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CLINICAL RESEARCH

Blood Pressure and Dapagliflozin in Heart Failure With Mildly Reduced or Preserved Ejection Fraction

DELIVER

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ABSTRACT

BACKGROUND Optimizing systolic blood pressure (SBP) in heart failure (HF) with preserved ejection fraction carries a Class I recommendation but with limited evidence. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have antihypertensive effects across cardiovascular disease.

OBJECTIVES The authors examined the interplay between SBP and treatment effects of dapagliflozin on SBP and cardiovascular outcomes.

METHODS The authors analyzed 6,263 DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure) participants and related baseline and mean achieved SBP categories (<120, 120-129, 130-139, ≥140 mm Hg) to the primary outcome (cardiovascular death or worsening HF), secondary outcomes, and safety events. They analyzed whether the blood pressure–lowering effects of dapagliflozin accounted for its treatment effects by adjusting for the change in SBP from baseline to 1 month.

RESULTS The average age was 72 ± 10 years and 44% were women. SBP <120 mm Hg was associated with higher HF and mortality events, although amputation and stroke risk increased with higher SBP. Dapagliflozin reduced SBP by 1.8 (95% CI: 1.1-2.5) mm Hg compared with placebo at 1 month. The treatment effect of dapagliflozin on the primary outcome and Kansas City Cardiomyopathy Questionnaire total symptom score was consistent across SBP (interaction $P = 0.15$ and $P = 0.98$, respectively). Adverse events between arms were similar across SBP categories. The treatment effect was not accounted for by reducing blood pressure.

CONCLUSIONS In DELIVER, risk by SBP was augmented in the lowest and highest categories and varied by endpoint examined. Dapagliflozin modestly decreased SBP compared with placebo. Dapagliflozin was similarly efficacious and safe across the range of baseline SBP. The beneficial effects of dapagliflozin were not accounted for by the changes in SBP. (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure [DELIVER]; NCT03619213) (J Am Coll Cardiol HF 2023;11:76–89) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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Hypertension is particularly common in patients with heart failure with preserved ejection fraction (HFpEF),[1-6] and its relevance to the HFpEF syndrome has been underscored by inclusion into diagnostic algorithms.[7,8] Because hypertension may drive disease progression in HFpEF through several pathways (including left ventricular hypertrophy, coronary microvascular disease, diastolic dysfunction, abnormal ventricular arterial coupling, and end-organ dysfunction), control of hypertension may represent an important therapeutic target in HFpEF.[1,9-11] Concordantly, blood pressure (BP) control remains the sole Class I recommendation in HFpEF in recent guidelines, though with limited supporting evidence.[12] While strict BP control is essential to reducing incident HF risk, as demonstrated in SPRINT (Systolic Blood Pressure Intervention Trial), the exclusion of patients with prevalent HF limits extrapolation to this population.[13]

Several randomized controlled trials of therapies that reduce BP have been studied in HFpEF.[2-5,14] However, the antihypertensive effects of sodium-glucose cotransporter 2 (SGLT2) inhibitors are increasingly recognized, particularly among those with comorbidities common in HFpEF.[15] In this prespecified subgroup analysis in DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure),[16] we sought to understand the prognostic influence of baseline and mean achieved SBP on clinical outcomes, analyze the impact of dapagliflozin on SBP, evaluate the effect of dapagliflozin on clinical outcomes in relation to baseline SBP, and assess whether the SBP-lowering effect of dapagliflozin accounted for its treatment effects.

METHODS

THE DELIVER STUDY DESIGN. The design of the DELIVER study has been described in detail previously.[17] Briefly, DELIVER is an international, randomized, double-blind, parallel-group, event-driven trial comparing the efficacy and safety of dapagliflozin with placebo in patients with HF and mildly reduced or preserved left ventricular ejection fraction (LVEF). DELIVER enrolled adults 40 years of age or older with signs and symptoms of HF (New York Heart Association functional class II-IV), LVEF of >40%, elevated concentrations of N-terminal pro-B-type natriuretic peptide (degree of elevation depending on presence or absence of atrial fibrillation/flutter), and evidence of structural heart disease (increased left atrial size or left ventricular hypertrophy). Patients were enrolled both as outpatients and as inpatients in the setting of a hospitalization for worsening HF. The primary endpoint for the trial was a composite of cardiovascular death or worsening HF event (either a HF hospitalization or an urgent HF visit). The study was approved by institutional review boards or ethics committees at individual study sites, and all patients signed written informed consent.

Key exclusion criteria included a screening estimated glomerular filtration rate (eGFR) <25 mL/min/1.73 m^2, recent cardiovascular event, and SBP <95 or ≥160 mm Hg (if not on treatment with ≥3 BP-lowering medications) or ≥180 mm Hg (irrespective of number of treatments). Detailed exclusion criteria are listed elsewhere.[17] All 6,263 DELIVER patients had an available baseline SBP, and therefore no patients were excluded for this analysis.

STUDY OUTCOMES. Endpoints studied in this analysis include time to first occurrence of the primary composite outcome (worsening HF episodes [urgent HF visit or HF hospitalization] or cardiovascular death), HF hospitalization, cardiovascular death, and all-cause mortality. For safety assessment, we analyzed several adverse events including limb amputation, diabetic ketoacidosis, myocardial infarction, and stroke, among others.

STATISTICAL ANALYSIS. Baseline characteristics grouped by clinical categories of baseline SBP (<120, 120-129, 130-139, ≥140 mm Hg, which approximated quartiles) were described using mean ± SD and

ACRONYMS AND ABBREVIATIONS

BP = blood pressure

EF = ejection fraction

eGFR = estimated glomerular filtration rate

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

LVEF = left ventricular ejection fraction

SBP = systolic blood pressure

SGLT2 = sodium-glucose cotransporter 2

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TABLE 1 Baseline Clinical Characteristics by SBP Categories

