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ORIGINAL RESEARCH PAPER

Cardio-Renal-Metabolic Overlap, Outcomes, and Dapagliflozin in Heart Failure With Mildly Reduced or Preserved Ejection Fraction

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ABSTRACT

BACKGROUND Cardio-renal-metabolic (CRM) conditions are individually common among patients with heart failure (HF), but the prevalence and influence of overlapping CRM conditions in this population have not been well-studied.

OBJECTIVES This study aims to evaluate the impact of overlapping CRM conditions on clinical outcomes and treatment effects of dapagliflozin in HF.

METHODS In this post hoc analysis of DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure), we evaluated the prevalence of comorbid CRM conditions (atherosclerotic cardiovascular disease, chronic kidney disease, and type 2 diabetes), their impact on the primary outcome (cardiovascular death or worsening HF), and treatment effects of dapagliflozin by CRM status.

RESULTS Among 6,263 participants, 1,952 (31%), 2,245 (36%), and 1,236 (20%) had 1, 2, and 3 additional CRM conditions, respectively. HF alone was uncommon (13%). Greater CRM multimorbidity was associated with older age, higher body mass index, longer-duration HF, worse health status, and lower left ventricular ejection fraction. Risk of the primary outcome increased with higher CRM overlap, with 3 CRM conditions independently associated with highest risk of primary events (adjusted HR: 2.16 [95% CI: 1.72-2.72]; $P < 0.001$) compared with HF alone. Relative benefits of dapagliflozin on the primary outcome were consistent irrespective of the type of CRM overlap ($P_{interaction} = 0.773$) and by the number of CRM conditions ($P_{interaction} = 0.734$), with greatest absolute benefits among those with highest CRM multimorbidity. Estimated 2-year numbers needed to treat with dapagliflozin to prevent 1 primary event were approximately 52, 39, 33, and 24 for participants with 0, 1, 2, and 3 additional CRM conditions at baseline, respectively. Adverse events between treatment arms were similar across the CRM spectrum.

CONCLUSIONS CRM multimorbidity was common and associated with adverse outcomes among patients with HF and left ventricular ejection fraction >40% in DELIVER. Dapagliflozin was safe and effective across the CRM spectrum, with greater absolute benefits among those with highest CRM overlap (Dapagliflozin Evaluation to Improve the LIVEs of Patients With Preserved Ejection Fraction Heart Failure [DELIVER]; NCT03619213). (J Am Coll Cardiol HF 2023;■:■-■)

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ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

CKD = chronic kidney disease

CRM = cardio-renal-metabolic

eGFR = estimated glomerular filtration rate

HFmrEF = heart failure with mildly reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire-Total Symptom Score

SGLT2 = sodium-glucose cotransporter 2

T2D = type 2 diabetes mellitus

Because of shared pathways of disease onset and progression, cardio-renal-metabolic (CRM) comorbidities—namely, atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), and type 2 diabetes mellitus (T2D)—are common among patients with heart failure (HF). When present, they are associated with substantial and often amplified risk of adverse outcomes.[1,2] Despite important therapeutic opportunities at these intersections, patients with HF and CRM conditions are frequently undertreated, which in turn contributes to progression of organ failure.[3,4] In this context, overlapping CRM conditions have received increasing attention in contemporary multispeciality clinical guidance documents, and interdisciplinary efforts have additionally convened explicitly to synthesize care optimization strategies at the high-risk CRM intersection.[5-14]

Despite these concerns, the prevalence and additive influence of overlapping CRM conditions in heart failure with mildly reduced ejection fraction (HFmrEF) or heart failure with preserved ejection fraction (HFpEF) have not been well-studied. Similarly, whether the relative and absolute benefits of sodium-glucose cotransporter-2 (SGLT2) inhibitors differ by CRM status in these populations remains uncertain. Finally, whether patients with HFmrEF or HFpEF without other established indications for SGLT2 inhibitors benefit from treatment optimization is of clinical interest. In this exploratory analysis of the DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) trial, we examine whether the benefits of dapagliflozin may vary according to type and extent of CRM overlap.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The trial design, baseline characteristics, and primary results of DELIVER have been previously reported.[15,16] In brief, DELIVER was an international, multicenter, randomized, double-blind, parallel-group, event-driven trial comparing the efficacy and safety of dapagliflozin with placebo in patients with HF and mildly reduced, preserved, or improved left ventricular ejection fraction (LVEF). DELIVER enrolled patients ≥40 years of age with HF and an LVEF >40% (documented by echocardiography or cardiac magnetic resonance within the 12 months preceding enrollment), NYHA functional class II-IV symptoms, elevated concentrations of N-terminal pro-B-type natriuretic peptide, and evidence of structural heart disease (increased left atrial size or left ventricular hypertrophy). Both ambulatory and hospitalized patients were eligible for enrollment. Key exclusion criteria included recent (within 4 weeks pre-enrollment) receipt or intolerance of an SGLT2 inhibitor, type 1 diabetes, estimated glomerular filtration rate (eGFR) <25 mL/min/1.73 m^2, uncontrolled hypertension, body mass index (BMI) >50 kg/m^2, the presence of an alternative diagnosis accounting for the patient's symptoms (eg, anemia), uncorrected primary valvular disease, and known infiltrative cardiomyopathy, myocarditis, or hypertrophic cardiomyopathy. DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure; NCT03619213) conforms with the principles outlined in the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board or ethics committee at each participating site and all participants provided written informed consent.

ASSESSMENT OF CRM STATUS IN DELIVER. For the purposes of this analysis, the trial population was divided into categories based on the presence or absence of comorbid CRM conditions at baseline. Consistent with contemporary multidisciplinary guidance documents, CRM conditions in this analysis included ASCVD, CKD, and T2D.[13] ASCVD was defined by coronary artery disease (including history of

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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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TABLE 1 Baseline Characteristics by Number of CRM Conditions

