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Association of Carbohydrate Antigen 125 on the Response to Dapagliflozin in Patients With Heart Failure

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ABSTRACT

BACKGROUND Elevated circulating carbohydrate antigen 125 (CA125) is a marker of congestion and a predictor of outcomes in acute heart failure (HF). Less is known about CA125 in chronic ambulatory HF with reduced ejection fraction.

OBJECTIVES This study examined the association between baseline CA125 (and changes in CA125) and outcomes in patients with HF with reduced ejection fraction in the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; NCT03036124) trial and its relationship with the effect of dapagliflozin.

METHODS The primary outcome was a composite of a first episode of worsening HF or cardiovascular death. CA125 was measured at baseline and 12 months following randomization.

RESULTS Median baseline CA125 was 13.04 U/mL (IQR: 8.78-21.13 U/mL) in 3,123 of 4,774 patients with available data. Compared with CA125 ≤35 U/mL (upper limit of normal), patients with CA125 >35 U/mL were at a higher risk of the primary outcome (adjusted HR: 1.59; 95% CI: 1.29-1.96). The adjusted risks of the primary outcome relative to quartile 1 (Q1) (≤8.78 U/mL) were as follow: Q2, 8.79-13.04 U/mL (HR: 0.94; 95% CI: 0.71-1.24); Q3, 13.05-21.13 U/mL (HR: 1.22; 95% CI: 0.94-1.59); Q4, ≥21.14 U/mL (HR: 1.63; 95% CI: 1.28-2.09). The beneficial effect of dapagliflozin compared with placebo on the primary outcome was consistent whether CA125 was analyzed in quartiles (interaction $P = 0.13$) or as a continuous variable (interaction $P = 0.75$). The placebo-corrected relative change in CA125 at 12 months was −5.2% (95% CI: −10.6% to 0.5%; $P = 0.07$).

CONCLUSIONS In DAPA-HF, elevated CA125 levels were an independent predictor of the risk of worsening HF or cardiovascular death. Dapagliflozin reduced the risk of worsening HF or cardiovascular death regardless of baseline CA125. (J Am Coll Cardiol 2023;82:142-157) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The presence of congestion, the clinical hallmark of the syndrome of heart failure (HF), is associated with worse outcomes in patients with heart failure with reduced ejection fraction (HFrEF).[1,2] The assessment of congestion and timely implementation of decongestive treatments is limited by the lack of sensitivity and specificity of clinical examination findings. Moreover, implanted hemodynamic monitoring devices have shown that increases in intracardiac filling pressures often precede clinically evident congestion by days or weeks. However, these devices are expensive and serial pressure monitoring adds complexity to patient management.[1,3] Newer imaging techniques may also have greater sensitivity than clinical examination in detecting raised intravascular and intracardiac pressures, but regular application of these is also labor-intensive and expensive. Carbohydrate antigen 125 (CA125) is synthesized by epithelial cells of serosal surfaces such as the peritoneum, pleura, and pericardium. CA125 lubricates mesothelial luminal surfaces to reduce mechanical stress and adhesion between tissue layers. CA125 may also be involved in inflammatory and immune response and tissue repair.[4]

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Although best known as a circulating biomarker used to monitor ovarian cancer, CA125 levels correlate with volume overload, and CA125 is a potential measure of congestion in patients with HF.[4] Elevated CA125 concentrations correlate with invasively measured filling pressures and with established biomarkers of congestion, including N-terminal pro-B-type natriuretic peptide (NT-proBNP), and are an independent predictor of outcomes in patients hospitalized with worsening HF.[4-6] Less is known about the association between elevated CA125 concentrations (and changes in CA125) with outcomes in patients with chronic, ambulatory HFrEF.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors reduce the risk of cardiovascular death and worsening HF in patients with HFrEF.[7] One of the suggested mechanisms of benefit of SGLT2 inhibition is an increase in natriuresis and osmotic diuresis along with a reduction in interstitial fluid (ie, a reduction in congestion).[8-11] Therefore, in this post hoc exploratory analysis, we hypothesized that this treatment would be more effective in patients with elevated CA125 levels and reduce CA125 concentration. We tested this hypothesis in the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial. We also analyzed the association between baseline CA125 levels (and change in CA125) and outcomes in DAPA-HF.[12,13]

METHODS

DAPA-HF was a prospective, randomized, double-blind, placebo-controlled trial that examined the efficacy and safety of dapagliflozin 10 mg once daily, compared with a placebo, in patients with HFrEF.[12,13] Ethics committees at each participating site approved the protocol, and each patient gave written informed consent.

STUDY PATIENTS. Eligible adults were in NYHA functional class II to IV, had left ventricular ejection fraction (LVEF) ≤40%, had elevated NT-proBNP level, and were optimally treated with pharmacologic and device therapy, according to local guidelines. Key exclusion criteria included symptoms of hypotension or systolic blood pressure <95 mm Hg, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, and type 1 diabetes. Patients were excluded if they had evidence of current acute decompensated HF or were hospitalized because of decompensated HF <4 weeks before enrollment. A full list of exclusion criteria was provided in the design paper.[13]

MEASUREMENT OF CA125. CA125 was measured at baseline and 12 months following randomization. Venous blood samples were collected and stored at −20 °C or colder until shipped on dry ice to the central repository, where they were stored at −80 °C or colder until thawed for analysis. CA125 was measured at the University of Glasgow using the Elecsys CA 125 II assay run on an automated platform (Cobas e 411, Roche Diagnostics). The coefficient of variation over 2 levels was ≤6.0%. The limit of blank of the assay is 0.6 U/mL. For this analysis, patients with CA125 concentrations ≤0.6 U/mL were assigned a value of 0.3 U/mL (ie, one-half the limit of blank).

TRIAL OUTCOMES. The primary outcome was the composite of time to first worsening HF or cardiovascular death. An episode of worsening HF was

ABBREVIATIONS AND ACRONYMS

AUC = area under the curve

CA125 = carbohydrate antigen 125

eGFR = estimated glomerular filtration rate

GDF = growth differentiation factor

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

hsTnT = high-sensitivity troponin T

KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire total symptom score

LVEF = left ventricular ejection fraction

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

SGLT2 = sodium-glucose co-transporter-2

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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TABLE 1 Baseline Characteristics by Baseline CA125 Concentration Using Cutoff of ≤35 U/mL

