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

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on behalf of the DELIVER Committees, Investigators, Sponsor and Participants

HFSA Annual Scientific Meeting 2022, Washington, DC

HARVARD MEDICAL SCHOOL

Brigham and Women's Hospital
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University of Glasgow

DAPAHF

DELIVER

Disclosures

- **Presenter Disclosures:** Dr. Desai reports institutional research grant support from Abbott, Alnylam, AstraZeneca, Bayer, Novartis, and Pfizer as well as personal consulting fees/speaking honoraria from Abbott, Alnylam, AstraZeneca, Avidity, Axon Therapeutics, Bayer, Biofourmis, Boston Scientific, Cytokinetics,GlaxoSmithKline, Medpace, Merck, Novartis, Parexel, Regeneron, Roche, Verily

- **Trial Sponsors:** The DELIVER and DAPA-HF Trials were funded by AstraZeneca

Background

- Addition of the SGLT2 inhibitor dapagliflozin to standard treatment reduced the risk of CV death or worsening HF events in randomized trials of patients with chronic HF and reduced EF (≤40%, DAPA-HF) or mildly reduced or preserved EF (>40%, DELIVER)

- DAPA-HF and DELIVER were not individually powered to test the effect of dapagliflozin on overall mortality or key secondary outcomes, including specific causes of death

- Analysis of the pooled cohorts from DAPA-HF and DELIVER was prespecified in the SAP to assess the effect of dapagliflozin on clinical outcomes, including cause of death

