A Pre-Specified Meta-Analysis of DELIVER and EMPEROR-Preserved

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Disclosures

- **Presenter Disclosures:** Dr. Vaduganathan has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, Novartis, Pharmacosmos, Relypsa, Roche Diagnostics, and Sanofi, speaker engagements with AstraZeneca, Novartis, and Roche Diagnostics, and participates on clinical trial committees for studies sponsored by Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics.

- **Trial Sponsors:** The DELIVER and DAPA-HF were funded by AstraZeneca, the EMPEROR trials were funded by Boehringer Ingelheim and Eli Lilly, and SOLOIST-WHF was funded by Sanofi and Lexicon Pharmaceuticals

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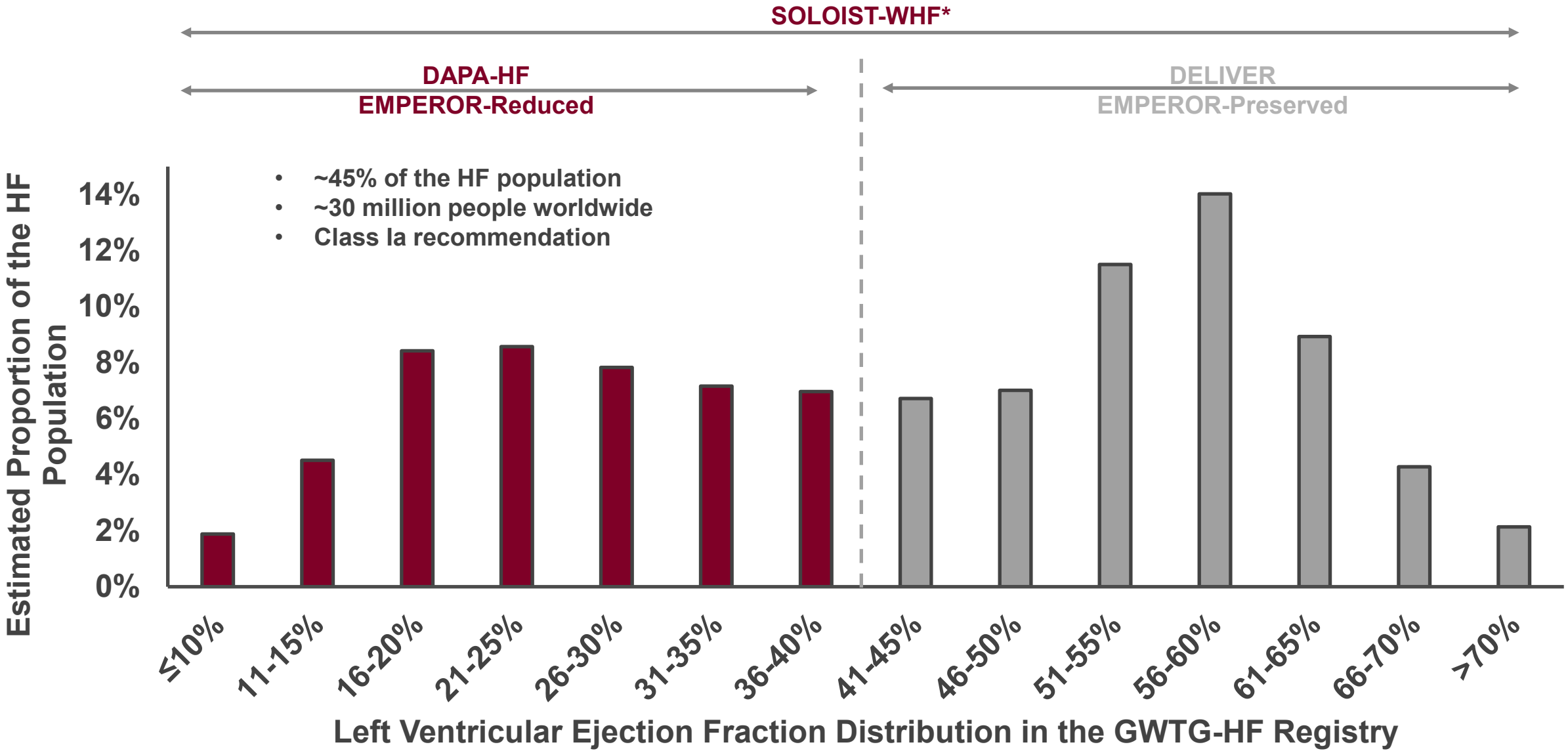
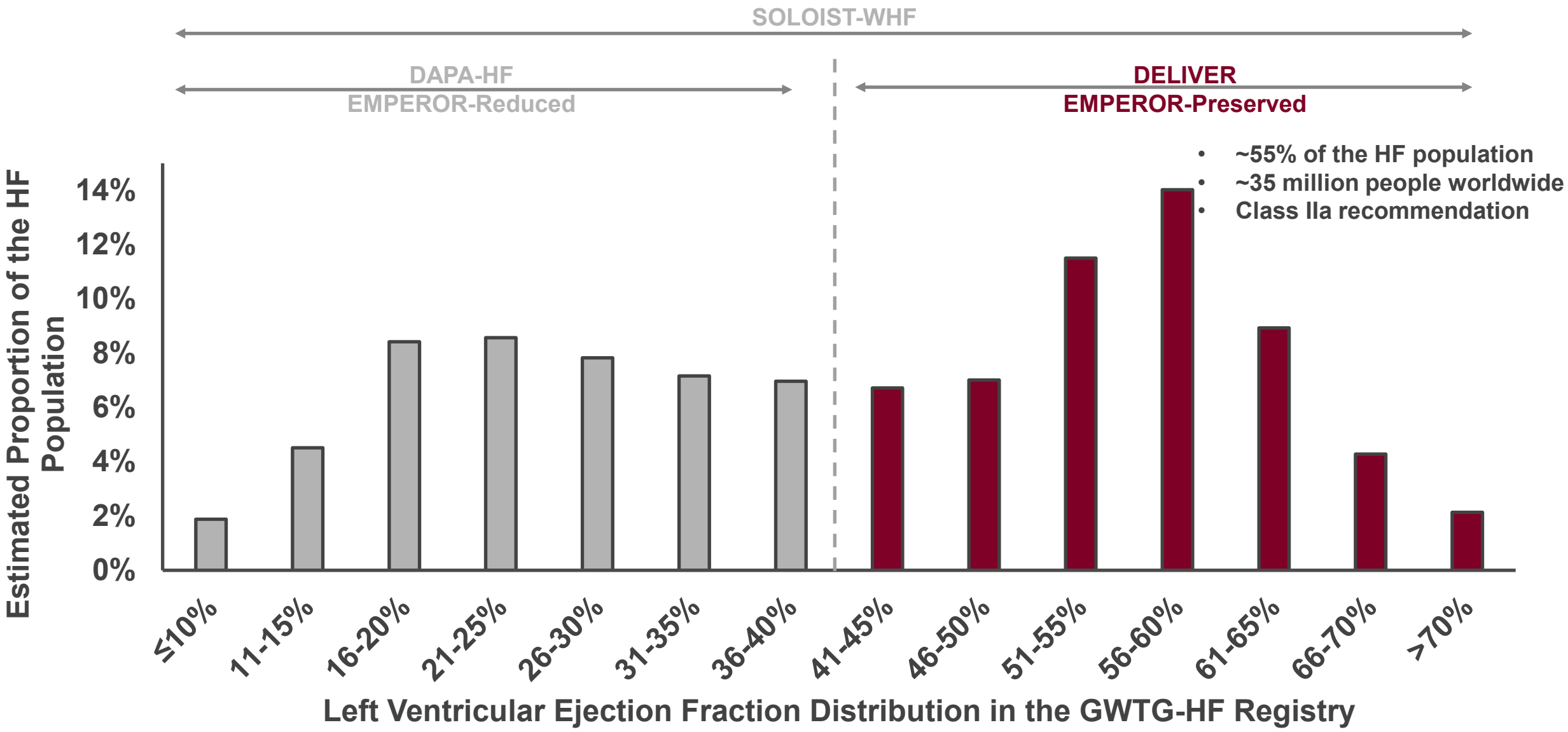
SGLT2 Inhibitors are Established as a Standard of Care in HFrEF