	Number of Additional CRM Conditions				
	0 (n = 830)	**1 (n = 1,952)**	**2 (n = 2,245)**	**3 (n = 1,236)**	***P* Value**
Age, y	69.6 ± 10.1	71.2 ± 10.1	72.4 ± 9.2	72.4 ± 8.6	<0.001
Age groups, y					<0.001
≤65	258 (31.1)	514 (26.3)	485 (21.6)	247 (20.0)	
66-75	314 (37.8)	716 (36.7)	865 (38.5)	517 (41.8)	
>75	258 (31.1)	722 (37.0)	895 (39.9)	472 (38.2)	
Men	426 (51.3)	1,053 (53.9)	1,285 (57.2)	752 (60.8)	<0.001
Race					0.031
White	553 (66.6)	1,402 (71.8)	1,609 (71.7)	875 (70.8)	
Asian	186 (22.4)	356 (18.2)	457 (20.4)	275 (22.2)	
Black or African American	19 (2.3)	49 (2.5)	57 (2.5)	34 (2.8)	
American Indian or Alaska Native	22 (2.7)	77 (3.9)	62 (2.8)	28 (2.3)	
Other	50 (6.0)	68(3.5)	60 (2.7)	24 (1.9)	
Geographic region					0.450
Europe and Saudi Arabia	371 (44.7)	938 (48.1)	1,105 (49.2)	591 (47.8)	
Asia	184 (22.2)	345 (17.7)	438 (19.5)	259 (21.0)	
Latin America	179 (21.6)	426 (21.8)	388 (17.3)	188 (15.2)	
North America	96 (11.6)	243 (12.4)	314 (14.0)	198 (16.0)	
History of AFF	535 (64.5)	1,163 (59.6)	1,220 (54.3)	634 (51.3)	<0.001
History of stroke[a]	2 (0.2)	106 (5.4)	266 (11.8)	223 (18.0)	<0.001
History of dyslipidemia	333 (40.1)	1,112 (57.0)	1,571 (70.0)	974 (78.8)	<0.001
History of type 2 diabetes mellitus	0 (0.0)	417 (21.4)	1,250 (55.7)	1,139 (92.2)	<0.001
History of COPD	65 (7.8)	196 (10.0)	273 (12.2)	158 (12.8)	<0.001
History of noncoronary revascularization	0 (0.0)	21 (1.1)	62 (2.8)	57 (4.6)	<0.001
History of sleep apnea	43 (5.2)	129 (6.6)	179 (8.0)	134 (10.8)	<0.001
History of myocardial infarction	0 (0.0)	341 (17.5)	746 (33.2)	552 (44.7)	<0.001
History of hypertension	640 (77.1)	1,682 (86.2)	2,067 (92.1)	1,164 (94.2)	<0.001
History of chronic kidney disease	0 (0.0)	298 (15.3)	714 (31.8)	754 (61.0)	<0.001
Prior HF hospitalization	276 (33.3)	714 (36.6)	956 (42.6)	593 (48.0)	<0.001
Coronary artery disease	0 (0.0)	647 (33.1)	1,453 (64.7)	1,118 (90.5)	<0.001
Atherosclerotic cardiovascular disease	0 (0.0)	718 (36.8)	1,644 (73.2)	1,236 (100.0)	<0.001
Smoking status					<0.001
Current	69 (8.3)	148 (7.6)	179 (8.0)	88 (7.1)	
Former	242 (29.2)	657 (33.7)	880 (39.2)	482 (39.0)	
Never	519 (62.5)	1,147 (58.8)	1,186 (52.8)	666 (53.9)	
Baseline body mass index, kg/m^2	29.1 ± 6.3	29.8 ± 6.2	29.8 ± 6.1	30.5 ± 5.9	<0.001
Body mass index groups, kg/m^2					<0.001
<18.5 (underweight)	12 (1.4)	17 (0.9)	19 (0.8)	6 (0.5)	
18.5-24.9 (normal weight)	229 (27.7)	435 (22.3)	469 (20.9)	210 (17.0)	
25.0-29.9 (overweight)	256 (30.9)	636 (32.6)	768 (34.3)	413 (33.4)	
30.0-34.9 (class I obesity)	191 (23.1)	486 (24.9)	560 (25.0)	337 (27.3)	
35.0-39.9 (class II obesity)	90 (10.9)	244 (12.5)	274 (12.2)	190 (15.4)	
≥40 (class III obesity)	50 (6.0)	133 (6.8)	152 (6.8)	80 (6.5)	
Time from diagnosis of HF to baseline					<0.001
0-3 mo	98 (11.8)	184 (9.4)	203 (9.0)	83 (6.7)	
>3-6 mo	74 (8.9)	191 (9.8)	214 (9.5)	113 (9.1)	
>6-12 mo	125 (15.1)	282 (14.5)	301 (13.4)	134 (10.8)	
>1-2 y	119 (14.4)	345 (17.7)	347 (15.5)	184 (14.9)	
>2-5 y	207 (25.0)	466 (23.9)	567 (25.3)	329 (26.6)	
>5 y	206 (24.8)	480 (24.6)	613 (27.3)	393 (31.8)	
NYHA functional class at baseline					<0.001
I	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	
II	658 (79.3)	1,535 (78.6)	1,663 (74.1)	857 (69.3)	
III	171 (20.6)	413 (21.2)	573 (25.5)	374 (30.3)	
IV	0 (0.0)	4 (0.2)	9 (0.4)	5 (0.4)	
KCCQ-TSS at baseline	71.9 ± 21.9	70.8 ± 22.0	70.6 ± 21.7	66.5 ± 23.0	<0.001

Continued on the next page

TABLE 1 Continued

	Number of Additional CRM Conditions				
	0 (n = 830)	1 (n = 1,952)	2 (n = 2,245)	3 (n = 1,236)	*P* Value
Baseline LVEF, %	54.7 ± 9.0	54.5 ± 8.8	54.1 ± 8.8	53.4 ± 8.5	<0.001
Pooled LVEF groups, %					<0.001
≤40	0 (0.0)	4 (0.2)	0 (0.0)	0 (0.0)	
41-49	260 (31.3)	626 (32.1)	765 (34.1)	461 (37.3)	
50-59	297 (35.8)	699 (35.8)	818 (36.4)	442 (35.8)	
≥60	273 (32.9)	623 (31.9)	662 (29.5)	333 (26.9)	
Baseline NT-proBNP, pg/mL	941 (623-1,531)	1,010 (634-1,720)	1,022 (616-1,795)	1,056 (615-1,897)	0.002
NT-proBNP in AFF, pg/mL	1,219 (885-1,830)	1,367 (967-2,187)	14,78 (985-2,396)	1,584 (1,088-2,597)	<0.001
NT-proBNP when no AFF, pg/mL	615 (438-1,075)	692 (458-1,190)	729 (460-1,325)	784 (506-1,500)	<0.001
Baseline ECG AFF	437 (52.7)	894 (45.8)	908 (40.5)	405 (32.8)	<0.001
Baseline systolic blood pressure, mm Hg	127.6 ± 15.7	127.4 ± 15.4	128.4 ± 15.2	129.6 ± 15.2	<0.001
Baseline diastolic blood pressure, mm Hg	75.2 ± 10.1	74.6 ± 10.5	73.6 ± 10.3	72.5 ± 10.2	<0.001
Baseline HbA_{1c}, %	5.7 ± 0.4	6.1 ± 1.0	6.8 ± 1.5	7.6 ± 1.6	<0.001
Baseline pulse, beats/min	72.1 ± 11.7	71.2 ± 11.9	71.8 ± 11.8	70.9 ± 11.5	0.120
Baseline creatinine, μmol/L	78.6 ± 14.0	93.9 ± 25.8	106.1 ± 30.7	125.3 ± 31.0	<0.001
Baseline eGFR, mL/min/1.73 m^2	77.3 ± 12.2	66.1 ± 18.6	58.2 ± 18.6	47.1 ± 12.6	<0.001
eGFR ≥60 mL/min/1.73 m^2	829 (100.0)	1,290 (66.1)	934 (41.6)	139 (11.2)	<0.001
Loop diuretic agents	603 (72.7)	1,459 (74.7)	1,736 (77.3)	1,013 (82.0)	<0.001
ACE inhibitor	293 (35.3)	710 (36.4)	856 (38.1)	436 (35.3)	0.770
ARB	269 (32.4)	705 (36.1)	817 (36.4)	481 (38.9)	0.006
ARNI	48 (5.8)	96 (4.9)	93 (4.1)	64 (5.2)	0.390
Beta-blocker	674 (81.2)	1,599 (81.9)	1,867 (83.2)	1,037 (83.9)	0.060
MRA	365 (44.0)	861 (44.1)	953 (42.4)	488 (39.5)	0.014
Pacemaker	83 (10.0)	187 (9.6)	249 (11.1)	143 (11.6)	0.070
ICD	7 (0.8)	40 (2.0)	38 (1.7)	28 (2.3)	0.090