	≤35 U/mL (n = 2,743)	>35 U/mL (n = 380)	*P* Value
Randomized to dapagliflozin	1,384 (50.5)	195 (51.3)	0.75
Age, y	67.1 ± 10.5	68.4 ± 9.5	0.020
Sex			0.18
Female	617 (22.5)	74 (19.5)	
Male	2,126 (77.5)	306 (80.5)	
Race			0.003
White	2,124 (77.4)	326 (85.8)	
Black	80 (2.9)	7 (1.8)	
Asian	528 (19.2)	46 (12.1)	
Other	11 (0.4)	1 (0.3)	
NYHA functional class			<0.001
II	1,938 (70.7)	213 (56.1)	
III	796 (29.0)	166 (43.7)	
IV	9 (0.3)	1 (0.3)	
Heart rate, beats/min	70.5 ± 11.1	73.5 ± 11.7	<0.001
Systolic blood pressure, mm Hg	122.8 ± 15.8	120.0 ± 14.9	0.002
Left ventricular ejection fraction, %	31.4 ± 6.7	30.1 ± 6.9	<0.001
Median NT-proBNP, pg/mL	1,331 (821-2,308)	2,910 (1,422-5,604)	<0.001
AF on baseline ECG	1,824 (1,205-2,948)	2,647 (1,439-5,319)	<0.001
No AF on baseline ECG	1,200 (743-2,097)	3,058 (1,351-5,737)	<0.001
Median hsTnT, ng/L	19.4 (13.3-28.9)	26.0 (17.4-41.8)	<0.001
Median KCCQ-TSS[a]	79.2 (61.5-93.8)	65.6 (52.1-85.4)	<0.001
KCCQ—patient-reported peripheral edema in last 2 wk on awakening			<0.001
Every morning	145 (5.5)	36 (10.0)	
3 or more times a week, but not every day	133 (5.1)	32 (8.9)	
1-2 times a week	267 (10.2)	59 (16.3)	
Less than once a week	363 (13.8)	46 (12.7)	
Never over the past 2 weeks	1,717 (65.4)	188 (52.1)	
Body mass index, kg/m^2	28.7 ± 6.0	27.5 ± 5.5	<0.001
Investigator-reported cause of heart failure			0.015
Ischemic	1,606 (58.5)	252 (66.3)	
Nonischemic	937 (34.2)	105 (27.6)	
Unknown	200 (7.3)	23 (6.1)	
Medical history			
Hospitalization for heart failure	1,231 (44.9)	182 (47.9)	0.27
Time from last hospitalization for heart failure to randomization			0.069
0-3 mo	182 (14.8)	42 (23.1)	
>3-6 mo	234 (19.0)	31 (17.0)	
>6-12 mo	260 (21.1)	39 (21.4)	
>1-2 y	191 (15.5)	28 (15.4)	
>2-5 y	209 (17.0)	21 (11.5)	
>5 y	155 (12.6)	21 (11.5)	
Atrial fibrillation	1,093 (39.8)	181 (47.6)	0.004
Type 2 diabetes	1,136 (41.4)	163 (42.9)	0.58
Estimated GFR, mL/min/1.73 m^2 of body surface area	65.7 ± 18.8	60.6 ± 18.0	<0.001
Estimated GFR rate <60 mL/min/1.73 m^2	1,068 (38.9)	200 (52.8)	<0.001
Device therapy			
Implantable cardioverter-defibrillator[b]	846 (30.8)	127 (33.4)	0.31
Cardiac-resynchronization therapy[c]	226 (8.2)	33 (8.7)	0.77

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either a hospitalization for HF or an urgent visit resulting in intravenous HF therapy that did not lead to hospital admission.[13] In this analysis, we compared the effect of dapagliflozin, to placebo, on the primary composite outcome, the individual components of cardiovascular death and worsening HF events, total HF hospitalizations and cardiovascular death, death from any cause, and the change from baseline to 8 months in the Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) using a scale from 0 to 100, with a higher score indicating fewer symptoms and a ≥5 change considered clinically meaningful. We also examined the post hoc exploratory endpoints of sudden cardiac death and death caused by worsening HF.

STATISTICAL ANALYSIS. In this analysis, CA125 was examined according to subgroups defined by the reported upper limit of normal of 35 U/mL, the median value, and quartiles.[4,14] Baseline characteristics were compared across these groups by the Pearson chi-square test for categorical variables and the Student's *t*-test or Wilcoxon rank-sum test for continuous variables, as appropriate.

The relationship between CA125 levels at baseline and outcomes was analyzed using Cox proportional hazards models adjusted for a history of hospitalization for HF (not included in the model for all-cause mortality) and treatment. Further adjustment was performed for other variables associated with outcomes in HFrEF: age, sex, heart rate, systolic blood pressure, body mass index, ischemic etiology of HF, LVEF, NYHA functional class, atrial fibrillation, and eGFR. Additional models included further adjustment for log NT-proBNP, log high-sensitivity troponin T (hsTnT), and log growth differentiation factor (GDF)-15. The annualized slope of change in eGFR over time from day 14 to day 720 of follow-up according to CA125 levels was analyzed using a mixed model for repeated measurements (adjusted for baseline values, visit, randomized treatment and interaction of treatment, and visit with a random intercept and slope per patient). The relationship between CA125 as a continuous variable and outcomes was analyzed using restricted cubic splines with 3 knots and adjusted for the same factors detailed herein. The association between change in CA125 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 CA125 data. The additional predictive value of CA125 to the PREDICT-HF risk model and

NT-proBNP alone in predicting the composite outcome of cardiovascular death or hospitalization for HF was examined using the area under the curve (AUC) from receiver-operating characteristic curves following logistic regression models using log-transformed CA125 and NT-proBNP and the additional predictive value expressed using a continuous net reclassification index and integrated discrimination improvement metric with 95% CIs (1,000× bootstrapping).[15] 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 previously described.[16] The association between CA125 and circulating other biomarkers was examined using linear regression models using log-transformed variables where appropriate.

The effect of dapagliflozin compared to placebo on each outcome was calculated as HR and 95% CI

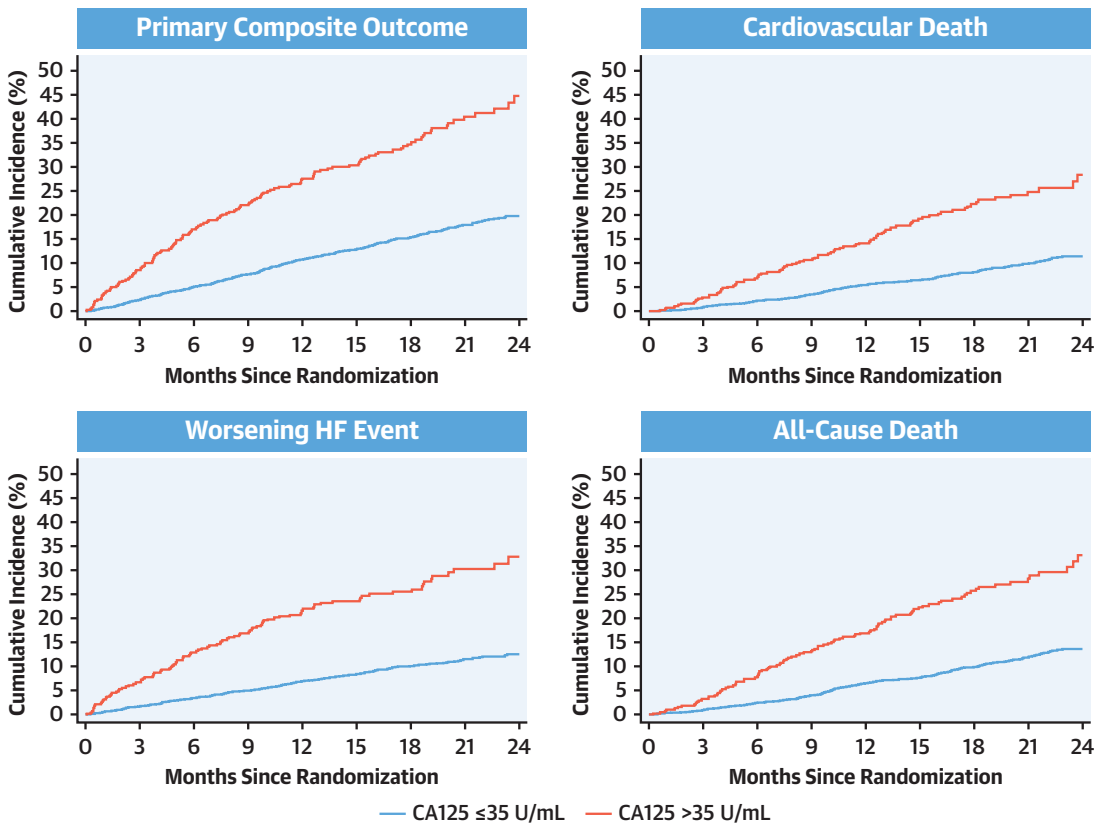
TABLE 1 Continued

	≤35 U/mL (n = 2,743)	>35 U/mL (n = 380)	*P* Value
Heart failure medication			
Any diuretic	2,305 (84.0)	344 (90.5)	<0.001
Loop diuretic	2,214 (80.7)	335 (88.2)	<0.001
Mean furosemide equivalent dose, mg	45.6 ± 68.0	52.6 ± 48.6	0.07
Non-loop diuretic	278 (10.1)	37 (9.7)	0.81
ACE inhibitor/ARB	2,254 (82.2)	311 (81.8)	0.87
Sacubitril/valsartan	337 (12.3)	42 (11.1)	0.49
Beta-blocker	2,627 (95.8)	364 (95.8)	0.99
Mineralocorticoid receptor antagonist	1,952 (71.2)	274 (72.1)	0.70
Digitalis	403 (14.7)	76 (20.0)	0.007

Values are n (%), mean ± SD, or median (IQR). Percentages may not total 100 because of rounding. [a]KCCQ-TSS ranges from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. A score of 75 or higher is considered to reflect satisfactory health status. [b]Either implantable cardioverter-defibrillator or cardiac resynchronization therapy with a defibrillator. [c]Cardiac-resynchronization therapy with or without a defibrillator.

