SGLT2 Inhibitors in Patients with Heart Failure with Mildly Reduced or Preserved Ejection Fraction: A Pre-Specified Meta-Analysis of DELIVER and EMPEROR-Preserved

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Disclosure

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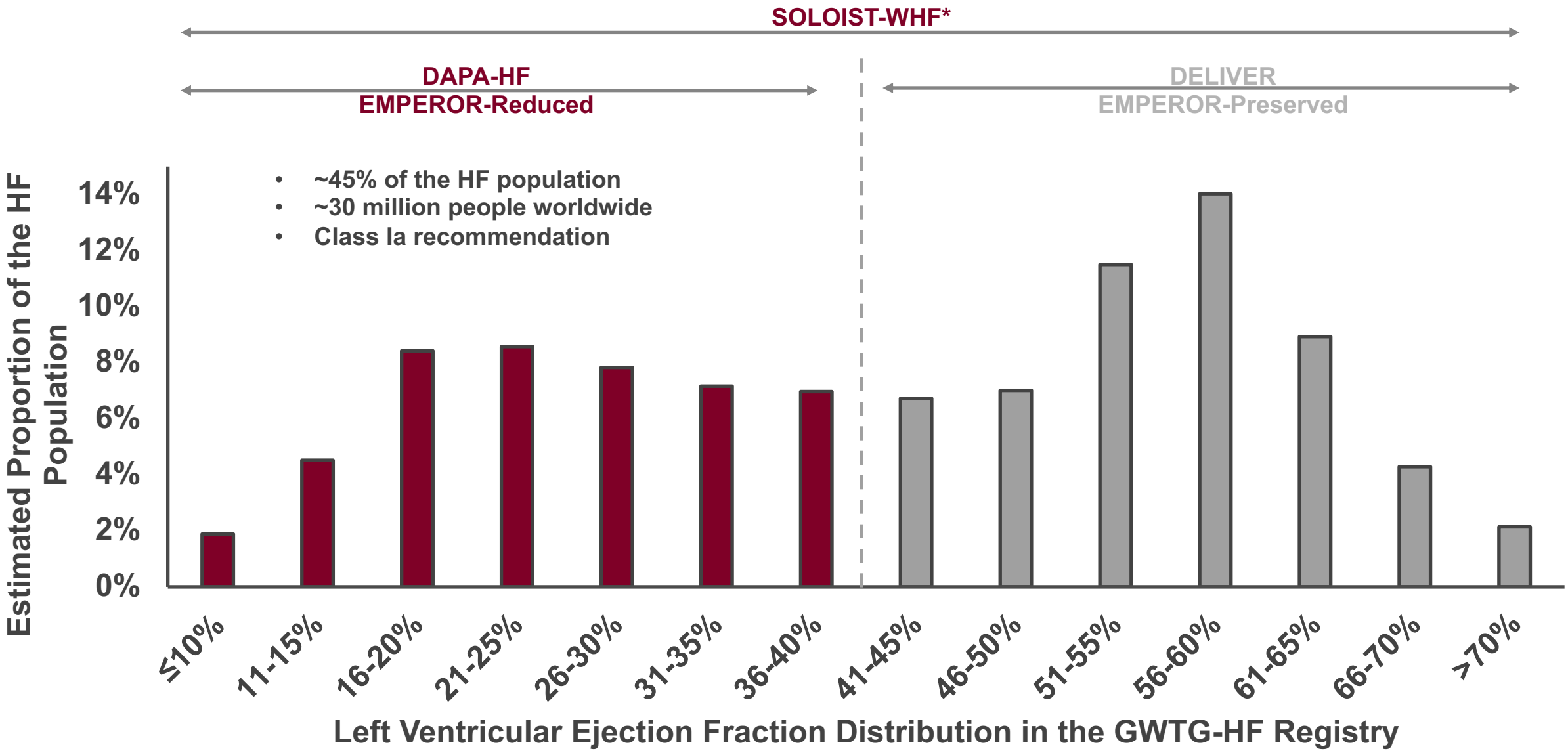
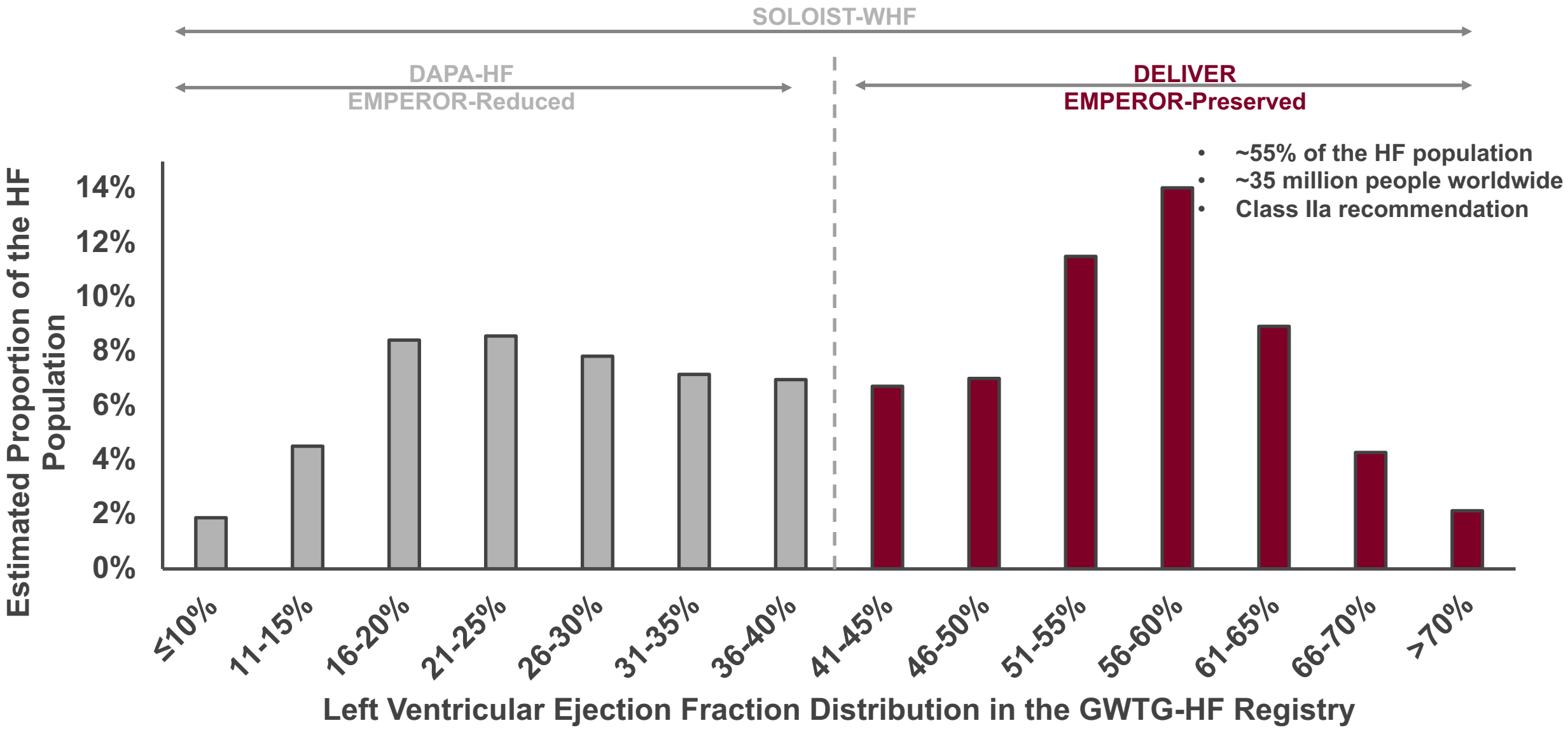
SGLT2 Inhibitors are Established as a Standard of Care in HFrEF