	SBP <120 mm Hg (n = 1,809)	SBP 120-129 mm Hg (n = 1,535)	SBP 130-139 mm Hg (n = 1,514)	SBP ≥140 mm Hg (n = 1,405)	*P* Value
Age, y	71.2 ± 10.0	71.7 ± 9.5	72.1 ± 9.3	71.9 ± 9.3	0.043
Men	1,056 (58.4)	854 (55.6)	876 (57.9)	730 (52.0)	0.001
Race					<0.001
White	1,113 (61.5)	1,139 (74.2)	1,160 (76.6)	1,027 (73.1)	
Asian	525 (29.0)	266 (17.3)	226 (14.9)	257 (18.3)	
Black or African American	46 (2.5)	31 (2.0)	23 (1.5)	59 (4.2)	
American Indian or Alaska Native	68 (3.8)	44 (2.9)	41 (2.7)	36 (2.6)	
Other	57 (3.2)	55 (3.6)	64 (4.2)	26 (1.9)	
Geographic region					<0.001
Europe and Saudi Arabia	645 (35.7)	778 (50.7)	849 (56.1)	733 (52.2)	
Asia	512 (28.3)	254 (16.5)	212 (14.0)	248 (17.7)	
Latin America	328 (18.1)	298 (19.4)	289 (19.1)	266 (18.9)	
North America	324 (17.9)	205 (13.4)	164 (10.8)	158 (11.2)	
History					
AFF	1,117 (61.7)	870 (56.7)	848 (56.0)	717 (51.0)	<0.001
Stroke	174 (9.6)	155 (10.1)	144 (9.5)	124 (8.8)	0.71
Type 2 diabetes mellitus	708 (39.1)	679 (44.2)	710 (46.9)	709 (50.5)	<0.001
COPD	220 (12.2)	168 (10.9)	167 (11.0)	137 (9.8)	0.20
Sleep apnea	182 (10.1)	109 (7.1)	95 (6.3)	99 (7.1)	<0.001
Myocardial infarction	485 (26.8)	423 (27.6)	396 (26.2)	335 (23.8)	0.12
Prior HF hospitalization	781 (43.2)	609 (39.7)	595 (39.3)	554 (39.4)	0.06
Any coronary artery disease	877 (48.5)	804 (52.4)	796 (52.6)	687 (48.9)	0.027
Any atherosclerotic cardiovascular disease	994 (54.9)	899 (58.6)	888 (58.7)	771 (54.9)	0.034
Smoking status					0.007
Current	122 (6.7)	112 (7.3)	132 (8.7)	118 (8.4)	
Former	716 (39.6)	550 (35.8)	511 (33.8)	484 (34.4)	
Never	971 (53.7)	873 (56.9)	871 (57.5)	803 (57.2)	
Baseline BMI, kg/m^2	28.8 ± 6.2	29.8 ± 6.0	30.2 ± 5.9	30.7 ± 6.2	<0.001
BMI group					<0.001
<18.5 kg/m^2 (underweight)	29 (1.6)	6 (0.4)	7 (0.5)	12 (0.9)	
18.5-24.9 kg/m^2 (normal weight)	506 (28.0)	316 (20.6)	286 (18.9)	235 (16.7)	
25.0-29.9 kg/m^2 (overweight)	591 (32.7)	547 (35.6)	506 (33.4)	429 (30.6)	
30.0-34.9 kg/m^2 (class I obesity)	378 (20.9)	381 (24.8)	411 (27.2)	404 (28.8)	
35.0-39.9 kg/m^2 (class II obesity)	196 (10.9)	184 (12.0)	204 (13.5)	214 (15.3)	
≥40 kg/m^2 (class III obesity)	106 (5.9)	101 (6.6)	99 (6.5)	109 (7.8)	
Time from diagnosis of HF to baseline					0.85
0-3 mo	180 (10.0)	141 (9.2)	130 (8.6)	117 (8.3)	
3-6 mo	163 (9.0)	148 (9.6)	135 (8.9)	146 (10.4)	
6-12 mo	230 (12.7)	202 (13.2)	219 (14.5)	191 (13.6)	
1-2 y	296 (16.4)	233 (15.2)	248 (16.4)	218 (15.5)	
2-5 y	437 (24.2)	393 (25.6)	384 (25.4)	355 (25.3)	
>5 y	499 (27.6)	417 (27.2)	398 (26.3)	378 (26.9)	
NYHA functional class at baseline					0.38
I	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	
II	1,363 (75.3)	1,155 (75.2)	1,125 (74.3)	1,070 (76.2)	
III	436 (24.1)	376 (24.5)	388 (25.6)	331 (23.6)	
IV	9 (0.5)	4 (0.3)	1 (0.1)	4 (0.3)	
Baseline LVEF, %	53.6 ± 9.0	54.0 ± 8.6	54.0 ± 8.6	55.2 ± 8.7	<0.001
LVEF group					<0.001
≤40%	2 (0.1)	1 (0.1)	0 (0.0)	1 (0.1)	
41%-49%	697 (38.5)	510 (33.2)	525 (34.7)	380 (27.0)	
50%-59%	590 (32.6)	577 (37.6)	532 (35.1)	557 (39.6)	
≥60%	520 (28.7)	447 (29.1)	457 (30.2)	467 (33.2)	

Continued on the next page

TABLE 1 Continued

	SBP <120 mm Hg (n = 1,809)	SBP 120-129 mm Hg (n = 1,535)	SBP 130-139 mm Hg (n = 1,514)	SBP ≥140 mm Hg (n = 1,405)	*P* Value
Baseline NT-proBNP, pg/mL	1,097 (668-1,884)	1,015 (626-1,747)	1,024 (621-1,743)	907 (562-1,596)	<0.001
NT-proBNP in AFF (ECG)	1,439 (996-2,210)	1,373 (924-2,161)	1,386 (962-2,231)	1,390 (962-2,323)	0.47
NT-proBNP when no AFF (ECG)	734 (484-1,417)	725 (461-1,316)	718 (470-1,316)	682 (450-1,135)	0.026
Baseline ECG AFF	867 (47.9)	663 (43.2)	627 (41.4)	487 (34.7)	<0.001
Baseline SBP, mm Hg	110.1 ± 6.8	124.5 ± 2.9	134.3 ± 3.0	149.0 ± 7.9	<0.001
Baseline DBP, mm Hg	67.9 ± 8.8	73.2 ± 8.7	76.3 ± 8.8	79.9 ± 11.0	<0.001
Baseline HbA_{1c}, %	6.4 ± 1.3	6.6 ± 1.4	6.6 ± 1.4	6.7 ± 1.5	<0.001
Baseline pulse, beats/min	72.2 ± 12.7	71.2 ± 10.7	70.9 ± 10.9	71.5 ± 12.5	0.006
Baseline creatinine, μmol/L	103.3 ± 30.6	100.9 ± 29.9	102.7 ± 31.6	102.8 ± 32.4	0.13
Baseline eGFR, mL/min/1.73 m^2	60.9 ± 19.4	61.7 ± 19.2	61.0 ± 19.1	60.4 ± 18.9	0.32
eGFR ≥60 mL/min/1.73 m^2	899 (49.7)	786 (51.2)	790 (52.2)	717 (51.0)	0.54
Loop diuretics	1,440 (79.6)	1,178 (76.7)	1,138 (75.2)	1,055 (75.1)	0.006
ACE inhibitor	593 (32.8)	587 (38.2)	603 (39.9)	512 (36.5)	<0.001
ARB	579 (32.0)	544 (35.4)	558 (36.9)	591 (42.1)	<0.001
ARNI	158 (8.7)	60 (3.9)	51 (3.4)	32 (2.3)	<0.001
Beta-blocker	1,528 (84.5)	1,263 (82.3)	1,259 (83.2)	1,127 (80.3)	0.017
MRA	933 (51.6)	655 (42.7)	632 (41.8)	447 (31.8)	<0.001
Pacemaker	218 (12.1)	160 (10.4)	160 (10.6)	124 (8.8)	0.033
ICD	48 (2.7)	27 (1.8)	24 (1.6)	14 (1.0)	0.005

Values are mean ± SD, n (%), or median (IQR).