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; AF = atrial fibrillation; CA125 = carbohydrate antigen 125; ECG = electrocardiogram; GFR = glomerular filtration rate; hsTnT = high-sensitivity troponin T; KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire total symptom score; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

FIGURE 1 Outcomes According to CA125 Using the Cutoff of ≤35 U/mL



The cumulative incidences of the primary composite outcome, worsening heart failure (HF) event, death from cardiovascular causes, and death from any cause were estimated with the use of the Kaplan-Meier method according to baseline carbohydrate antigen 125 (CA125) using the cutoff of ≤35 U/mL.

TABLE 2 Outcomes According to Baseline CA125 Concentration Using Cutoff of ≤35 U/mL

	≤35 U/mL (n = 2,743)	>35 U/mL (n = 380)
Primary composite endpoint[a]	436 (15.9)	140 (36.8)
Event rate per 100 person-years	11.1 (10.1-12.2)	30.1 (25.5-35.5)
Unadjusted HR	1.00 (referent)	2.68 (2.21-3.24)
Adjusted HR—model 1	1.00 (referent)	2.34 (1.92-2.84)
Adjusted HR—model 2	1.00 (referent)	1.59 (1.29-1.96)
Adjusted HR—model 3	1.00 (referent)	1.53 (1.24-1.89)
Cardiovascular death	238 (8.7)	86 (22.6)
Event rate per 100 person-years	5.8 (5.1-6.6)	16.4 (13.3-20.3)
Unadjusted HR	1.00 (referent)	2.83 (2.21-3.63)
Adjusted HR—model 1	1.00 (referent)	2.32 (1.80-2.99)
Adjusted HR—model 2	1.00 (referent)	1.47 (1.11-1.93)
Adjusted HR—model 3	1.00 (referent)	1.40 (1.05-1.01)
Worsening HF event[a]	270 (9.8)	99 (26.0)
Event rate per 100 person-years	6.9 (6.1-7.8)	21.2 (17.5-25.9)
Unadjusted HR	1.00 (referent)	3.04 (2.41-3.82)
Adjusted HR—model 1	1.00 (referent)	2.71 (2.14-3.44)
Adjusted HR—model 2	1.00 (referent)	1.87 (1.46-2.41)
Adjusted HR—model 3	1.00 (referent)	1.79 (1.38-2.31)
All-cause mortality	289 (10.5)	102 (26.8)
Event rate per 100 person-years	7.0 (6.3-7.9)	19.5 (16.0-23.6)
Unadjusted HR	1.00 (referent)	2.77 (2.21-3.47)
Adjusted HR—model 1	1.00 (referent)	2.35 (1.87-2.97)
Adjusted HR—model 2	1.00 (referent)	1.55 (1.21-2.00)
Adjusted HR—model 3	1.00 (referent)	1.45 (1.12-1.88)
Total HF hospitalizations and cardiovascular death[b]	625	239
Event rate per 100 person-years	15.3 (14.1-16.5)	45.8 (40.3-52.0)
Unadjusted RR	1.00 (referent)	2.98 (2.57-3.46)
Adjusted RR—model 1	1.00 (referent)	2.54 (2.18-2.96)
Adjusted RR—model 2	1.00 (referent)	1.72 (1.46-2.03)
Adjusted RR—model 3	1.00 (referent)	1.64 (1.38-1.94)
Sudden cardiac death	104 (3.8)	26 (6.8)
Event rate per 100 person-years	2.5 (2.1-3.1)	5.0 (3.4-7.3)
Unadjusted HR	1.00 (referent)	1.96 (1.27-3.01)
Adjusted HR—model 1	1.00 (referent)	1.61 (1.04-2.50)
Adjusted HR—model 2	1.00 (referent)	1.04 (0.65-1.67)
Adjusted HR—model 3	1.00 (referent)	0.99 (0.61-1.61)
Heart failure death	56 (2.0)	32 (8.4)
Event rate per 100 person-years	1.4 (1.0-1.8)	6.1 (4.3-8.6)
Unadjusted HR	1.00 (referent)	4.48 (2.90-6.92)
Adjusted HR—model 1	1.00 (referent)	3.31 (2.11-5.19)
Adjusted HR—model 2	1.00 (referent)	2.11 (1.29-3.45)
Adjusted HR—model 3	1.00 (referent)	1.98 (1.20-3.27)
Slope of change in eGFR per year, mL/min/1.73 m^2	−1.77 (−2.06 to −1.49)	−2.84 (−3.66 to −2.01)

Values are n (%), event rate (95% CI), HR (95% CI), RR (95% CI), or n, unless otherwise indicated. Unadjusted analyses include factors for randomized treatment and history of HF hospitalization (not in the model for all-cause mortality), and are stratified by diabetes status. Adjusted analyses include factors for randomized treatment, history of HF hospitalization, age, sex, heart rate, systolic blood pressure, body mass index, ischemic etiology of heart failure, left ventricular ejection fraction, NYHA functional class, atrial fibrillation, and eGFR (model 1) and the same factors including log NT-proBNP and log hsTnT (model 2) and log NT-proBNP, log hsTnT, and log GDF-15 (model 3). Models 1, 2, and 3 were stratified by diabetes status. [a]The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or death from cardiovascular causes. [b]Risk estimate presented is a rate ratio.

eGFR = estimated glomerular filtration rate; GDF = growth differentiation factor; HF = heart failure; RR = rate ratio; other abbreviations as in Table 1.