*SOLOIST-WHF evaluated an SGLT1/2 inhibitor

Vaduganathan M et al. *JAMA Cardiology.* 2021.

SGLT2 Inhibitors Benefits are Less Well-Established in LVEF>40%



Vaduganathan M et al. *JAMA Cardiology.* 2021.

Meta-Analytic Structure

1

DELIVER and EMPEROR-Preserved (N=12,251)

- Prespecified prior to unblinding of DELIVER
- Meta-analytic protocol registered with PROSPERO (CRD42022327527)
- Individual participant-level data from DELIVER used to harmonize endpoint definitions and subgroups

2

Totality of Evidence of SGLT2i in HF (N=21,947)

5 trials with n>1,000 based on systematic search

- DELIVER and EMPEROR-Preserved
- DAPA-HF and EMPEROR-Reduced
- SOLOIST-WHF*

*SOLOIST-WHF evaluated an SGLT1/2 inhibitor

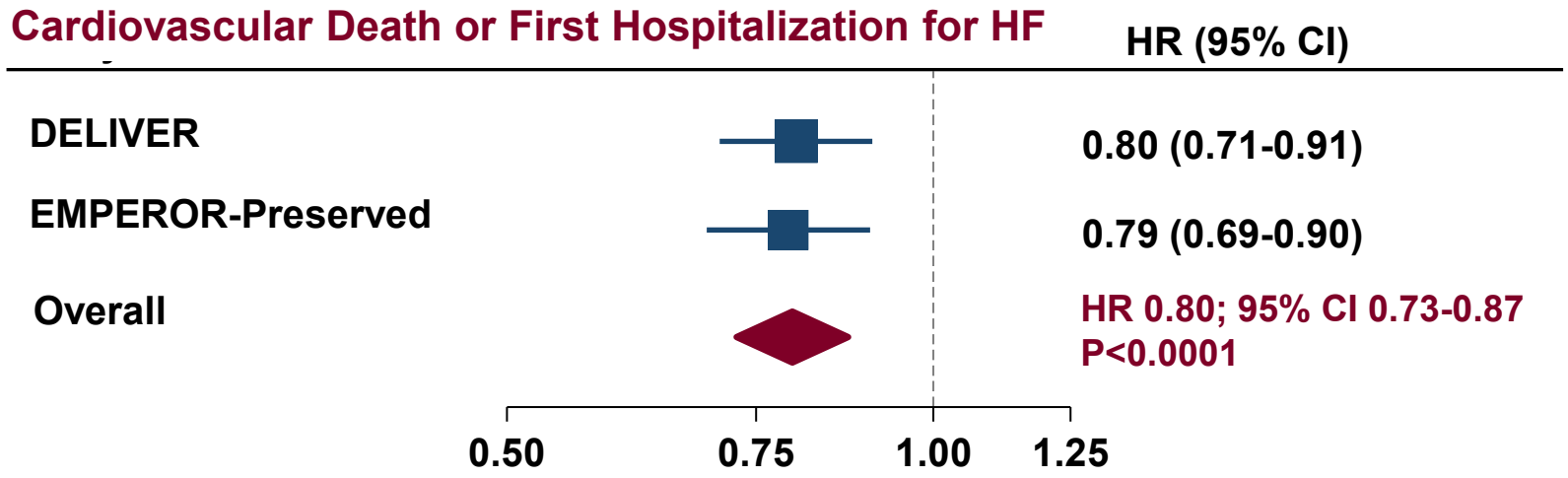
Key Eligibility Criteria in DELIVER and EMPEROR-Preserved

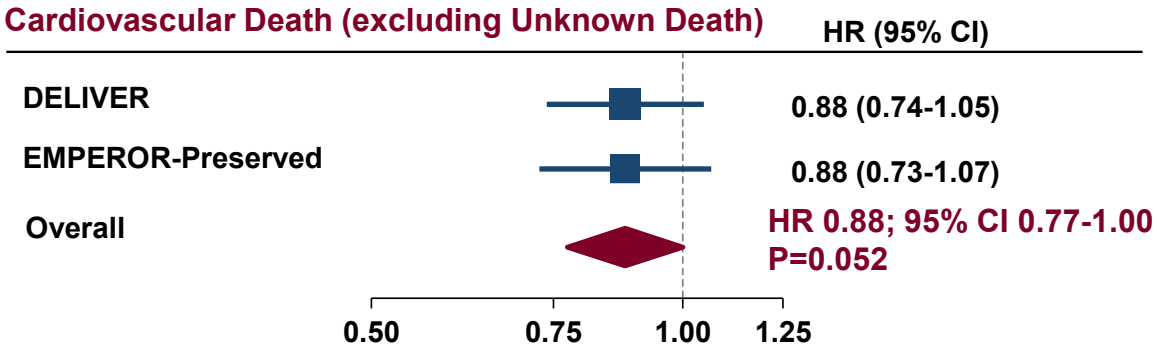
Key Inclusion Criteria	DELIVER	EMPEROR-Preserved
Symptomatic HF	NYHA class II-IV	NYHA class II-IV
Cardiac Structure and Function	LVEF>40% and evidence of structural heart disease	LVEF>40% and either evidence of structural heart disease or history of HF hospitalization within 12mo
Prior LVEF≤40% with Improved LVEF to >40%	Included	Excluded
Elevated NT-proBNP	• ≥300 pg/mL (without AF) or • ≥600 pg/mL (with AF)	• >300 pg/mL (without AF) or • >900 pg/mL (with AF)
Setting of Enrollment	Ambulatory or hospitalized included as long as off intravenous HF therapies	Acute decompensated HF within 1 week of screening excluded
Diuretics	At least intermittent need for diuretics	Stable oral diuretics for ≥1 week
Body mass index	≤50kg/m^2	<45kg/m^2
Estimated glomerular filtration rate	≥25 mL/min/1.73 m^2	≥20 mL/min/1.73 m^2