ACE = angiotensin-converting enzyme; AFF = atrial fibrillation/flutter; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BMI = body mass index; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycosylated hemoglobin; HF = heart failure; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure.

median (IQR) or percentage as appropriate for the levels of measurement and distributions of the variables.[18] The SBP categories were compared using analysis of variance (or nonparametric equivalent when appropriate) for continuous variables and chi-square tests (or Fisher exact test when appropriate) for categorical variables.

The association between baseline SBP categories and efficacy outcomes were assessed using crude and multivariable-adjusted Cox regression, using the lowest SBP category as the referent group. In a complementary analysis using restricted cubic splines, we examined the continuous association between SBP and all outcomes. Four knots placed at the 5th, 35th, 65th, and 95th percentiles were used for all outcomes. Multivariable models adjusted for similar baseline covariates used in previous analyses of SBP in HFpEF, including region, atrial fibrillation, creatinine, diabetes mellitus, New York Heart Association functional class, heart rate, sex, age, race, smoking status, ejection fraction (EF), and treatment group (model 1).[5,6] As competing risks regression models used previously for relevant analyses yielded very similar results in DELIVER,[16] Cox models were employed here. In addition, while a proportional hazards assumption violation was noted in DELIVER,[16,19] alternative modeling produced similar results, and therefore the violation was not considered to threaten the original approach. We repeated these analyses using mean achieved SBP as a time-updated covariate, which was updated at each BP ascertainment to represent the average observed BP up to that time point.[5,20] We additionally modeled SBP using the last observed value. The relationship between SBP categories and adverse events was assessed using chi-square tests.

We next determined the placebo-adjusted change in SBP from baseline to follow-up at the 1-month follow-up visit using linear regression, adjusting for baseline SBP values. Interaction terms between treatment and baseline SBP, LVEF, and eGFR were tested. We assessed the placebo-corrected differences in Kansas City Cardiomyopathy Questionnaire domains from baseline to 32 weeks using linear regression.

Finally, to assess whether the change in SBP accounted for the beneficial effects of dapagliflozin, we generated Cox models assessing the relationship between treatment assignment and outcomes adjusting for baseline SBP and change in SBP between baseline and the 1-month visit.[6] Analyses were performed using STATA version 14, and a 2-sided value of $P < 0.05$ was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS. The baseline characteristics of the 6,263 DELIVER participants stratified

TABLE 2 Event Rates and Crude and Adjusted HRs for Efficacy Outcomes by Baseline SBP Category

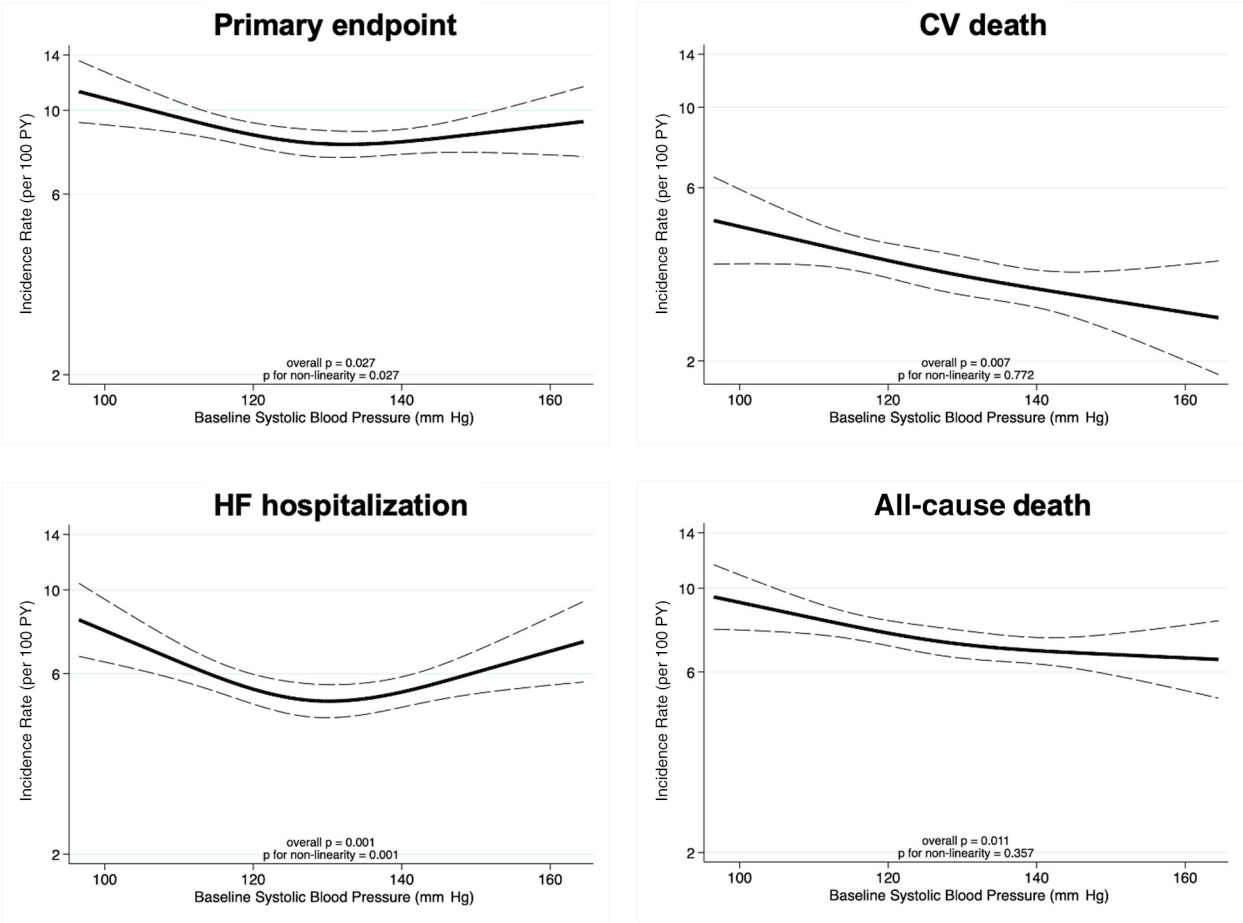
	SBP <120 mm Hg (n = 1,809)	SBP 120-129 mm Hg (n = 1,535)	SBP 130-139 mm Hg (n = 1,514)	SBP ≥140 mm Hg (n = 1,405)
Primary composite				
Number of events	348	260	269	245
Event rate, per 100 PY	9.7	8.2	8.5	8.2
Unadjusted HR (95% CI) (overall $P = 0.202$)	Ref.	0.85 (0.73-1.00); $P = 0.057$	0.89 (0.76-1.04); $P = 0.150$	0.87 (0.74-1.03); $P = 0.101$
Adjusted HR (95% CI) (overall $P = 0.329$)	Ref.	0.89 (0.75-1.05); $P = 0.154$	0.90 (0.77-1.06); $P = 0.222$	0.87 (0.73-1.03); $P = 0.099$
CV death				
Number of events	168	121	112	91
Event rate, per 100 PY	4.4	3.6	3.3	2.8
Unadjusted HR (95% CI) (overall $P = 0.001$)	Ref.	0.77 (0.61-0.98); $P = 0.031$	0.70 (0.55-0.90); $P = 0.004$	0.62 (0.48-0.80); $P < 0.001$
Adjusted HR (95% CI) (overall $P = 0.004$)	Ref.	0.81 (0.64-1.03); $P = 0.082$	0.72 (0.56-0.92); $P = 0.008$	0.64 (0.50-0.84); $P < 0.001$
HF hospitalization				
Number of events	240	160	176	171
Event rate, per 100 PY	6.7	5.0	5.5	5.7
Unadjusted HR (95% CI) (overall $P = 0.137$)	Ref.	0.79 (0.64-0.96); $P = 0.020$	0.88 (0.72-1.08); $P = 0.220$	0.91 (0.75-1.11); $P = 0.376$
Adjusted HR (95% CI) (overall $P = 0.257$)	Ref.	0.81 (0.66-1.00); $P = 0.045$	0.90 (0.74-1.10); $P = 0.303$	0.90 (0.74-1.11); $P = 0.330$
All-cause death				
Number of events	318	243	251	211
Event rate, per 100 PY	8.3	7.1	7.4	6.5
Unadjusted HR (95% CI) (overall $P = 0.006$)	Ref.	0.81 (0.68-0.96); $P = 0.014$	0.82 (0.69-0.96); $P = 0.017$	0.75 (0.63-0.89); $P = 0.001$
Adjusted HR (95% CI) (overall $P = 0.013$)	Ref.	0.84 (0.71-0.99); $P = 0.037$	0.82 (0.69-0.97); $P = 0.021$	0.76 (0.63-0.91); $P = 0.002$

