JAMA Cardiology | Original Investigation

Effect of Dapagliflozin on Cause-Specific Mortality in Patients With Heart Failure Across the Spectrum of Ejection Fraction

A Participant-Level Pooled Analysis of DAPA-HF and DELIVER

Akshay S. Desai, MD, MPH; Pardeep S. Jhund, MBCHB, PhD; Brian L. Claggett, PhD; Muthiah Vaduganathan, MD, MPH; Zi Michael Miao, MS; Toru Kondo, MD, PhD; Ebrahim Barkoudah, MD; Abdel Brahimi, MD; Eugene Connolly, MBChB; Peter Finn, MD; Ninian N. Lang, MBChB, PhD; Finnian R. Mc Causland, MBBCh, MMSc; Martina McGrath, MBBCh; Mark C. Petrie, MD; John J. V. McMurray, MD; Scott D. Solomon, MD

IMPORTANCE In 2 trials enrolling patients with heart failure (HF) across the spectrum of ejection fraction (EF), dapagliflozin has been shown to reduce the rate of the composite of worsening HF events or death from cardiovascular (CV) causes.

OBJECTIVE To examine the effects of dapagliflozin on cause-specific CV and non-CV mortality across the spectrum of EF.

DESIGN, SETTING, AND PARTICIPANTS This was a participant-level, pooled, prespecified secondary analysis of data from the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure, or DAPA-HF trial (participant left ventricular EF [LVEF] ≤40%), and Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure, or DELIVER trial (participant LVEF >40%), to assess the effects of randomized treatment on cause-specific mortality. The trials assigned adjacent populations of patients with chronic HF, New York Heart Association class II-IV symptoms, and elevated natriuretic peptides to treatment with dapagliflozin (10 mg, once daily) or placebo. The primary outcome for each study was a composite of worsening HF events (hospitalization or urgent heart failure visits) or CV death. Clinical outcomes, including all deaths, were adjudicated as to cause by clinical end points committees blinded to treatment assignment.

INTERVENTION Dapagliflozin vs placebo.

MAIN OUTCOMES AND MEASURES The mode of death in relation to baseline EF was examined, as well as the effect of randomized treatment on cause-specific death in Cox regression models. Relationships with continuous EF were modeled using Poisson regression.

RESULTS Of 11 007 patients in the pooled data set, there were 1628 deaths during follow-up (mean [SD] age, 71.7 [10.3] years; 1139 male [70.0%]). Of those who died, 872 (53.5%) were ascribed to CV deaths, 487 (29.9%) to non-CV deaths, and 269 (16.5%) to undetermined causes. Of CV deaths, 289 (33.1%; this represented 17.8% of total deaths) were due to HF, 441 (50.6%; 27.1% of total deaths) were sudden, 69 (7.9%; 4.2% of total deaths) were due to stroke, 47 (5.4%; 2.9% of total deaths) to myocardial infarction, and 26 (3.0%; 1.6% of total deaths) were due to other CV causes. The proportion of non-CV deaths was higher in those with higher EF. In the pooled population, across the spectrum of EF, treatment with dapagliflozin was associated with lower rates of CV death (hazard ratio [HR], 0.86; 95% CI, 0.75-0.98; *P* = .02), principally due to lower rates of sudden death (HR, 0.84; 95% CI, 0.70-1.01; *P* = .07) and HF death (HR, 0.88; 95% CI, 0.70-1.11; *P* = .30), with little difference in rates of death from stroke or MI.

CONCLUSIONS AND RELEVANCE In a pooled analysis of patients with HF in the DAPA-HF and DELIVER randomized clinical trials, across the full spectrum of LVEF, dapagliflozin significantly reduced risks of CV death with contributions from lower rates of sudden death and death from progressive HF.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03036124, NCT03619213

JAMA Cardiol. doi:10.1001/jamacardio.2022.3736
Published online October 3, 2022.

Supplemental content

Author Affiliations: Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts (Desai, Claggett, Vaduganathan, Miao, Barkoudah, Brahimi, Finn, Solomon); British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (Jhund, Kondo, Connolly, Lang, Petrie, McMurray); Renal Division, Brigham and Women's Hospital, Boston, Massachusetts (Mc Causland, McGrath).

Corresponding Author: Akshay S. Desai, MD, MPH, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115 (adesai@bwh.harvard.edu).

Data from recent clinical trials of ambulatory patients with chronic heart failure (HF) across the spectrum of ejection fraction (EF) suggest that treatment with sodium-glucose cotransporter 2 (SGLT-2) inhibitors reduces the risk of the composite of worsening HF events or death from cardiovascular (CV) causes. However, individual trials have been underpowered to examine the effects of SGLT2 inhibition on overall mortality and specific causes of death. Better understanding the effects of SGLT2 inhibition on different causes of death might provide greater insight into the pathophysiologic mechanisms that support the observed clinical benefits, which largely remain obscure.

