Dapagliflozin in Heart Failure with Improved Ejection Fraction The DELIVER Trial

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

HARVARD MEDICAL SCHOOL
Brigham and Women's Hospital
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DELIVER

Disclosures

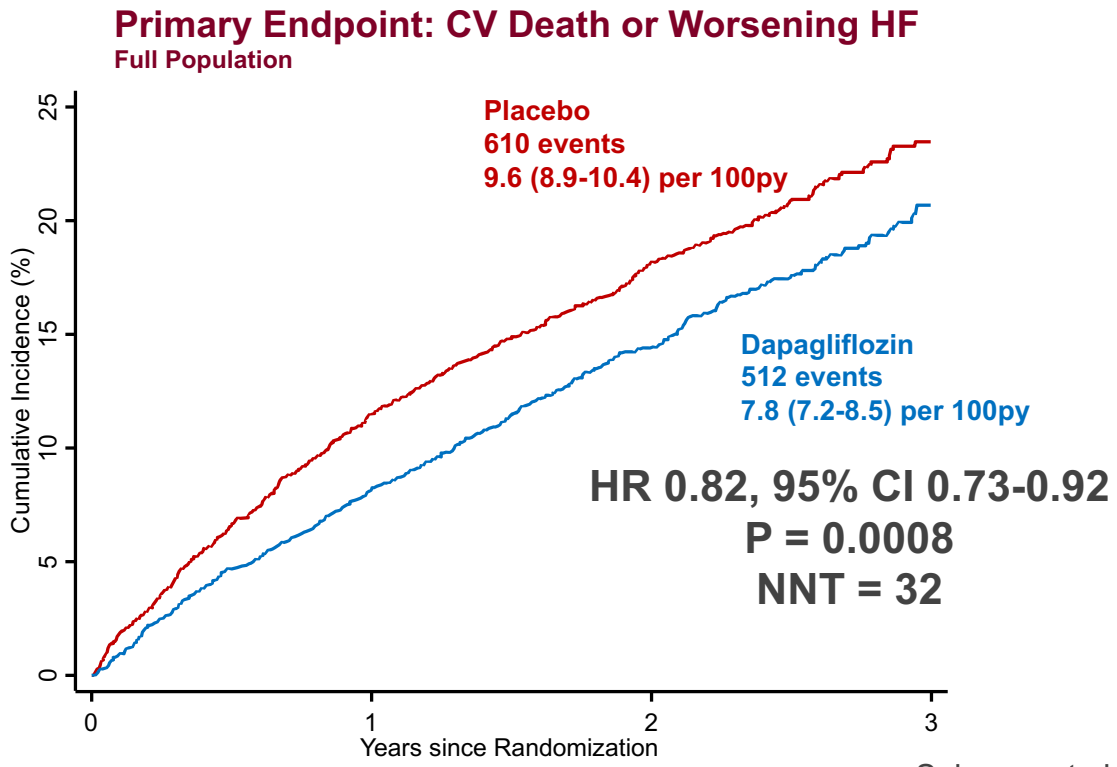
- Dr. Vardeny has received research support from AstraZeneca, Bayer, and Cardurion
- The DELIVER trial was funded by AstraZeneca

Background and Rationale

- Heart failure (HF) with improved ejection fraction (HFimpEF) has been recently defined as HF with previously reduced left ventricular ejection fraction (LVEF) of 40% or less, and a subsequent measurement of LVEF that increased to greater than 40%, although other definitions have varied
- Advances in the treatment of HFrEF with disease modifying therapies has resulted in a rapid growth of the pool of patients with HFimpEF
- Recent HF guidelines recommend that patients with HFimpEF continue treatment with guideline-directed medical therapies to avoid relapse and worsening of left ventricular function
- Previous therapeutic heart failure outcomes trials, have explicitly excluded individuals with HFimpEF
- Whether initiation of specific new pharmacologic therapies might improve clinical outcomes in these patients is unknown.