Multivariable analyses adjusted for region, atrial fibrillation, creatinine, diabetes mellitus, NYHA functional class, heart rate, sex, age, race, smoking status, and treatment group.
CV = cardiovascular; PY = person-years; Ref. = reference; other abbreviations as in Table 1.

by SBP categories are shown in Table 1. The overall average age was 72 ± 10 years, 44% were women, the majority were White, and the mean baseline BP was 128 ± 15/74 ± 10 mm Hg. Higher SBP category was associated with older age, White race, female sex, higher diastolic BP and heart rate, higher body mass index, less frequent atrial fibrillation and sleep apnea, and more frequent diabetes mellitus and coronary artery disease. Higher SBP category was also associated with higher LVEF and lower N-terminal pro-B-type natriuretic peptide ($P < 0.05$ for all comparisons). Regarding medications, higher SBP category was associated with more frequent use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers and less frequent use of loop diuretics, angiotensin receptor neprilysin inhibitors, beta-blockers, and mineralocorticoid antagonists. There was no difference in eGFR across categories.

ASSOCIATION OF SBP WITH CARDIOVASCULAR EVENTS. In crude analyses of the efficacy outcomes using SBP categories (Table 2), SBP category was not associated with the primary outcome (overall $P = 0.20$). Specifically, compared with the lowest SBP category, the HRs for the primary outcome among SBP categories 2 to 4 were 0.85 (95% CI: 0.73-1.00), 0.89 (95% CI: 0.76-1.04), and 0.87 (95% CI: 0.74-1.03). The risk for cardiovascular death and all-cause mortality decreased with increasing SBP category (overall $P = 0.001$ and $P = 0.006$, respectively). Multivariable adjustment (Table 2) showed similar patterns as observed in the crude analysis. When analyzed using continuous splines, a U-shaped relationship was observed between SBP category and risk for the primary outcome and HF hospitalization with the nadir risk ~130 mm Hg for both outcomes ($P < 0.05$ for both comparisons) (Figure 1). Increasing SBP was linearly associated with lower rates of cardiovascular and all-cause mortality ($P < 0.05$ for overall relationship). Adverse events that were common in higher SBP categories included amputation ($P = 0.005$), stroke ($P = 0.017$), and myocardial infarction ($P = 0.06$) (Table 3).

FIGURE 1 Relationship Between Baseline Continuous Systolic Blood Pressure and Outcomes



Unadjusted incidence rates (per 100 PY) using spline analysis for the primary endpoint, cardiovascular (CV) death, heart failure (HF) hospitalization, and all-cause death, according to systolic blood pressure at baseline. The interrupted lines are 95% CI. PY = person-years.

TABLE 3 Adverse Events by Baseline SBP Category

	SBP <120 mm Hg (n = 1,809)	SBP 120-129 mm Hg (n = 1,535)	SBP 130-139 mm Hg (n = 1,514)	SBP ≥140 mm Hg (n = 1,405)	*P* Value
Any SAE (including outcome = death)	807 (44.6)	658 (43.0)	656 (43.4)	663 (47.3)	0.08
Any AE leading to discontinuation of IP	117 (6.5)	76 (5.0)	96 (6.4)	74 (5.3)	0.17
Any AE leading to interruption of IP	278 (15.4)	217 (14.2)	225 (14.9)	210 (15.0)	0.81
Any amputation	5 (0.3)	7 (0.5)	15 (1.0)	17 (1.2)	0.005
Any potential risk factor AE for amputation affecting lower limbs	114 (6.3)	96 (6.3)	83 (5.5)	94 (6.7)	0.58
Any definite or probable diabetic ketoacidosis	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0.10
Any MI	27 (1.5)	40 (2.6)	33 (2.2)	39 (2.8)	0.06
Any stroke	51 (2.8)	44 (2.9)	47 (3.1)	65 (4.6)	0.017
Any major hypoglycemic event	5 (0.3)	0 (0.0)	5 (0.3)	3 (0.2)	0.19
Any SAE or DAE suggestive of volume depletion	27 (1.5)	17 (1.1)	15 (1.0)	15 (1.1)	0.54
Any renal SAE or DAE	51 (2.8)	28 (1.8)	34 (2.3)	39 (2.8)	0.22

Values are n (%).

AE = adverse event; DAE = adverse events leading to discontinuation of study drug; IP = investigational product; MI = myocardial infarction; SAE = serious advent event; SBP = systolic blood pressure.