Compared with those with HF and reduced EF, patients with HF and mildly reduced and preserved EF experience a higher proportionate contribution of non-CV mortality to overall death rates, in line with the greater burden of associated comorbid medical illness observed in this population.[1,2] Nonetheless, data from clinical trials also suggest a substantial burden of CV mortality in HF and preserved EF that, as in HF and reduced EF, is attributed principally to sudden death or death from progressive HF.[3,4] Because the risk of ventricular arrhythmias or pump failure is likely to be lower in patients with HF and preserved EF, alternate mechanisms of disease progression, including worsening kidney function, pulmonary hypertension, or right ventricular failure, may play a greater role.[5] Accordingly, treatment effects on cause-specific mortality may vary according to EF.

A patient-level meta-analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) and Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trials examining treatment effects on the composite of CV death or worsening HF events as well as overall and CV mortality has been published, but it did not explore effects on cause-specific mortality.[6] To better understand the effects of dapagliflozin on cause-specific mortality across the spectrum of EF, we pooled data from the DAPA-HF and DELIVER trials, which both randomly assigned patients with symptomatic HF to treatment with dapagliflozin or placebo but enrolled adjacent populations with HF and reduced EF (EF ≤40%) and HF with mildly reduced or preserved ejection fraction (EF >40%), respectively.

Key Points

Question Is the effect of dapagliflozin on cardiovascular (CV) mortality driven by effects on particular causes of CV death?

Findings In this pooled analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) and Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trials including 1628 patient deaths, treatment with dapagliflozin led to a 14% lower risk of CV death regardless of ejection fraction, principally due to lower rates of sudden death and HF death, with little difference in rates of death from stroke or MI.

Meaning Regardless of ejection fraction, dapagliflozin-associated reductions in CV mortality in patients with HF are principally due to lower rates of HF and sudden death.

Methods

The detailed design and principal results of the DAPA-HF and DELIVER trials have been previously reported (Supplement 1 and Supplement 2).[7-10] Both were similarly designed as international, prospective, randomized, placebo-controlled trials of dapagliflozin in patients with symptomatic HF and elevated natriuretic peptide levels, but the qualifying left ventricular EF (LVEF) for enrollment differed between the studies. In the DAPA-HF trial, 4744 patients with chronic HF, LVEF of 40% or less, New York Heart Association II-IV symptoms, and plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) level of 600 pg/mL or greater (≥400 pg/mL if hospitalized for HF within 12 months; ≥900 pg/mL if in atrial fibrillation or flutter on baseline electrocardiogram) receiving guideline-recommended medical therapy were randomly assigned to treatment with dapagliflozin, 10 mg, once daily or matching placebo over a median follow-up period of 18.2 months. In the DELIVER trial, 6263 patients with chronic HF, LVEF greater than 40%, New York Heart Association II-IV symptoms, NT-proBNP level of 300 pg/mL or greater (≥600 pg/mL if in atrial fibrillation/flutter on the baseline electrocardiogram), and evidence of structural heart disease (left atrial enlargement or left ventricular hypertrophy) who required at least intermittent diuretic therapy were randomly assigned to treatment with dapagliflozin, 10 mg, once daily or matching placebo over a median follow-up period of 27.6 months. Patients with type 1 diabetes, symptomatic hypotension, systolic blood pressure less than 95 mm Hg, or reduced estimated glomerular filtration rate (eGFR; <30 mL/min/1.73 m^2 for DAPA-HF; <25 mL/min/1.73 m^2 for DELIVER) were excluded from both studies. Patients from the following race categories were included: American Indian or Alaska Native, Asian, Black or African American, White, or other (ie, Native Hawaiian or Pacific Islander or not otherwise specified by patients or investigators). Race data was gathered from the initial studies to help inform generalizability of the study results beyond the population studied. The primary outcome in both trials was time to the first occurrence of the composite of CV death or worsening HF, defined as either an unplanned hospitalization or an urgent visit for HF requiring intravenous therapy. Both studies were approved by institutional review boards or ethics committees at each of the participating sites before enrollment of the first patients, and all patients provided written informed consent for participation.

Clinical outcomes, including death, were centrally adjudicated in each trial according to standardized criteria[11] (eAppendices 1 and 2 in Supplement 3) by a clinical events committee blinded to study drug assignment. For both studies, the primary cause of death was classified by the clinical events committee as CV or non-CV. Where a specific CV or non-CV cause could not be assigned (due to ambiguity or lack of sufficient data regarding the circumstances of death), the cause of death was classified as undetermined. CV deaths were further subclassified by the clinical events committee as sudden

deaths or nonsudden deaths due to myocardial infarction (MI), HF, stroke, or other CV causes. Death due to MI was defined as death by any CV mechanism within 30 days of a clinical MI. Sudden death was defined as unexpected death in an otherwise stable patient, not within 30 days of an MI. Death due to HF was defined as death in the context of clinically worsening symptoms and/or signs of HF with no other apparent cause. Death due to stroke was assigned if deaths occurred as a result of an ischemic or hemorrhagic stroke defined by clinical or imaging criteria.