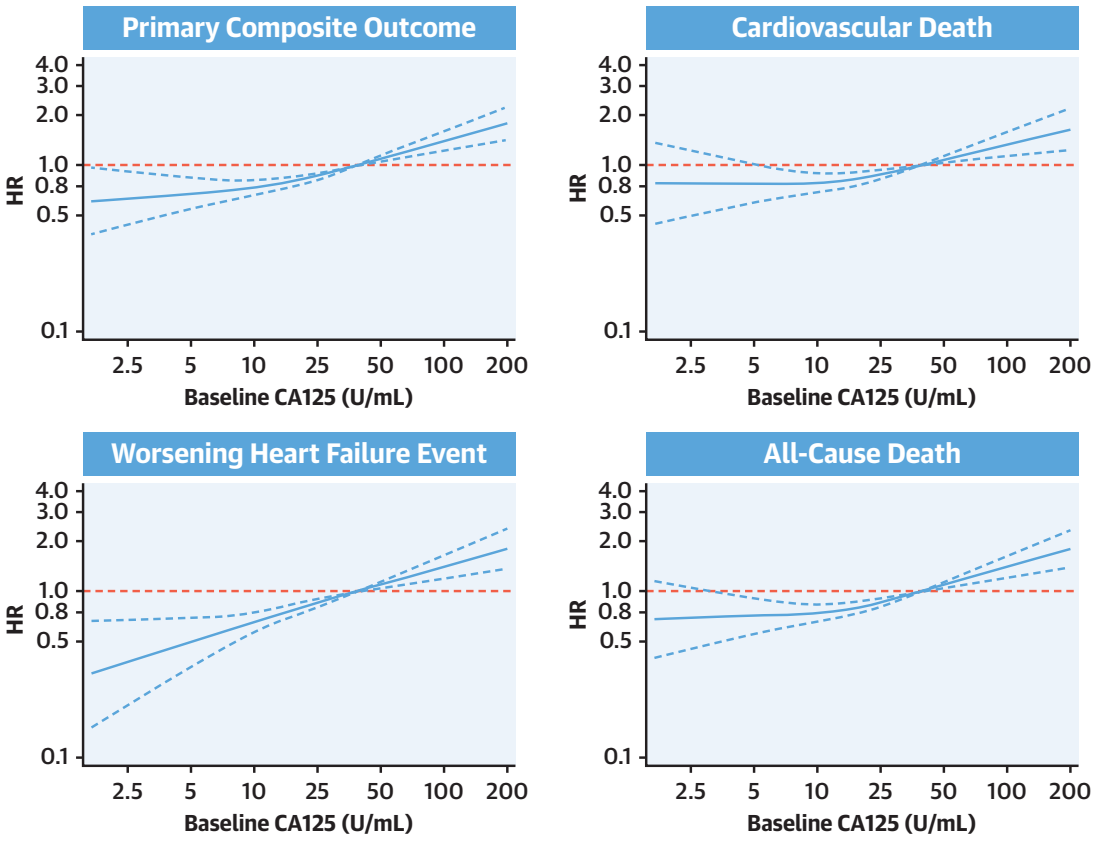
derived from Cox proportional hazards models adjusted for a history of hospitalization for HF and treatment assignment and stratified by baseline diabetes status, as prespecified in the statistical analysis plan for the main trial. The effect of dapagliflozin on the composite endpoint of recurrent (first and total) HF hospitalizations and cardiovascular death was examined using a semiparametric proportional rates model.[12] The proportion of patients in each treatment group reporting a clinically meaningful change (≥5 points) in KCCQ-TSS was analyzed using methods previously described.[12] The effect of dapagliflozin on the primary outcome according to baseline CA125, analyzed as a continuous variable, was examined using a fractional polynomial analysis. The effect of dapagliflozin on CA125 between baseline and 12 months is presented as a relative difference calculated from a linear regression model adjusted for log-transformed baseline and 12-month values. All analyses were performed using Stata 17 (StataCorp) and SAS version 9.4 (SAS Institute). A value of $P < 0.05$ was considered statistically significant.

RESULTS

Of the 4,744 patients randomized in DAPA-HF, 3,123 (66%) had a baseline measurement of CA125 and 2,427 (78%) of these had a second measurement at 12 months. The distribution of CA125 at baseline is displayed in Supplemental Figure 1. At baseline, mean and median CA125 levels were 23.38 ± 44.1 U/mL and 13.04 U/mL (IQR: 8.78-21.13 U/mL), respectively. Median CA125 did not differ significantly between men (12.69 U/mL [IQR: 8.91-20.08 U/mL]) and women (13.13 U/mL [IQR: 8.75-21.68 U/mL]; $P = 0.65$). Baseline CA125 was elevated above 35 U/mL (the upper limit of normal) in 380 patients (12.2%).

PATIENT CHARACTERISTICS. Baseline characteristics according to cutoff (≤35 or >35 U/mL) and median (<13.04 or ≥13.04 U/mL) CA125 concentrations are displayed in **Table 1** and Supplemental Table 1, respectively. Patients with higher concentrations of CA125 were older; more frequently were in worse NYHA functional class; had higher heart rate, NT-proBNP, and hsTnT concentrations; and lower mean systolic blood pressure, LVEF, eGFR, body mass index, and median KCCQ-TSS. Patients with higher CA125 levels more frequently reported peripheral edema on their KCCQ compared to those with lower CA125. Among those who had been hospitalized with HF, individuals with higher CA125 levels had been discharged more recently than those with lower

FIGURE 2 **Association Between Outcomes and Baseline CA125**



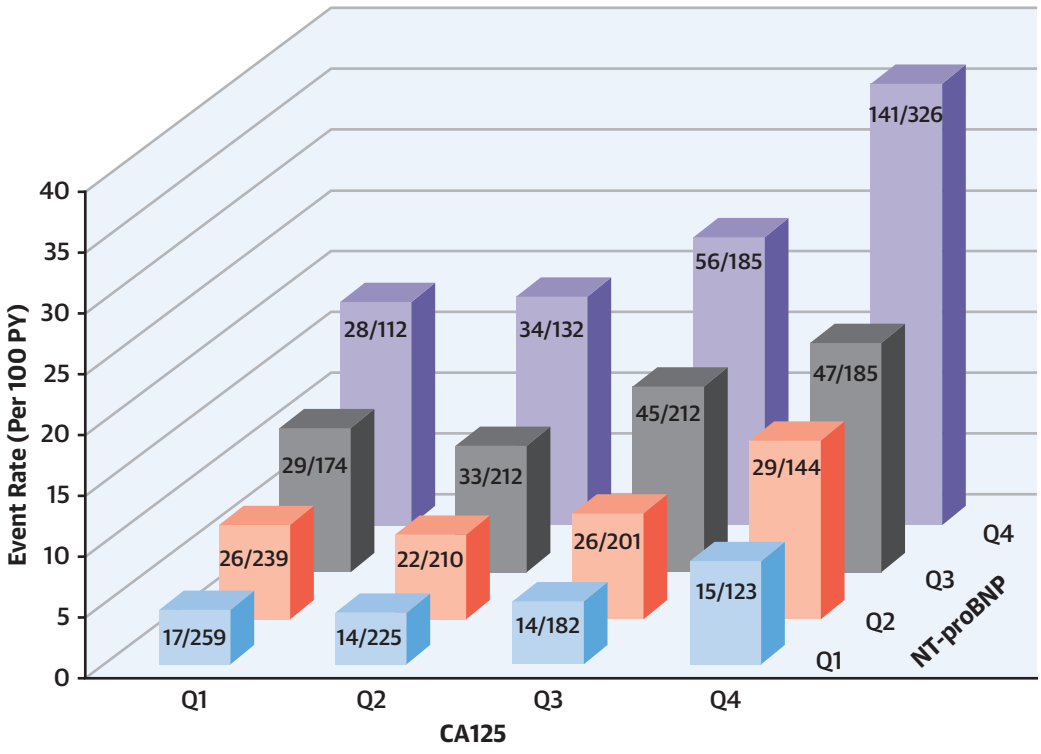
The **solid blue line** represents a continuous HR calculated from an adjusted restricted cubic spline (3 knots). The **dashed blue lines** represent the 95% CI around the HR estimate. The **dashed red line** represents an HR of 1.00. The point of reference (HR: 1.00) is the carbohydrate antigen 125 (CA125) concentration of 35 U/mL.

levels. A history of atrial fibrillation was more frequent in patients with higher CA125 levels. Compared with those with lower concentrations, patients with higher CA125 levels were more frequently taking a diuretic (and the mean dose was higher) and digoxin.

CORRELATION OF CA125 WITH NT-proBNP, hsTnT, eGFR, AND GDF-15. The correlations between baseline log-transformed CA125 and log-transformed NT-proBNP and between log-transformed CA125 and eGFR are displayed in Supplemental Figure 2. Per unit increase in log-NT-proBNP, log-hsTnT, and log-GDF-15 was associated with an increase in log-CA125 of 0.31 (95% CI: 0.28-0.35; $P < 0.001$), 0.26 (95% CI: 0.21-0.30; $P < 0.001$) and 0.22 (95% CI: 0.19-0.26; $P < 0.001$), respectively. Per unit increase in eGFR was associated with a decrease in log-CA125 of 0.01 (95% CI: 0.01-0.00; $P < 0.001$).