TABLE 4 Event Rates and Crude and Adjusted HRs for Outcomes by Time-Updated Mean Achieved SBP Quartile

	SBP <120 mm Hg	SBP 120-129 mm Hg	SBP 130-139 mm Hg	SBP ≥140 mm Hg
Primary composite				
Number of events	338	301	257	226
Event rate, per 100 PY	9.9	8.0	7.8	9.3
Unadjusted HR (95% CI) (overall $P = 0.027$)	Ref.	0.83 (0.71-0.97); $P = 0.022$	0.81 (0.69-0.95); $P = 0.010$	0.95 (0.80-1.13); $P = 0.560$
Adjusted HR (95% CI) (overall $P = 0.04$)	Ref.	0.84 (0.72-0.99); $P = 0.035$	0.80 (0.68-0.95); $P = 0.010$	0.94 (0.79-1.12); $P = 0.488$
CV death				
Number of events	166	137	112	77
Event rate, per 100 PY	4.5	3.4	3.2	2.9
Unadjusted HR (95% CI) (overall $P = 0.002$)	Ref.	0.75 (0.60-0.94) $P = 0.013$	0.70 (0.55-0.89) $P = 0.003$	0.64 (0.49-0.84) $P = 0.001$
Adjusted HR (95% CI) (overall $P < 0.001$)	Ref.	0.71 (0.56-0.89); $P = 0.003$	0.65 (0.50-0.82); $P < 0.001$	0.60 (0.45-0.79); $P < 0.001$
HF hospitalization				
Number of events	243	174	173	157
Event rate, per 100 PY	7.0	4.6	5.2	6.4
Unadjusted HR (95% CI) (overall $P < 0.001$)	Ref.	0.67 (0.56-0.82); $P < 0.001$	0.76 (0.63-0.93); $P = 0.006$	0.92 (0.75-1.12); $P = 0.406$
Adjusted HR (95% CI) (overall $P = 0.003$)	Ref.	0.71 (0.59-0.87); $P < 0.001$	0.80 (0.65-0.97); $P = 0.025$	0.95 (0.77-1.17); $P = 0.636$
All-cause death				
Number of events	317	288	248	170
Event rate, per 100 PY	8.6	7.2	7.0	6.4
Unadjusted HR (95% CI) (overall $P = 0.005$)	Ref.	0.82 (0.70-0.96); $P = 0.014$	0.80 (0.68-0.95); $P = 0.009$	0.74 (0.62-0.89); $P = 0.002$
Adjusted HR (95% CI) (overall $P < 0.001$)	Ref.	0.77 (0.65-0.90); $P = 0.001$	0.73 (0.61-0.86); $P < 0.001$	0.68 (0.56-0.82); $P < 0.001$

Multivariable analyses adjusted for region, atrial fibrillation, creatinine, diabetes mellitus, NYHA class, heart rate, sex, age, race, smoking status, and treatment group. Time-updated, mean achieved SBP uses average SBP as a time-updated covariate, which is updated at each blood pressure ascertainment to represent the average observed blood pressure up to that time point.

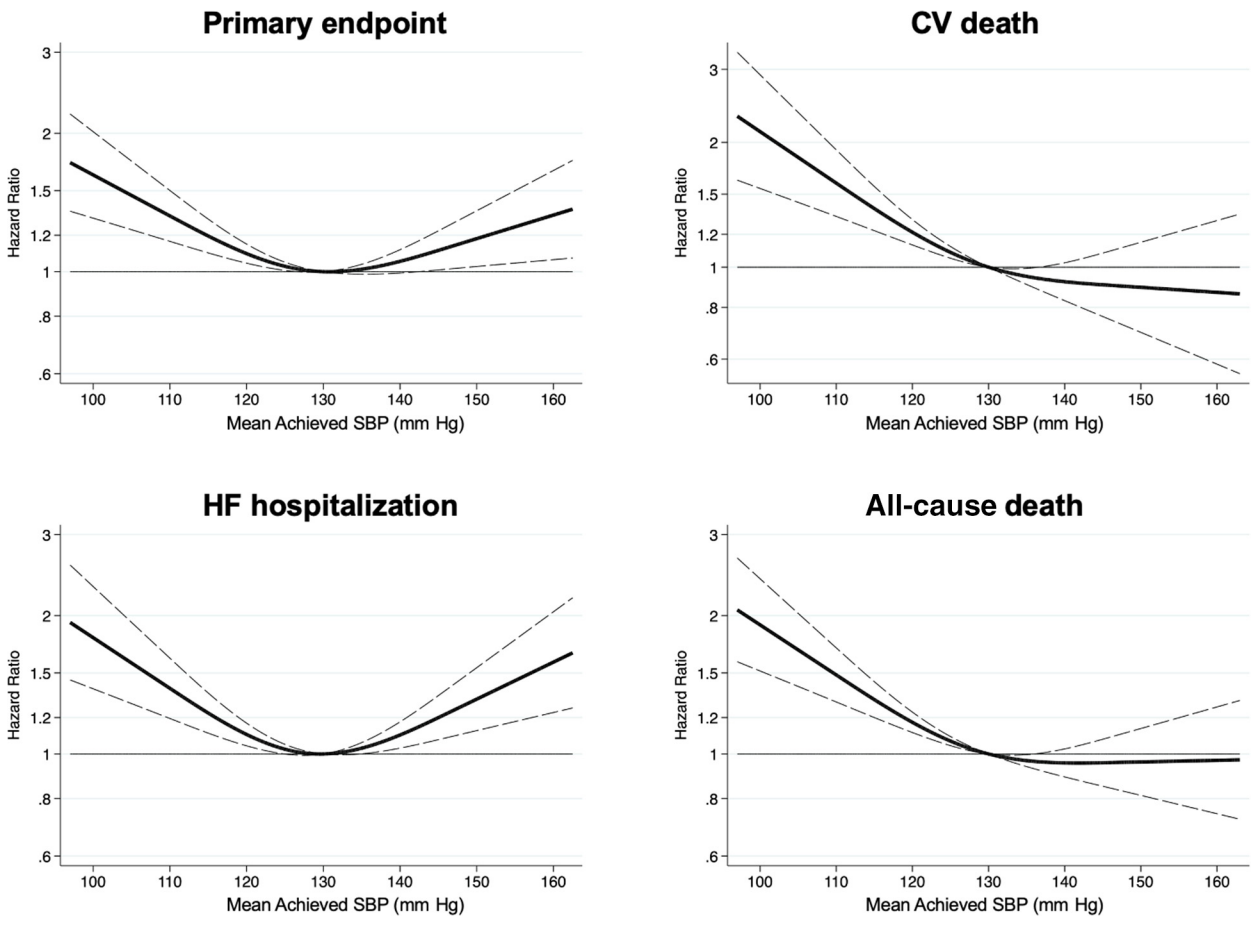
Abbreviations as in Tables 1 and 2.