In this prespecified secondary analysis, conducted from July 1, 2022, to September 6, 2022, we examined the adjudicated mode of death (CV, non-CV, undetermined) as well as specific causes of CV death (HF, sudden death, MI, stroke, other CV) in the pooled population of the 2 trials as a whole and in subgroups defined by baseline LVEF categories. We used cut points proposed by the Universal Definition of Heart Failure and emerging clinical consensus and as outlined in the academic statistical analysis plan for the DELIVER trial (≤40%, 41%-49%, 50%-59%, ≥60%). Although in DAPA-HF deaths from undetermined cause were treated as CV deaths for the primary end point analysis, these deaths were considered separately for this pooled analysis, as was done in the DELIVER trial. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Statistical Analysis

Baseline characteristics were summarized for patients who died according to the mode of death (CV, non-CV, undetermined) using means, SDs, medians, and IQRs for continuous variables and counts and percentages for categorical variables. Rates were estimated as the number of events over the total duration of follow-up and expressed as a rate per 100 patient-years. The effect of randomized treatment on cause-specific death was estimated in Cox regression models. Sensitivity analyses were conducted to adjust for the competing risk of death from other causes using the method of Fine and Gray. Associations between continuous variables and incidence rates were estimated using Poisson regression, with potential nonlinearity accommodated by using polynomial (eg, quadratic, cubic) terms. Treatment effects according to EF were modeled using restricted cubic splines and graphically displayed as a plot of the treatment hazard ratio (HR) across the range of EF. All analyses were conducted in Stata, version 17.0 (StataCorp), with 2-sided $P < .05$ used as the threshold for statistical significance.

Results

Between-trial heterogeneity was tested prior to pooling of patient-level data between the trials; there was no evidence of between trial heterogeneity with regard to the effect of treatment on CV death ($Q = 0.47$; $I^2 = 0\%$; $P = .50$). Among 11 007 patients in the pooled analysis, there were 1628 deaths during follow-up (mean [SD] age, 71.7 [10.3] years; 1139 male [70.0%]; 489 female [30.0%]). Of those who died, 872 (53.5%) were ascribed to CV deaths, 487 (29.9%) to non-CV deaths, and 269 (16.5%) to undetermined causes. Of CV deaths, 289 (33.1%; this represented 17.8% of total deaths) were due to HF, 441 (50.6%; 27.1% of total deaths) were sudden, 69 (7.9%; 4.2% of total deaths) were due to stroke, 47 (5.4%; 2.9% of total deaths) to MI, and 26 (3.0%; 1.6% of total deaths) were due to other CV causes (eFigure in Supplement 3). Patients from the following race categories were included: 32 American Indian or Alaska Native (2.0%), 250 Asian (15.4%), 55 Black or African American (3.4%), 1232 White (75.7%), and 59 other (3.6%). Clinical characteristics at baseline for the 1628 patients who died are summarized by cause of death in **Table 1**. Compared with those dying of non-CV or undetermined death, patients who died of CV causes tended to be younger (mean [SD] age, 70.6 [10.7] years vs non-CV, 74.0 [8.9] years; undetermined, 71.3 [10.8] years) and to have a lower baseline LVEF (mean [SD] EF, 42.2% [14.1%] vs non-CV, 50.0% [12.2%]; undetermined, 43.0% [13.6%]), lower systolic blood pressure (mean [SD], 122.9 [15.8] mm Hg vs non-CV, 127.3 [16.1] mm Hg; undetermined, 123.8 [17.3] mm Hg), higher rate of prior HF hospitalization (457 [52.4%] vs non-CV, 214 [43.9%]; undetermined 130 [48.3%]), and higher NT-proBNP (median [IQR], 1942 [1032-4086] ng/L vs non-CV, 1333 [813-2649] ng/L; undetermined, 1848 [995-4014] ng/L) (Table 1).

The breakdown of adjudicated cause of death according to baseline EF categories is shown in **Table 2** and **Figure 1**. The proportion of deaths attributed to CV causes (overall and by specific cause) was inversely correlated with EF, principally due to higher proportions of sudden and HF death in the lower EF categories. Despite higher proportionate contribution of non-CV deaths to overall death rates in the highest EF category (>60%), 39.6% of deaths (112 of 283) were ascribed to CV causes, with 19.1% (54 of 283; 1.3 per 100 patient-years) due to sudden death and 12.7% (36 of 283; 0.9 per 100 patient-years) due to death from progressive HF. Across the full range of continuous EF, higher rates of overall mortality with lower EF were contributed principally by higher rates of both sudden and nonsudden (principally HF associated) mortality, with lesser variation in rates of non-CV death (**Figure 2**).

The effects of treatment with dapagliflozin compared with placebo on cause-specific mortality are displayed in **Figure 3**. In the pooled population, treatment with dapagliflozin was associated with lower rates of all-cause death, CV death (HR, 0.86; 95% CI, 0.75-0.98; $P = .02$), and the composite of CV death or unknown death (HR, 0.86; 95% CI, 0.76-0.97; $P = .01$). This reduction in CV death was driven principally by lower rates of sudden death (HR, 0.84; 95% CI, 0.70-1.01; $P = .07$) and, to a lesser extent, HF death (HR, 0.88; 95% CI, 0.70-1.11; $P = .30$), with little difference in rates of death from stroke or MI. There was no difference between dapagliflozin and placebo in rates of non-CV death (HR, 1.01; 95% CI, 0.84-1.20; $P = .94$). These results were consistent in sensitivity analyses accounting for competing risk of death from other causes. As with the effect on CV death, the effect of dapagliflozin compared with placebo on sudden death and HF death was consistent across EF assessed as a continuous variable (**Figure 4**).