*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.

Nested Meta-Analytic Structure

1

DELIVER and EMPEROR-Preserved

- 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

- 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

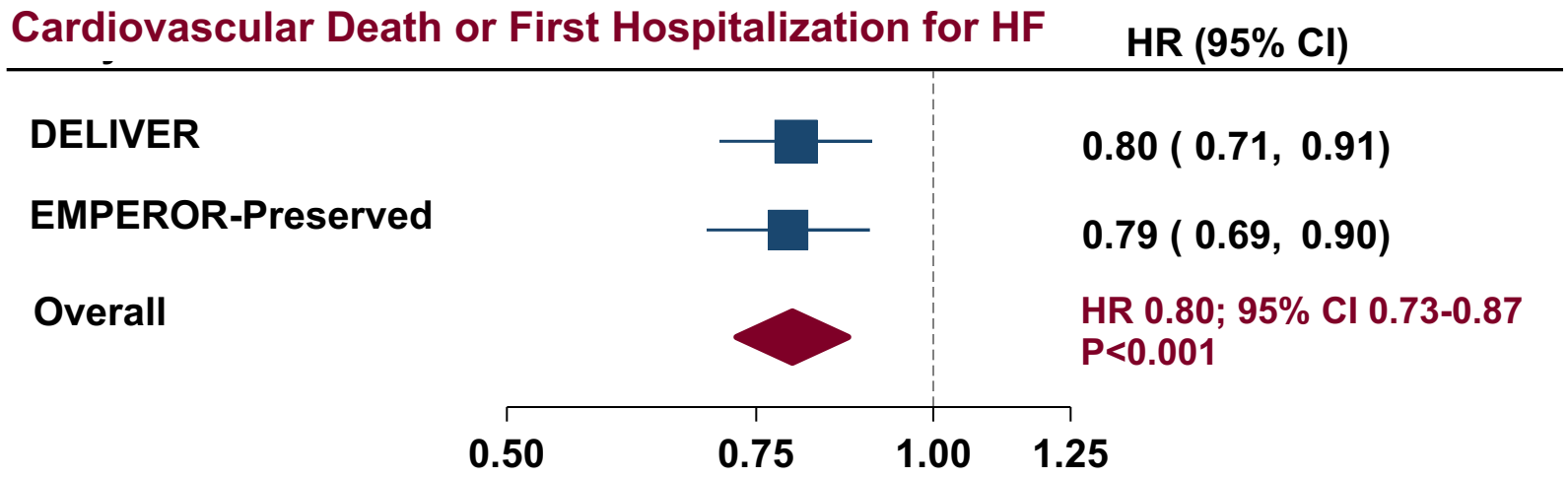
Key Eligibility Criteria in DELIVER and EMPEROR-Preserved