OUTCOMES ACCORDING TO BASELINE CA125. The cumulative incidence of the primary composite outcome, its components, and all-cause mortality, according to baseline CA125 concentration (≤35 or >35 U/mL), are shown in **Figure 1** (and by quartiles in Supplemental Figure 3). When using the cutoff value of 35 U/mL, the risks of the primary and the secondary morbidity/mortality outcomes were higher in patients with elevated CA125 concentrations in both unadjusted and adjusted analyses with and without adjustment for NT-proBNP, hsTnT, and GDF-15 (**Table 2**). When considering cause-specific cardiovascular mortality, the risk of death caused by worsening HF, but not sudden cardiac death, was

FIGURE 3 Primary Composite Endpoint by Quartiles of Baseline CA125 and NT-proBNP



The data presented in each bar are the number of events per number of patients. There was no significant interaction between carbohydrate antigen 125 (CA125) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) and the risk of the primary outcome (interaction $P = 0.10$). PY = patient-years.

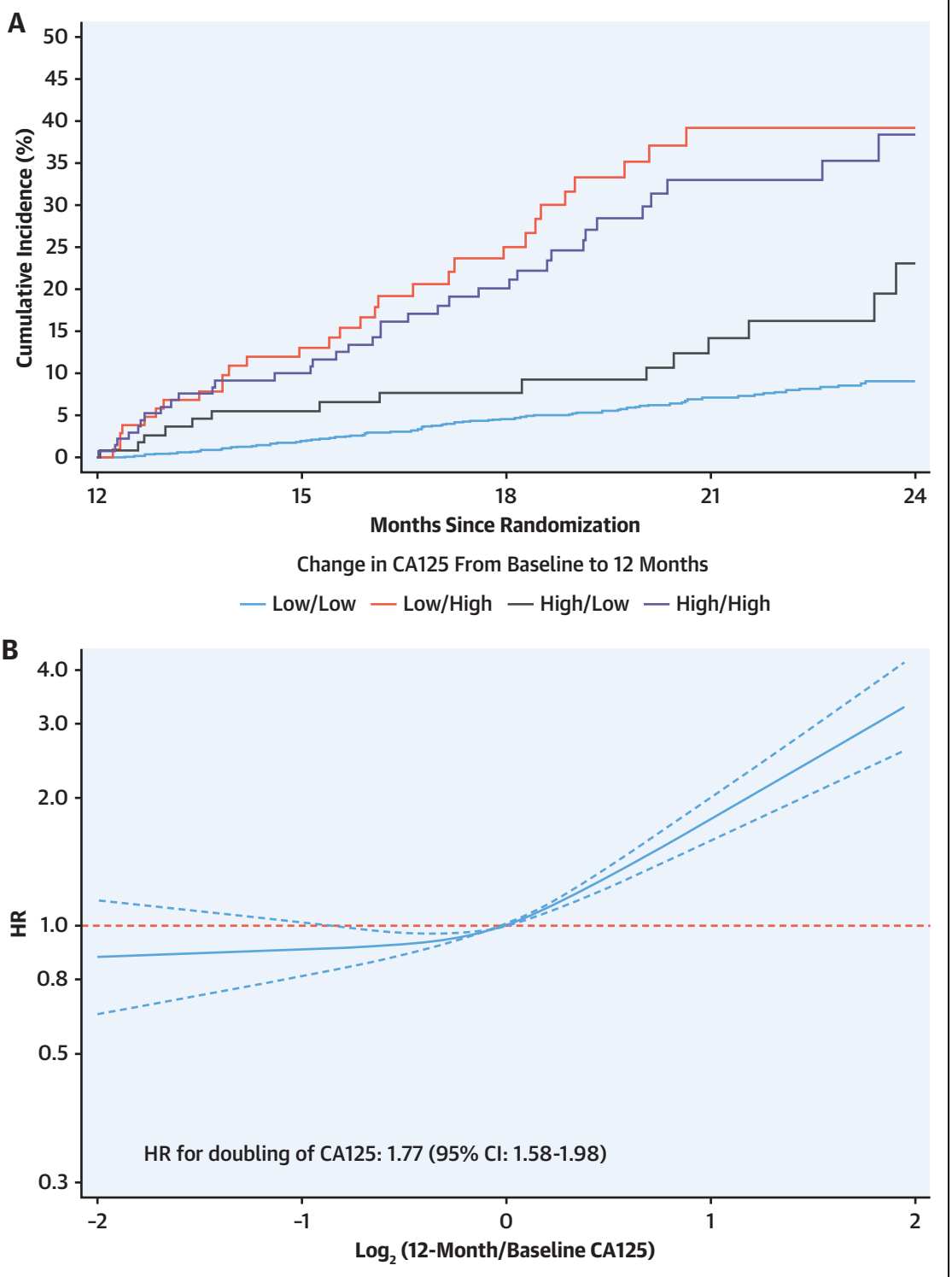
significantly higher in adjusted analyses in patients with CA125 >35 U/mL (Table 2). In analyses by quartiles, the risk of the primary composite outcome was higher after adjustment among those in quartile 4 (Q4) (≥21.14 U/mL), but not in Q2 and Q3, relative to Q1 (≤8.78 U/mL) (Supplemental Table 2). However, the risk of the secondary endpoint of worsening HF was higher in Q3 (13.05-21.13 U/mL) as well as Q4 compared to Q1 (Supplemental Table 2). The associations between CA125 analyzed as a continuous variable and outcomes are displayed in Figure 2, Supplemental Table 3, and Supplemental Figure 4.

Renal function declined over time to a greater degree in patients with CA125 >35 U/mL with an annual slope of change of −2.84 mL/min/1.73 m^2 (95% CI: −3.66 to −2.01 mL/min/1.73 m^2) compared with −1.77 mL/min/1.73 m^2 (95% CI: −2.06 to −1.49 mL/min/1.73 m^2) in patients with concentrations ≤35 U/mL, P for comparison = 0.02 (Table 2).

Figure 3 displays the incidence rate of the primary composite outcome according to quartiles of baseline CA125 and NT-proBNP. There was a stepwise increment in the rate of the primary composite outcome within each quartile of NT-proBNP with increasing CA125 concentrations. Compared to those in the lowest quartile of both NT-proBNP and CA125, those in the highest quartiles of both biomarkers were at an over 3-fold higher risk of the primary composite outcome (adjusted HR: 3.43; 95% CI: 2.22-5.30). There was no significant interaction between CA125 and NT-proBNP and the risk of the primary outcome (interaction $P = 0.10$).

PREDICTIVE VALUE OF CA125. When added to the PREDICT-HF risk model (AUC: 0.715) for the composite of cardiovascular death and HF hospitalization, baseline CA125 level provided additional prognostic information (combination of PREDICT

FIGURE 4 **Outcomes and Change in CA125 at 12 Months From Baseline**



(A) The cumulative incidence of the primary outcome in a landmark analysis from 12 months postrandomization is displayed by groups of baseline and 12-month carbohydrate antigen 125 (CA125) concentrations. Low = CA125 ≤35 U/mL; high = CA125 >35 U/mL. **(B)** The subsequent risk of the primary composite outcome is displayed according to the change in CA125 concentration from baseline to 12 months. HR for the primary outcome according to the $\log_2$-transformed ratio of 12 months to baseline CA125 were modeled using adjusted restricted cubic spline analysis. The referent point is patients with no change in CA125. The **dashed lines** represent 95% CIs of the HR estimates. A value of 1.0 on the x-axis represents a doubling in CA125 from baseline to 12 months.

