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ORIGINAL RESEARCH ARTICLE

Outpatient Worsening Among Patients With Mildly Reduced and Preserved Ejection Fraction Heart Failure in the DELIVER Trial

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BACKGROUND: Hospitalization is recognized as a sentinel event in the disease trajectory of patients with heart failure (HF), but not all patients experiencing clinical decompensation are ultimately hospitalized. Outpatient intensification of diuretics is common in response to symptoms of worsening HF, yet its prognostic and clinical relevance, specifically for patients with HF with mildly reduced or preserved ejection fraction, is uncertain.

METHODS: In this prespecified analysis of the DELIVER trial (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure), we assessed the association between various nonfatal worsening HF events (those requiring hospitalization, urgent outpatient visits requiring intravenous HF therapies, and outpatient oral diuretic intensification) and rates of subsequent mortality. We further examined the treatment effect of dapagliflozin on an expanded composite end point of cardiovascular death, HF hospitalization, urgent HF visit, or outpatient oral diuretic intensification.

RESULTS: In DELIVER, 4532 (72%) patients experienced no worsening HF event, whereas 789 (13%) had outpatient oral diuretic intensification, 86 (1%) required an urgent HF visit, 585 (9%) had an HF hospitalization, and 271 (4%) died of cardiovascular causes as a first presentation. Patients with a first presentation manifesting as outpatient oral diuretic intensification experienced rates of subsequent mortality that were higher (10 [8–12] per 100 patient-years) than those without a worsening HF event (4 [3–4] per 100 patient-years) but similar to rates of subsequent death after an urgent HF visit (10 [6–18] per 100 patient-years). Patients with an HF hospitalization as a first presentation of worsening HF had the highest rates of subsequent death (35 [31–40] per 100 patient-years). The addition of outpatient diuretic intensification to the adjudicated DELIVER primary end point (cardiovascular death, HF hospitalization, or urgent HF visit) increased the overall number of patients experiencing an event from 1122 to 1731 (a 54% increase). Dapagliflozin reduced the need for outpatient diuretic intensification alone (hazard ratio, 0.72 [95% CI, 0.64–0.82]) and when analyzed as a part of an expanded composite end point of worsening HF or cardiovascular death (hazard ratio, 0.76 [95% CI, 0.69–0.84]).

CONCLUSIONS: In patients with HF with mildly reduced or preserved ejection fraction, worsening HF requiring oral diuretic intensification in ambulatory care was frequent, adversely prognostic, and significantly reduced by dapagliflozin.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03619213.

Key Words: disease progression ■ heart failure ■ heart failure, diastolic ■ heart failure, systolic ■ hospitalization ■ sodium-glucose transporter 2 inhibitor

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Clinical Perspective

What Is New?

- Outpatient oral diuretic intensification is a frequent first manifestation of worsening heart failure (HF) occurring in 1 in 8 patients with mildly reduced or preserved ejection fraction in the DELIVER trial (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure).
- Oral diuretic intensification carries a risk of subsequent mortality similar to an urgent HF visit and is preceded by clinically significant declines in health status.
- Treatment with dapagliflozin significantly reduces the full spectrum of worsening HF events, including outpatient oral diuretic intensification.
- Inclusion of outpatient oral diuretic intensification in a broader composite worsening HF end point greatly increases the number of clinical events.

What Are the Clinical Implications?

- Oral diuretic intensification occurring in ambulatory care is frequent and prognostically important, and its occurrence may represent a clinically meaningful juncture to interrupt the progression of HF.
- The addition of outpatient oral diuretic intensification to the traditional composite end point of cardiovascular death and worsening HF allows a broader capture of clinically meaningful events and may have implications for future clinical trial design.

Nonstandard Abbreviations and Acronyms

HF	heart failure
KCCQ	Kansas City Cardiomyopathy Questionnaire
SGLT2	sodium-glucose cotransporter-2
TSS	Total Symptoms Score

In the DELIVER trial (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure), treatment with dapagliflozin resulted in significant and sustained reductions in worsening heart failure (HF) events.[1] Although HF hospitalization is well established as a sentinel event in the disease trajectory of patients with HF,[2] worsening HF may manifest across various clinical settings. Such progression may result in HF hospitalization, emergency department visit, or management without hospitalization through intravenous diuretic administration or intensification of oral diuretic therapy.[3] Outpatient oral diuretic intensification is a frequent occurrence, and such events represent a potential opportunity for intervention to prevent downstream hospitalization and resultant health care resources. The frequency and clinical implications of outpatient oral diuretic intensification have been characterized among patients with HF with reduced ejection fraction.[4,5] However, the prognostic relevance of outpatient worsening may differ among patients with HF with mildly reduced and preserved ejection fraction.

Previous studies have demonstrated the prognostic significance of nonhospitalized visits requiring short-term intravenous diuretic administration.[6–8] There has been increasing global emphasis on the management of HF decompensation in the outpatient setting to potentially avert hospitalization.[9] The US Food and Drug Administration standardized definitions for cardiovascular and stroke end point events in clinical trials also include nonhospitalized HF events requiring intravenous therapies as a potential cardiovascular end point.[10] Because outpatient oral diuretic intensification occurs considerably more frequently and may be modifiable by treatment, inclusion of these events in a composite end point could provide more complete capture of HF events and may have implications for the conduct of future clinical trials.

In this prespecified analysis of the DELIVER trial, we assessed the prognostic importance of the spectrum of worsening HF events, including outpatient oral diuretic intensification. We also examined the potential value of the inclusion of outpatient oral diuretic intensification in an expanded composite outcome in a contemporary population of patients with HF with mildly reduced and preserved ejection fraction.

METHODS

Study Design

The DELIVER trial study design and primary results have been previously described.[1] In brief, the DELIVER trial was a double-blind, randomized controlled trial in which the effect of 10 mg of dapagliflozin once daily versus placebo was evaluated among ambulatory or hospitalized patients >40 years of age with symptomatic HF (New York Heart Association class II–IV) and at least intermittent diuretic requirement, left ventricular ejection fraction >40%, evidence of structural heart disease, and elevated natriuretic peptides. Patients were excluded if they received an sodium-glucose cotransporter-2 (SGLT2) inhibitor in the 4 weeks before randomization, experienced previous intolerance to SGLT2 inhibitors, had a history of type 1 diabetes, screening estimated glomerular filtration rate <25 mL·min^{-1}·1.73 m^{-2}, or systolic blood pressure <95 mm Hg. The study protocol received approval by the ethics committees at each study site, and participants provided written informed consent.