Values are mean ± SD, n (%), or median (IQR). [a]Hemorrhagic or ischemic stroke.

ACE = angiotensin-converting enzyme; AFF = atrial fibrillation/flutter; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; COPD = chronic obstructive pulmonary disease; CRM = cardio-renal-metabolic; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HbA_{1c} = hemoglobin A1c; HF = heart failure; ICD = implantable cardioverter-defibrillator; KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire–Total Symptom Score; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid antagonist; NT-probing = N-terminal pro-B-natriuretic peptide.

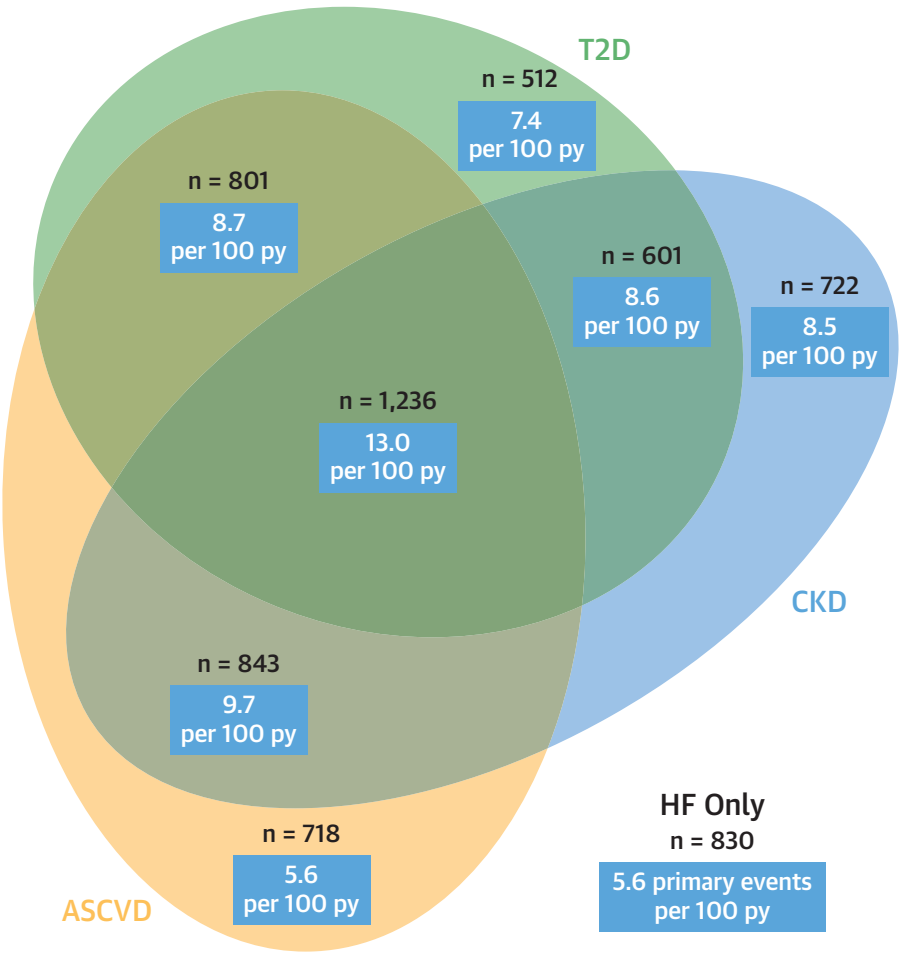
coronary atherosclerosis, myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention), cerebrovascular disease (defined as ischemic stroke), or peripheral artery disease (defined as carotid artery stenosis or noncoronary revascularization). Baseline CKD was identified by either history of CKD or baseline eGFR <60 mL/min/1.73 m^2.[17] T2D was identified by history of T2D, history of or prevalent use of an antihyperglycemic therapy (unless explicitly prescribed for an indication other than T2D), or baseline glycated hemoglobin (HbA_{1c}) level of ≥6.5%.

CLINICAL OUTCOMES IN DELIVER. The primary endpoint of DELIVER was the composite of cardiovascular death or worsening HF event (inclusive of hospitalization for HF or an urgent HF visit requiring intravenous HF therapy). Secondary endpoints were cardiovascular death, all-cause death, as well as cardiovascular death and total (first and recurrent) HF events, and patient symptom burden as assessed by the Kansas City Cardiomyopathy Questionnaire-Total Symptom Score (KCCQ-TSS) at 8 months. All clinical events were adjudicated by a blinded Clinical Endpoints Committee at Brigham and Women's Hospital (Boston, Massachusetts, USA) and University of Glasgow (Glasgow, United Kingdom).

SAFETY OUTCOMES. Per protocol, only serious adverse events (AEs), AEs leading to study drug discontinuation, and selected other AEs (eg, amputation events) were collected.[18] The incidence of safety events was compared by treatment arm within CRM categories among participants who received ≥1 dose of randomized treatment.

STATISTICAL ANALYSIS. Normally distributed data are reported as mean ± SD, non-normally distributed data as median (IQR), and categorical variables as frequencies and percentages. Study participants were categorized by CRM status, expressed as either number (0, 1, 2, or 3) or type (ASCVD, CKD, and/or T2D) of additional overlapping CRM conditions.