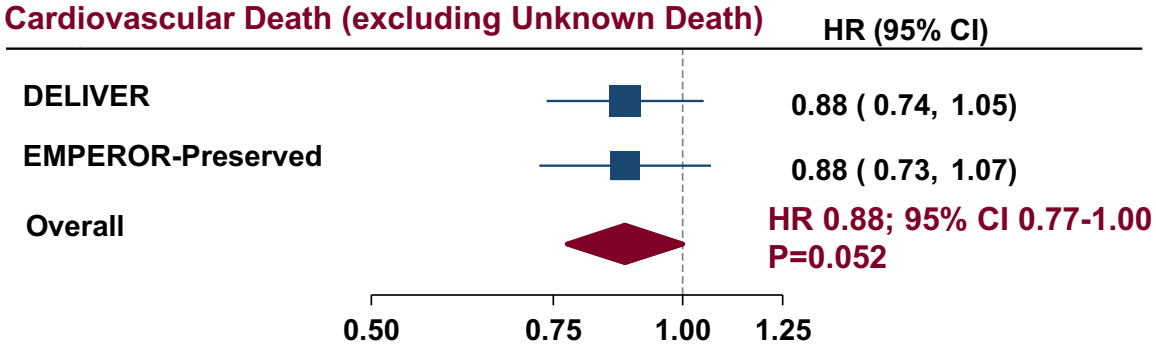
Key Inclusion Criteria	DELIVER	EMPEROR-Preserved
Symptomatic HF	NYHA class II-IV	NYHA class II-IV
Cardiac Structure and Function	LVEF>40% and evidence of structural heart disease	LVEF>40% and either evidence of structural heart disease or history of HF hospitalization within 12mo
Prior LVEF≤40% with 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

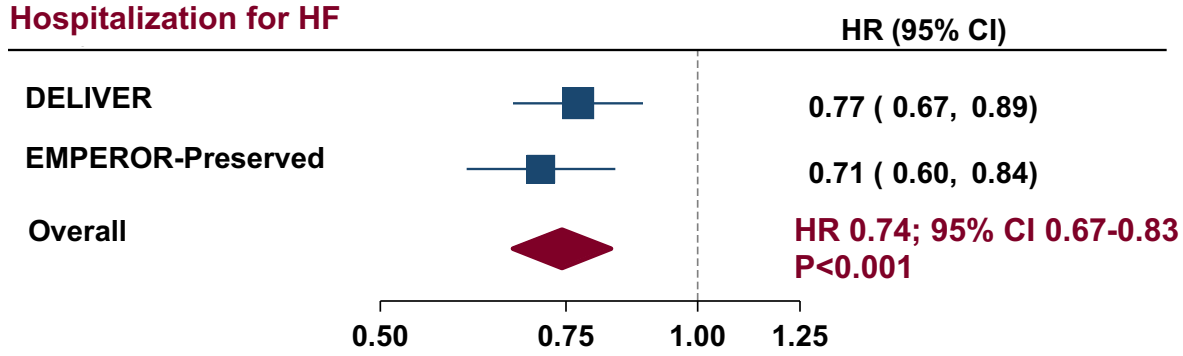
Baseline Characteristics & Background Medical Therapy