DAPA-HF and DELIVER Pooled Dataset

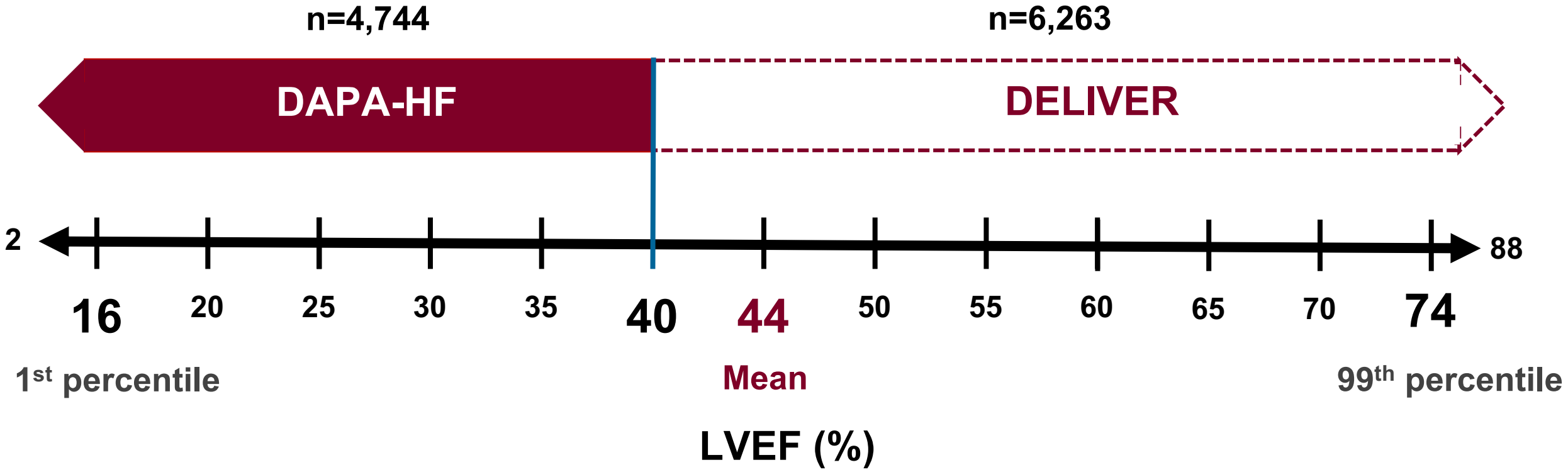
DELIVER

DAPAHF

Dapagliflozin 10mg once daily vs placebo

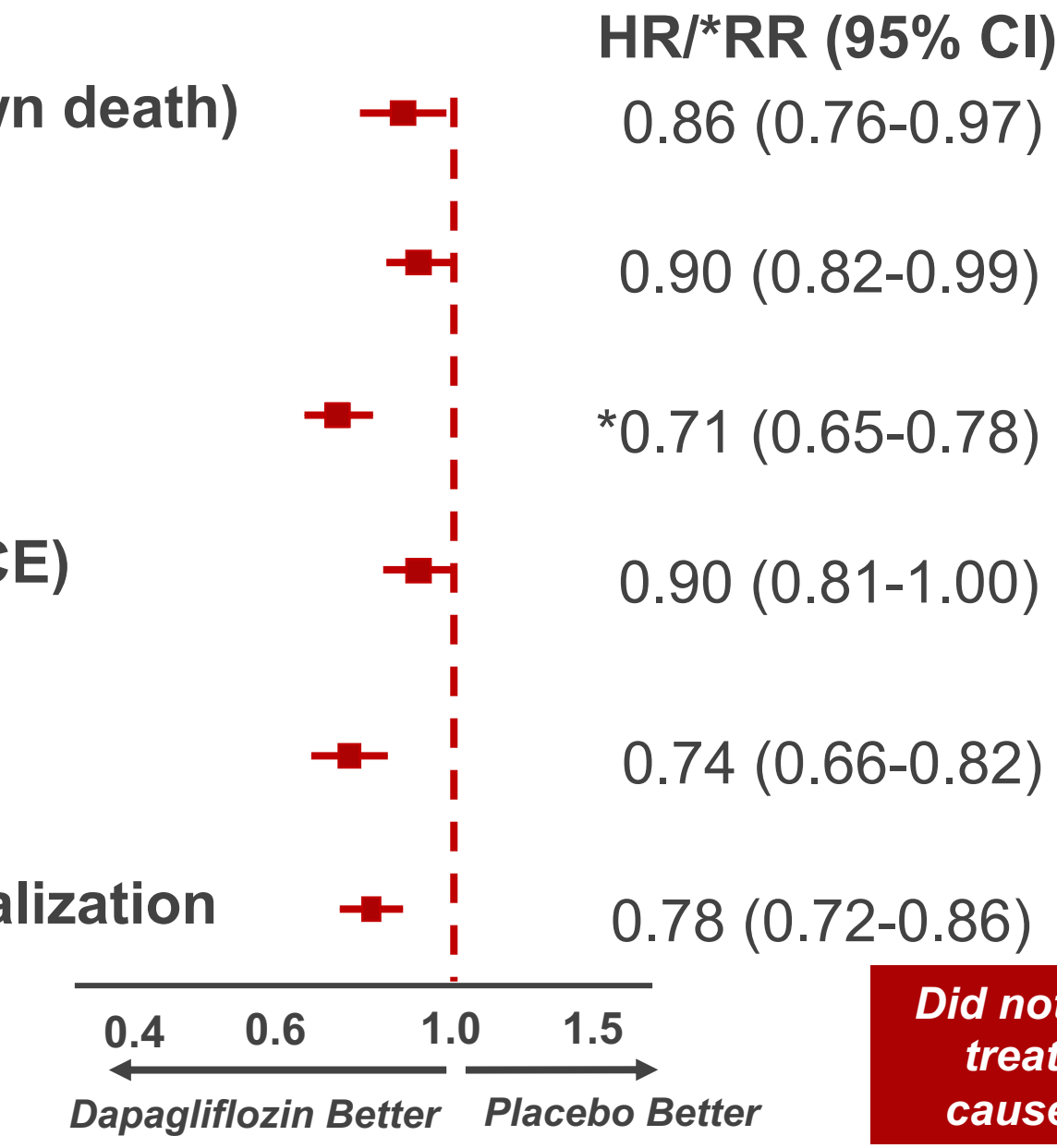
Median follow-up = 22 (IQR 17-30) months