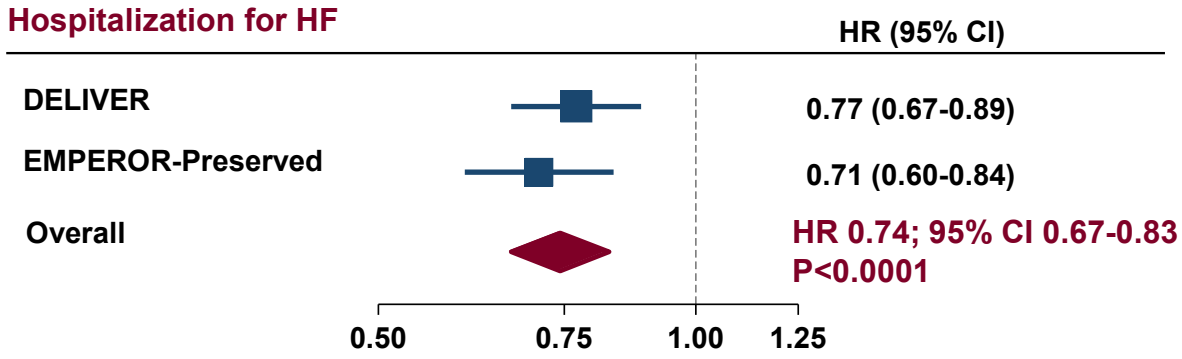
Baseline Characteristics & Background Medical Therapy

	DELIVER (N=6,263)	EMPEROR-Preserved (N=5,988)
Enrollment Period	2018-2021	2017-2020
Sites	350 sites in 20 countries	622 sites in 23 countries
Median Follow-up (years)	2.3	2.2
Complete Follow-up (%)	99%	97%
Age (years)	72 ± 10	72 ± 9
Women	44%	45%
Systolic BP (mmHg)	128 ± 15	132 ± 16
BMI, kg/m^2	30 ± 6	30 ± 6
LVEF (%)	54 ± 9	54 ± 9
NYHA Class 2	75%	82%
NYHA Class 3 or 4	25%	18%
History of Atrial Fibrillation or Flutter	57%	51%
Diabetes Mellitus	45%	49%
Hospitalization for HF within Last 12mo	26%	23%
Loop Diuretics	77%	68%
ACEi/ARB/ARNI	77%	81%
β-blockers	83%	86%
MRA	43%	37%

DELIVER and EMPEROR-Preserved Meta-Analysis:
↓ 20% (13-27%) Relative Risk Reduction of Primary Endpoint with Consistent Reductions in Both Components