	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

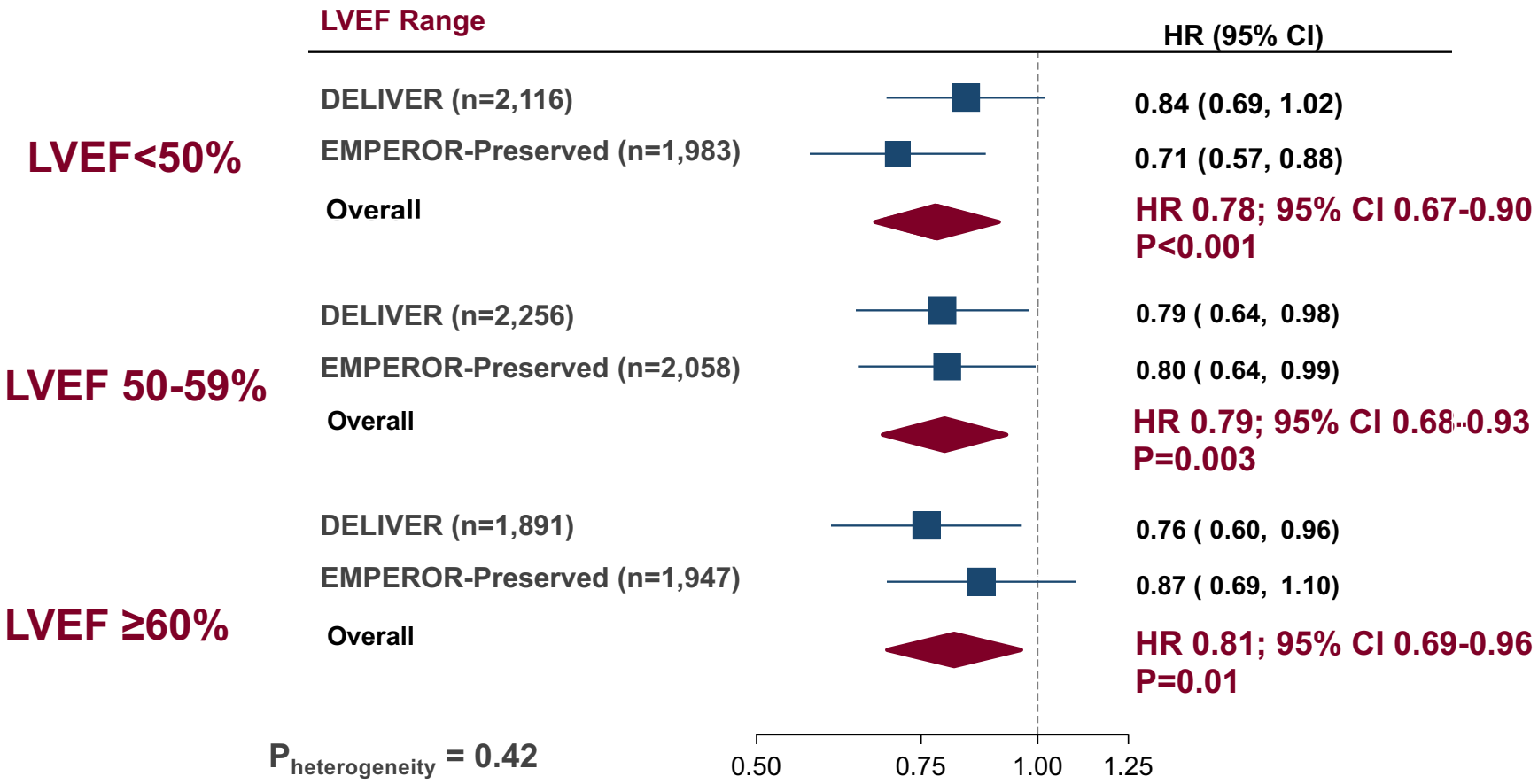




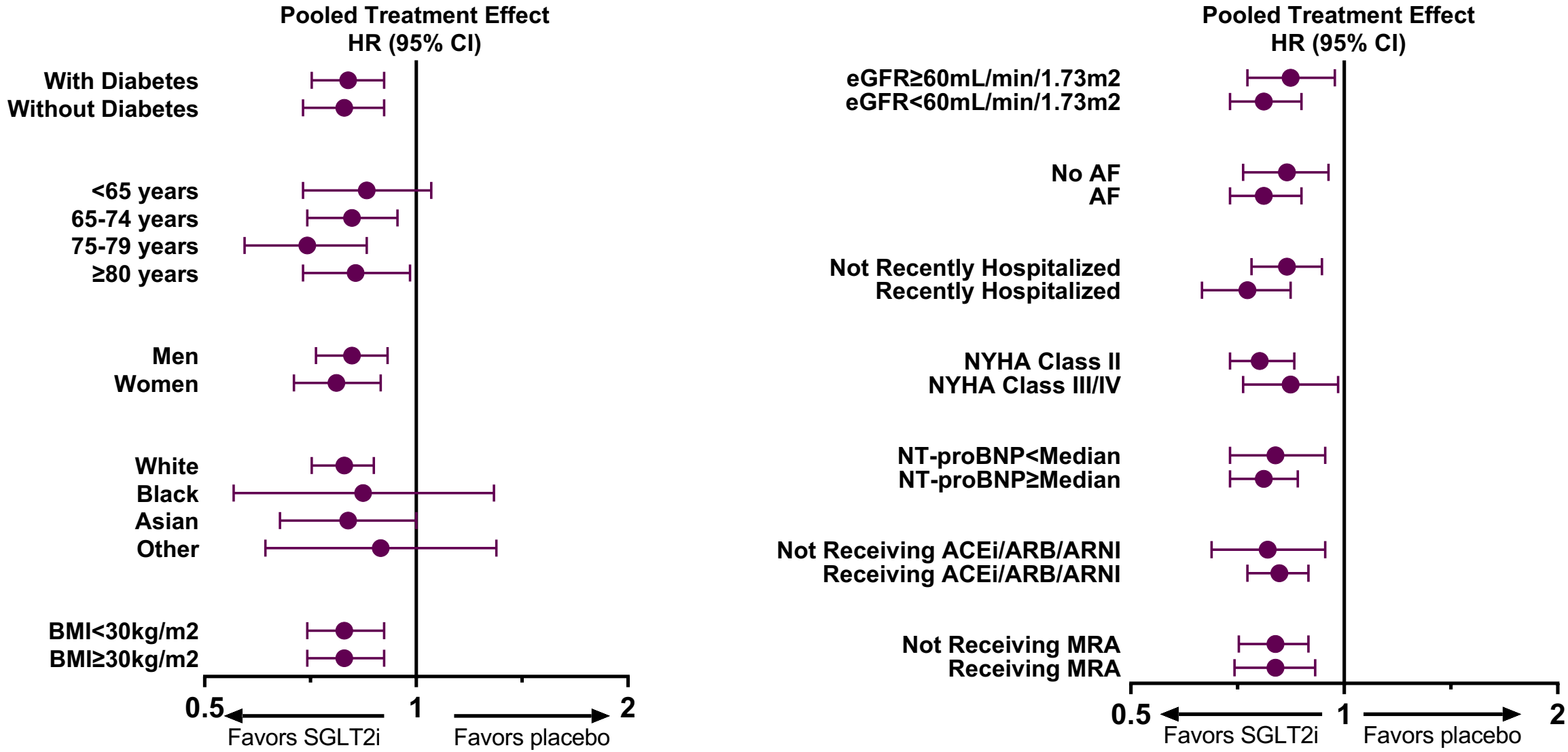


$P_{heterogeneity}$ >0.10 for all endpoints

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