Clinical End Points

The primary end point in DELIVER was a composite of cardiovascular death or first worsening HF event, including

hospitalization for HF or an urgent HF visit. An urgent HF visit was defined as an emergency department or outpatient visit requiring intravenous therapy. To provide a more complete picture of treatment effects on the burden of worsening HF, including outpatient worsening, an expanded composite outcome was constructed by adding diuretic intensification to the primary composite outcome. Diuretic intensification was defined as any new oral loop diuretic initiation (among those not taking loop diuretics at baseline) or sustained increase in dose of ≥30 days (among those taking diuretics at baseline).

Statistical Analysis

Baseline characteristics were compared according to the following mutually exclusive categories defining a first worsening HF event: no worsening HF, outpatient oral diuretic intensification, urgent HF visit requiring intravenous therapy, HF hospitalization, and cardiovascular death. We also compared the clinical course after an urgent HF visit and an outpatient oral diuretic intensification. Data are reported as mean±SD, median (interquartile range) for nonnormal distributions, and frequency (percentage) for categorical variables. Student *t* test, Pearson χ^2 test, and ANOVA were used when appropriate.

Ascertainment of diuretic dose information has been previously detailed.[11] In brief, all patients with information on diuretic treatment were included in this analysis. For patients taking diuretics, those without reliable diuretic dose information were excluded from analyses of diuretic dose. In DELIVER, of the 13 357 diuretic records identified, 3586 records (275) were excluded, leaving 9771 records (73%) for analysis. No imputation was performed. Among patients taking a loop diuretic, a total daily dose equivalent to 80 mg of oral furosemide was calculated using the following equivalency: bumetanide 1 mg, torsemide 20 mg, azosemide 60 mg, and ethacrynic acid 100 mg were considered equivalent to 80 mg of oral furosemide.[12,13] When there were missing or insufficient diuretic dose data, patients were excluded at that specific time point and included again at the next available time point.

We also assessed the cumulative incidence of all-cause mortality after a first nonfatal worsening HF event (including those requiring hospitalization for HF, urgent HF visit, and outpatient oral diuretic intensification) relative to those who did not experience a worsening HF event using Cox proportional hazards models. The time scale for patients with and without a worsening HF event was time after worsening HF event and time from randomization, respectively. Among patients experiencing outpatient diuretic intensification, we separately assessed the risk of subsequent mortality after varying degrees of loop diuretic dose escalation. Increase in furosemide equivalent dose above baseline was analyzed as a continuous variable using restricted cubic splines. Models were adjusted for baseline loop diuretic dose and landmarked at the time of loop diuretic dose increase.

We characterized the temporal trajectory of the Kansas City Cardiomyopathy Questionnaire (KCCQ) Total Symptom Score (TSS) before and after the first nonfatal "outpatient" and "inpatient" worsening HF events using repeated-measures linear regression models, with patient-level random intercepts and with time represented using restricted cubic splines with fixed knots at time zero and at 1, 2, and 6 months before and after an HF event according to previously established methodology.[14,15] "Outpatient" worsening was defined as an outpatient oral diuretic intensification or urgent HF visit, and "inpatient" worsening denoted HF hospitalization. The average trajectory of KCCQ TSS that would have been observed if patients were continuously monitored before and after the HF event was estimated by integrating all available KCCQ TSS data from prespecified trial visits, when KCCQ TSS was assessed (at randomization, 1 month, 4 months, and 8 months, according to the DELIVER trial protocol). KCCQ-TSS data were plotted relative to time, which was defined as the number of months preceding or immediately after the HF event. KCCQ-TSS after an HF event was modeled only among survivors.

Treatment effect of dapagliflozin on the primary composite outcome, its components, and the exploratory extended composite outcome including oral diuretic intensification were evaluated in time-to-first event analyses using Cox regression and displayed in Kaplan-Meier curves. Cox proportional hazards assumptions were violated in the primary end point analysis of the DELIVER trial and were felt not to undermine any qualitative findings as a model free estimate of treatment effect yielded nearly identical results. In this analysis, no violations of Cox proportional hazards assumptions were identified for the new models, estimating treatment effects on outpatient oral diuretic intensification and on an expanded worsening HF end point inclusive of oral diuretic intensification. In view of the variation in clinical importance of cardiovascular death, HF hospitalization, urgent HF visit, and outpatient oral diuretic intensification, we evaluated the treatment effect of dapagliflozin versus placebo by win ratio analysis that accounts for the timing and relative importance of each outcome.[16]

The sponsor (AstraZeneca) is committed to sharing access to participant-level data and supporting clinical documents from eligible studies. The trial data availability is according to separate criteria and processes outlined here: https://www.astrazenecaclinicaltrials.com/our-transparency-commitments/. All analyses were performed using STATA (Stat Corp., College Station, TX). A *P* value of <0.05 was considered to be statistically significant.

RESULTS

Manifestations of First Worsening HF Events

Of the 6263 patients who underwent randomization in DELIVER, 4532 patients (72%) experienced no worsening HF and 1731 patients (28%) experienced a worsening HF event during trial follow-up. First worsening HF events manifested as an outpatient oral diuretic intensification in 789 patients (45% of first worsening HF events and 13% of total patients), urgent HF visit requiring intravenous diuretics in 86 patients (5% of first worsening HF events and 1.4% of total patients), HF hospitalization in 585 patients (34% of first worsening HF events and 9.3% of total patients), and death related to cardiovascular causes in 271 patients (16% of first worsening HF events and 4.3% of total patients; Figure 1).

