (and other hemodynamic derangements) compared with SGLT2 inhibition, as clearly do the surgical interventions. Alternatively, the lack of effect of dapagliflozin on IGFBP-7 levels, despite the therapeutic benefits of SGLT2 inhibition in HF, may mean that IGFBP-7 reflects a pathophysiologic pathway (or pathways) different from that altered by treatment with dapagliflozin.

In the population as a whole, there was a small increase in IGFBP-7 concentration in both treatment arms at 1 year, perhaps reflecting a trend to higher levels over time due to aging and overall progression of the HF syndrome. In those in the highest IGFBP-7 tertile, there was a fall in concentration in both treatment arms, which was likely multifactorial, reflecting regression toward the mean over time and survivor bias due to more patients with a high IGFBP-7 at baseline dying before the repeated measurement at 1 year.

Finally, the benefits of dapagliflozin were consistent across the range of IGFBP-7 levels measured at baseline in DAPA-HF.

STUDY LIMITATIONS. This was a post hoc analysis and conducted within a clinical trial setting among selected patients. Whether the relationship between IGFBP-7 levels and outcomes would be similar in a broader population is unknown. We did not have detailed echocardiographic information, which meant we could not explore the previously described relationship between IGFBP-7 and markers of diastolic dysfunction. This study used a commercially available IGFBP-7 assay that is intended for research use only and the interassay coefficient of variation was higher than is usually reported for clinically validated biomarker assays. This may have resulted in some nondifferential misclassification bias which would tend to bias associations to the null. Our model performance may be overoptimistic because we used the same data to model the coefficients and model performance, so external validation is required.

CONCLUSIONS

Elevation of IGFBP-7 in ambulant patients with HFrEF was associated with worse clinical outcomes, even after adjustment for important clinical characteristics, NT-proBNP, and hsTnT. The benefits of

dapagliflozin were consistent across the range of IGFBP-7 concentrations at baseline in DAPA-HF and dapagliflozin did not reduce IGFBP-7.

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Dr Inzucchi has membership on scientific/research advisory boards for Boehringer Ingelheim, AstraZeneca, Intarcia, Lexicon, Janssen, Sanofi, Merck & Co, and Novo Nordisk; has received research supplies to Yale University from Takeda; and has participated in medical educational projects for which unrestricted funding from Boehringer Ingelheim, Eli Lilly, and Merck & Co was received by Yale University. Dr Køber has received speaker honoraria from Novartis, AstraZeneca, Novo, and Boehringer Ingelheim. Dr Kosiborod has received grant and research support from AstraZeneca; grant and honoraria from Boehringer Ingelheim; and honoraria from Sanofi, Amgen, Novo Nordisk, Merck (Diabetes), Janssen, Bayer, Novartis, Eli Lilly, and Vifor Pharma. Dr Ljungman has received personal fees and financial reimbursement through her institution from AstraZeneca during the conduct of the study and personal fees from Novartis and Pfizer outside of the submitted work. 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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: IGFBP-7 shows promise as an informative biomarker in HFrEF and may provide incremental prognostic information above that provided from NT-proBNP and hsTnT.

TRANSLATIONAL OUTLOOK: We do not fully understand the pathophysiologic pathways that result in elevation of IGFBP-7 in HFrEF, and given that it provides prognostic information above that of NT-proBNP, it may reflect pathophysiologic pathways different from those measured by conventional biomarkers. Further research in this area could improve our understanding of disease mechanisms in HF and potentially identify therapeutic targets.

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