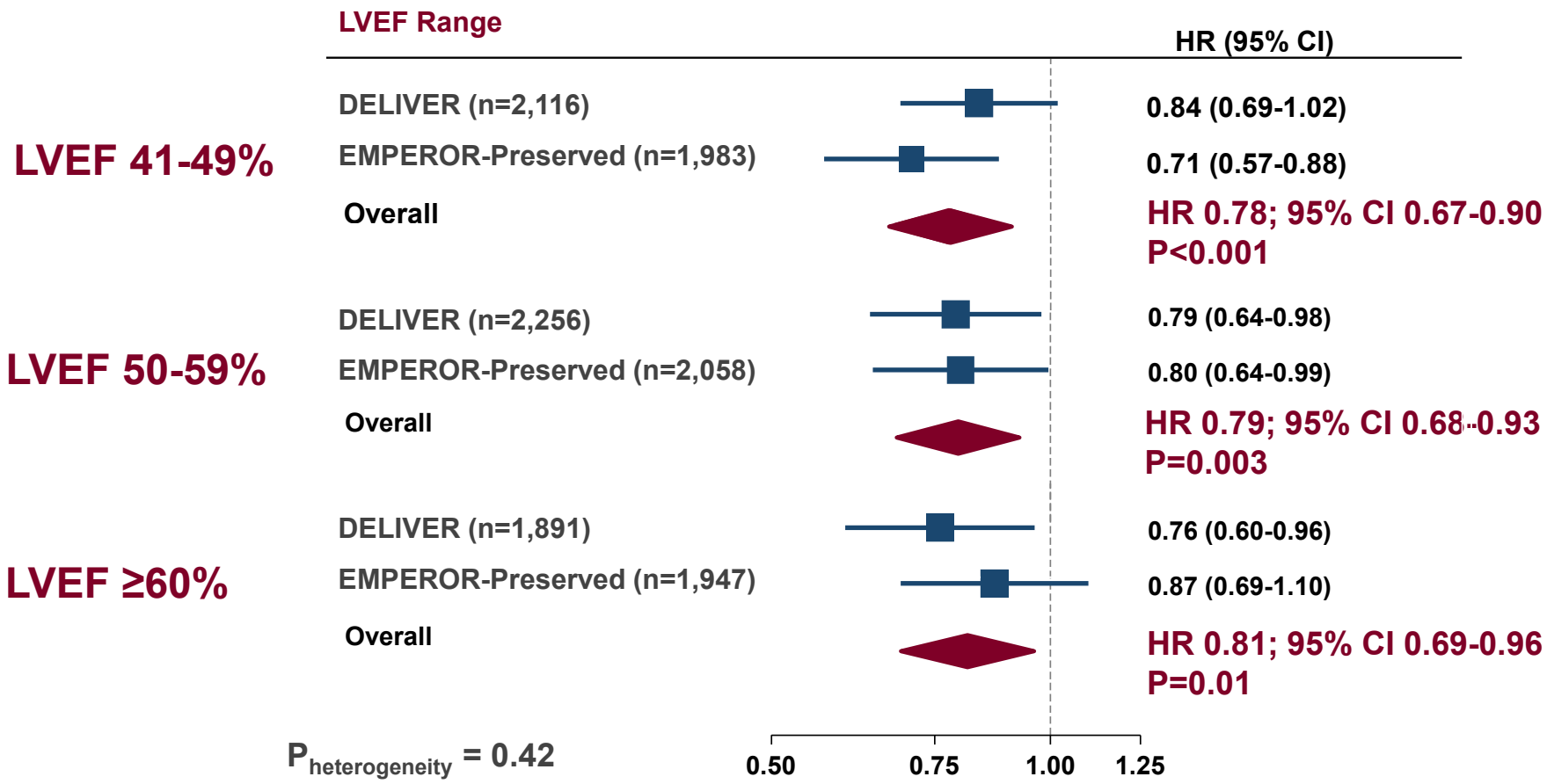




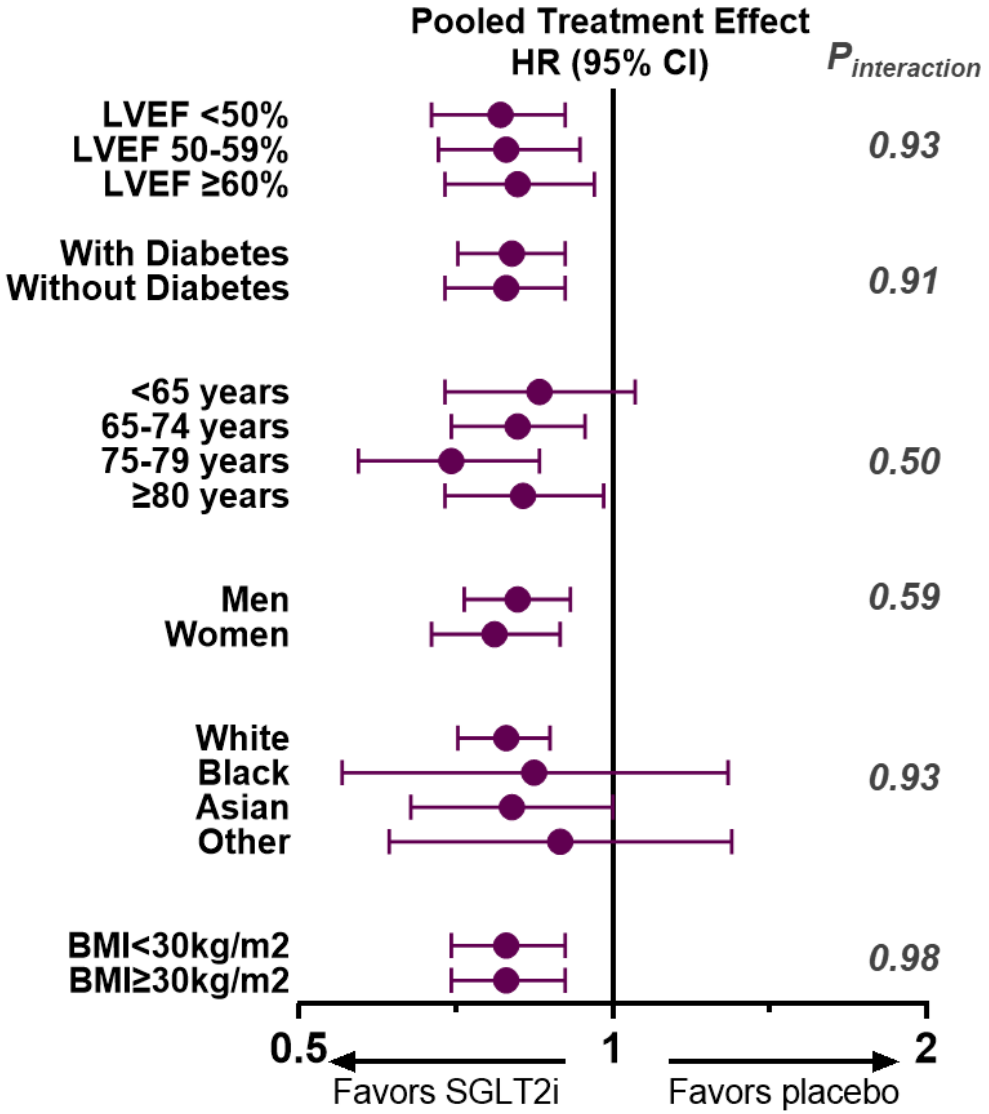


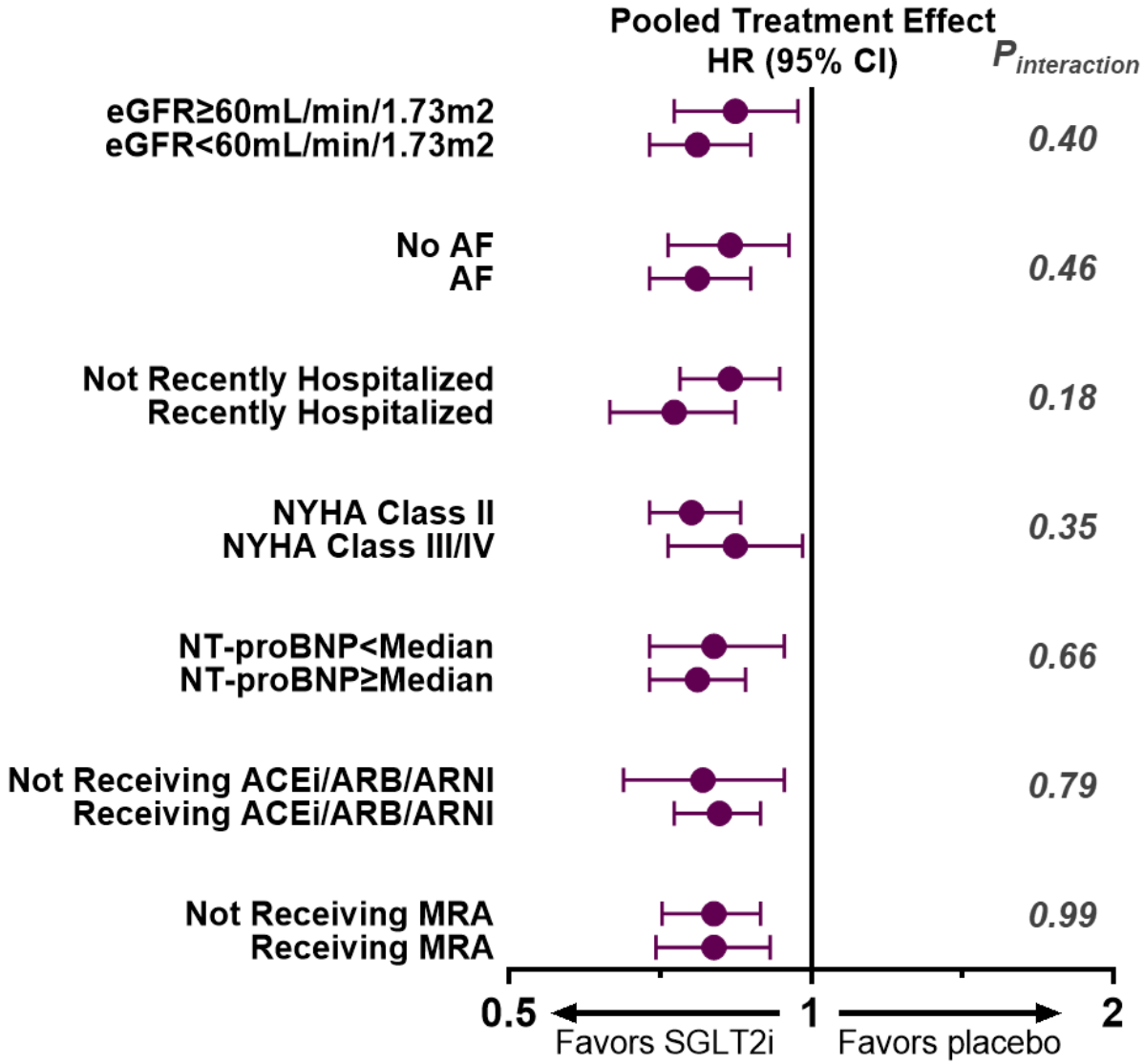
$P_{heterogeneity}$ >0.40 for all endpoints