Baseline Characteristics

Baseline characteristics of randomly assigned patients according to their first manifestation of worsening HF are

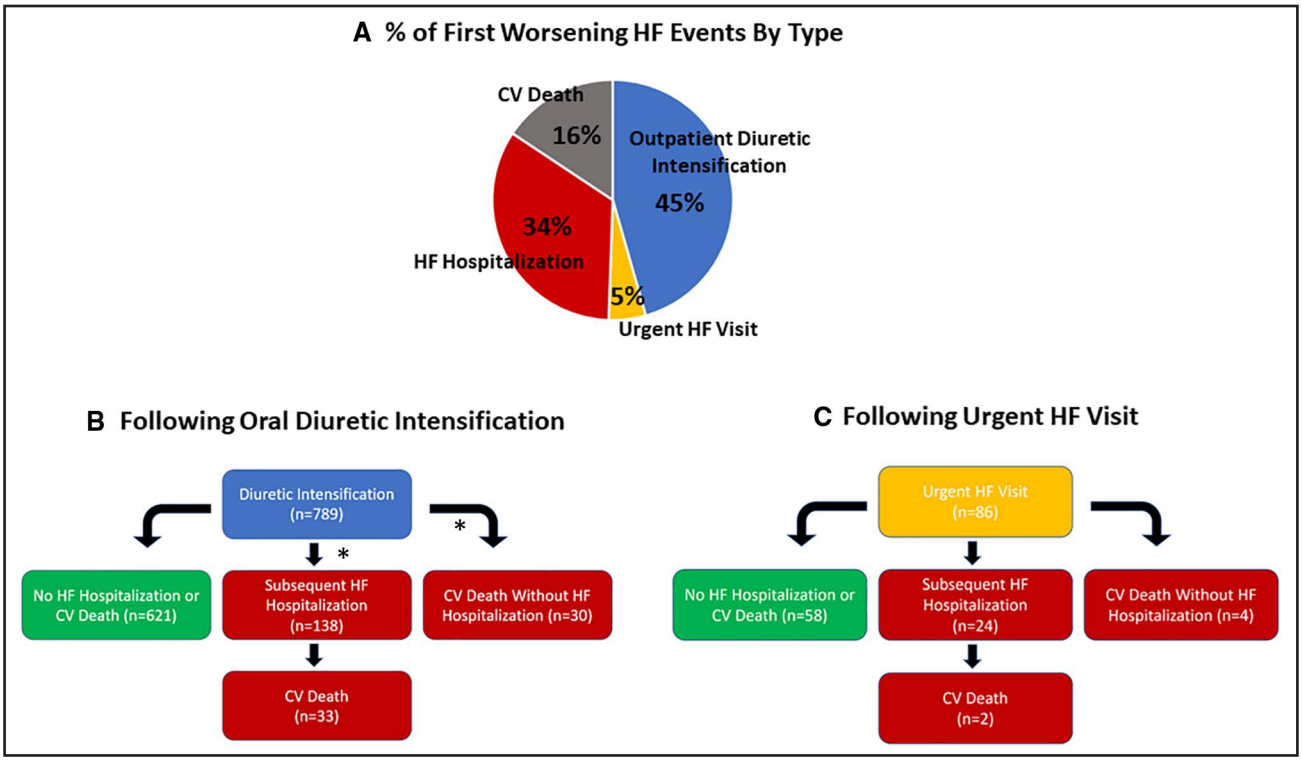

Figure 1. Manifestations of first worsening HF events.
Breakdown of first worsening HF events by type (**A**) and pathways of worsening heart failure after oral diuretic intensification (**B**) and urgent HF visit (**C**). *A total of 28 patients experienced an urgent HF visit after oral diuretic intensification. CV indicates cardiovascular; and HF, heart failure.

described in Table 1. Patients experiencing outpatient oral diuretic intensification as a first worsening HF event had higher ejection fraction, less severe HF symptoms, higher baseline KCCQ TSS, and a generally lower burden of comorbidities compared with patients experiencing other worsening HF events. Such patients were more often prescribed beta-blocker but less often prescribed a mineralocorticoid receptor antagonist or loop diuretic compared with patients experiencing other worsening HF events.

Clinical Course After Outpatient Oral Diuretic Intensification Versus Urgent HF Visit

The clinical course after the first outpatient oral diuretic intensification and urgent visit requiring intravenous diuretic administration are described in Figure 1. Among patients experiencing outpatient oral diuretic intensification, 621 (78%) did not experience progression (subsequent HF hospitalization of cardiovascular death), 138 (18%) had a subsequent HF hospitalization, of whom 33 died of cardiovascular causes, and 30 (4%) experienced cardiovascular death without HF hospitalization. Among those experiencing an urgent HF visit, 58 patients (67%) did not experience HF progression, 24 (28%) were subsequently hospitalized for HF, of whom 2 died of cardiovascular causes, and 4 patients (5%) experienced cardiovascular death without a preceding HF hospitalization.

Prognosis After First Nonfatal Worsening HF Event

Patients with a first presentation of worsening HF manifesting as an outpatient diuretic intensification experienced rates of subsequent all cause death that were higher (incidence rate, 10 [95% CI, 8–12 per 100 patient-years]) compared with those without a worsening HF event (incidence rate, 4 [95% CI, 3–4 per 100 patient-years]), but similar to rates of subsequent death after an urgent HF visit (incidence rate, 10 [95% CI, 6–18 per 100 patient-years]; Figure 2). Patients with an HF hospitalization as a first presentation of worsening HF had the highest rates of subsequent death (incidence rate, 35 [95% CI, 31–40 per 100 patient-years]).

Among patients experiencing outpatient diuretic intensification, dose augmentation up to increases (above baseline) of ≈80 mg of furosemide dose equivalents was associated with incrementally higher subsequent risk of mortality (Figure 2).