CENTRAL ILLUSTRATION **Prevalence of Overlapping CRM Conditions and Primary Event Rates in DELIVER by CRM Status**



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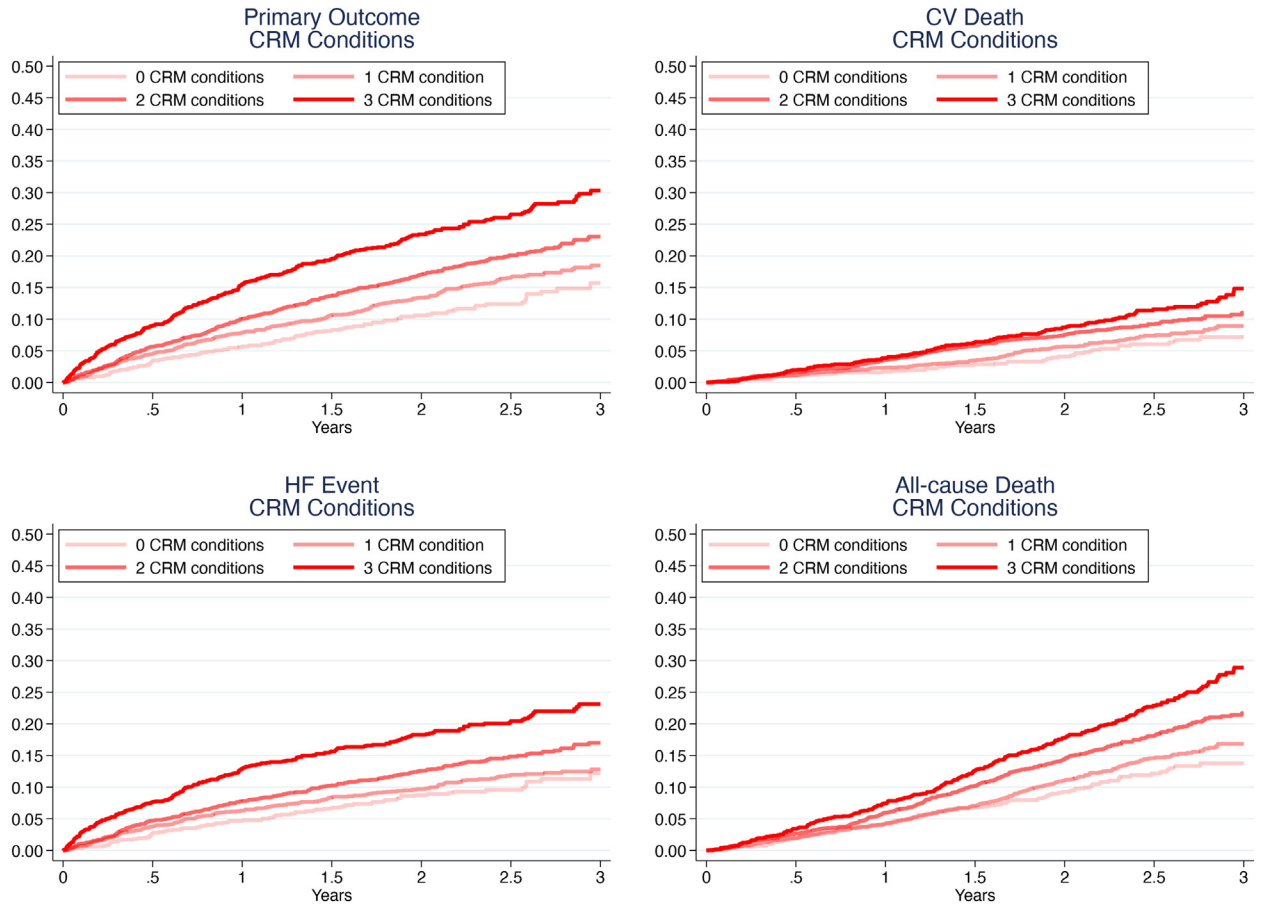
Euler diagram shows the prevalence of individual and overlapping additional cardio-renal-metabolic (CRM) conditions among DELIVER participants, as well as primary event rates for each CRM status, per 100 patient-years. ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; HF = heart failure; py = patient-years; T2D = type 2 diabetes.

Differences in baseline characteristics of trial participants by CRM status at baseline were summarized for each group. The association between baseline CRM status and clinical outcomes was adjusted for covariates determined a priori: age, sex, race, geographic region, and baseline LVEF. HRs and 95% CIs were calculated for time-to-first endpoints using Cox proportional hazard models, whereas rate ratios and 95% CIs were calculated for recurrent event endpoints based on the Lin-Wei-Yang-Ying model.[19] Treatment effects of dapagliflozin vs placebo were examined, including interaction terms for effect modification by CRM category. Values of $P < 0.05$ were considered statistically significant, and P values for each subgroup analysis were not adjusted for multiple comparisons as the tests were exploratory and interpreted descriptively. Statistical analyses were performed using STATA version 17.0 (StataCorp, College Station, Texas, USA).

RESULTS

PATIENT CHARACTERISTICS. Across 6,263 participants in DELIVER, 1,952 (31%), 2,245 (36%), and 1,236 (20%) had 1, 2, and 3 additional CRM conditions, respectively (Table 1). HF alone was uncommon (n = 830; 13%). The prevalence of CRM overlap was similarly substantial irrespective of HF subtype in

FIGURE 1 **Kaplan-Meier Curves for Selected Endpoints by Number of Overlapping CRM Conditions**