TABLE 3 Effect of Dapagliflozin Compared With Placebo According to Quartiles of Baseline CA125 Concentration

	Q1 (n = 784) ≤8.78 U/mL		Q2 (n = 779) 8.79-13.04 U/mL	
	Dapagliflozin	Placebo	Dapagliflozin	Placebo
Primary composite outcome[a]				
No. of events	53/409 (13.0)	47/375 (12.5)	39/398 (9.8)	64/381 (16.8)
Rate	9.1 (6.9-11.9)	8.8 (6.6-11.7)	6.4 (4.7-8.8)	11.8 (9.2-15.0)
HR	0.99 (0.67-1.47)		0.54 (0.36-0.80)	
Cardiovascular death				
No. of events	34/409 (8.3)	25/375 (6.7)	19/398 (4.8)	31/381 (8.1)
Rate	5.7 (4.1-8.0)	4.5 (3.0-6.6)	3.1 (2.0-4.8)	5.4 (3.8-7.7)
HR	1.17 (0.69-1.96)		0.57 (0.32-1.00)	
Worsening heart failure event[a]				
No. of events	27/409 (6.6)	26/375 (6.9)	23/398 (5.8)	39/381 (10.2)
Rate	4.6 (3.2-6.8)	4.8 (3.3-7.1)	3.8 (2.5-5.7)	7.2 (5.2-9.8)
HR	0.94 (0.55-1.61)		0.52 (0.31-0.86)	
All-cause death				
No. of events	42/409 (10.3)	28/375 (7.5)	25/398 (6.3)	35/381 (9.2)
Rate	7.0 (5.2-9.5)	5.0 (3.5-7.3)	4.0 (2.7-6.0)	6.1 (4.4-8.5)
HR	1.31 (0.81-2.12)		0.66 (0.40-1.11)	
Total heart failure hospitalizations and cardiovascular death				
No. of events	69	58	50	87
Rate	11.6 (9.1-14.7)	10.5 (8.1-13.6)	8.1 (6.1-10.7)	15.3 (12.4-18.9)
Rate ratio	1.06 (0.68-1.64)		0.52 (0.33-0.81)	
KCCQ-TSS				
Mean (95% CI) change in score at 8 months	4.0 (2.3 to 5.8)	1.4 (−0.4 to 3.3)	3.8 (2.1 to 5.5)	1.5 (−0.3 to 3.4)
Patients with ≥5, point improvement at 8 months, %	58.8 (53.6-63.9)	50.0 (44.4-55.5)	57.7 (52.6-62.9)	48.2 (43.0-53.4)
OR	1.19 (1.03-1.38)		1.22 (1.05-1.42)	
Patients with ≥5-point deterioration at 8 months, %	23.5 (19.2-27.8)	32.0 (26.9-37.0)	23.8 (19.4-28.1)	33.6 (28.7-38.5)
OR	0.81 (0.69-0.96)		0.78 (0.66-0.91)	

Values are n/N (%), rate (95% CI), HR (95% CI), OR (95% CI), mean (95% CI), or % (95% CI), unless otherwise indicated. Event rates presented per 100 patient-years. HRs and 95% CIs were estimated with the use of Cox regression models, stratified according to diabetes status, with a history of hospitalization for heart failure and treatment-group assignment as explanatory variables (for all-cause mortality history of hospitalization for heart failure was not included in the model). aThe primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or death from cardiovascular causes.

Q1 = quartile 1; other abbreviations as in Table 1.

Continued on the next page

HF + CA125; AUC: 0.731) with a continuous net reclassification index of 20.5% (95% CI: 10.4%-31.2%) and integrated discrimination improvement of 1.7% (95% CI: 0.7%-3.1%), and the *P* value for comparison of AUC was $P < 0.001$ (Supplemental Figure 5). The AUC for NT-proBNP alone was 0.691 and for CA125 was 0.631.

RELATIONSHIP BETWEEN CHANGES IN CA125 AND OUTCOMES. Figure 4A displays the cumulative incidence of the primary composite outcome in a landmark analysis from 12 months according to whether patients had a low (≤35 U/mL) or high (>35 U/mL) CA125 at baseline and 12 months. Relative to patients who had a low CA125 both at baseline and 12 months, those who started low and subsequently had a high CA125 at 12 months had an HR of 5.90 (95% CI: 3.94-8.83), and those who were high at both time points had an HR of 5.13 (95% CI: 3.53-7.48). Figure 4B displays the association between change in CA125 assessed as a continuous variable: a doubling of CA125 from baseline to 12 months was associated with an HR for the primary composite of 1.77 (95% CI: 1.58-1.98).

The change in CA125 from baseline to 12 months was inversely correlated with change in diuretic dose ($r = -0.07$; $P = 0.001$) but not with change in weight over the same time ($r < 0.01$; $P = 0.96$).

EFFECT OF DAPAGLIFLOZIN ACCORDING TO BASELINE CA125. The effect of dapagliflozin compared with placebo on the primary outcome and the secondary morbidity/mortality outcomes is presented by CA125 quartiles in Table 3 and as a continuous variable in Figure 5. The benefit of dapagliflozin in reducing the risk of the primary composite outcome was consistent

TABLE 3 Continued

Q3 (n = 780) 13.05-21.13 U/mL		Q4 (n = 780) ≥21.14 U/mL		Interaction *P* Value
Dapagliflozin	Placebo	Dapagliflozin	Placebo	
61/384 (15.9)	80/396 (20.2)	109/388 (28.1)	123/392 (31.4)	
10.9 (8.5-14.0)	14.7 (11.8-18.3)	21.5 (17.8-25.9)	24.3 (20.3-28.9)	
0.75 (0.54-1.04)		0.89 (0.68-1.15)		0.13
34/384 (8.9)	37/396 (9.3)	64/388 (16.5)	80/392 (20.4)	
5.8 (4.1-8.1)	6.3 (4.5-8.7)	11.6 (9.1-14.8)	14.2 (11.4-17.7)	
0.92 (0.57-1.46)		0.81 (0.58-1.12)		0.25
38/384 (9.9)	59/396 (14.9)	76/388 (19.6)	81/392 (20.7)	
6.8 (4.9-9.3)	10.9 (8.4-14.0)	15.0 (12.0-18.8)	16.0 (12.8-19.9)	
0.64 (0.42-0.95)		0.94 (0.69-1.28)		0.17
37/384 (9.6)	49/396 (12.4)	79/388 (20.4)	96/392 (24.5)	
6.3 (4.6-8.7)	8.3 (6.3-11.0)	14.3 (11.5-17.8)	17.1 (14.0-20.8)	
0.76 (0.49-1.16)		0.83 (0.62-1.12)		0.17
91	127	176	206	
15.7 (12.7-19.2)	21.6 (18.1-25.7)	31.8 (27.5-36.9)	36.9 (32.2-42.3)	
0.74 (0.51-1.07)		0.87 (0.65-1.15)		0.13
4.9 (3.0, 6.8)	3.1 (1.0, 5.1)	7.2 (5.0, 9.4)	5.0 (2.8, 7.3)	0.90
56.1 (50.9-61.2)	52.2 (47.1-57.4)	55.3 (50.2-60.4)	50.8 (45.4-56.1)	
1.08 (0.92-1.25)		1.08 (0.92-1.26)		0.84
25.5 (21.0-29.9)	32.0 (27.3-36.8)	29.2 (24.5-34.0)	33.2 (28.3-38.2)	
0.85 (0.73-1.00)		0.92 (0.79-1.08)		0.70