To understand the relationship between change in BP and subsequent risk, we analyzed the relationship between time-updated, mean achieved SBP and study outcomes, using category 1 (<120 mm Hg) as the referent arm (Table 4). Results were overall similar to the baseline SBP analysis, with modest differences observed. Specifically, the relationship with the primary outcome was significant ($P = 0.04$), and when compared with the lowest SBP category, the adjusted HRs among mean achieved SBP categories 2 to 4 were 0.84 (95% CI: 0.72-0.99), 0.80 (95% CI: 0.68-0.95), and 0.94 (95% CI: 0.79-1.12). Also, the risk for cardiovascular death and all-cause mortality did not continue to decrease above 130 mm Hg (Figure 2). Analysis of SBP using the last observed value also yielded similar findings to analysis of mean achieved SBP, though the relationship with the primary outcome was not significant on unadjusted or adjusted analysis (Supplemental Table 1).

INTERPLAY OF DAPAGLIFLOZIN AND SBP. Overall, dapagliflozin reduced SBP by 1.8 mm Hg (95% CI: 1.1-2.5 mm Hg; $P < 0.001$) at the 1-month visit compared with placebo (Central Illustration, Supplemental Table 2). Dapagliflozin had a similar BP-lowering effect across the 4 SBP baseline categories at the 1-month visit (interaction $P = 0.16$). Similarly, the BP-lowering effect was similar across baseline eGFR (interaction $P = 0.30$), as well as LVEF (interaction $P = 0.33$).

Baseline SBP did not modify the relationship between dapagliflozin and the primary outcome (interaction $P = 0.15$), cardiovascular death (interaction $P = 0.73$), HF hospitalization (interaction $P = 0.10$), and all-cause death (interaction $P = 0.16$) (Figure 3). Likewise, the beneficial effects of dapagliflozin on Kansas City Cardiomyopathy Questionnaire domains were consistent across SBP categories (Table 5), and corresponding interaction P values for the total symptom, clinical summary, and overall summary scores were 0.98, 0.97, and 0.98, respectively. Adverse events by treatment arm were generally similar across SBP categories, including no differences by treatment arm in adverse events in the lowest SBP category (Supplemental Tables 3 to 6).

FIGURE 2 Adjusted Relationship Between Time-Updated, Mean Achieved SBP, and Clinical Outcomes



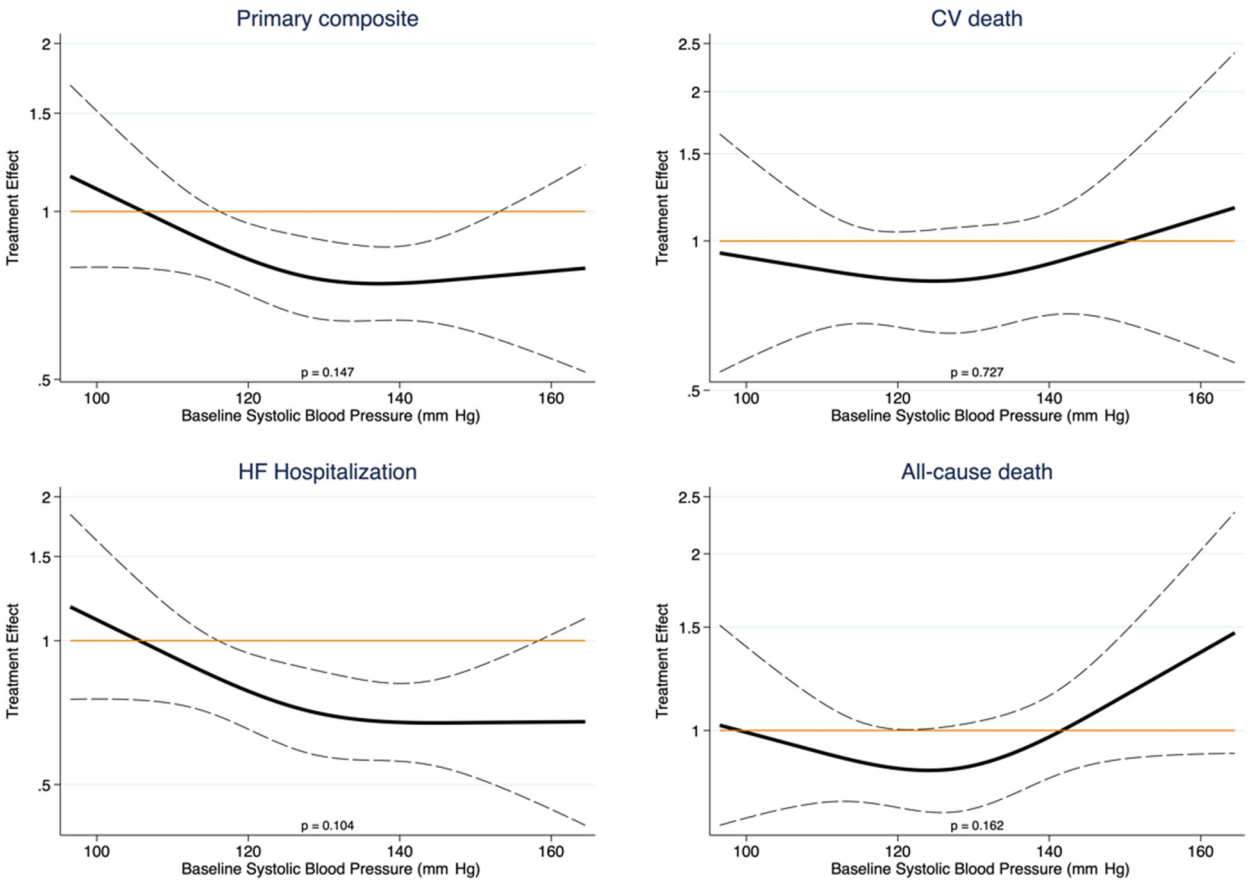
HRs (using referent systolic blood pressure [SBP] = 130 mm Hg) are depicted for the primary endpoint, CV death, HF hospitalization, and all-cause death, according to time-updated, mean achieved SBP. The interrupted lines are 95% CI. Abbreviations as in Figure 1.

RELATIONSHIP BETWEEN CHANGE IN SBP AND TREATMENT EFFECT. To determine whether the treatment effects of dapagliflozin were mediated by BP reduction, we performed Cox regression, adjusting for change in SBP at the 1-month visit, for the outcomes improved by dapagliflozin in DELIVER. Adjusting for the change in SBP minimally attenuated the treatment effect of dapagliflozin (Table 6).