Pooled dataset n=11,007



McMurray JJV et al Eur J Heart Fail. 2019;21:665-675 and Solomon SD et al Eur J Heart Fail 2021;23:1217-1225

DAPA-HF/DELIVER Pooled: Initial Findings



Consistent Effects, regardless of LVEF

Did not further examine treatment effect on cause-specific death

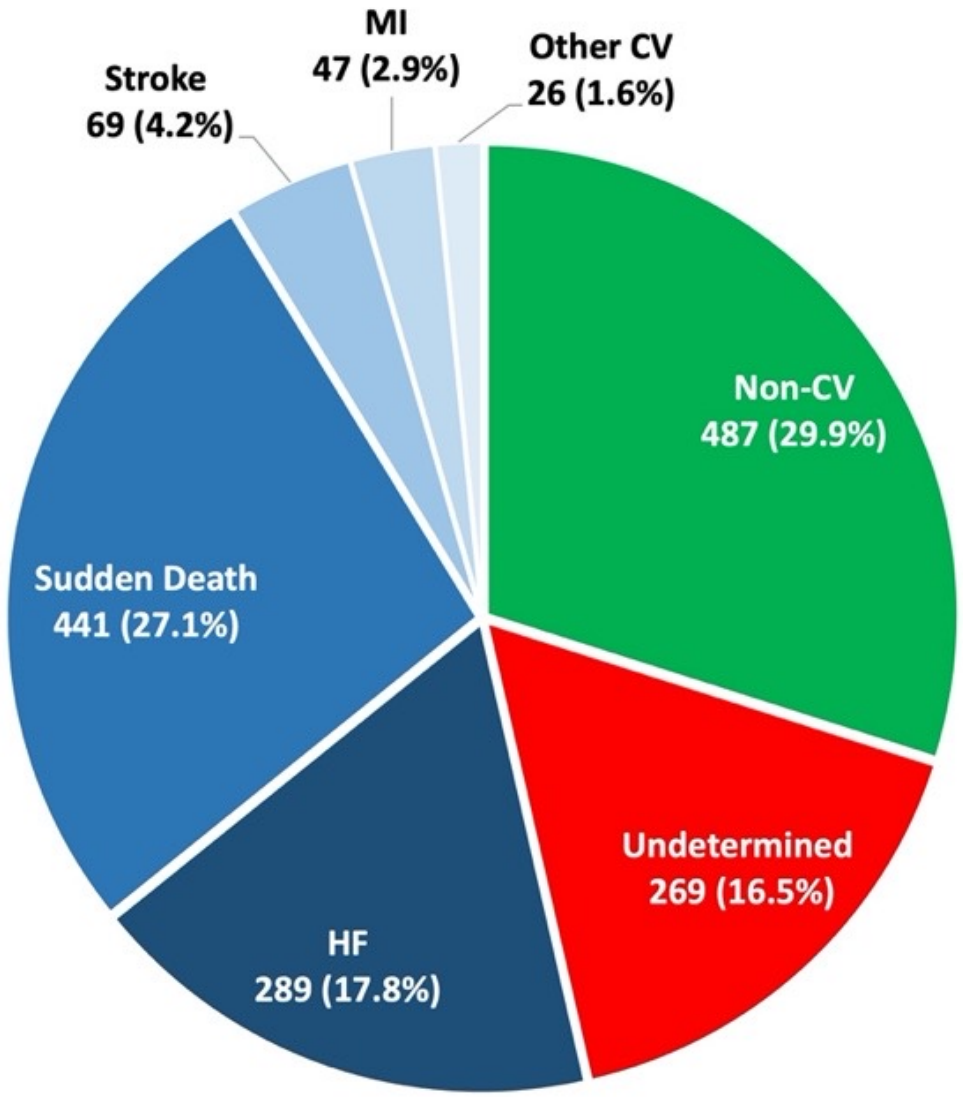
Jhund P, et al. Nature Medicine 2022; 28: 1956-1964