Health Status Trajectories Before and After Outpatient and Inpatient Worsening HF Events

Among those patients who experienced a worsening HF event in the time frame during which KCCQ

Table 1. Baseline Characteristics

Characteristics	First worsening heart failure event					*P* value
	No worsening HF event (n=4532)	Diuretic intensification (n=789)	Urgent HF visit (n=86)	HF hospitalization (n=585)	Cardiovascular death (n=271)	
Randomly assigned to dapagliflozin, n (%)	2362 (52.1)	328 (41.6)	42 (48.8)	268 (45.8)	131 (48.3)	<0.001
Age	71±10	73±9	70±10	72±10	73±10	<0.001
Male sex, n (%)	2511 (55.4)	432 (54.8)	49 (57.0)	352 (60.2)	172 (63.5)	0.022
Race and ethnicity, n (%)						<0.001
White	3201 (70.6)	541 (68.6)	65 (75.6)	430 (73.5)	202 (74.5)	
Asian	904 (19.9)	202 (25.6)	13 (15.1)	125 (21.4)	30 (11.1)	
Black and African American	103 (2.3)	24(3.0)	6 (7.0)	18 (3.1)	8 (3.0)	
American Indian	158 (3.5)	8 (1.0)	1 (1.2)	7 (1.2)	15 (5.5)	
Other*	166 (3.7)	14(1.8)	1 (1.2)	5 (0.9)	16 (5.9)	
Region, n (%)						<0.001
Europe and Saudi Arabia	2177 (48.0)	352 (44.6)	50 (58.1)	281 (48.0)	145 (53.5)	
Asia	870 (19.2)	194 (24.6)	13 (15.1)	120 (20.5)	29 (10.7)	
Latin America	927 (20.5)	111 (14.1)	8 (9.3)	64 (10.9)	71 (26.2)	
North America	558 (12.3)	132 (16.7)	15 (17.4)	120 (20.5)	26 (9.6)	
Body mass index, kg/m^2	30±6	30±6	32±7	30±7	29±6.4	<0.001
Systolic blood pressure, mm Hg	128±15	128±17	131±16	128±17	128±15	0.42
Pulse, bpm	71±12	71±12	73±12	74±12	73±12	<0.001
Estimated glomerular filtration rate	62±19	58±18	60±23	56±19	60±20	<0.001
Creatinine	100±30	107±33	109±37	112±34	106±33	<0.001
NT pro-BNP	929 [582–1576]	1133 [717–1948]	1375 [794–2286]	1463 [850–2628]	1329 [702–2728]	<0.001
New York Heart Association class, n (%)						<0.001
II	3505 (77.3)	585 (74.1)	63 (73.3)	384 (65.6)	176 (64.9)	
III	1018 (22.5)	202 (25.6)	23 (26.7)	193 (33.0)	95 (35.1)	
IV	9 (0.2)	2 (0.3)	0 (0.0)	7 (1.2)	0 (0.0)	
KCCQ TSS	75 [57–90]	71 [52–85]	67 [49–2]	67 [48–84]	65 [47–82]	<0.001
Left ventricular ejection fraction, %	54±9	55±9	53±8	54±9	52±9	<0.001
Previous HF hospitalization, n (%)	1708 (37.7)	305 (38.7)	43 (50.0)	352(60.2)	131 (48.3)	<0.001
Atrial fibrillation/flutter, n (%)	2424 (53.5)	484 (61.3)	48 (55.8)	370 (63.2)	139 (51.3)	<0.001
Chronic kidney disease, n (%)	1150 (25.4)	286 (36.2)	32 (37.2)	224 (38.3)	74 (27.3)	<0.001
Chronic obstructive pulmonary disease, n (%)	441 (9.7)	95 (12.1)	5 (5.8)	107 (18.3)	44 (16.2)	<0.001
Type 2 diabetes, n (%)	1943 (42.9)	363 (46.0)	54 (62.8)	309 (52.8)	137 (50.6)	<0.001
Dyslipidemia, n (%)	137 (50.6)	544 (68.9)	67 (77.9)	383 (65.5)	179 (66.1)	<0.001
Hypertension, n (%)	3991 (88.1)	711 (90.1)	81 (94.2)	519 (88.7)	251 (92.6)	0.039
Myocardial infarction, n (%)	1179 (26.0)	165 (20.9)	21 (24.4)	174 (29.7)	100 (36.9)	<0.001
Valvular heart disease, n (%)	1159 (25.6)	210 (26.6)	23 (26.7)	193 (33.0)	80 (29.5)	0.003
Beta-blocker, n (%)	3791 (83.6)	638 (81.1)	76 (88.4)	458 (78.3)	214 (79.0)	0.002
Angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker or angiotensin receptor-neprilysin inhibitor, n (%)	3517 (77.6)	596 (75.7)	70 (81.4)	433 (74.0)	216 (79.7)	0.16
Mineralocorticoid receptor antagonist, n (%)	1949 (43.0)	298 (37.9)	32 (37.2)	263(45.0)	125 (46.1)	0.024
Loop diuretic, n (%)	3424 (75.6)	554 (70.4)	74 (86.0)	541 (92.5)	218 (80.4)	<0.001
Baseline furosemide equivalent dose, mg	34±50	35±50	53±66	68±88	44±57	<0.001

HF indicates heart failure; KCCQ TSS, Kansas City Cardiomyopathy Questionnaire Total Symptoms Score; and NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

*Other race includes Native Hawaiian or Pacific Islander or race not otherwise specified by patients or investigators.