DISCUSSION

In the largest trial to date of patients with HF with mildly reduced or preserved EF, both baseline and time-updated, mean achieved SBP <120 mm Hg generally identified patients at the highest risk for HF hospitalization and mortality. However, amputation and stroke events increased with increasing SBP category. Dapagliflozin reduced SBP by ~2 mm Hg, compared with placebo, by the 1-month visit; this effect was consistently observed across baseline SBP and LVEF. Dapagliflozin provided consistent treatment benefits with respect to cardiovascular events and HF-related health status regardless of baseline SBP, and the safety profile of dapagliflozin was similar to placebo across SBP categories. Finally, the treatment effect was not significantly accounted for by the changes in SBP. These analyses provide new insight into the relationship between SBP and outcomes in HF with mildly reduced or preserved EF, demonstrate the efficacy and safety of dapagliflozin

FIGURE 3 Treatment Effect of Dapagliflozin on Trial Outcomes Across Baseline SBP



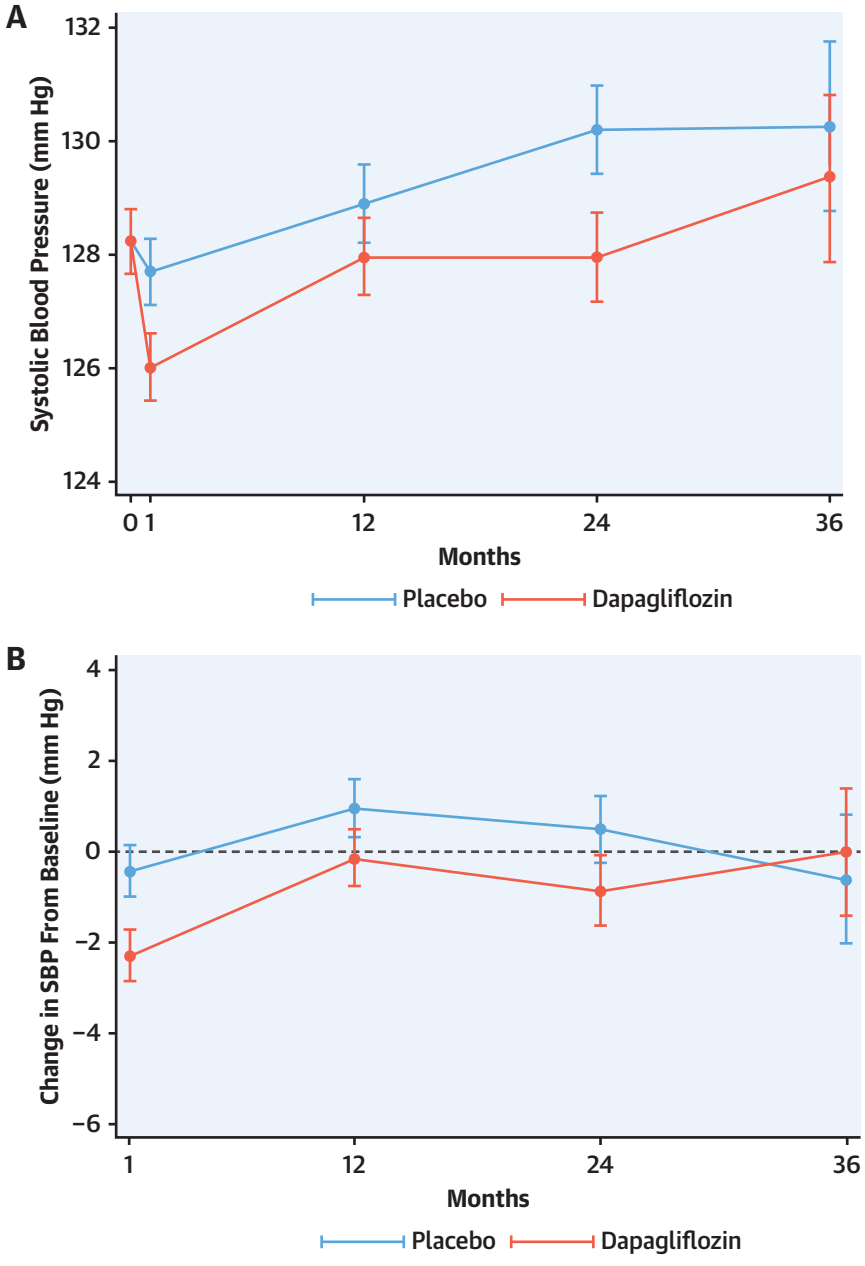
The HRs of dapagliflozin vs placebo on several outcomes are shown as continuous splines by baseline SBP. Interrupted lines represent 95% CI. *P* value shown for treatment by continuous SBP interaction term. Abbreviations as in Figures 1 and 2.

regardless of baseline SBP, and suggest that SBP reduction with dapagliflozin is not responsible for its treatment benefits in this patient population.

The optimal SBP in HFpEF remains controversial.[1] In the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial, no significant relationship between SBP quartiles and outcomes was demonstrated in patients with HFpEF. However, continuous spline analysis displayed a U-shaped relationship with cardiovascular events.[6] In the PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) trial, baseline and time-updated SBP 120 to 129 mm Hg identified the lowest-risk participants across several cardiovascular and renal endpoints.[5]

In DELIVER, the risk by SBP was heterogeneous with respect to the outcome study. Modeling both baseline and mean achieved SBP, the risk for HF hospitalization was U-shaped, with the lowest risk at ~130 mm Hg. However, analysis of baseline and mean achieved SBP rendered modestly different results. Using baseline SBP, increasing SBP was generally associated with lower mortality, though this risk did not continue to decrease past ~130 mm Hg when assessed using mean achieved SBP. Furthermore, when evaluating adverse events, increasing SBP category was associated with higher risk of vascular

CENTRAL ILLUSTRATION **Treatment Effects on SBP Over Time**



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(A) Systolic blood pressure (SBP) during follow-up for dapagliflozin- and placebo-treated patients shown separately. **(B)** The difference in SBP from baseline at each follow-up visit shown by treatment arm. **Bars** represent 95% CI.