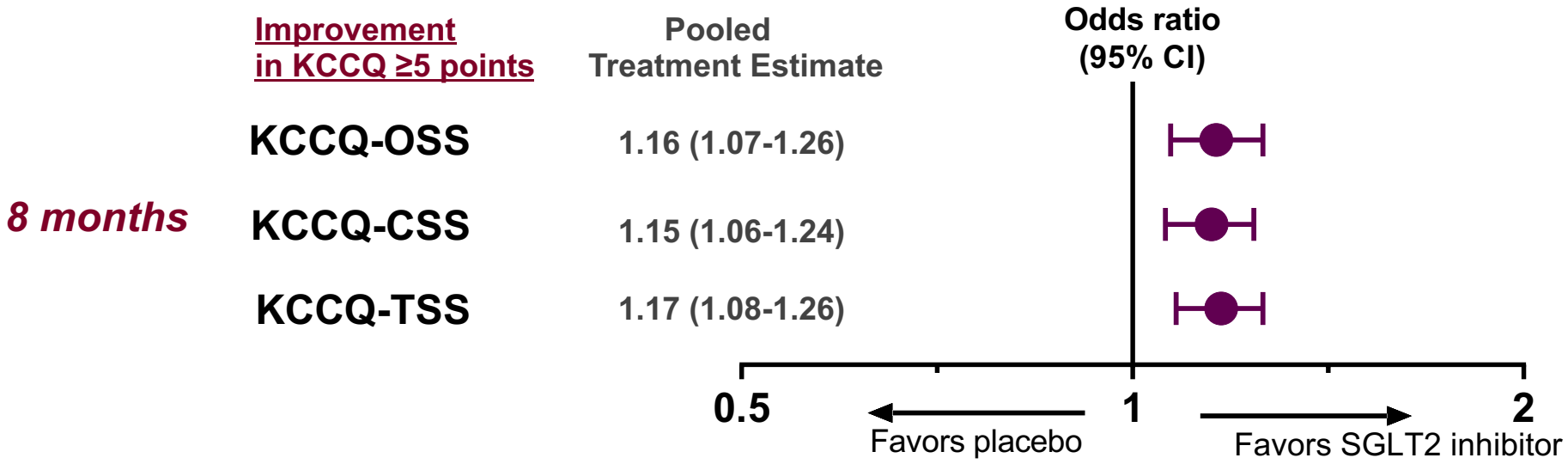


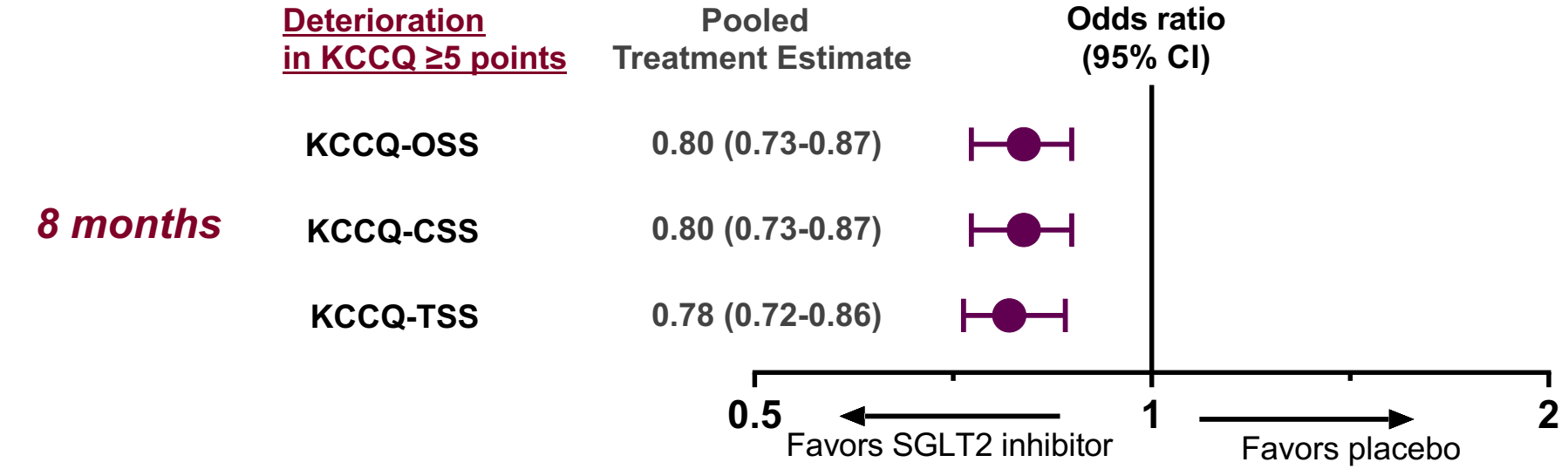
DELIVER and EMPEROR-Preserved Meta-Analysis:
No Significant Heterogeneity in Primary Endpoint across 13 Subgroups