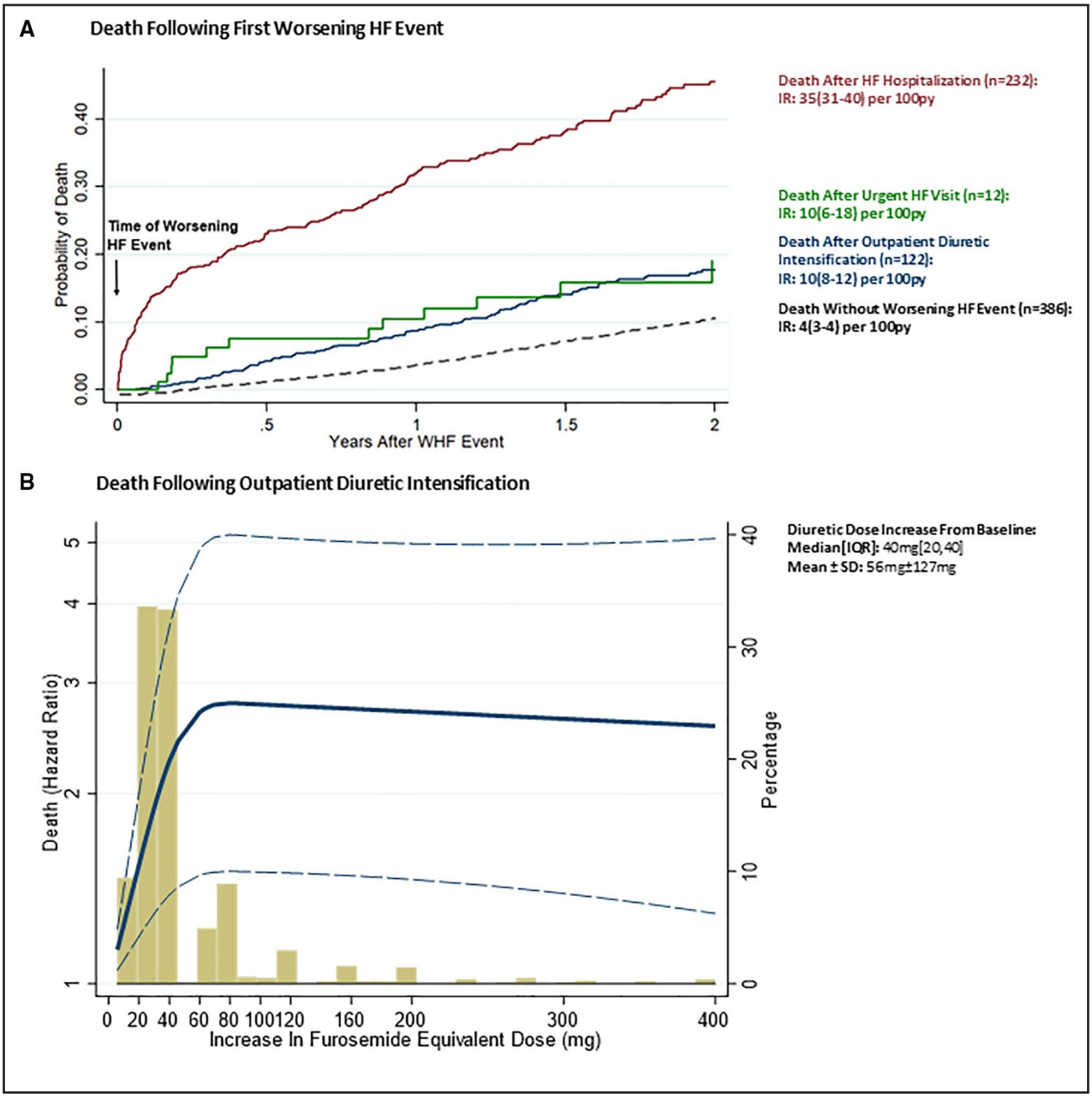

Figure 2. Prognosis after first nonfatal worsening HF event.
A, Death after first worsening HF events. Time scale for patients with first worsening HF events (red, green, and blue lines) is time after worsening HF event, and time scale for patients without worsening HF event (black dotted line) is time from randomization. **B**, Death after a varying degree of loop diuretic dose escalation (from baseline) expressed as furosemide equivalent dose (mg). HF indicates heart failure; IQR, interquartile range; py, patient-years; and WHF, worsening heart failure.

assessment was available, health status was observed to decline before both outpatient and inpatient worsening events (Figure 3). Declines in health status before outpatient worsening events (≈10 points) were less steep than declines before inpatient worsening events (≈25 points). A quick recovery in health status was observed after the HF event regardless of clinical setting.

Treatment Effects of Dapagliflozin on First Worsening HF Events

Dapagliflozin relative to placebo consistently reduced the occurrence of first nonfatal worsening HF events, including outpatient oral diuretic intensification (hazard ratio, 0.72 [95% CI, 0.64–0.82]; Table 2). The addition of outpatient oral diuretic intensification to the primary