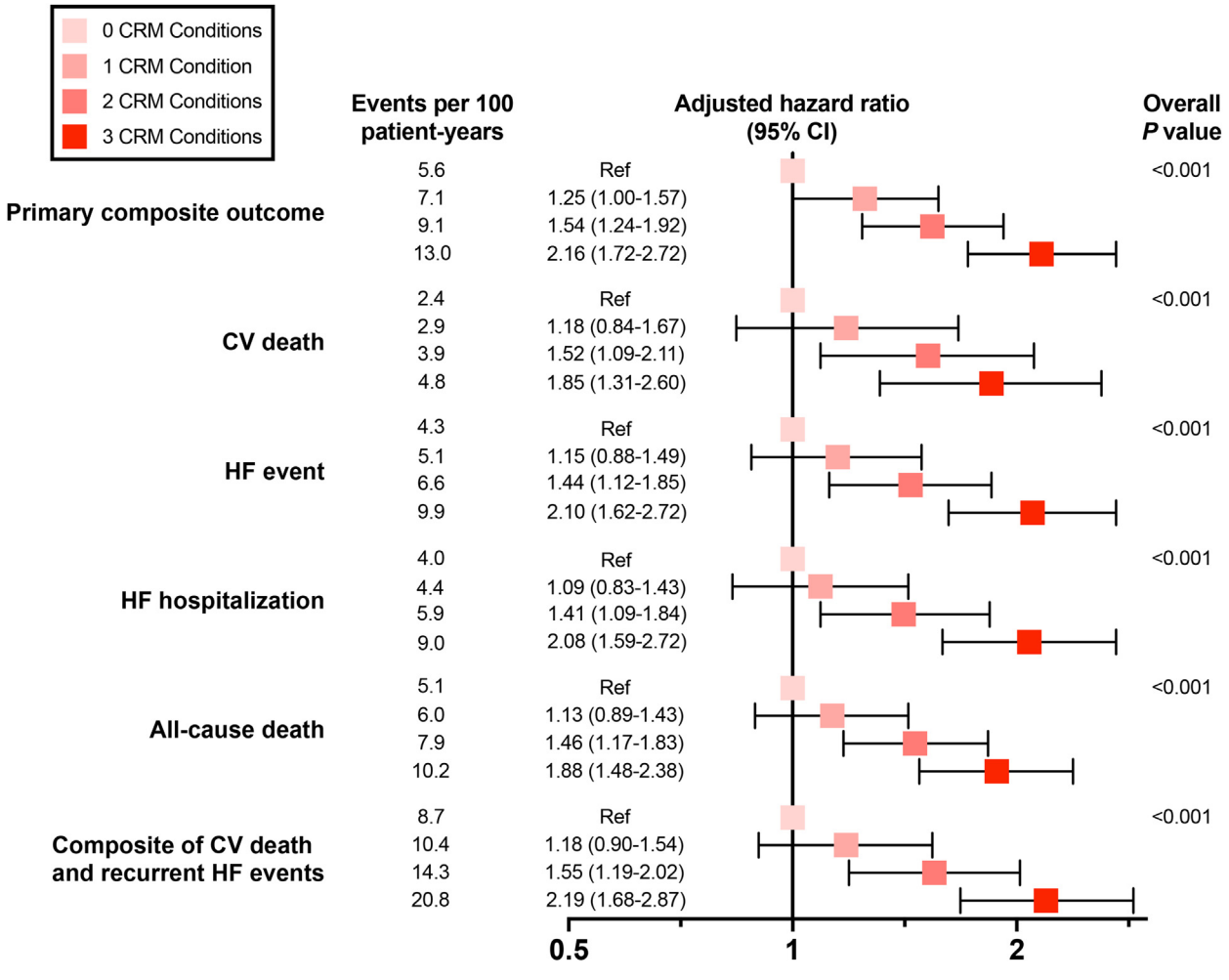


HF = heart failure; CRM = cardio-renal-metabolic; CV = cardiovascular.

DELIVER, with coexisting HF, ASCVD, CKD, and T2D observed in 22% and 19% of participants with HFmrEF and HFpEF, respectively (Supplemental Table 1). Compared with participants without additional CRM conditions (ie, HF only), participants with a higher number of comorbid CRM conditions tended to be older and male, and more often had dyslipidemia, hypertension, prior smoking, prior HF hospitalization, longer-duration HF, lower LVEF, and worse baseline health status as evaluated by both NYHA functional class and KCCQ-TSS. Greater CRM multimorbidity at baseline was additionally associated with higher BMI, systolic blood pressure, and natriuretic peptides. Participants with a higher number of CRM comorbidities were more often treated with loop diuretic agents and angiotensin receptor blockers (ARBs), and less often treated with mineralocorticoid receptor antagonists (MRAs).

When evaluated by type of CRM condition, 3,598 (57%) DELIVER participants had ASCVD, 3,402 (54%) had CKD, and 3,150 (50%) had T2D. Having all 3 CRM conditions (ASCVD + CKD + T2D) in addition to HF was the single most common CRM status (**Central Illustration**), followed by ASCVD + CKD (n = 843; 13%) (Supplemental Table 2). Participants with CKD or CKD + T2D tended to be female, whereas those with ASCVD or ASCVD + T2D tended to be male. Participants with a CRM status that included T2D generally exhibited a higher BMI, whereas those including ASCVD were more likely to have dyslipidemia. Significant between-group variation was observed for selected pharmacotherapies; participants with CKD-containing CRM statuses tended to be more often treated with loop diuretic agents and ARBs, and less often treated with MRAs. No between-group differences were observed for angiotensin-converting

FIGURE 2 Risk of Primary and Secondary Endpoints Stratified by Number of Overlapping CRM Conditions



Abbreviations as in Figure 1.

enzyme inhibitors, angiotensin receptor neprilysin inhibitors, or beta-blockers.

CLINICAL OUTCOMES BY CRM STATUS. During a median follow-up of 2.3 years, higher CRM overlap was associated with a graded increase in risk of clinical outcomes (Figure 1). Having 3 CRM conditions was independently associated with the highest risk of the primary outcome (adjusted HR [aHR]: 2.16 [95% CI: 1.72-2.72]), HF hospitalization (aHR: 2.08 [95% CI: 1.59-2.72]), cardiovascular death (aHR: 1.85 [95% CI: 1.31-2.60]), and all-cause death (aHR: 1.88 [95% CI: 1.48-2.38]) as compared with HF alone; similar findings were observed for other key outcomes (Figure 2). Significant between-group variation in the risk of the primary outcome, individual components of the primary outcome, and other outcomes was also observed when evaluated by type of CRM overlap (P for all comparisons < 0.001), with highest risk similarly observed for participants with ASCVD + CKD + T2D (Supplemental Table 3).