Methods

- Participant level data pooled across the 2 trials (no statistical heterogeneity)
- Deaths in each trial were centrally adjudicated by a blinded CEC and classified according to primary cause (CV, non-CV, unknown)
  - CV deaths further subclassifed according to specific cause (HF, Sudden, MI Stroke, Other) according to standardized criteria[1]
- Effect of randomized treatment on cause-specific mortality estimated in Cox proportional hazards models (sensitivity analyses adjusting for competing risk)
- Treatment effects according to EF modelled using restricted cubic splines

[1]Hicks K, et al. J Am Coll Cardiol 2018; 71: 1021-34

Cause of Death DAPA+DELIVER (N=11007, 1628 deaths)



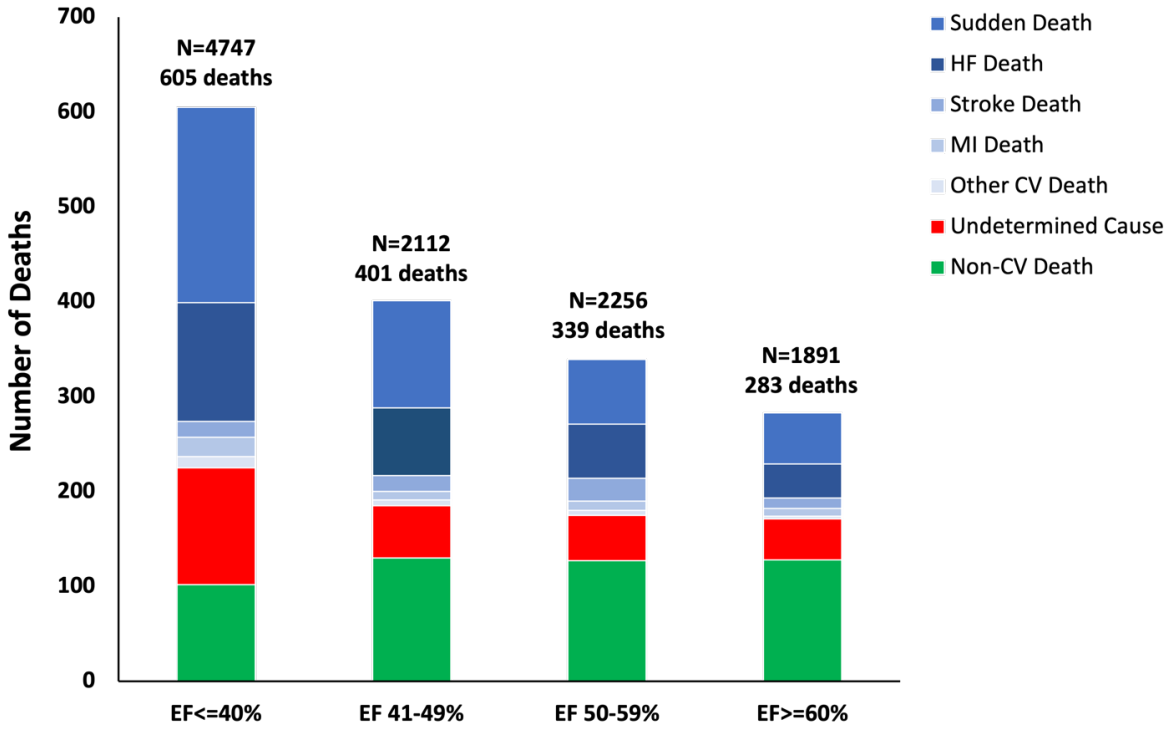
Baseline Characteristics of Patients who Died by Cause