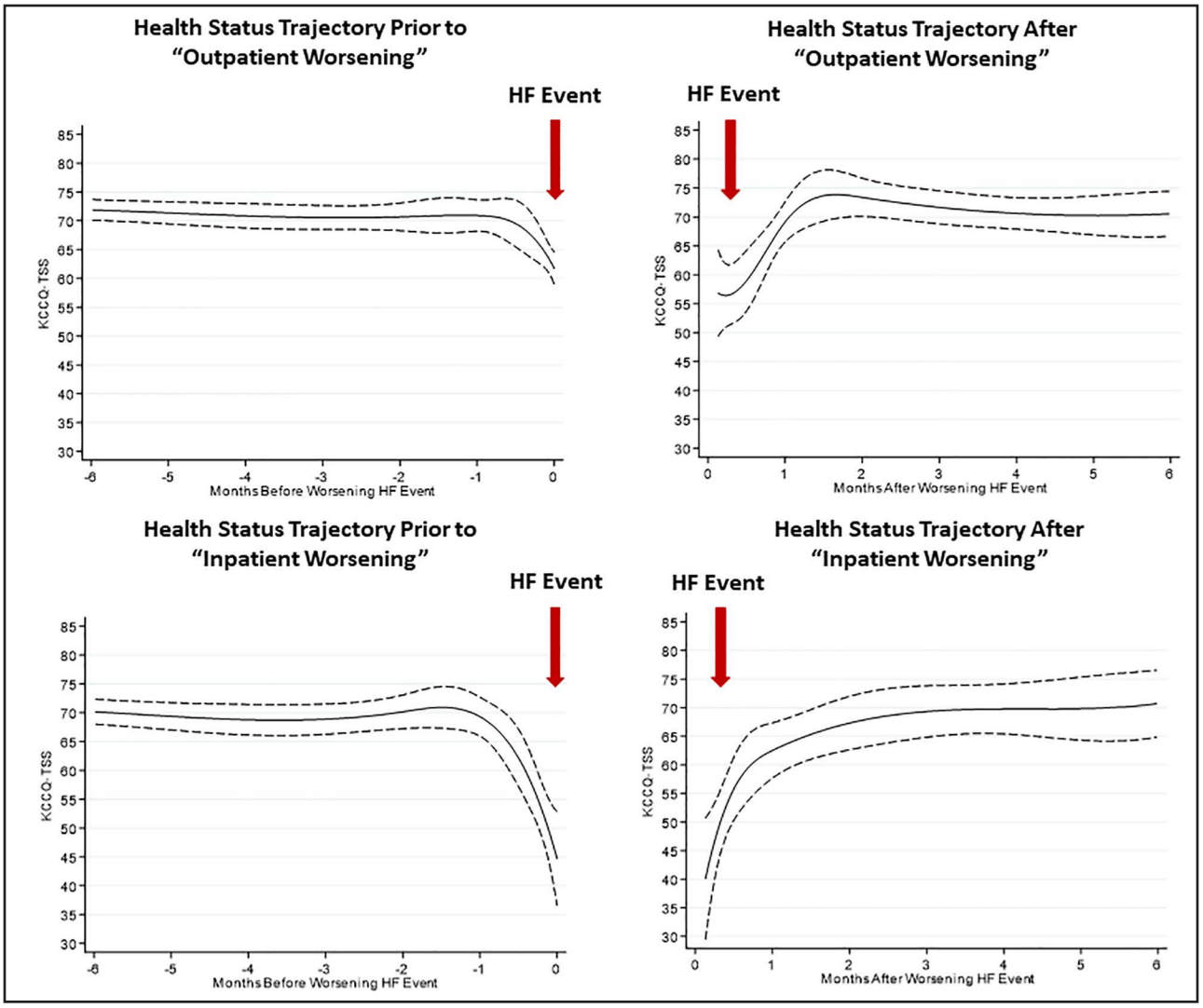

Figure 3. KCCQ-TSS health status trajectories before and after first outpatient or inpatient worsening HF event.
HF indicates heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; and TSS, Total Symptoms Score.

composite outcome of worsening HF and cardiovascular death increased the number of events from 1122 to 1731 (54% increase). Consistent with the primary findings of the DELIVER trial, treatment with dapagliflozin resulted in a 24% risk reduction in the expanded composite outcome of cardiovascular death, worsening HF event (requiring intravenous therapies), or outpatient oral diuretic intensification (hazard ratio, 0.76 [95% CI, 0.69–

Table 2. Treatment Effect of Dapagliflozin Vs Placebo on Facets of Worsening Heart Failure

Outcome	Dapagliflozin, No. of events	Placebo, No. of events	Hazard ratio* (95% CI)
Cardiovascular death	231	261	0.88 (0.74–1.05)
HF hospitalization	329	418	0.77 (0.67–0.89)
Urgent HF visit	60	78	0.76 (0.55–1.07)
Outpatient oral diuretic intensification	440	588	0.72 (0.64–0.82)
HF hospitalization or urgent HF visit	368	455	0.79 (0.69–0.91)
Cardiovascular death or HF hospitalization	475	577	0.80 (0.71–0.91)
Cardiovascular death or HF hospitalization or urgent HF visit	512	610	0.82 (0.73–0.92)
Cardiovascular death or HF hospitalization or urgent HF Visit or outpatient diuretic intensification	769	962	0.76 (0.69–0.84)

HF indicates heart failure.
*Unadjusted hazard ratios.

0.84]; Figure 4). These results remained consistent in win ratio analysis: win ratio for cardiovascular death followed by HF hospitalization, urgent HF visit, and then outpatient oral diuretic intensification in decreasing level of priority was 1.29 (95% CI, 1.17–1.42); 1/win ratio 0.78 (95% CI, 0.70–0.85).

DISCUSSION

In this prespecified analysis of the DELIVER trial, among patients with mildly reduced or preserved ejection fraction HF, we found that: (1) outpatient oral diuretic intensification was a frequent (1 in 8 patients) first manifestation of worsening HF; (2) outpatient oral diuretic intensification was similarly prognostic to an urgent HF visit requiring intravenous therapies and was preceded by clinically meaningful declines in health status; and (3) treatment with dapagliflozin significantly reduced the need for outpatient oral diuretic escalation. Taken together, these data suggest that oral diuretic intensification occurring in ambulatory care is frequent and prognostically important, and its occurrence may represent a clinically meaningful juncture to interrupt the progression of HF. These findings also support the consideration of adding outpatient oral diuretic intensification to a worsening HF composite end point in HF trials and may have implications for future trial design.

Hospitalization is well established as a destabilizing event in the clinical trajectory of patients with HF and carries significant risk of mortality and economic burden.[17] Worsening HF may also be managed in the outpatient setting either through oral diuretic intensification or intravenous diuretic administration in an outpatient HF unit, short-stay unit, observation unit, or the emergency department. In this analysis of patients with HF with mildly reduced or preserved ejection fraction, those experiencing worsening in the ambulatory setting managed with oral diuretic intensification had lower long-term mortality compared with patients experiencing HF hospitalization but similar rates of death compared with those experiencing an urgent HF visit requiring intravenous therapies. These observations are consistent with results from the PARAGON-HF trial (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction).[8] On the other hand, in patients with HF with reduced ejection fraction, outpatient and inpatient worsening events appear to carry overlapping prognostic trajectories.[5–7] Potential explanations may be related to differences in risk profile due to a more contemporary HF population in DELIVER or underlying phenotypic differences between patients with reduced and preserved ejection fraction. It should also be noted that there were slight differences in the exact definition of outpatient intensification used between studies. In our analysis, outpatient diuretic intensification was defined as any new oral loop diuretic initiation (among those not taking loop diuretics at baseline) or sustained increase in dose of ≥30 days (among those taking diuretics at baseline). In similar analyses in DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure), outpatient intensification was inclusive of any HF therapy including diuretic.

Health-related quality of life is a significant predictor of mortality and hospitalization and has been shown to decline significantly in the period preceding HF