DELIVER and EMPEROR-Preserved Meta-Analysis: Consistent Reductions in Primary Endpoint across LVEF Range, including among LVEF ≥60%

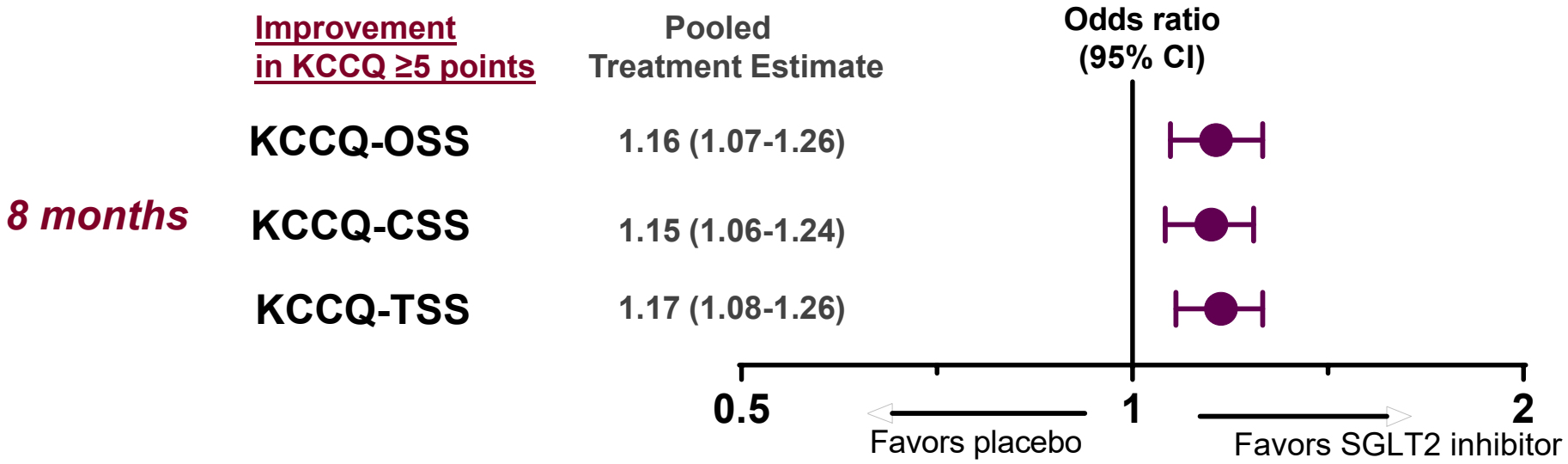


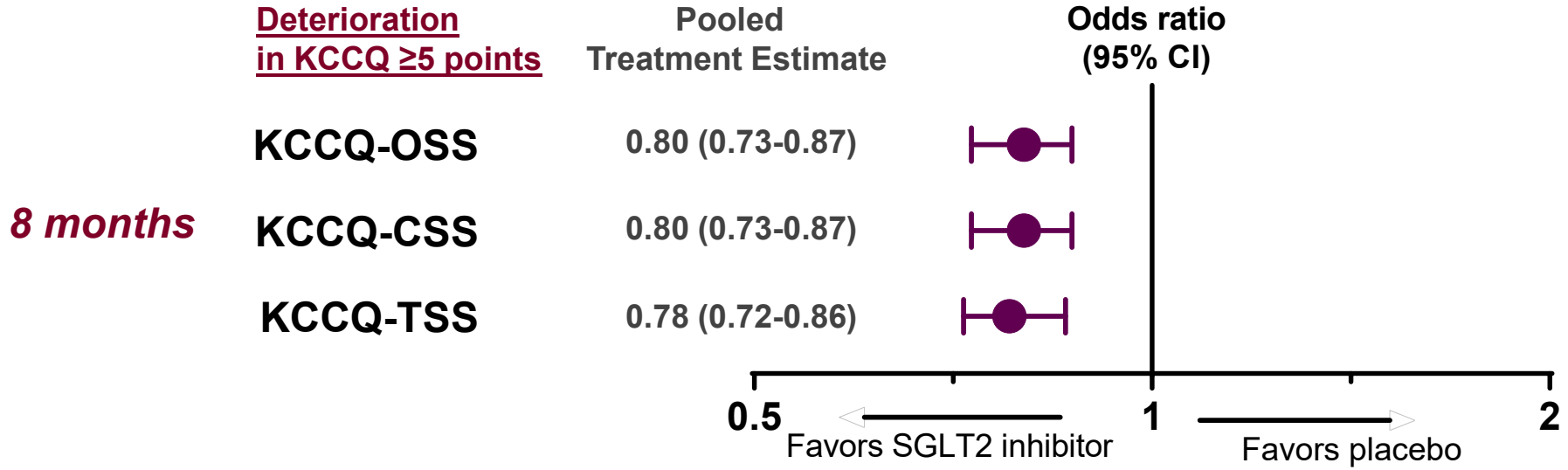
DELIVER and EMPEROR-Preserved Meta-Analysis:
No Significant Heterogeneity in Primary Endpoint across 13 Subgroups