$P_{interaction}$>0.10 for all subgroups

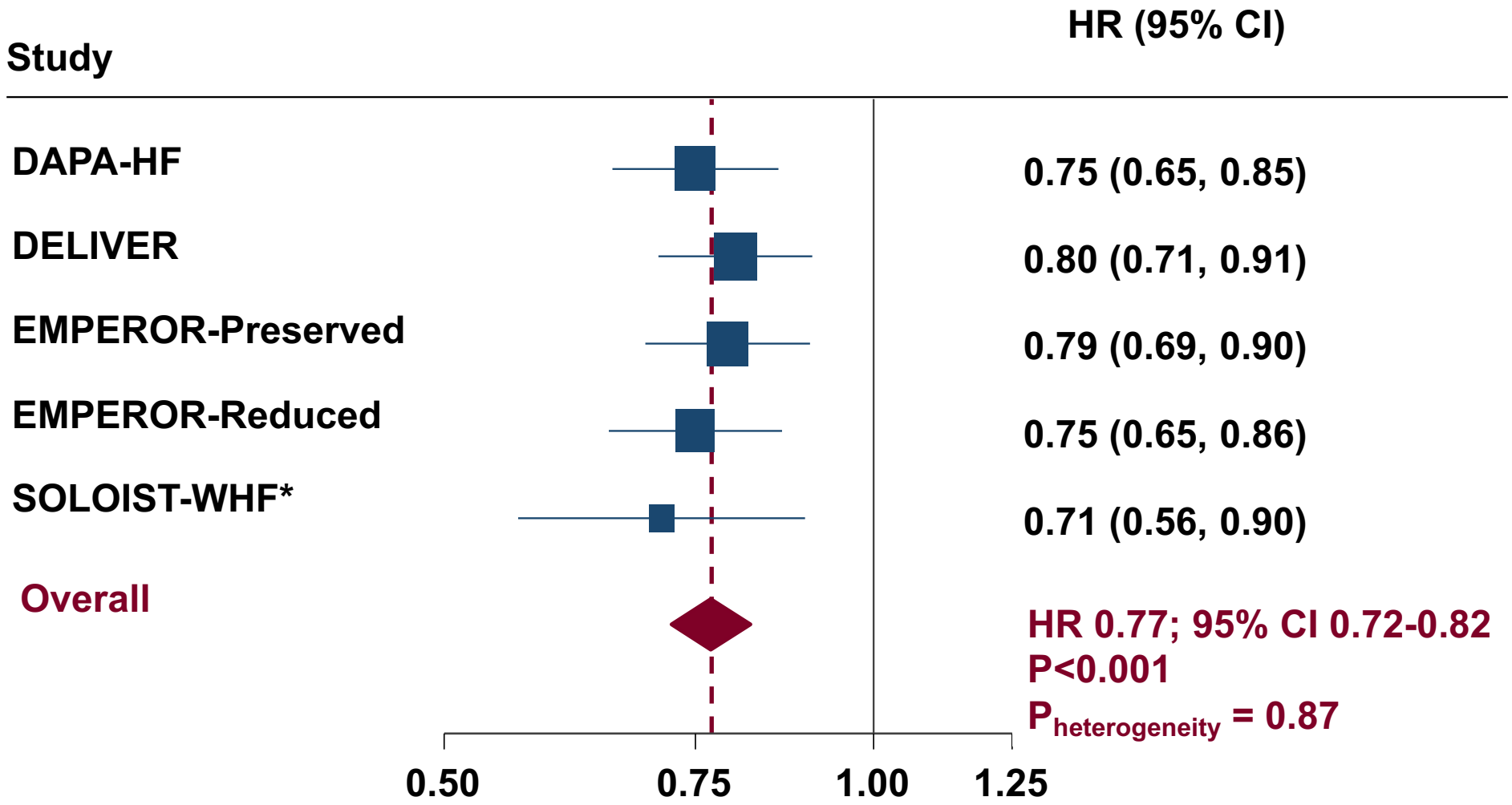
DELIVER and EMPEROR-Preserved Meta-Analysis: Greater Clinically Meaningful Improvement and Lesser Deterioration in Multiple Domains of Health Status with SGLT2i