Table 1. Baseline Characteristics by Cause of Death for Patients Who Died During Follow-up of DAPA-HF + DELIVER (N = 1628)

Characteristic	No. (%)		
	CV death (n = 872)	Non-CV death (n = 487)	Undetermined (n = 269)
Baseline LVEF, mean (SD), %	42.2 (14.1)	50.0 (12.2)	43.0 (13.6)
Randomized treatment	404 (46.3)	245 (50.3)	124 (46.1)
Age, mean (SD), y	70.6 (10.7)	74.0 (8.9)	71.3 (10.8)
Sex			
Male	628 (72.0)	316 (64.9)	195 (72.5)
Female			
Region			
Asia/Pacific	127 (14.6)	55 (11.3)	55 (20.4)
Europe and Saudi Arabia	460 (52.8)	247 (50.7)	125 (46.5)
North America	109 (12.5)	74 (15.2)	31 (11.5)
South America	176 (20.2)	111 (22.8)	58 (21.6)
Race			
American Indian or Alaska Native	20 (2.3)	11 (2.3)	1 (0.4)
Asian	131 (15.0)	59 (12.1)	60 (22.3)
Black or African American	32 (3.7)	12 (2.5)	11 (4.1)
White	667 (76.5)	378 (77.6)	187 (69.5)
Other[a]	22 (2.5)	27 (5.5)	10 (3.7)
Baseline pulse, beats/min	72.3 (12.0)	71.6 (11.7)	73.0 (11.3)
Blood pressure, mean (SD), mm Hg			
Baseline systolic	122.9 (15.8)	127.3 (16.1)	123.8 (17.3)
Baseline diastolic	72.6 (10.2)	72.8 (10.1)	73.0 (10.3)
Baseline body mass index,[b] mean (SD)	28.6 (6.3)	29.6 (6.1)	28.2 (6.3)
History of hypertension	728 (83.5)	433 (88.9)	220 (81.8)
History of diabetes	423 (48.5)	241 (49.5)	129 (48.0)
History of atrial fibrillation	436 (50.0)	262 (53.8)	139 (51.7)
Prior HF hospitalization	457 (52.4)	214 (43.9)	130 (48.3)
NYHA class at baseline			
II	516 (59.2)	336 (69.0)	148 (55.0)
III	349 (40.0)	148 (30.4)	113 (42.0)
IV	7 (0.8)	3 (0.6)	8 (3.0)
Baseline KCCQ-TSS, mean (SD)	65.0 (22.8)	66.8 (21.6)	65.9 (23.9)
Baseline NT-proBNP, median (IQR), ng/L	1942 (1032-4086)	1333 (813-2649)	1848 (995-4014)
Baseline eGFR, mean (SD), mL/min/1.73 m^2	58.5 (18.9)	56.5 (19.0)	58.5 (20.4)
Baseline creatinine, mean (SD), μmol/L	112.2 (34.5)	111.0 (34.0)	112.8 (35.6)
Loop diuretics	751 (86.1)	416 (85.4)	223 (82.9)
ACEi or ARB	663 (76.0)	360 (73.9)	201 (74.7)
ARNI	55 (6.3)	31 (6.4)	15 (5.6)
ACEi or ARB or ARNI	716 (82.1)	388 (79.7)	216 (80.3)
β-Blocker	746 (85.6)	421 (86.4)	238 (88.5)
MRA	520 (59.6)	235 (48.3)	150 (55.8)
Digitalis	106 (12.2)	27 (5.5)	43 (16.0)
CRT-D or CRT-P	48 (5.5)	18 (3.7)	9 (3.3)
CRT-D or ICD	127 (14.6)	37 (7.6)	24 (8.9)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; CV, cardiovascular; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; LVEF, left ventricular ejection fraction; MRA, mineralcorticoid receptor antagonist; NT-proBNP, N-terminal pro–brain natriuretic peptide.

SI conversion factor: To convert serum creatinine to milligrams per deciliter, divide by 88.4.

[a] Other race includes Native Hawaiian or Pacific Islander or race not otherwise specified by patients or investigators.

[b] Calculated as weight in kilograms divided by height in meters squared.

Discussion

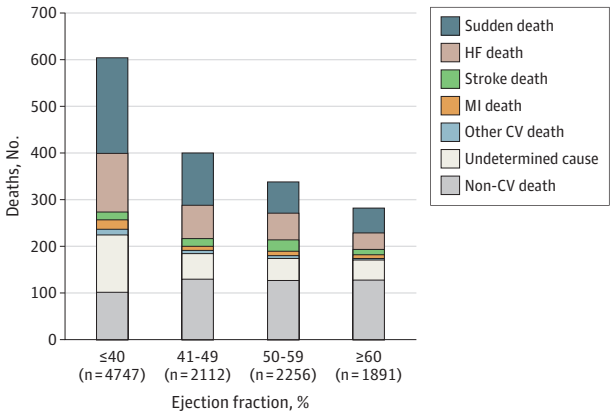
In this participant-level, pooled, prespecified secondary analysis of cause-specific mortality in the DAPA-HF and DELIVER randomized clinical trials reflecting the experience of 11 007 patients with HF across the full spectrum of LVEF, the reductions in CV death with dapagliflozin were driven principally by lower rates of sudden death and, to a lesser extent, death from progressive HF. These treatment effects appeared to be consistent across EF levels, despite higher rates of overall CV, sudden, and HF-associated deaths among patients with lower