DELIVER
DAPAHF

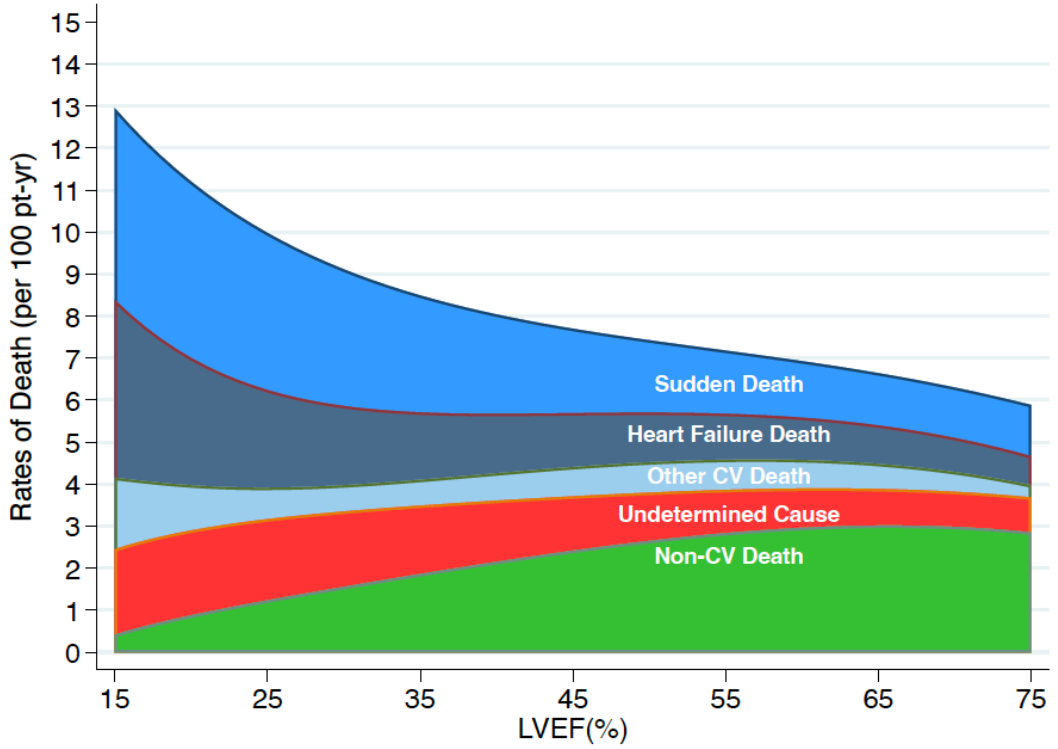
	CV Death (N=872)	Non-CV Death (N=487)	Undetermined (N=269)
Age (years)	71 ± 11	74 ± 9	71 ± 11
Men	72.0%	64.9%	72.5%
NYHA Class 2, %	59.2%	69.0%	55.0%
History of AF	50.0%	53.8%	51.7%
Diabetes Mellitus	48.5%	49.5%	48.0%
HF Hospitalization within 12 mos	52.4%	43.9%	48.3%
eGFR	59 ± 19	57 ± 19	59 ± 20
Systolic BP (mmHg)	123 ± 16	127 ± 16	124 ± 17
BMI, kg/m^2	29 ± 6	30 ± 6	28 ± 6
NTproBNP, median [IQR]	1942 [1032 , 4086]	1333 [813, 2649]	1848 [995, 4014]
LVEF (%)	42 ± 14	50 ± 12	43 ± 14