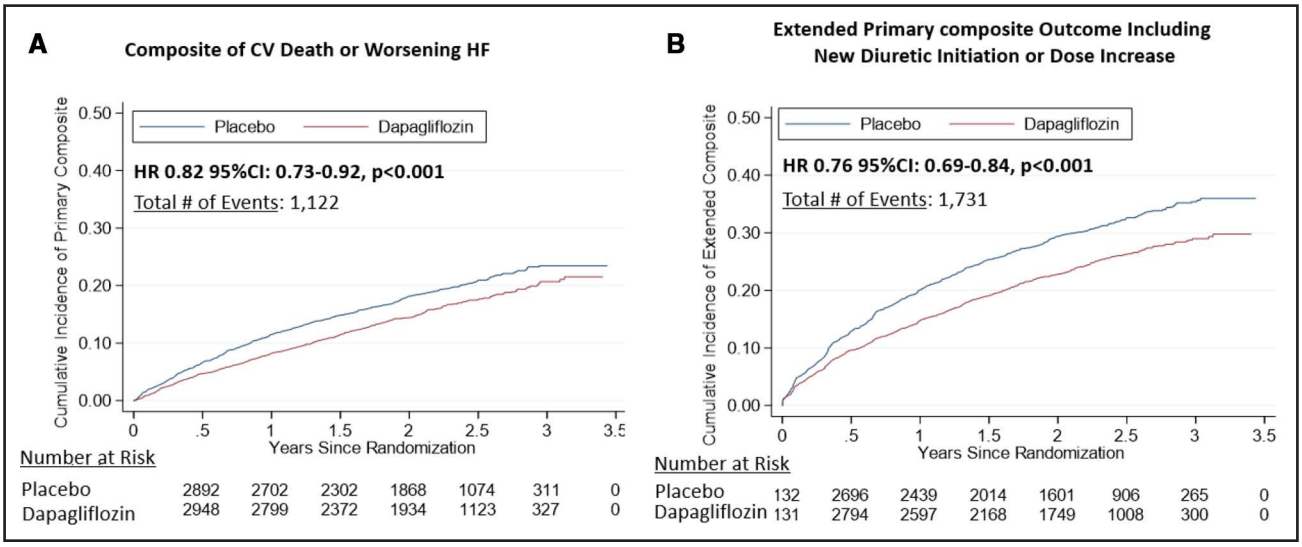

Figure 4. Treatment effect on the DELIVER primary composite outcome of cardiovascular death or worsening HF (HF hospitalization or urgent HF visit) and the extended composite outcome including oral diuretic intensification.
CV indicates cardiovascular; HF, heart failure; and HR, hazard ratio.

hospitalization.[15,18] In this report, we demonstrate that the trajectories of patients experiencing outpatient worsening were also characterized by steep declines in health-related quality of life that preceded the HF event and quickly rebounded after the event. It is important to note that a large majority (more than two-thirds) of outpatient worsening episodes did not result in HF hospitalization. When outpatient worsening is followed by HF hospitalization, outpatient oral diuretic increase may identify patients earlier in their trajectory of worsening. The quick recovery in health status after worsening events suggests that the related health status declines may be modifiable. These data further underscore outpatient worsening events, including those requiring oral diuretic intensification, as clinically meaningful opportunities to interrupt HF progression.

Urgent HF visits requiring intravenous diuretics are increasingly included as a component of the primary composite end point in clinical trials of pharmacological therapies in HF.[1,19] In ambulatory care settings, worsening HF episodes are more commonly treated with intensification of oral therapies than with intravenous diuretics. In this analysis, ≈1 in 8 patients experienced a first worsening HF event manifesting as oral diuretic intensification in the outpatient setting compared with <1 in 10 patients with an urgent HF visit requiring intravenous diuretic administration. Outpatient worsening occurs on a spectrum; focusing exclusively on those requiring intravenous therapies may underestimate the actual burden of disease. In this analysis, the inclusion of outpatient oral diuretic intensification in an expanded composite outcome led to >50% increase in the total number of events. Furthermore, dapagliflozin reduced both the primary composite outcome and the expanded composite to a similar extent. This suggests that these events may be therapeutically responsive to discern and support their use as a potential efficacy signal. As such, consideration of this expanded end point in clinical trials may effectively reduce sample size, duration of follow-up time required to accrue target events, and related study costs.

SGLT2 inhibitors robustly reduce HF hospitalizations across the spectrum of ejection fraction. Secondary analyses have further demonstrated the clinical benefits of these agents to prevent worsening HF events of varying severity (including those requiring escalation of therapy beyond standard intravenous diuretics).[20–22] In this analysis, treatment with dapagliflozin significantly reduced outpatient oral diuretic intensification and is consistent with findings from DAPA-HF in patients with reduced ejection fraction.[5] These data highlight another facet of the benefit of SGLT2 inhibitors to prevent the full spectrum of worsening HF events, including outpatient worsening.

These data must be evaluated in the context of important limitations. Outpatient worsening events defined as oral diuretic intensification were not formally adjudicated. Information regarding specific signs and symptoms of HF was not used to corroborate worsening HF in this group of patients with oral diuretic intensification specifically. The definition of outpatient oral diuretic intensification was limited to patients experiencing a new loop diuretic initiation or dose increase, because loop diuretics represent the mainstay of management of acute decompensated HF. Augmentation through thiazide diuretics or other nonloop diuretics was not considered given the inherent limitations in the dose conversion between loop diuretics and nonloop diuretics. Last, we did not separately assess visits to the emergency department without subsequent hospital admission.

Conclusions

Overall, outpatient oral diuretic intensification was a frequent first manifestation of worsening HF occurring in 1 in 8 patients with HF with mildly reduced or preserved ejection fraction in the DELIVER trial. The subsequent trajectory of patients experiencing outpatient worsening is characterized by both an increased risk of mortality and a steep decline in health status, highlighting these events as important junctures to interrupt HF progression. Dapagliflozin consistently reduced the full spectrum of worsening HF events, including those that transpired exclusively in the outpatient setting. Addition of oral diuretic intensification to the primary composite end point led to an important increment in clinically meaningful events. These data underscore that oral diuretic intensification in the ambulatory setting, while seemingly benign, carries important prognostic significance and its requirement is significantly reduced with the SGLT2 inhibitor dapagliflozin. These data further support the potential consideration of an expanded worsening HF end point that is inclusive of oral diuretic intensification in future HF clinical trials.