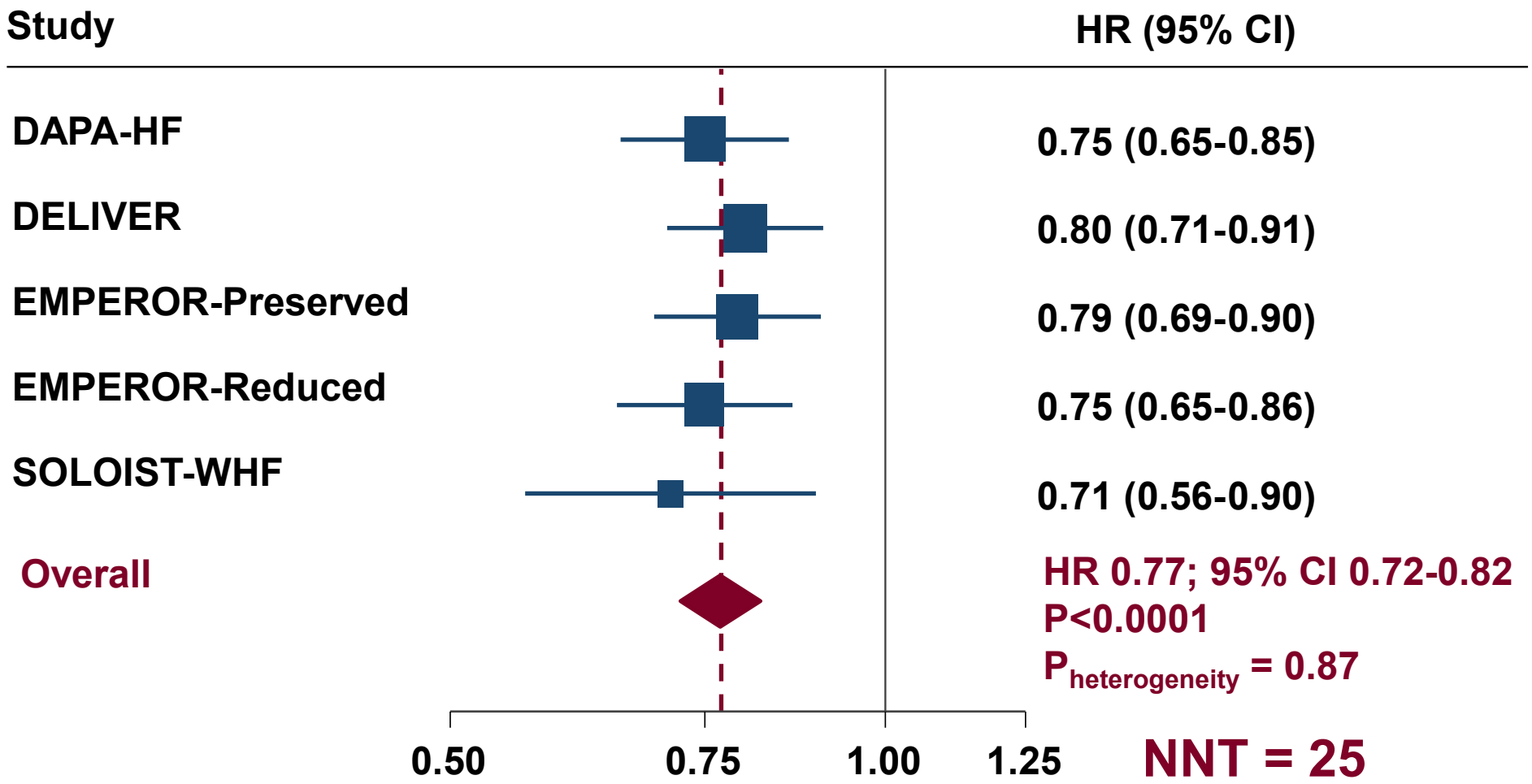
DELIVER and EMPEROR-Preserved Meta-Analysis: Greater Clinically Meaningful Improvement and Lesser Deterioration in Multiple Domains of Health Status with SGLT2i



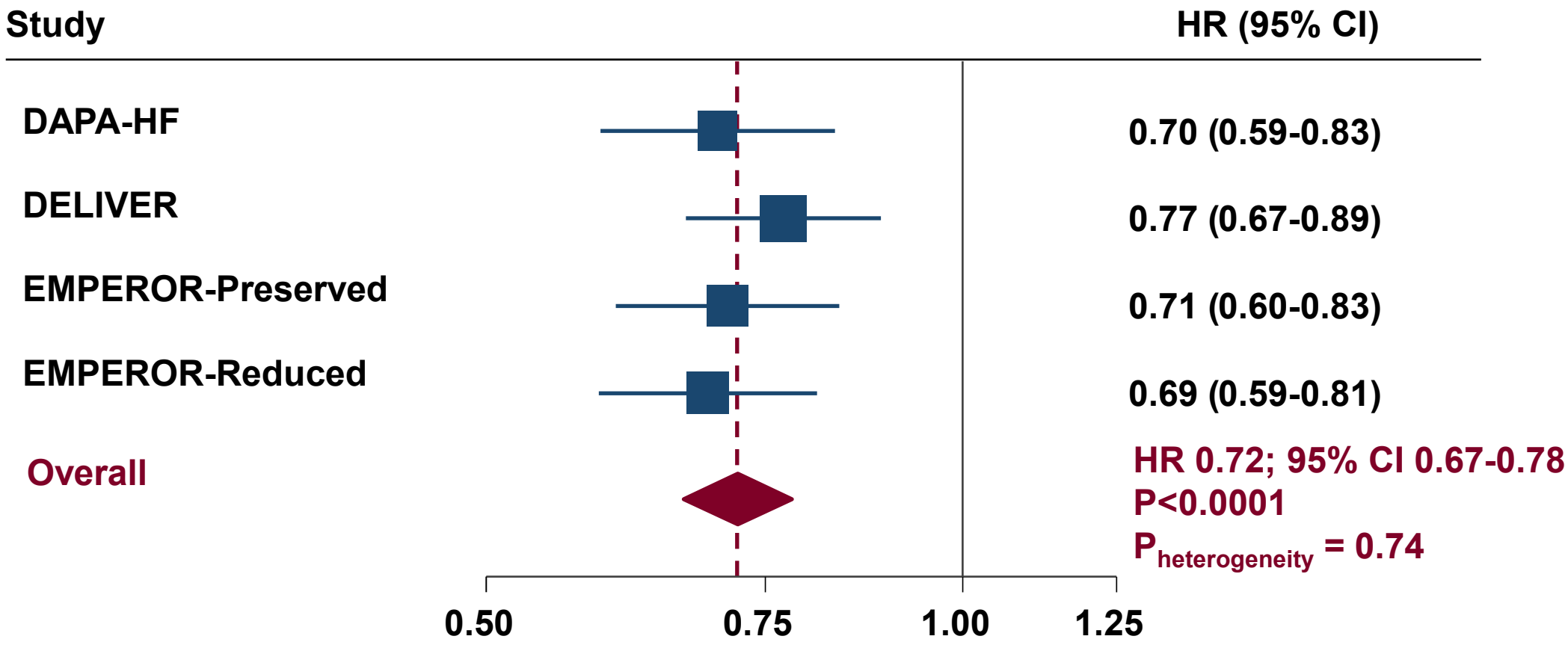


P≤0.01 for all meta-analytic estimates without heterogeneity observed between 2 trials