2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure. J Card Fail. 2022 May;28(5):e1-e167

Background and Objective



Solomon et al. N Engl J Med 2022

- DELIVER permitted enrollment of patients with prior LVEF ≤ 40% if they fulfilled LVEF entry criteria on enrollment (LVEF > 40%)
- **The objective of this analysis was to assess the efficacy and safety of dapagliflozin in patients with heart failure with improved ejection fraction**

DELIVER Study Design

Randomized, double-blind, placebo-controlled trial testing the hypothesis that dapagliflozin would reduce cardiovascular death or worsening heart failure in patients with heart failure and mildly reduced or preserved ejection fraction

DELIVER

Eligibility Criteria

- Age ≥ 40 years
- NYHA class II-IV
- LVEF > 40

(including prior LVEF ≤ 40%)

- Structural Heart Disease (LVH or LA Enlargement)
- Elevated Natriuretic Peptides (> 300 pg/ml or 600 pg/ml in AFF)
- Either Ambulatory or Hospitalized for Heart Failure

Double-blind Treatment period

Dapagliflozin 10mg once daily

Event Driven (1117 estimated events)

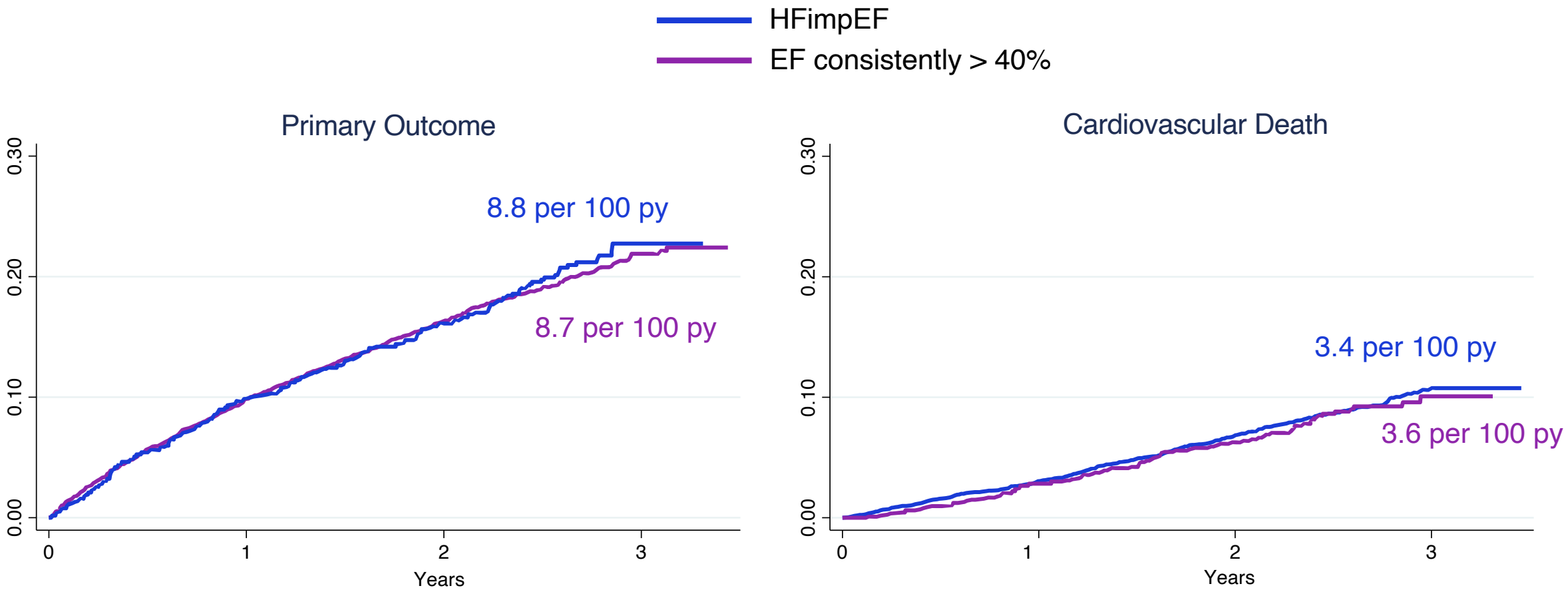
Placebo

Solomon et al. Eur J Heart Fail 2021

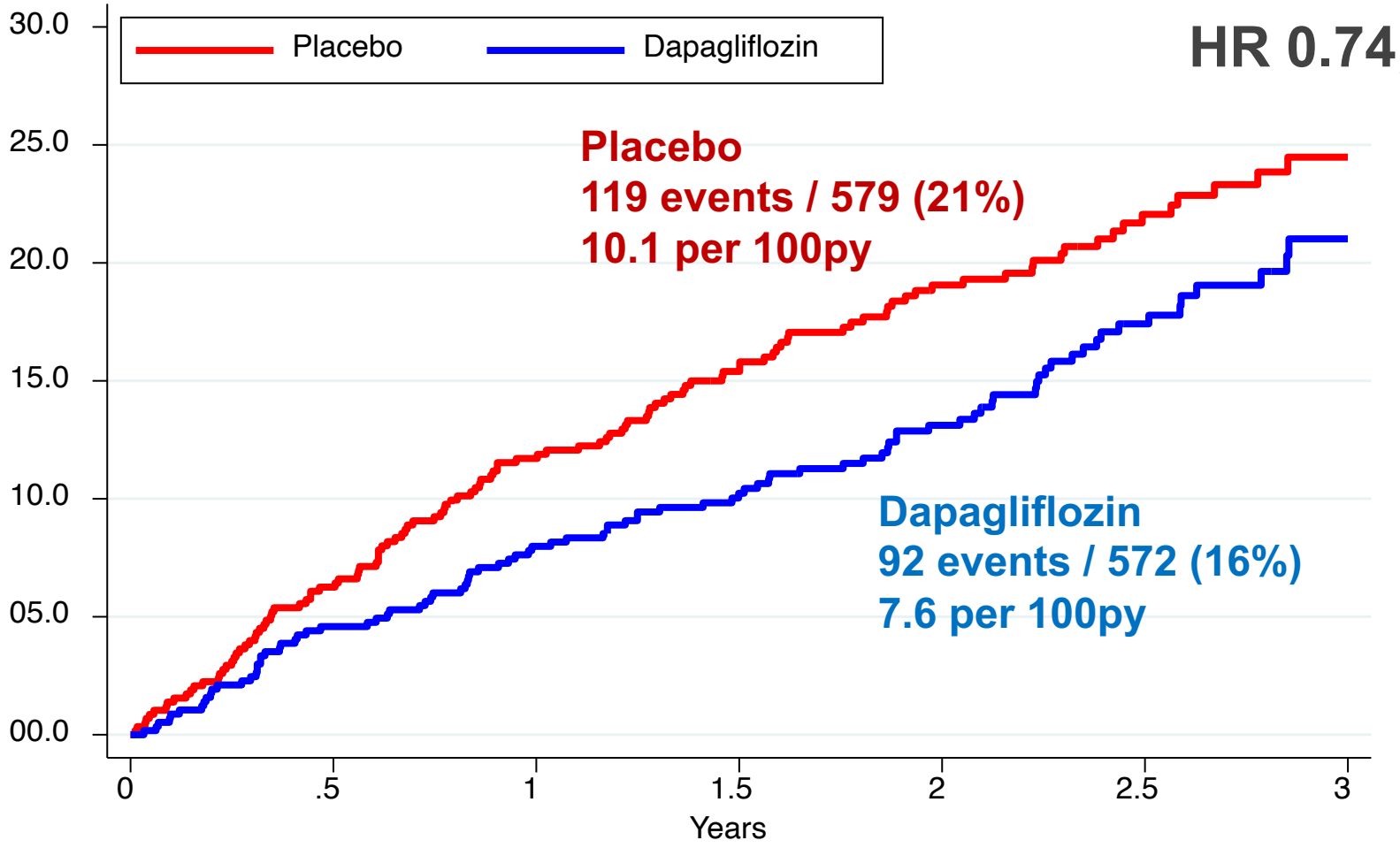
Baseline Characteristics by HFimpEF Status