Table 2. Incidence and Proportion of Deaths by Cause According to EF at Baseline Among Patients Who Died, Pooled DAPA-HF and DELIVER Populations (N = 11 007)

Cause of death	EF ≤40% (n = 4747)		EF ≤49% (n = 2112)		EF 50%-59% (n = 2256)		EF ≥60% (n = 1891)		*P* value	
	No. (% of deaths)	Rate/100 PY	No. (% of deaths)	Rate/100 PY	No. (% of deaths)	Rate/100 PY	No. (% of deaths)	Rate/100 PY	Proportions	Incidence rates
Total deaths	605 (100)	8.8	401 (100)	8.8	339 (100)	6.7	283 (100)	6.7	NA	<.001
CV death	380 (62.8)	5.6	216 (53.9)	4.7	164 (48.4)	3.2	112 (39.6)	2.7	<.001	<.001
HF	125 (20.7)	1.8	71 (17.7)	1.6	57 (16.8)	1.1	36 (12.7)	0.9	<.001	<.001
Sudden death	206 (34.0)	3.0	113 (28.2)	2.5	68 (20.1)	1.3	54 (19.1)	1.3	<.001	<.001
Stroke	17 (2.8)	0.2	17 (4.2)	0.4	24 (7.1)	0.5	11 (3.9)	0.3	.71	.46
MI	20 (3.3)	0.3	9 (2.2)	0.2	10 (2.9)	0.2	8 (2.8)	0.2	.12	.25
Other CV	12 (2.0)	0.2	6 (1.5)	0.1	5 (1.5)	0.1	3 (1.1)	0.1	.30	.06
Non-CV	102 (16.9)	1.5	130 (32.4)	2.9	127 (37.5)	2.5	128 (45.2)	3.0	<.001	.001
Unknown	123 (20.3)	1.8	55 (13.7)	1.2	48 (14.2)	0.9	43 (15.2)	1.0	.02	<.001
Non-CV + unknown	225 (37.2)	3.3	185 (46.1)	4.1	175 (51.6)	3.4	171 (60.4)	4.0	<.001	.97
CV + unknown	503 (83.1)	7.3	271 (67.6)	6.0	212 (62.5)	4.2	155 (54.8)	3.7	<.001	<.001

Abbreviations: CV, cardiovascular; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure; EF, ejection fraction; HF, heart failure; NA, not applicable; PY, patient-year.

Figure 1. Number of Deaths by Adjudicated Cause and Ejection Fraction Category for Pooled DAPA-HF and DELIVER Populations



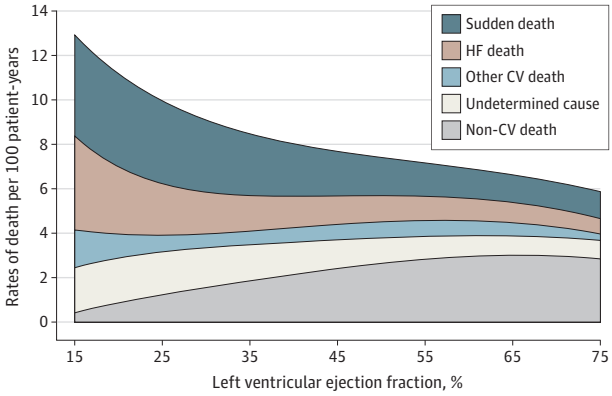
CV indicates cardiovascular; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure; HF, heart failure; MI, myocardial infarction.

EF. Rates of death from stroke, MI, and other CV causes were relatively low and did not appear to vary across the spectrum of EF. Although the proportionate contribution of non-CV death to overall mortality was greater in the higher EF categories, overall rates of non-CV death were relatively consistent across all patients except those with the lowest baseline EF and were not influenced by dapagliflozin treatment. Together, these data support the consistent benefits of dapagliflozin on CV mortality regardless of EF.

As in other clinical trial populations,[1-3] we observed that overall mortality rates tracked closely with LVEF, driven principally by rising rates of sudden death and death from progressive HF with declining EF. When analyzing rates of cause-specific CV mortality according to categories defined by the recently proposed Universal Definition of Heart Failure, rates of CV death and its key components were similar in patients with HF and mildly reduced EF (41%-49%) to those with HF and reduced EF (≤40%) but substantially lower in those with HF and preserved EF (>50%), with only slight differences between those with EF of 51% to 59% and those with EF of 60% or greater. The higher proportionate contribution of non-CV death with rising EF may be partly responsible for the limited progress in reducing the burden of overall mortality in patients with HF and preserved EF using CV therapies. Nonetheless, CV mortality accounted for 40% to 50% of deaths in patients with HF and preserved EF, with the largest proportion of these adjudicated as sudden deaths. These data underscore the important contribution of sudden death and death from progressive HF to overall mortality in HF with preserved EF. Importantly, however, it remains unclear if the mechanisms driving sudden death and HF death in those with preserved EF are the same as that in those with reduced EF. Sudden death in those with HF and reduced EF is often ascribed to arrhythmic death, but the risk for ventricular arrhythmias is typically lower in those with higher EF. As well, since overall cardiac output is often preserved even in end-stage HF with preserved EF, mechanisms other than pump failure (such as pulmonary hypertension, right ventricular failure, or worsening kidney function) may account for death due to HF in this population.