Meta-Analysis of 5 Large Placebo-Controlled Trials:
↓ 23% (18-28%) Relative Risk Reduction of Primary Endpoint (CV Death or HF Hospitalisation)

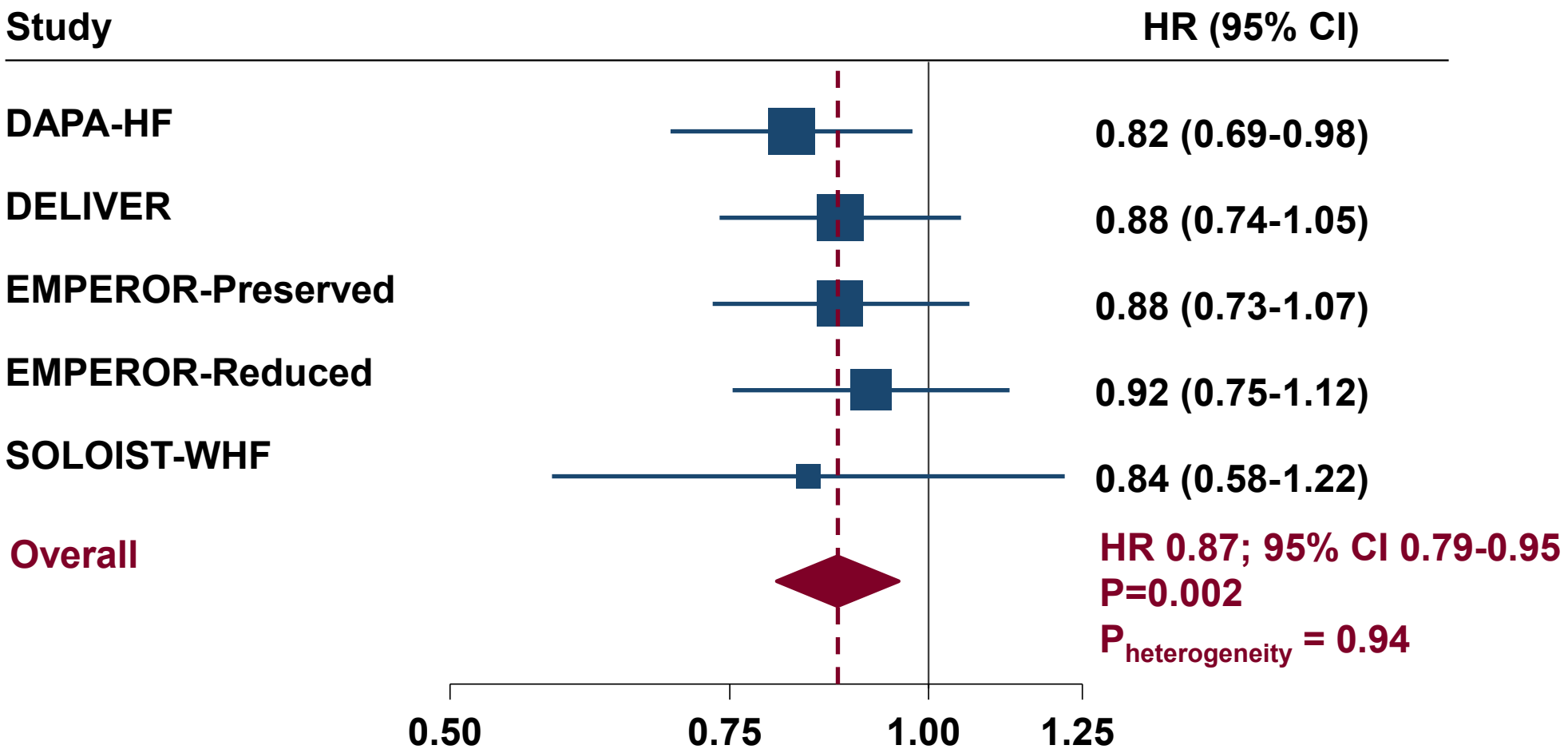


Meta-Analysis of 4 Large Placebo-Controlled Trials:
↓ 28% (22-33%) Relative Risk Reduction of Hospitalisation for HF