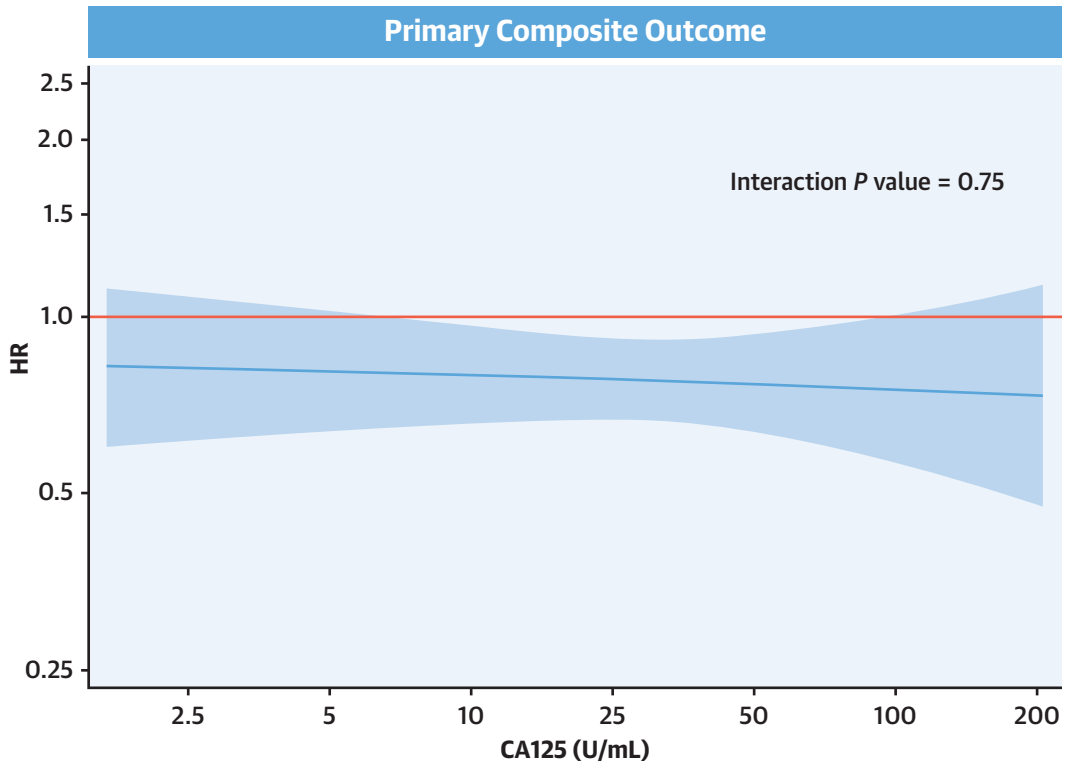
across the quartiles: Q1, HR: 0.99 (95% CI: 0.67-1.47); Q2, HR: 0.54 (95% CI: 0.36-0.80); Q3, HR: 0.75 (95% CI: 0.51-1.04); Q4, HR: 0.89 (95% CI: 0.68-1.15); interaction $P = 0.13$. When assessed as a continuous variable, there was a consistency of benefit of dapagliflozin across the range of CA125 at baseline in DAPA-HF (interaction $P = 0.75$). A similar consistency of benefit of dapagliflozin was seen across the CA125 quartiles for the secondary morbidity/mortality outcomes and the effect on KCCQ-TSS (all interaction $P > 0.10$) (Table 3).

EFFECT OF DAPAGLIFLOZIN ON CA125 CONCENTRATIONS. In the dapagliflozin group, the mean change in CA125 from baseline to 12 months was −1.29 U/mL (95% CI: −4.05 to 1.46 U/mL) and the corresponding change in the placebo group was 0.69 U/mL (95% CI: −1.40 to 2.79 U/mL); placebo-corrected relative change of −5.2% (95% CI: −10.6% to 0.5%; $P = 0.07$). There was no modification of the effect according to CA125 ≤35 or >35 U/mL (interaction $P = 0.79$), quartiles of CA125 (interaction $P = 0.63$), < or ≥ median NT-proBNP (interaction $P = 0.22$), diabetes status (interaction $P = 0.75$), or whether patients were taking a diuretic (interaction $P = 0.63$). In patients with a history of previous HF hospitalization, dapagliflozin reduced CA125 with a placebo-corrected change of −11.7% (95% CI: −4.2% to −18.7%) with no effect in those without a history of hospitalization (0.8%; 95% CI: −7.3% to 9.5%), interaction $P = 0.03$.

DISCUSSION

CA125 is a circulating glycoprotein, encoded by *MUC16*, which is predominantly synthesized by mesothelial cells in the pericardium, pleura, and peritoneum.[4] It is also produced by epithelial ovarian tumors and has an established role in the monitoring of ovarian cancer.[17] Production of CA125 is thought to be up-regulated in response to the activation of mesothelial cells by increased mechanical and hydrostatic stress and inflammatory cytokines.[4,18] Elevated levels of CA125 are present in up to two-thirds of patients with worsening HF and correlate

FIGURE 5 **Effect of Dapagliflozin Compared With Placebo According to Baseline CA125**

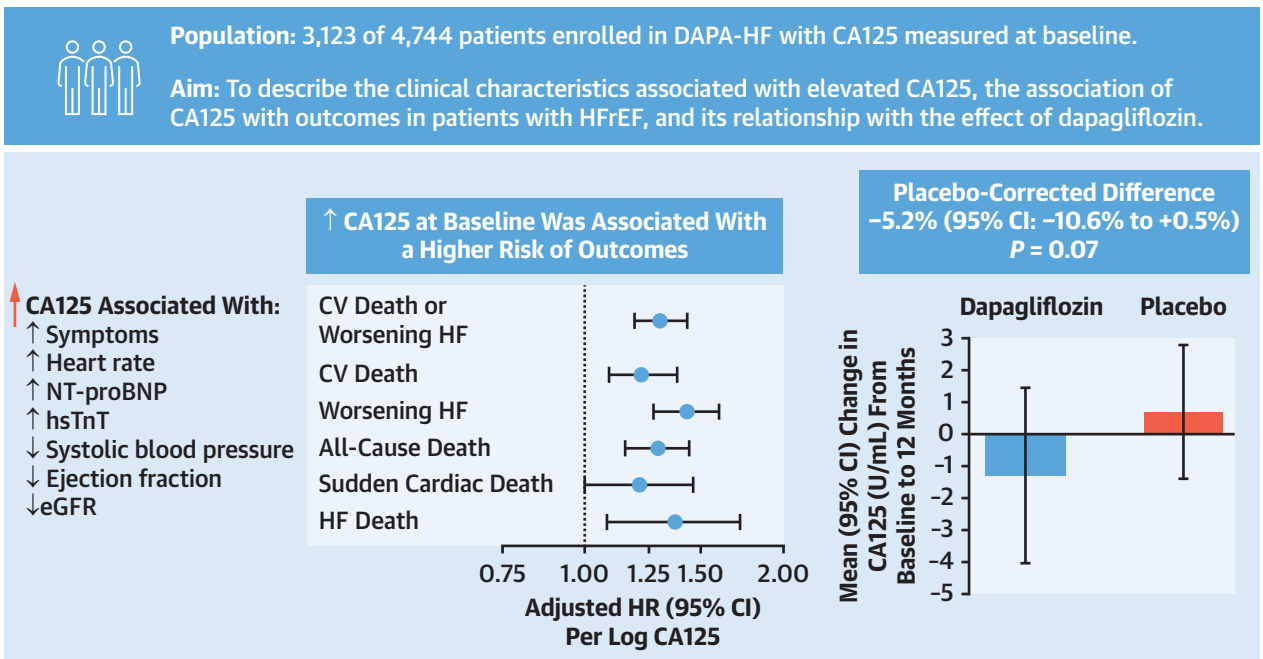


The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or death from cardiovascular causes. The **solid blue line** represents a continuous HR, and the **solid red line** represents a HR of 1.00 (ie, no difference between treatments). The **shaded area** represents the 95% CI around the HR. CA125 = carbohydrate antigen 125.

with biomarkers of congestion (NT-proBNP, adrenomedullin, the presence of pleural or pericardial effusions, and echocardiographic and invasive markers of elevated filling pressures) and inflammation (interleukin-6 and GDF-15).[4] In patients discharged following hospitalization for worsening HF, a CA125-guided therapy strategy (aiming for a level ≤35 U/mL) to tailor decongestive treatments reduced the risk of mortality and rehospitalization.[14] Due to its potential as a circulating biomarker of congestion, research into its role in the management of patients with HF has to date largely focused on patients hospitalized with worsening HF. This post hoc exploratory analysis from DAPA-HF is, to our knowledge, the largest description of CA125 in a cohort of patients with chronic ambulatory HFrEF, the majority of whom were clinically "stable" in NYHA functional class II and were at least 4 weeks from an episode of worsening HF with over one-half of patients having never been hospitalized for worsening HF.