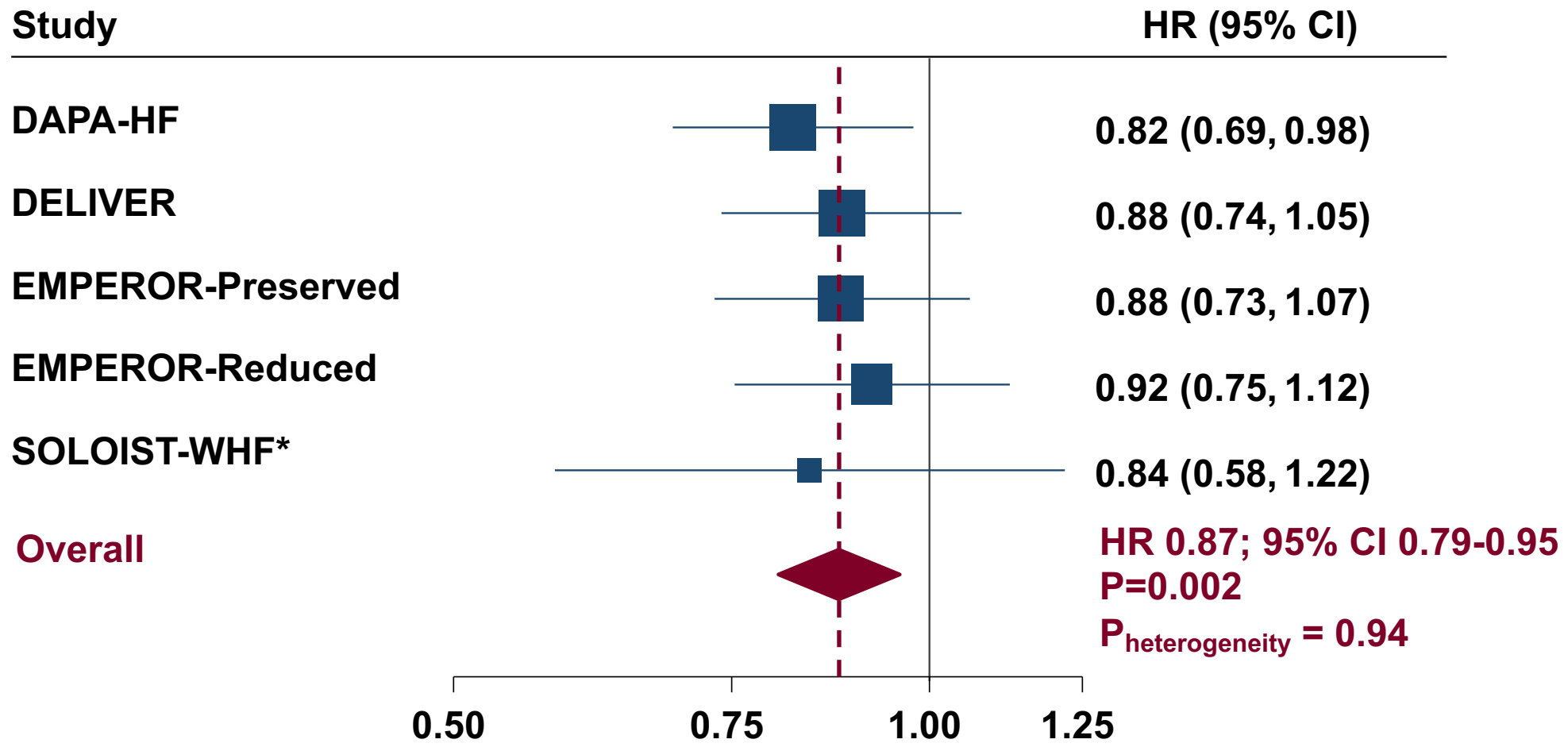
P≤0.01 for all meta-analytic estimates without heterogeneity observed between 2 trials

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



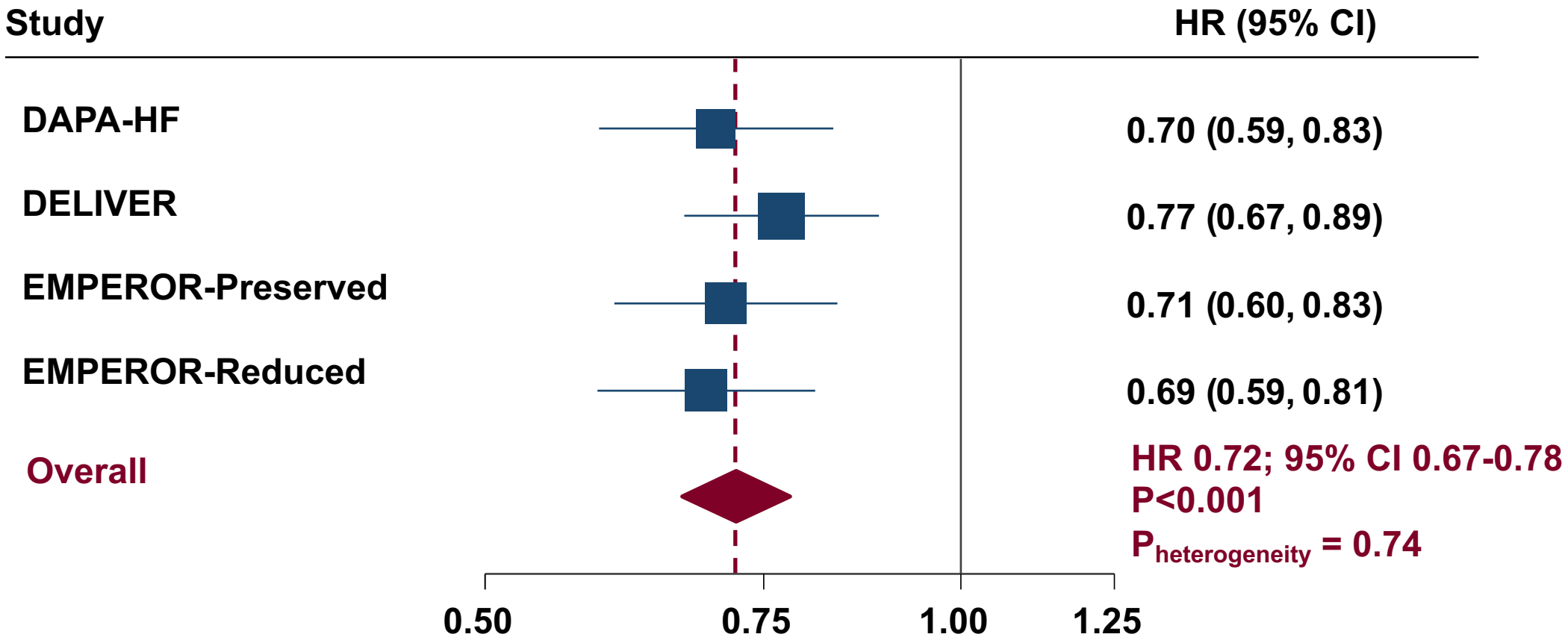
*SOLOIST-WHF evaluated an SGLT1/2 inhibitor