Adjudicated Cause of Death by LVEF

Number of Deaths by Cause

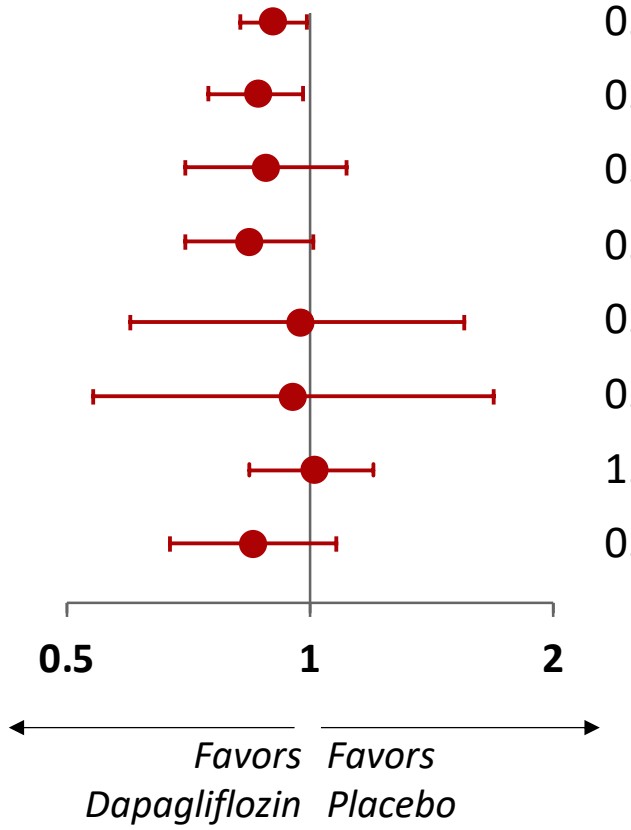


Incidence Rates of Death by Cause



Effect of Dapagliflozin on Cause-Specific Mortality

	Dapagliflozin Events (rate/100 pt-yr) (N=5504)	**Placebo** Events (rate/100 pt-yr) (N=5503)	**HR (95% CI)**	P
All-Cause Death	773 (7.4)	855 (8.3)	0.90 (0.82-0.99)	0.032
CV Death	404 (3.9)	468 (4.5)	0.86 (0.75-0.98)	0.024
HF Death	136 (1.3)	153 (1.5)	0.88 (0.70-1.11)	0.296
Sudden Death	202 (1.9)	239 (2.3)	0.84 (0.70-1.01)	0.067
Stroke Death	34 (0.3)	35 (0.3)	0.97 (0.60-1.55)	0.896
MI Death	23 (0.2)	24 (0.2)	0.95 (0.54-1.69)	0.870
Non-CV Death	245 (2.4)	242 (2.3)	1.01 (0.84-1.20)	0.937
Unknown Death	124 (1.2)	145 (1.4)	0.85 (0.67-1.08)	0.181