TREATMENT EFFECTS OF DAPAGLIFLOZIN BY BASELINE CRM STATUS. The relative benefits of dapagliflozin on the primary composite outcome were consistent irrespective of number of CRM conditions at baseline (HR: 0.74 [95% CI: 0.50-1.10] for 0 CRM conditions; HR: 0.90 [95% CI: 0.72-1.14] for 1 CRM condition; HR: 0.83 [95% CI: 0.68-1.00] for 2 CRM conditions; HR: 0.77 [95% CI: 0.62-0.97] for 3

TABLE 2 Rate of Primary Outcome and Efficacy of Dapagliflozin vs Placebo on the Primary Composite Endpoint Stratified by CRM Status

CRM Status	n (%)	Total Primary Events	Rate per 100 patient-years (95% CI)			Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)[b]	Treatment Effect (Dapagliflozin vs Placebo)	
			Overall	Dapagliflozin	Placebo			RR (95% CI)	$P_{interaction}$
None (HF only)	830 (13.3)	99	5.6 (4.6-6.8)	4.8 (3.6-6.4)	6.5 (5.0-8.5)	Ref.	Ref.	0.74 (0.50-1.10)	0.773
ASCVD only	718 (11.5)	88	5.6 (4.6-6.9)	5.2 (3.8-7.0)	6.1 (4.6-8.0)	1.01 (0.76-1.35)	0.95 (0.71-1.27)	0.83 (0.55-1.27)	
CKD only	722 (11.5)	126	8.5 (7.2-10.1)	7.6 (5.9-9.9)	9.4 (7.4-11.9)	1.52 (1.17-1.98)	1.53 (1.17-1.99)	0.80 (0.56-1.14)	
T2D only	512 (8.2)	80	7.4 (6.0-9.3)	7.9 (5.8-10.7)	7.0 (5.1-9.6)	1.33 (0.99-1.79)	1.35 (1.01-1.82)	1.12 (0.72-1.74)	
ASCVD + CKD	843 (13.5)	165	9.7 (8.4-11.3)	9.3 (7.4-11.7)	10.1 (8.2-12.4)	1.74 (1.35-2.23)	1.60 (1.24-2.06)	0.93 (0.69-1.27)	
ASCVD + T2D	801 (12.8)	149	8.7 (7.4-10.2)	7.3 (5.7-9.3)	10.3 (8.3-12.7)	1.57 (1.21-2.02)	1.49 (1.16-1.93)	0.71 (0.52-0.99)	
CKD + T2D	601 (9.6)	104	8.6 (7.1-10.5)	8.1 (6.1-10.7)	9.2 (7.1-12.0)	1.54 (1.17-2.03)	1.55 (1.18-2.05)	0.89 (0.60-1.31)	
ASCVD + CKD + T2D	1,236 (19.7)	311	13.0 (11.6-14.5)	11.3 (9.6-13.3)	14.8 (12.8-17.2)	2.31 (1.84-2.90)	2.17 (1.73-2.72)	0.77 (0.62-0.97)	

[a]Adjusted for baseline age, sex, race, geographic region, and left ventricular ejection fraction. [b]$P < 0.001$ for comparison across CRM categories.
ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; RR = rate ratio; T2D = type 2 diabetes; other abbreviations as in Table 1.

CRM conditions; $P_{interaction} = 0.734$) or type of CRM overlap ($P_{interaction} = 0.773$) (Table 2). Similar findings were observed for the individual components of the primary outcome and for other outcomes (Figure 3, Supplemental Table 4).

Because of higher baseline risk, the absolute benefits of dapagliflozin on the primary composite outcome were greatest among participants with a higher number of CRM conditions at baseline. Applying an overall relative treatment effect estimate of HR: 0.82 in DELIVER, the stepwise increase in background risk for 0, 1, 2, and 3 additional CRM conditions at baseline would be expected to translate into estimated 2-year numbers needed to treat of approximately 52, 39, 33, and 24, respectively (Table 3). Findings were qualitatively similar when evaluated by type of CRM overlap (Supplemental Table 5).

Between 0 and 8 months, participants irrespective of CRM overlap experienced improvements in KCCQ-TSS after treatment with dapagliflozin vs placebo (mean difference, $^{+}3.6$ [95% CI: $^{+}1.2$ to $^{+}6.0$] for 3 CRM conditions; $^{+}1.7$ [95% CI: $^{+}0.1$ to $^{+}3.4$] for 2 CRM conditions; $^{+}2.6$ [95% CI: $^{+}0.9$ to $^{+}4.2$] for 1 CRM condition; $^{+}2.3$ [95% CI: -0.4 to $^{+}5.1$] for 0 CRM conditions; $P_{interaction} = 0.120$). When evaluated by type of CRM overlap, participants with T2D alone (mean difference $^{+}5.9$ [95% CI: $^{+}2.6$ to $^{+}9.2$]; $P < 0.001$), CKD + T2D (mean difference, $^{+}5.1$ [95% CI: $^{+}1.7$ to $^{+}8.5$]; $P = 0.003$), and ASCVD + CKD + T2D (mean difference, $^{+}3.6$ [95% CI: $^{+}1.2$ to $^{+}6.0$]; $P = 0.004$) exhibited the highest absolute improvements in KCCQ-TSS with dapagliflozin compared with placebo at 8 months (Supplemental Table 6).

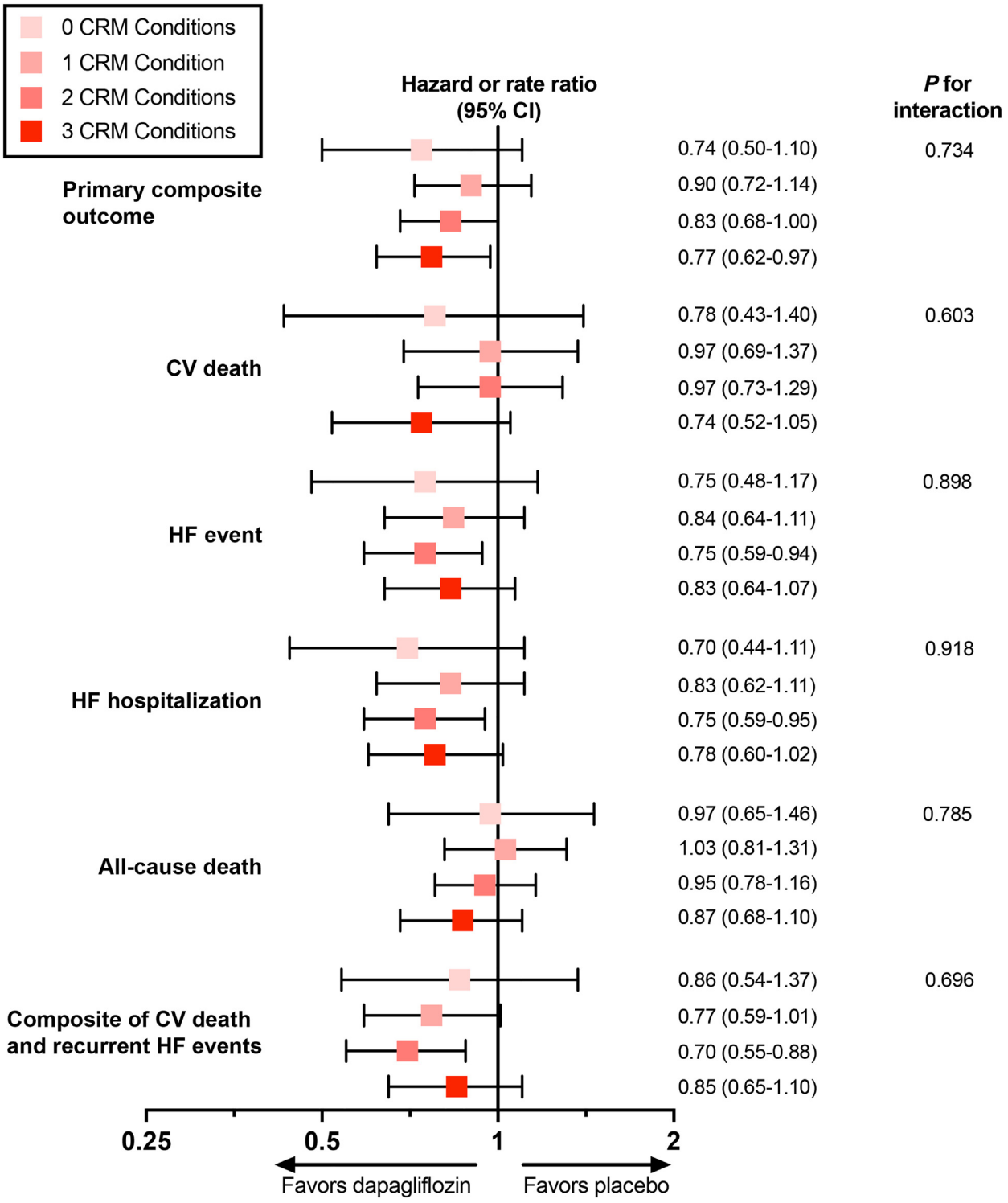
SAFETY OUTCOMES BY CRM STATUS. Overall, serious AEs with either dapagliflozin or placebo were more commonly reported among participants with a higher number of CRM conditions at baseline. However, there were no significant between-group differences in the incidence of AEs leading to drug discontinuation (Supplemental Table 7). Serious AEs, kidney AEs, amputation events, and other AEs including those suggestive of volume depletion were generally well-balanced between treatment arms within CRM categories (Table 4).