(amputation and stroke) events. Overall, these findings suggest that the risk by SBP may be conditional on the endpoint studied. While HF-related events and mortality increased with lower SBP, amputation and stroke events increased with higher SBP. The association between low SBP and HF and mortality events could be causally related but might also identify a sicker patient population with confounding

TABLE 5 Effect of Dapagliflozin on HF-Related Health Status Across SBP Categories

SBP Category/KCCQ Domain	Baseline		Month 8		Difference Between Dapagliflozin and Placebo Arms (95% CI)	*P* Value
	Dapagliflozin	Placebo	Dapagliflozin	Placebo		
<120 mm Hg (n = 1,235)						
Total symptom score	70.4 ± 22.1	71.8 ± 21.7	80.7 ± 18.6	78.7 ± 20.5	2.5 (0.6-4.4)	0.009
Clinical summary score	68.4 ± 21.0	70.1 ± 20.6	78.1 ± 18.4	76.1 ± 19.9	2.6 (0.9-4.3)	0.003
Overall summary score	66.1 ± 20.8	67.7 ± 20.2	80.7 ± 18.6	78.7 ± 20.5	2.6 (0.7-4.4)	0.007
120-129 mm Hg (n = 1,102)						
Total symptom score	69.1 ± 23.1	70.5 ± 21.7	77.9 ± 19.4	76.3 ± 20.7	2.4 (0.4-4.4)	0.017
Clinical summary score	67.2 ± 21.4	69.0 ± 20.2	75.2 ± 18.6	74.2 ± 19.5	2.1 (0.3-4.0)	0.02
Overall summary score	65.5 ± 20.7	67.4 ± 19.7	77.9 ± 19.4	76.3 ± 20.7	2.7 (0.6-4.7)	0.01
130-139 mm Hg (n = 1,089)						
Total symptom score	70.1 ± 22.1	68.6 ± 21.3	79.5 ± 18.0	75.8 ± 20.4	2.7 (0.8-4.7)	0.006
Clinical summary score	68.7 ± 20.7	67.4 ± 19.7	77.0 ± 17.6	73.5 ± 19.3	2.6 (0.7-4.4)	0.007
Overall summary score	66.9 ± 20.2	66.0 ± 19.2	79.5 ± 18.0	75.8 ± 20.4	2.9 (0.9-4.9)	0.004
≥140 mm Hg (n = 985)						
Total symptom score	69.5 ± 23.3	69.8 ± 22.2	78.6 ± 19.4	76.4 ± 20.6	2.1 (−0.0 to 4.1)	0.05
Clinical summary score	67.8 ± 21.6	67.9 ± 20.3	75.9 ± 18.8	73.5 ± 19.4	2.1 (0.2 to 4.0)	0.027
Overall summary score	66.8 ± 21.3	66.8 ± 19.7	78.6 ± 19.4	76.4 ± 20.6	1.9 (−0.2 to 4.0)	0.07

Values are mean ± SD, unless otherwise indicated.
KCCQ = Kansas City Cardiomyopathy Questionnaire; other abbreviations as in Table 1.

conditions or more aggressive treatment. Conversely, the association between higher SBP and vascular events is analogous to other populations across cardiovascular disease.[21] It is important to highlight that these previous studies as well as DELIVER did not randomize BP targets (like SPRINT). Overall, the heterogeneous results of DELIVER, coupled with the observational nature of the present and previous analyses, underscore the need for randomized trials in this space. Notably, dapagliflozin provided consistent benefit with respect to efficacy endpoints and HF-related health status, and adverse events were similar across SBP categories. These results may therefore reassure clinicians that in the context of the modest BP lowering effect, initiation of SGLT2 inhibitors (even among patients in the lower end of the SBP spectrum studied in DELIVER) is both efficacious and safe.

TABLE 6 Landmark Analysis of 1-Month Change in SBP and Treatment Effect of Dapagliflozin

Efficacy Outcome	Unadjusted HR: Dapagliflozin vs Placebo (95% CI)	*P* Value	Adjusted HR: Dapagliflozin vs Placebo (95% CI)[a]	*P* Value
Primary composite endpoint	0.82 (0.73-0.92)	0.001	0.85 (0.75-0.96)	0.01
HF hospitalization	0.77 (0.67-0.89)	<0.001	0.80 (0.68-0.93)	0.004

Analyses were landmarked at the 1-month visit. [a]Adjusted for baseline SBP and 1-month SBP.
Abbreviations as in Table 1.

The BP-lowering effects of SGLT2 inhibitors have been recognized across the spectrum of cardiovascular disease. SGLT2 inhibitors reduce BP likely through several pathways, including weight loss, proximal tubule inhibition of fluid and electrolyte reabsorption, volume loss, sympathoinhibition, lowering of uric acid, and decrease in arterial stiffness.[22-27] A meta-analysis of participants with type 2 diabetes mellitus showed a placebo-corrected reduction with dapagliflozin of 3.6 mm Hg in hypertensive participants and 2.6 mm Hg in nonhypertensive participants.[28] However, the antihypertensive effects of SGLT2 inhibitors can be robust, for example, with an ~8- to 10-mm Hg placebo-corrected decrease in daytime SBP among diabetic groups as assessed by ambulatory monitoring.[29,30] Office-based assessments of BP control, as in DELIVER, could underestimate the effect size compared with ambulatory monitoring.[15] For comparison with other therapies tested in large trials in HFpEF, the SBP-lowering effect of SGLT2 inhibitors (1-2 mm Hg for dapagliflozin and empagliflozin)[31] is less compared with spironolactone or sacubitril-valsartan (4-5 mm Hg), for example.[5,6] In general, the effects of SGLT2 inhibitors on BP in patients with HF generally seem mildly diminished compared with non-HF populations. Concordantly, in the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial in patients with HF and EF ≤40%, dapagliflozin reduced SBP by 2.5 mm Hg compared with placebo.[32]

Thus, the BP effects of dapagliflozin in HFpEF or mildly reduced EF are modest, and unsurprisingly, do not account for the beneficial effects as shown in our mediation analysis.

STUDY LIMITATIONS. Ambulatory BP monitoring, rather than office BP measurements, may provide a more accurate assessment of the BP effects of dapagliflozin, as has been previously demonstrated.[15] In addition, although DELIVER is the largest trial in HF with mildly reduced or preserved EF to date, the trial may have been underpowered to detect more subtle relationships of SBP categories with some outcomes. Finally, exclusion criteria based on BP and renal function may somewhat limit generalizability of our results.

CONCLUSIONS

SBP <120 mm Hg was generally associated with higher risk of HF and mortality events, though amputation and stroke events increased with higher SBP. Dapagliflozin modestly decreased SBP compared with placebo. Dapagliflozin provided consistent treatment benefits across baseline SBP with respect to cardiovascular events and HF-related health status and was similarly safe even among participants in the lowest SBP category. The beneficial treatment effects of dapagliflozin were independent of changes in BP.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Dapagliflozin was similarly beneficial and safe across the spectrum of SBP studied in DELIVER. Dapagliflozin modestly reduced BP (~2 mm Hg) compared with placebo, and this did not result in more treatment interruption across SBP categories, including the lowest category (<120 mm Hg).

TRANSLATIONAL OUTLOOK: As the BP-lowering effect of dapagliflozin did not account for its beneficial treatment effects, future studies are needed to clarify the mechanisms responsible for the treatment effects of SGLT2 inhibitors in patients with HF and mildly reduced or preserved EF.

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KEY WORDS blood pressure, dapagliflozin, heart failure hospitalization, heart failure with preserved ejection fraction, SGLT2

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