CA125 levels in DAPA-HF were significantly lower than those reported in acute HF populations with only 12% of patients having a level >35 U/mL.[4,6,14] Several features suggest that patients with higher levels of CA125 had more severe HF including higher NT-proBNP and hsTnT levels, lower ejection fraction, and lower (worse) KCCQ-TSS (**Central Illustration**). Consistent with this, the incidence of the primary composite outcome and secondary morbidity/mortality outcomes was higher with increasing CA125 concentrations. This relationship persisted after adjustment for other prognostic features including NT-proBNP and hsTnT and was strongest for a worsening HF event (CA125 >35 U/mL; adjusted HR: 1.87) as compared with cardiovascular death (adjusted HR: 1.55). Moreover, elevated CA125 levels were an independent predictor of the risk of death from worsening HF (adjusted HR: 2.11) but not sudden cardiac death (adjusted HR: 1.04), which perhaps is reflective of their association with congestion. Consistent with

CENTRAL ILLUSTRATION **Carbohydrate Antigen 125 in Heart Failure With Reduced Ejection Fraction and Relationship With Dapagliflozin**



Docherty KF, et al. J Am Coll Cardiol. 2023;82(2):142–157.

Adjusted analyses include factors for randomized treatment, history of heart failure (HF) hospitalization, age, sex, heart rate, systolic blood pressure, body mass index, ischemic etiology of HF, left ventricular ejection fraction, NYHA functional class, atrial fibrillation, estimated glomerular filtration rate (eGFR), log N-terminal pro–B-type natriuretic peptide (NT-proBNP), and log high-sensitivity troponin T (hsTnT). The Cox models were stratified by diabetes status. CA125 = carbohydrate antigen 125; CV = cardiovascular; DAPA-HF = Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; HFrEF = heart failure with reduced ejection fraction.

this, there was an apparent linear relationship with a higher risk of worsening HF events with increasing CA125 across the full range of concentrations, whereas for cardiovascular and all-cause mortality the gradient of higher risk with increasing levels was less pronounced at CA125 concentrations ≤35 U/mL.

Furthermore, changes in CA125 identified patients with a worse prognosis; patients in whom CA125 increased above 35 U/mL at 1 year from baseline were at an approximate 6-fold higher risk of the primary composite outcome as compared with those in whom CA125 remained ≤35 U/mL. The finding from DAPA-HF that baseline CA125 and changes in CA125 were independent predictors of worsening HF and mortality in patients with chronic HFrEF adds to the existing literature describing this association in small cohorts in patients with chronic ambulatory HF (without adjustment for natriuretic peptides) and in patients with worsening HF including after adjustment for NT-proBNP.[5,6,19-21]

Strategies using NT-proBNP concentrations as a marker of congestion have not been demonstrated to reduce morbidity or mortality in patients with HFrEF.[22] The use of NT-proBNP alone as a marker of elevated left-sided filling pressures may not be sufficient to fully assess patient congestion status; indeed, in the PARADIGM-HF trial, the total number of physical signs of systemic and pulmonary congestion was independently predictive of outcomes including after adjustment for natriuretic peptide levels.[2] Measurement of CA125 may provide additional information regarding systemic congestion: in a cohort of patients with severe functional tricuspid regurgitation and acute HF, CA125 outperformed NT-proBNP in predicting mortality; and in patients with acute HF, CA125, but not NT-proBNP, was predictive of the degree of renal venous congestion measured by ultrasound.[20,23] The modest positive correlation between NT-proBNP and CA125 seen in DAPA-HF and previous studies serves to highlight

that these 2 markers may be complementary to one another and not simply a surrogate for each other, as evidenced by the stepwise gradient in higher risk across combined quartiles of both biomarkers. Previous multibiomarker panels in HF reflecting different pathophysiologic pathways have suggested an incremental value of the addition of multiple biomarkers to clinical prediction models. However, the benefit of additional biomarkers on top of NT-proBNP alone is small and for some, including mid-regional pro-adrenomedullin as a marker of congestion, nonsignificant.[24,25] In DAPA-HF, baseline CA125 provided significant incremental predictive information (net reclassification index: 20.5%) on top of the comprehensive PREDICT-HF risk model, which includes NT-proBNP.[15] Future studies examining a combined NT-proBNP and CA125-guided treatment strategy are warranted to further explore the clinical utility of this result.

The efficacy of dapagliflozin compared with placebo in reducing the risk of cardiovascular death or worsening HF was consistent across the range of CA125 at baseline. This finding is consistent with previous reports of no modification of the effect of SGLT2 inhibitors in HFrEF by diuretic use, NT-proBNP levels, in patients with a history of previous HF hospitalization, or in patients assessed to have recently been volume-overloaded.[26-29]

It was initially suggested that one of the key mechanisms of benefit of SGLT2 inhibition in patients with chronic HF was an increase in natriuresis and diuresis along with a reduction in extravascular congestion. Indeed, a decongestive effect was suggested by the observed reduction in invasively measured pulmonary artery pressure after 12 weeks of treatment with empagliflozin.[11] However, mechanistic studies have reported that the natriuretic and diuretic effect of SGLT2 inhibitors is relatively short-lived and consistent with this, the reduction in NT-proBNP is relatively modest.[10,12,30,31] Small nonrandomized studies of SGLT2 inhibitors have reported a reduction in CA125 (but not in NT-proBNP) in patients with HF and type 2 diabetes.[32,33] In DAPA-HF, there was a 5% reduction in CA125 with dapagliflozin at 12 months that did not reach statistical significance ($P = 0.07$).

Overall, along with the small effect of SGLT2 inhibitors on NT-proBNP, these results suggest that in the long term, a decongestive effect is not the only mechanism and may not be one of the main mechanisms of the benefits of SGLT2 inhibitors in HF. We found a significant reduction in CA125 with dapagliflozin in patients who had previously been hospitalized for HF and not in those with no prior hospitalization. Whether the effect of SGLT2 inhibitors on decongestion in terms of a reduction in CA125 is more pronounced in patients with decompensated HF is unknown, although we did not observe any suggestion of a modification of treatment effect by baseline CA125 or NT-proBNP concentrations to support this hypothesis.

STUDY LIMITATIONS. We did not have information regarding the clinical assessment of congestion in patients enrolled in DAPA-HF and therefore were unable to describe the prevalence of these findings according to baseline CA125. CA125 was only measured at baseline and 1 year following randomization, and we were unable to exclude a significant effect of dapagliflozin on reducing CA125 at earlier time points. Biomarker collection was not performed in all participating countries in DAPA-HF and not all randomized patients in DAPA-HF were included. Therefore, there may be a degree of selection bias in these analyses. All analyses presented were performed post hoc and should be considered exploratory.

CONCLUSIONS

In DAPA-HF, elevated levels of CA125 at baseline were an independent predictor of the risk of worsening HF and mortality, and an increase in CA125 from baseline to 12 months was associated with a higher subsequent risk of worsening HF and cardiovascular death. The benefits of dapagliflozin were not modified by baseline CA125, and dapagliflozin, compared with placebo, did not significantly reduce levels of CA125 at 12 months after randomization.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Elevated levels of circulating CA125 are associated with a higher risk of morbidity and mortality in ambulatory patients with chronic heart failure and reduced left ventricular ejection fraction, but the benefit of dapagliflozin is maintained.

TRANSLATIONAL OUTLOOK: Measurement of CA125 in patients with HFrEF adds prognostic information to that of NT-proBNP, and future studies should evaluate the utility of both biomarkers to guide therapy in patients with HFrEF.

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