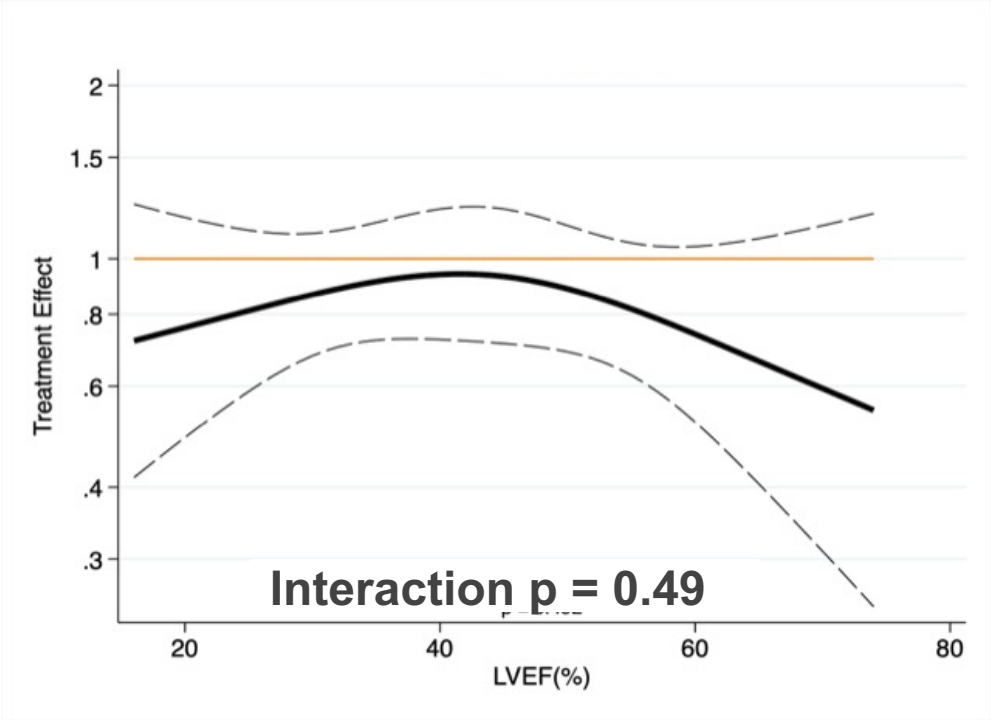


Effects of Dapagliflozin on Cause-Specific Mortality according to LVEF

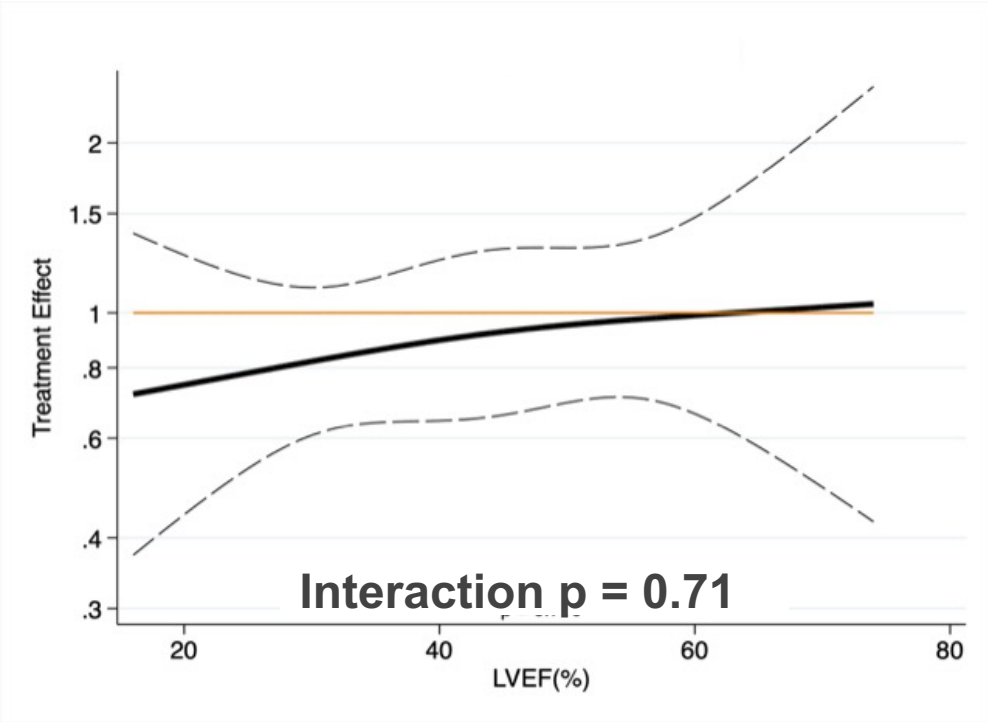
DELIVER

DAPAHF

Sudden Death



Heart Failure Death



Conclusions

- In this pooled analysis of the DAPA-HF and DELIVER trials
  - Overall death rates were higher in patients with lower EF due to higher rates of CV death (particularly sudden death and HF death) with declining EF
  - Rates of non-CV death were relatively constant across EF categories, but the proportionate contribution of non-CV death to overall mortality was higher in those with higher EF
  - Dapagliflozin reduced CV death principally due to reduction in sudden death and death from progressive heart failure
  - Dapagliflozin did not influence the risk of death from other CV causes including MI and stroke
  - Effects of dapagliflozin on cause-specific mortality appeared consistent across the full range of EF

These data provide further evidence of CV death reductions with dapagliflozin across the spectrum of EF and offer additional mechanistic insights into the clinical benefits of SGLT2 inhibition in chronic HF

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We thank all the DELIVER Investigators and participants!

Simultaneously Published in *JAMA Cardiology*

Research

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Supplemental content

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

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

jamanetwork/2022/car/10_03_2022/hoi220064pap PAGE: right 1 SESS: 20 OUTPUT: Sep 20 14:0 2022

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JAMA Cardiology 2022; xx: xx-xx

Thank you!

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