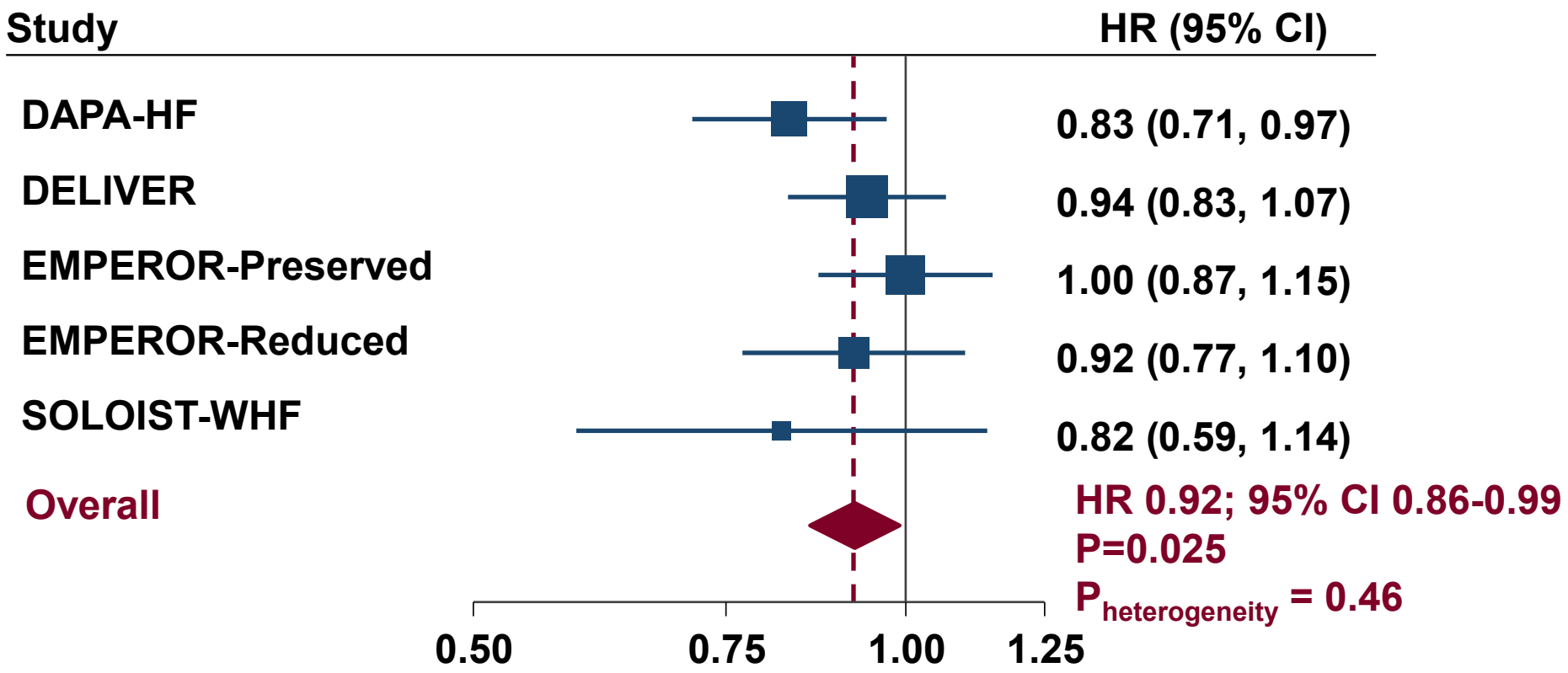


SOLOIST-WHF did not report this endpoint

Meta-Analysis of 5 Large Placebo-Controlled Trials:
↓ 13% (5-21%) Relative Risk Reduction of CV Death



Meta-Analysis of 5 Large Placebo-Controlled Trials:
↓ 8% (1-14%) Relative Risk Reduction of All Cause Death



Conclusions

- This meta-analysis of the 2 large, dedicated outcomes trials of SGLT2i in HF with mildly reduced or preserved ejection fraction confirms that the SGLT2i dapagliflozin and empagliflozin robustly reduced CV death or hospitalisation for HF.
- SGLT2i ameliorated symptoms and conferred clinically meaningful improvements in quality of life, with benefits seen rapidly within months of treatment initiation.
- The clinical benefit of SGLT2i appeared consistent across all 13 subgroups, and extended to patients with LVEF ≥60% as well as those already treated with other common HF therapies.
- The comprehensive meta-analysis of the 5 large outcomes trials encompassing over 20,000 participants with HF showed that SGLT2i extended survival, reduced morbid events, and improved overall health status.

The totality of evidence supports prioritizing the use of SGLT2 inhibitors in all patients with heart failure, irrespective of patient phenotype or care setting.

Simultaneously Published in *The Lancet*

SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials

Muthiah Vaduganathan, Kieran F Docherty*, Brian L Claggett, Pardeep S Jhund, Rudolf A de Boer, Adrian F Hernandez, Silvio E Inzucchi, Mikhail N Kosiborod, Carolyn S P Lam, Felipe Martinez, Sanjiv J Shah, Akshay S Desai, John J V McMurray†, Scott D Solomon†*

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Summary

Background SGLT2 inhibitors are strongly recommended in guidelines to treat patients with heart failure with reduced ejection fraction, but their clinical benefits at higher ejection fractions are less well established. Two large-scale trials, DELIVER and EMPEROR-Preserved, in heart failure with mildly reduced or preserved ejection fraction have been done, providing power to examine therapeutic effects on cardiovascular mortality and in patient subgroups when combined with the earlier trials in reduced ejection fraction.

Methods We did a prespecified meta-analysis of DELIVER and EMPEROR-Preserved, and subsequently included trials that enrolled patients with reduced ejection fraction (DAPA-HF and EMPEROR-Reduced) and those admitted to hospital with worsening heart failure, irrespective of ejection fraction (SOLOIST-WHF). Using trial-level data with harmonised endpoint definitions, we did a fixed-effects meta-analysis to estimate the effect of SGLT2 inhibitors on various clinical endpoints in heart failure The primary endpoint for this meta-analysis was time from randomisation to the occurrence of the composite of cardiovascular death or hospitalisation for heart failure. We assessed heterogeneity in treatment effects for the primary endpoint across subgroups of interest. This study is registered with PROSPERO, CRD42022327527.

Findings Among 12 251 participants from DELIVER and EMPEROR-Preserved, SGLT2 inhibitors reduced composite cardiovascular death or first hospitalisation for heart failure (hazard ratio 0·80 [95% CI 0·73–0·87]) with consistent reductions in both components: cardiovascular death (0·88 [0·77–1·00]) and first hospitalisation for heart failure (0·74 [0·67–0·83]). In the broader context of the five trials of 21 947 participants, SGLT2 inhibitors reduced the risk of composite cardiovascular death or hospitalisation for heart failure (0·77 [0·72–0·82]), cardiovascular death (0·87 [0·79–0·95]), first hospitalisation for heart failure (0·72 [0·67–0·78]), and all-cause mortality (0·92 [0·86–0·99]). These treatment effects for each of the studied endpoints were consistently observed in both the trials of heart failure with mildly reduced or preserved ejection fraction and across all five trials. Treatment effects on the primary endpoint were generally consistent across the 14 subgroups examined, including ejection fraction.

Interpretation SGLT2 inhibitors reduced the risk of cardiovascular death and hospitalisations for heart failure in a broad range of patients with heart failure, supporting their role as a foundational therapy for heart failure, irrespective of ejection fraction or care setting.

https://www.thelancet.com/

https://doi.org/10.1016/S0140-6736(22)01429-5

DELIVER at the ESC

Simultaneous Publications

The New England Journal of Medicine
Solomon et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

nature medicine
Jhund 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

THE LANCET
Vaduganathan et al. SGLT-2 Inhibitors in Patients with Heart Failure: A Comprehensive Meta-Analysis of 5 Randomized Placebo-Controlled Trials

JACC
Cunningham et al. Dapagliflozin in Hospitalized or Recently Hospitalized Heart Failure with Mildly Reduced or Preserved Ejection Fraction

JACC
Butt et al. Atrial Fibrillation and Dapagliflozin Efficacy in Patients with Preserved or Mildly Reduced Ejection Fraction

JACC
Vaduganathan et al. Estimated Event-Free Survival Benefits with Dapagliflozin in HF with Mildly Reduced or Preserved EF

Circulation
Butt et al. Efficacy and safety of dapagliflozin according to frailty in patients with heart failure: A prespecified analysis of the DELIVER trial

European Heart Journal
Adamson et al. Efficacy and safety of dapagliflozin according to body mass index in patients with heart failure: A prespecified analysis of the DELIVER trial

JACC Heart Failure
Myhre et al. Influence of NT-proBNP on Efficacy of Dapagliflozin in HF with Mildly Reduced or Preserved Ejection Fraction

European Journal of Heart Failure
Ostrominski et al. Dapagliflozin and New York Heart Association functional class in heart failure with mildly reduced or preserved ejection fraction: the DELIVER trial

Circulation: Heart Failure
Peikert et al. Efficacy and Safety of Dapagliflozin in Heart Failure With Mildly Reduced or Preserved Ejection Fraction According to Age: The DELIVER Trial