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REFERENCES

1. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, et al; DELIVER Trial Committees and Investigators. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2022;387:1089–1098. doi: 10.1056/NEJMoa2206286
2. Solomon SD, Dobson J, Pocock S, Skali H, McMurray JJ, Granger CB, Yusuf S, Swedberg K, Young JB, Michelson EL, et al; Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Investigators. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation*. 2007;116:1482–1487. doi: 10.1161/CIRCULATIONAHA.107.696906
3. Greene SJ, Bauersachs J, Brugts JJ, Ezekowitz JA, Lam CSP, Lund LH, Ponikowski P, Voors AA, Zannad F, Zieroth S, et al. Worsening heart failure: nomenclature, epidemiology, and future directions: JACC review topic of the week. *J Am Coll Cardiol*. 2023;81:413–424. doi: 10.1016/j.jacc.2022.11.023
4. Madelaire C, Gustafsson F, Stevenson LW, Kristensen SL, Køber L, Andersen J, D'Souza M, Biering-Sørensen T, Andersson C, Torp-Pedersen C, et al. One-year mortality after intensification of outpatient diuretic therapy. *J Am Heart Assoc*. 2020;9:e016010. doi: 10.1161/JAHA.119.016010
5. Docherty KF, Jhund PS, Anand I, Bengtsson O, Böhm M, de Boer RA, DeMets DL, Desai AS, Drozdz J, Howlett J, et al. Effect of dapagliflozin on outpatient worsening of patients with heart failure and reduced ejection fraction: a prespecified analysis of DAPA-HF. *Circulation*. 2020;142:1623–1632. doi: 10.1161/CIRCULATIONAHA.120.047480
6. Okumura N, Jhund PS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Swedberg K, Zile MR, Solomon SD, et al; PARADIGM-HF Investigators and Committees. Importance of clinical worsening of heart failure treated in the outpatient setting. *Circulation*. 2016;133:2254–2262. doi: 10.1161/CIRCULATIONAHA.115.020729
7. Skali H, Dwyer EM, Goldstein R, Haigney M, Krone R, Kukin M, Lichstein E, McNitt S, Moss AJ, Pfeffer MA, et al. Prognosis and response to therapy of first inpatient and outpatient heart failure event in a heart failure clinical trial: MADIT-CRT. *Eur J Heart Fail*. 2014;16:560–565. doi: 10.1002/ejhf.71
8. Vaduganathan M, Cunningham JW, Claggett BL, Causland FM, Barkoudah E, Finn P, Zannad F, Pfeffer MA, Rizkala AR, Sabarwal S, et al. Worsening heart failure episodes outside a hospital setting in heart failure with preserved ejection fraction: the PARAGON-HF trial. *JACC Heart Fail*. 2021;9:374–382. doi: 10.1016/j.jchf.2021.01.014
9. Vidic A, Chibnall JT, Hauptman PJ. Heart failure is a major contributor to hospital readmission penalties. *J Card Fail*. 2015;21:134–137. doi: 10.1016/j.cardfail.2014.12.002
10. Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, Solomon SD, Marler JR, Teerlink JR, Farb A, et al; Standardized Data Collection for Cardiovascular Trials Initiative (SCTI). 2017 cardiovascular and stroke endpoint definitions for clinical trials. *Circulation*. 2018;137:961–972. doi: 10.1161/CIRCULATIONAHA.117.033502
11. Chatur S, Vaduganathan M, Claggett B, Vardeny O, Desai AS, Jhund PS, de Boer RA, Lam CSP, Kosiborod MN, Shah SJ, et al. Dapagliflozin and diuretic utilization in heart failure with mildly reduced or preserved ejection fraction: the DELIVER trial. *Eur Heart J*. 2023;44:2930–2943. doi: 10.1093/eurheartj/ehad283
12. Jackson AM, Dewan P, Anand IS, Bělohlávek J, Bengtsson O, de Boer RA, Böhm M, Boulton DW, Chopra VK, DeMets DL, et al. Dapagliflozin and diuretic use in patients with heart failure and reduced ejection fraction in DAPA-HF. *Circulation*. 2020;142:1040–1054. doi: 10.1161/CIRCULATIONAHA.120.047077
13. Testani JM, Brisco MA, Turner JM, Spatz ES, Bellumkonda L, Parikh CR, Tang WH. Loop diuretic efficiency: a metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. *Circ Heart Fail*. 2014;7:261–270. doi: 10.1161/CIRCHEARTFAILURE.113.000895
14. Wolsk E, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber L, Lawson FC, Lewis EF, Maggioni AP, McMurray JJV, et al. Increases in natriuretic peptides precede heart failure hospitalization in patients with a recent coronary event and type 2 diabetes mellitus. *Circulation*. 2017;136:1560–1562. doi: 10.1161/CIRCULATIONAHA.117.029503
15. Vaduganathan M, Claggett BL, McMurray JJV, Solomon SD. Health status trajectories before and after hospitalization for heart failure. *Circulation*. 2022;145:1872–1874. doi: 10.1161/CIRCULATIONAHA.122.059282
16. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *Eur Heart J*. 2011;33:176–182. doi: 10.1093/eurheartj/ehr352
17. Greene SJ, Mentz RJ, Felker GM. Outpatient worsening heart failure as a target for therapy: a review. *JAMA Cardiol*. 2018;3:252–259. doi: 10.1001/jamacardio.2017.5250
18. Johansson I, Joseph P, Balasubramanian K, McMurray JJV, Lund LH, Ezekowitz JA, Kamath D, Alhabib K, Bayes-Genis A, Budaj A, et al; G-CHF Investigators. Health-related quality of life and mortality in heart failure: the global congestive heart failure study of 23 000 patients from 40 countries. *Circulation*. 2021;143:2129–2142. doi: 10.1161/CIRCULATIONAHA.120.050850

19. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, et al; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008. doi: 10.1056/NEJMoa1911303
20. Chatur S, Kondo T, Claggett BL, Docherty K, Miao ZM, Desai AS, Jhund PS, de Boer RA, Hernandez AF, Inzucchi SE, et al. Effects of dapagliflozin on heart failure hospitalizations according to severity of inpatient course: insights from DELIVER and DAPA-HF. *Eur J Heart Fail*. 2023;25:1364–1371. doi: 10.1002/ejhf.2912
21. Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, Carson P, Anand I, Doehner W, Haass M, et al. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: The EMPEROR-Reduced trial. *Circulation*. 2021;143:326–336. doi: 10.1161/CIRCULATIONAHA.120.051783
22. Packer M, Butler J, Zannad F, Filippatos G, Ferreira JP, Pocock SJ, Carson P, Anand I, Doehner W, Haass M, et al. Effect of empagliflozin on worsening heart failure events in patients with heart failure and preserved ejection fraction: EMPEROR-Preserved trial. *Circulation*. 2021;144:1284–1294. doi: 10.1161/CIRCULATIONAHA.121.056824