DISCUSSION

In this post hoc analysis, more than 4 in 5 participants with HFmrEF or HFpEF exhibited at least 1 other concomitant CRM condition, and 1 in 5 had all 3 CRM conditions in addition to HF. Greater CRM multimorbidity was incrementally associated with adverse clinical outcomes and worse patient-reported health status, and the relative treatment benefits of dapagliflozin on the primary composite outcome were consistent irrespective of the extent or type of CRM overlap. As expected, with greater baseline risk, higher absolute benefits of dapagliflozin on the primary endpoint were observed among participants with higher CRM overlap, whereas the safety profile of dapagliflozin vs placebo was similar within CRM groups. Although relatively infrequent, patients with HF alone (without coexisting CRM comorbidities) who do not have alternative indications for SGLT2 inhibitor derived consistent benefits from dapagliflozin in DELIVER. Taken together, these findings support the expanding focus on integrative strategies to optimize outcomes among patients with HF and CRM multimorbidity and highlight the overall clinical value of dapagliflozin across the spectrum of CRM overlap.

Numerous prospective randomized trials have shown the concordant cardiometabolic and kidney benefits of SGLT2 inhibitors, and emerging data additionally support the potential utility of SGLT2

FIGURE 3 Effect of Dapagliflozin vs Placebo on Primary and Secondary Endpoints Stratified by Number of Overlapping CRM Conditions



Abbreviations as in Figure 1.

TABLE 3 Number Needed to Treat to Prevent 1 Primary Event With 1, 2, and 3 Years of Treatment by Number of Overlapping CRM Conditions

CRM Category	Estimated Risk Difference (%)	Number Needed to Treat
0 CRM conditions		
Year 1	1.3	78.1
Year 2	1.9	52.0
Year 3	3.3	30.2
1 CRM condition		
Year 1	1.7	59.7
Year 2	2.5	39.2
Year 3	3.0	33.4
2 CRM conditions		
Year 1	2.0	50.9
Year 2	3.1	32.5
Year 3	3.9	25.9
3 CRM conditions		
Year 1	2.8	35.5
Year 2	4.2	23.9
Year 3	5.1	19.8

Estimated risk differences represent the difference between the observed primary event rate in the placebo arm and the estimated event rate in the dapagliflozin arm, calculated by applying an overall relative treatment effect estimate of HR: 0.82 over 1, 2, and 3 years of follow-up within CRM categories.

Abbreviation as in Table 1.

inhibitors in isolated ASCVD—a promising strategy that is being further evaluated in ongoing prospective trials including DAPA-MI (Dapagliflozin Effects on Cardiometabolic Outcomes in Patients With an Acute Heart Attack; NCT04564742) and EMPACT-MI (A Study to Test Whether Empagliflozin Can Lower the Risk of Heart Failure and Death in People Who Had a Heart Attack [Myocardial Infarction]; NCT04509674).[20-24] Individually, these conditions remain dominant sources of death and disability worldwide, but in the context of population aging and an expanding burden of shared risk factors, their coexistence within both populations and individual patients has become an increasingly recognized clinical and research priority.[13,25,26] Moreover, the emergence of pharmacotherapies capable of favorably modifying diverse disease pathways across multiple interconnected organ systems has fostered high-yield and unified treatment opportunities.

Previous trials have provided important insights into the safety and efficacy of SGLT2 inhibitors in selected populations with CRM overlap, such as in concomitant ASCVD and T2D, but less is known about impact of SGLT2 inhibitors among patients with wider CRM multimorbidity. We show that CRM overlap was exceedingly prevalent in DELIVER and associated with an incrementally higher risk of adverse outcomes. These findings extend prior data showing worse outcomes associated with specific HF-CRM intersections and amplify the importance of awareness of CRM multimorbidity among the wide range of clinicians actively engaged in the care of high-risk patients with HFmrEF and HFpEF.[3,4] The consistent safety profile and higher absolute treatment effects of dapagliflozin with increasing CRM overlap additionally solidifies SGLT2 inhibitors as a central part of multidisciplinary strategies to improve outcomes in these especially high-risk groups.