Given the likely variation in the pathophysiologic mechanisms driving CV mortality in patients with HF across the EF spectrum, our findings that showed a consistent effect of dapagliflozin on reductions of the key components of CV death regardless of EF are notable. In particular, the trend to lower rates of sudden death observed across the EF spectrum during dapagliflozin treatment, which only marginally missed the nominal threshold for statistical significance, highlight a possible effect of dapagliflozin on the substrate for sudden death that is independent of EF. These data amplify previous findings from DAPA-HF trial suggesting that dapagliflozin reduced the expanded composite of serious ventricular arrhythmia, cardiac arrest, or sudden death in patients with HF and reduced EF.[12] Whether this reflects a direct antiarrhythmic effect of SGLT2 inhibition remains unclear, but collectively, these

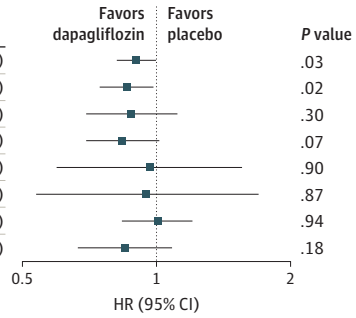
Figure 2. Variation in Incidence Rates of Death by Cause and Continuous Left Ventricular Ejection Fraction for Pooled DAPA-HF and DELIVER Populations



CV indicates cardiovascular; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure; HF, heart failure; MI, myocardial infarction.

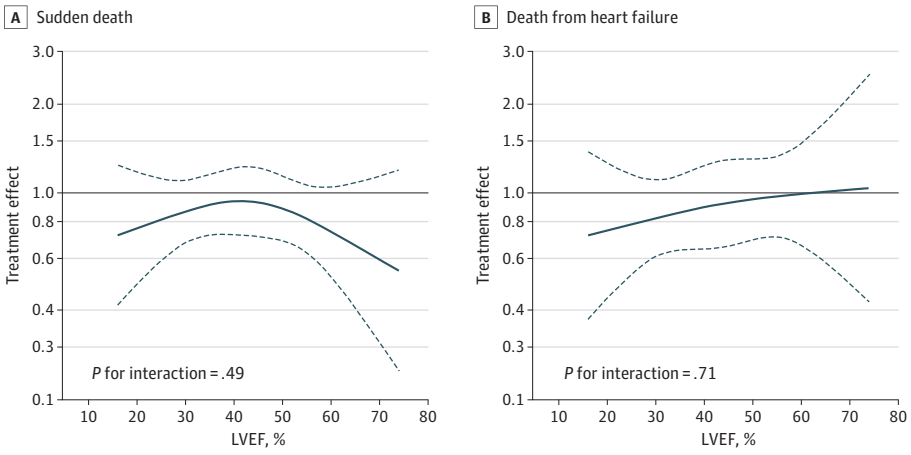
Figure 3. Effect of Dapagliflozin Compared With Placebo on Cause-Specific Mortality for the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) and Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) Populations

Outcome	Dapagliflozin Events, rate/ 100 patient-year (n = 5504)	Placebo Events, rate/ 100 patient-year (n = 5503)	HR (95% CI)	*P* value
All-cause death	773 (7.4)	855 (8.3)	0.90 (0.82-0.99)	.03
CV death	404 (3.9)	468 (4.5)	0.86 (0.75-0.98)	.02
HF death	136 (1.3)	153 (1.5)	0.88 (0.70-1.11)	.30
Sudden death	202 (1.9)	239 (2.3)	0.84 (0.70-1.01)	.07
Stroke death	34 (0.3)	35 (0.3)	0.97 (0.60-1.55)	.90
MI death	23 (0.2)	24 (0.2)	0.95 (0.54-1.69)	.87
Non-CV death	245 (2.4)	242 (2.3)	1.01 (0.84-1.20)	.94
Unknown death	124 (1.2)	145 (1.4)	0.85 (0.67-1.08)	.18



CV indicates cardiovascular; HR, hazard ratio; MI, myocardial infarction.

Figure 4. Effect of Dapagliflozin Across the Spectrum of Ejection Fraction



Effect of dapagliflozin on sudden death (A) and heart failure (B). The solid line depicts the continuous hazard ratio across the range of left ventricular ejection fraction (LVEF) and the dashed lines represent the 95% CIs from the Cox model. The overall effect of treatment in the pooled population is shown in each panel as an HR (95% CI) with the 2-sided *P* value for interaction between treatment assignment and LVEF.

findings provide further mechanistic support for the use of SGLT2 inhibitors as foundational treatment for symptomatic HF across the full spectrum of EF.