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

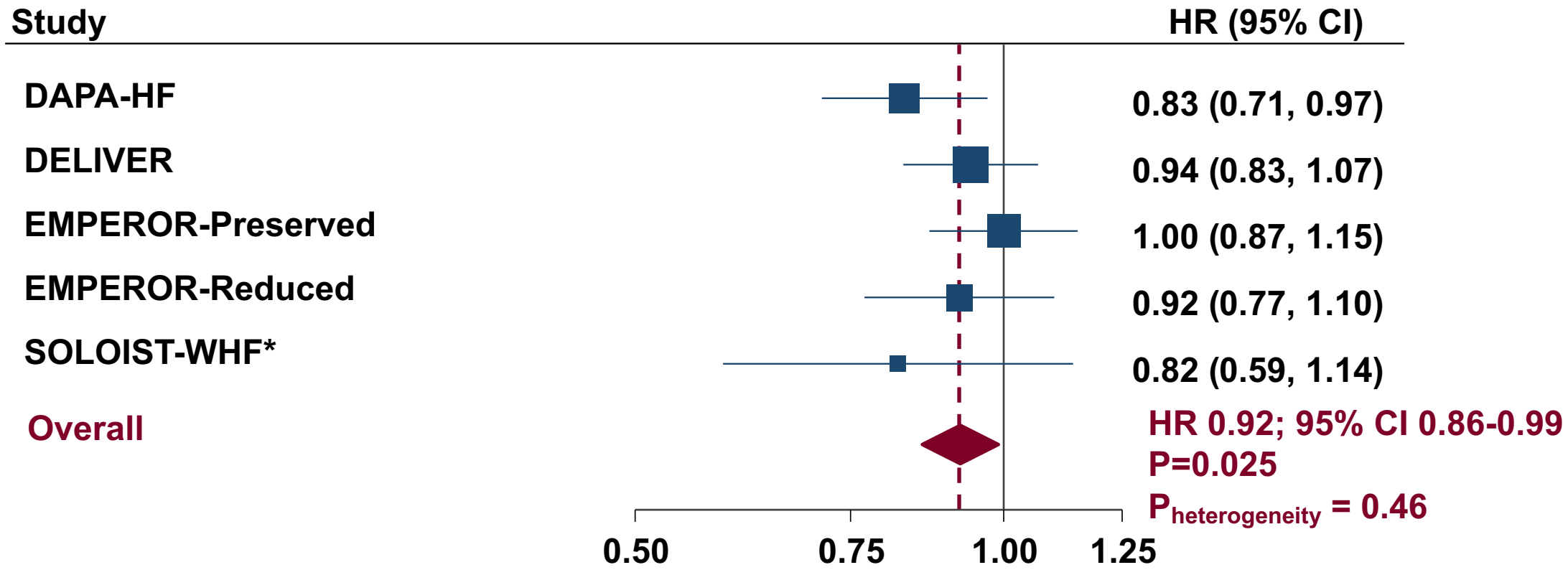


*SOLOIST-WHF evaluated an SGLT1/2 inhibitor

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



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



*SOLOIST-WHF evaluated an SGLT1/2 inhibitor

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 health status, with benefits seen rapidly within months of treatment initiation.
- The clinical benefit of SGLT2i appeared consistent across 13 subgroups, and extended to patients with LVEF ≥60% as well as those already treated with other common HF therapies.
- In the more comprehensive examination of the totality of evidence from 5 trials enrolling over 20,000 participants, SGLT2i reduced the risk of mortality and worsening HF across a broad range of patients with the syndrome of HF.

This comprehensive meta-analysis supports the role of SGLT2i as foundational therapy in the management of HF, irrespective of ejection fraction or care setting.

Simultaneously Published in *The Lancet*