Approximately 13% of DELIVER participants did not have a comorbid CRM condition at baseline. This population tended to be younger and more often female, with more recently diagnosed HF, higher

TABLE 4 Adverse Events for Dapagliflozin vs Placebo by Number of Overlapping CRM Conditions

	Number of Additional CRM Conditions							
	0		1		2		3	
Event	Placebo (n = 385)	Dapagliflozin (n = 445)	Placebo (n = 997)	Dapagliflozin (n = 995)	Placebo (n = 1,126)	Dapagliflozin (n = 1,119)	Placebo (n = 624)	Dapagliflozin (n = 612)
Any AE with outcome = death	39 (10.1)	41 (9.2)	118 (11.8)	109 (11.4)	154 (13.7)	148 (13.2)	110 (17.7)	103 (16.8)
Any SAE (including outcome = death)	132 (34.3)	161 (36.3)	395 (39.7)	404 (42.4)	554 (49.3)	467 (41.8)	342 (55.0)	329 (53.8)
Any AE leading to discontinuation of IP	17 (4.4)	23 (5.2)	51 (5.1)	53 (5.6)	64 (5.7)	66 (5.9)	49 (7.9)	40 (6.5)
Any AE leading to interruption of IP	44 (11.4)	30 (6.8)	127 (12.8)	131 (13.7)	204 (18.1)	163 (14.6)	119 (19.1)	112 (18.3)
Any AE possibly related to IP	22 (5.7)	31 (7.0)	67 (6.7)	77 (8.1)	95 (8.5)	92 (8.2)	51 (8.2)	73 (11.9)
Any amputation	0 (0.0)	0 (0.0)	5 (0.5)	4 (0.4)	8 (0.7)	3 (0.3)	12 (1.9)	12 (2.0)
Any potential risk factor AE for amputation affecting lower limbs	15 (3.9)	15 (3.4)	44 (4.4)	49 (5.1)	76 (6.8)	53 (4.7)	64 (10.3)	71 (11.6)
Any definite or probable diabetic ketoacidosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Any SAE or DAE suggestive of volume depletion	1 (0.3)	3 (0.7)	6 (0.6)	13 (1.4)	16 (1.4)	15 (1.3)	9 (1.4)	11 (1.8)
Any renal SAE or DAE	2 (0.5)	3 (0.7)	17 (1.7)	13 (1.4)	29 (2.6)	27 (2.4)	31 (5.0)	30 (4.9)

Values are n (%).

AE = adverse event; DAE = adverse events leading to drug discontinuation; IP = investigational product; SAE = serious adverse event; other abbreviation as in Table 1.

baseline functional status (~80% NYHA functional class II), and a greater burden of atrial fibrillation. Critically, although clinical events were less frequent in this group, relative treatment effects of dapagliflozin on both health status and time to first worsening HF events or cardiovascular mortality were similar when compared to higher-risk participants with CRM multimorbidity. Although concomitant CRM conditions were absent in this subpopulation, the burden of dyslipidemia, hypertension, and obesity—key risk factors for incident HF, ASCVD, CKD, and T2D—was substantial. Further, in follow-up, approximately 1 in 8 experienced the primary outcome. As such, patients with HFmrEF or HFpEF, even in the absence of other CRM conditions, still face important risks and appear to benefit from treatment optimization with SGLT2 inhibitors. As this class was initially established in the care of patients with T2D and CKD, it might be assumed that treatment benefits are only observed in HF in the context of these conditions. However, the HF-specific benefits of SGLT2 inhibitors observed in this analysis suggest that implementation of SGLT2 inhibitors in HFmrEF or HFpEF should still be prioritized even in the absence of these alternative indications for their use. Finally, in addition to improving HF status, the use of SGLT2 inhibitors in this population represents a critical opportunity to avert downstream CRM conditions and associated clinical events, health care expenditures, and health status erosion.

Recent registry-based analyses highlight limited or delayed implementation of novel HF pharmacotherapies;[4,27,28] these gaps in implementation appear especially prominent at CRM intersections.[29] These data provide clinical reassurance about the safety of SGLT2 inhibitors even in high-risk patients with CRM multimorbidity and support dedicated interventions to improve therapeutic optimization at CRM intersections. Novel care delivery strategies such as multidisciplinary clinics have been widely evaluated and implemented in oncology, offering earlier diagnosis and treatment, reduced health care fragmentation, improved patient experiences, and (in many cases) better outcomes.[30] Team-based cardiometabolic clinics have also seen early successes in improving secondary risk reduction among patients with cardiovascular disease and T2D.[14] As such, novel care delivery pathways constructed around HF and associated CRM overlap may offer a scalable approach to improving the outcomes and health care use of high-risk patients with these interconnected conditions.

STUDY LIMITATIONS. Several limitations of this analysis should be emphasized. First, exclusion of patients with eGFR <25 mL/min/1.73 m^2 may have resulted in underestimation of the prevalence of CKD, its associated overlap, and contribution to clinical events. Second, lack of capture of urine albumin excretion in DELIVER precluded further CKD categorization. Third, reliance on single HbA_{1c} measurements rather than other methods of glycemic assessment (eg, oral glucose tolerance testing) may have additionally influenced estimates of T2D in DELIVER. Contemporary guidelines recommend serial measurement of HbA1c before establishing a formal T2D diagnosis, and the glycemic status of some DELIVER participants may have been reclassified with further testing. Fourth, although we intentionally focused on the CRM intersection, we recognize that other comorbidities (eg, anemia, obstructive lung disease, and depression) importantly influence HF care.[31,32] Finally, we did not evaluate the severity and level of control of individual CRM conditions.

CONCLUSIONS

In this post hoc analysis, we show that most DELIVER participants had multiple CRM conditions; the quadruple intersection of HF, ASCVD, CKD, and T2D was the single most prevalent CRM status, and HF alone was uncommon. As such, more than 75% of DELIVER participants had at least 1 other contemporary indication for SGLT2 inhibitors. CRM multimorbidity was independently associated with adverse clinical outcomes among patients with HF and LVEF >40%. Dapagliflozin was well-tolerated, and its treatment benefits were consistent across the CRM spectrum. Although patients with substantial CRM overlap are anticipated to derive the greatest absolute risk reductions with SGLT2 inhibitor implementation, even those with HF alone and without any alternative indication for SGLT2 inhibitors experienced consistent benefits. Taken together, these findings support the expanding focus on integrative strategies to optimize outcomes among patients with CRM multimorbidity and highlight the overall clinical value of dapagliflozin for patients with HFmrEF and HFpEF across CRM intersections.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Contemporary HFmrEF and HFpEF uncommonly exist in isolation; CRM multimorbidity is highly prevalent in this population and independently predictive of adverse HF outcomes and death. In DELIVER, dapagliflozin was beneficial and well-tolerated across the CRM spectrum, with greatest absolute benefits among participants with highest CRM overlap at baseline.

TRANSLATIONAL OUTLOOK: These findings highlight the importance of SGLT2 inhibitors as a central part of holistic and interdisciplinary strategies to optimize outcomes for patients with HFmrEF and HFpEF. Broad implementation of SGLT2 inhibitors in this population offers the critical opportunity to not only improve HF status but also to treat or avert CRM multimorbidity.

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