Limitations

Our analysis should be viewed in the context of important limitations. Although the cause of death was adjudicated by an in-

dependent clinical events committee in both trials, accurate ascertainment of the cause of death is challenging in the absence of autopsy data (which was available in the minority of cases) and was, in many cases, made based on clinical inference from limited data regarding the circumstances of death. Despite its size, the pooled data set was underpowered to examine treatment effects on the specific components of CV death and may be confounded by the competing risk of death from other causes. Finally, these data from selected patients with HF recruited from selected clinical sites who were eligible for participation in a clinical trial may not accurately represent treatment effects among unselected patients with greater burden of comorbidities in clinical practice.

Conclusions

In this participant-level, pooled, prespecified secondary analysis of the DAPA-HF and DELIVER randomized clinical trials, we conclude that rates of CV death, principally sudden death and HF death, were higher among HF patients with lower EF, whereas non-CV deaths were largely consistent across the EF spectrum. Reductions in CV mortality with dapagliflozin across the CV spectrum appear to be associated with lower rates of sudden death and death from progressive HF. These data provide additional support for the use of SGLT2 inhibitors to treat patients with symptomatic HF, regardless of LVEF.

ARTICLE INFORMATION

Accepted for Publication: September 6, 2022.

Published Online: October 3, 2022. doi:10.1001/jamacardio.2022.3736

Author Contributions: Dr Desai had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Desai, Barkoudah, Petrie, Solomon.
Acquisition, analysis, or interpretation of data: Desai, Jhund, Claggett, Vaduganathan, Miao, Kondo, Barkoudah, Brahimi, Connolly, Finn, Lang, Mc Causland, McGrath, McMurray, Solomon.
Drafting of the manuscript: Desai, Claggett, Kondo, Barkoudah.
Critical revision of the manuscript for important intellectual content: Desai, Jhund, Vaduganathan, Miao, Barkoudah, Brahimi, Connolly, Finn, Lang, Mc Causland, McGrath, Petrie, McMurray, Solomon.
Statistical analysis: Jhund, Claggett, Miao, Kondo.
Obtained funding: Solomon.
Administrative, technical, or material support: Miao, Barkoudah.
Supervision: Desai, Petrie, Solomon.

Conflict of Interest Disclosures: Dr Desai reported receiving grants from AstraZeneca, Abbott, Alnylam, Bayer, and Novartis; consulting fees from AstraZeneca, Abbott, Alnylam, Amgen, Bayer, Biofourmis, Cytokinetics, GlaxoSmithKline, Medpace, Merck, Novartis, Parexel, Roche, Regeneron, Verily, Axon Therapeutics, Avidity, and New Amsterdam; and fees for data-safety monitoring board participant from Boston Scientific. Dr Jhund reported receiving received consulting, advisory board, and speaker fees from Novartis; advisory board fees from Cytogenetics; a grant from Boehringer Ingelheim; grant support from AstraZeneca and Novartis; advisory board fees from Boehringer Ingelheim; and fees for clinical trial work from Novo Nordisk and Bayer outside the submitted work. Dr Claggett reported receiving consulting fees from Boehringer Ingelheim, Cardurion, Corvia, and Novartis outside the submitted work. Dr Vaduganathan reported receiving grant support or advisory board fees from Amgen, AstraZeneca, American Regent, Baxter HealthCare, Bayer AG, Boehringer Ingelheim, Cytokinetics, Pharmacosmos, Relypsa, Novartis, Roche Diagnostics, Lexicon Pharmaceuticals, Galmed, Occlutech, Impulse Dynamics, Sanofi, and Tricog Health; speaker fees from AstraZeneca, Boehringer Ingelheim, Novartis, and Roche Diagnostics; and actively participates on clinical trial committees for studies sponsored by Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics outside the submitted work. Dr Kondo reported receiving lecture fees from Abbott Medical Japan, Ono Pharmaceutical, Otsuka Pharmaceutical, Novartis Pharma, AstraZeneca, Bristol Myers Squibb, and Abiomed Japan outside the submitted work. Dr Barkoudah reported receiving grants from Brigham and Women's Hospital, the National Institutes of Health/National Heart, Lung, and Blood Institute, Bristol Myers Squibb, and Janssen; personal fees from WebMD, Medscape, Janssen, Novartis, and Pfizer; and travel expenses from Alexion outside the submitted work. Dr Connolly reported receiving fees from University of Glasgow during the conduct of the study. Dr Lang reported receiving grants from AstraZeneca, Boehringer Ingelheim, and Roche and speaker/advisory fees from MyoKardia, Roche Pharma, Pharmacosmos, Astra Zeneca, Akero, and Novartis outside the submitted work. Dr Mc Causland reported receiving consulting fees from GlaxoSmithKline; personal fees from Advanced Instruments; and grants from Fifth Eye, the National Institute of Diabetes and Digestive and Kidney Diseases, Satellite Healthcare, and Advanced Medical outside the submitted work. Dr Petrie reported receiving personal fees from Astra Zeneca, Boehringer Ingelheim, Boehringer Ingelheim, Novo Nordisk, Roche, Siemens, Takeda, New Amsterdam, Abbvie, Bayer, Cardiorentis, Vifor, Alnylam, Novartis, and Pharmacosmos; grants from Pharmacosmos, NovoNordisk, SQ Innovations, Roche, Astra Zeneca, Vifor, Medtronic, Boston Scientific, Novartis; and research support from the British Heart Foundation Centre of Research Excellence Award. Dr McMurray reported receiving consultant fees or grant support from Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Cardurion, Amgen, Cytokinetics, Servier, Theracos, Dalcor, Pfizer, GlaxoSmithKline, Bristol Myers Squibb, Alnylam, Novartis; personal fees from Abbott, Alkem Metabolics, Corpus, Eris Lifesciences, Hikma, Lupin, Sun Pharmaceuticals, Medscape/Heart.Org, ProAdWise Communications, Radcliffe Cardiology, Servier, Ionis Pharmaceuticals, Cardurion, Boehringer Ingelheim, Sun Pharmaceuticals, Medsca; and research support from the British Heart Foundation Centre of Research Excellence Award outside the submitted work. Dr Solomon reported receiving grants from AstraZeneca, Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GlaxoSmithKline, Ionis, Lilly, Mesoblast, MyoKardia, National Institutes of Health/National Heart, Lung, and Blood Institute, Neurotronik, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos; and consultant fees from Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GlaxoSmithKline, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, Puretech Health outside the submitted work. No other disclosures were reported.

Funding/Support: The DAPA-HF and DELIVER trials were sponsored by AstraZeneca. In addition, this work was supported by grant RE/18/6/34217 from the British Heart Foundation Centre of Research Excellence (Drs Jhund and McMurray) and the Vera Melrose Heart Failure Research Fund.

Role of the Funder/Sponsor: The DAPA-HF and DELIVER studies were designed by the academic members of the respective executive committees in collaboration with representatives from AstraZeneca. The sponsor, AstraZeneca, was responsible for study supervision, site monitoring, and data collection for both trials. Data analysis of each trial was performed by AstraZeneca and independent academic statisticians at the University of Glasgow and the Brigham and Women's Hospital, Boston. This prespecified secondary analysis was conducted by an independent academic group at Brigham and Women's Hospital. All authors participated in the decision to submit the manuscript for publication with support from the study sponsor.

Meeting Presentation: This paper was presented at the HFSA Annual Scientific Meeting 2022; October 3, 2022; Washington, DC.

REFERENCES

1. Vaduganathan M, Patel RB, Michel A, et al. Mode of death in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2017;69(5):556-569. doi:10.1016/j.jacc.2016.10.078

2. Solomon SD, Wang D, Finn P, et al. Effect of candesartan on cause-specific mortality in heart failure patients: the Candesartan in Heart failure

Assessment of Reduction in Mortality and Morbidity (CHARM) program. *Circulation*. 2004;110 (15):2180-2183. doi:10.1161/01.CIR.0000144474.65922.AA

3. Desai AS, Vaduganathan M, Cleland JG, et al. Mode of death in patients with heart failure and preserved ejection fraction: insights from PARAGON-HF trial. *Circ Heart Fail*. 2021;14(12): e008597. doi:10.1161/CIRCHEARTFAILURE.121.008597

4. Desai AS, McMurray JJ, Packer M, et al. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. *Eur Heart J*. 2015;36(30): 1990-1997. doi:10.1093/eurheartj/ehv186

5. Greene SJ, Gheorghiade M. Matching mechanism of death with mechanism of action: considerations for drug development for hospitalized heart failure. *J Am Coll Cardiol*. 2014;64 (15):1599-1601. doi:10.1016/j.jacc.2014.06.1199

6. Jhund PS, Kondo T, Butt JH, et al. Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER. *Nat Med*. Published online August 27, 2022. doi:10.1038/s41591-022-01971-4

7. McMurray JJV, Solomon SD, Inzucchi SE, et al; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381 (21):1995-2008. doi:10.1056/NEJMoa1911303

8. Solomon SD, McMurray JJV, Claggett B, et al; DELIVER Trial Committees and Investigators. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. Published online August 27, 2022. doi:10.1056/NEJMoa2206286

9. McMurray JJV, DeMets DL, Inzucchi SE, et al; DAPA-HF Committees and Investigators. A trial to evaluate the effect of the sodium-glucose cotransporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). *Eur J Heart Fail*. 2019;21(5):665-675. doi:10.1002/ejhf.1432

10. Solomon SD, de Boer RA, DeMets D, et al. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. *Eur J Heart Fail*. 2021;23 (7):1217-1225. doi:10.1002/ejhf.2249

11. Hicks KA, Mahaffey KW, Mehran R, et al; Standardized Data Collection for Cardiovascular Trials Initiative (SCTI). 2017 Cardiovascular and stroke end point definitions for clinical trials. *J Am Coll Cardiol*. 2018;71(9):1021-1034. doi:10.1016/j.jacc.2017.12.048

12. Curtain JP, Docherty KF, Jhund PS, et al. Effect of dapagliflozin on ventricular arrhythmias, resuscitated cardiac arrest, or sudden death in DAPA-HF. *Eur Heart J*. 2021;42(36):3727-3738. doi:10.1093/eurheartj/ehab560