	HFimpEF N=1151	EF consistently > 40% N=5112	P-value
Age (years)	70.1 ± 10.0	72.0 ± 9.4	<0.001
Male Sex	67.2%	53.6%	<0.001
Baseline LVEF (%)	50.5 ± 8.3	55.0 ± 8.7	<0.001
Race			<0.001
White	67.2%	71.7%	
Black	3.1%	2.4%	
Asian	25.2%	19.2%	
Other	4.4%	6.7%	
NYHA Class II	79.8%	74.2%	<0.001
Type 2 Diabetes Mellitus	46.0%	44.5%	0.38
Implantable cardioverter defibrillator	5.1%	1.1%	<0.001
Medications			
Loop diuretics	76.8%	76.9%	0.96
ACEi/ARB	68.9%	73.4%	<0.001
Sacubitril/valsartan	13.2%	2.9%	<0.001
β-blocker	86.2%	81.9%	<0.001
Mineralocorticoid receptor antagonist (MRA)	50.4%	40.8%	<0.001

Similar Event Rates in Patients with HFimpEF and those with EF consistently over 40%



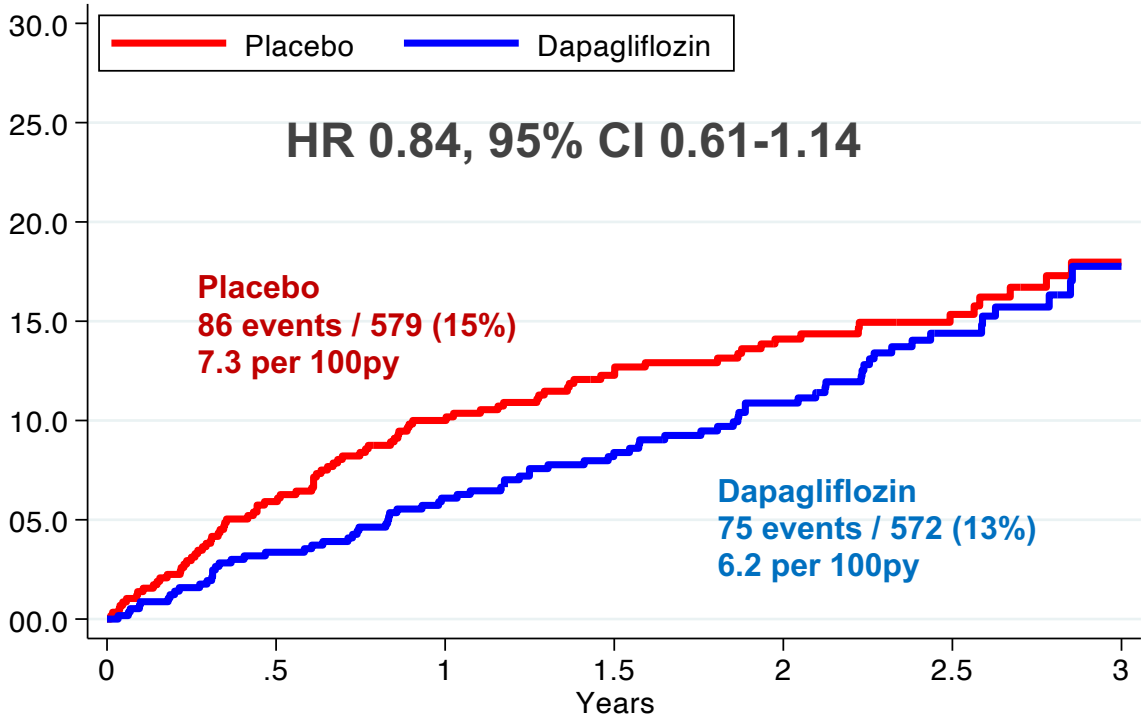
Primary Endpoint in Patients with HFimpEF (Cardiovascular Death or Worsening Heart Failure)



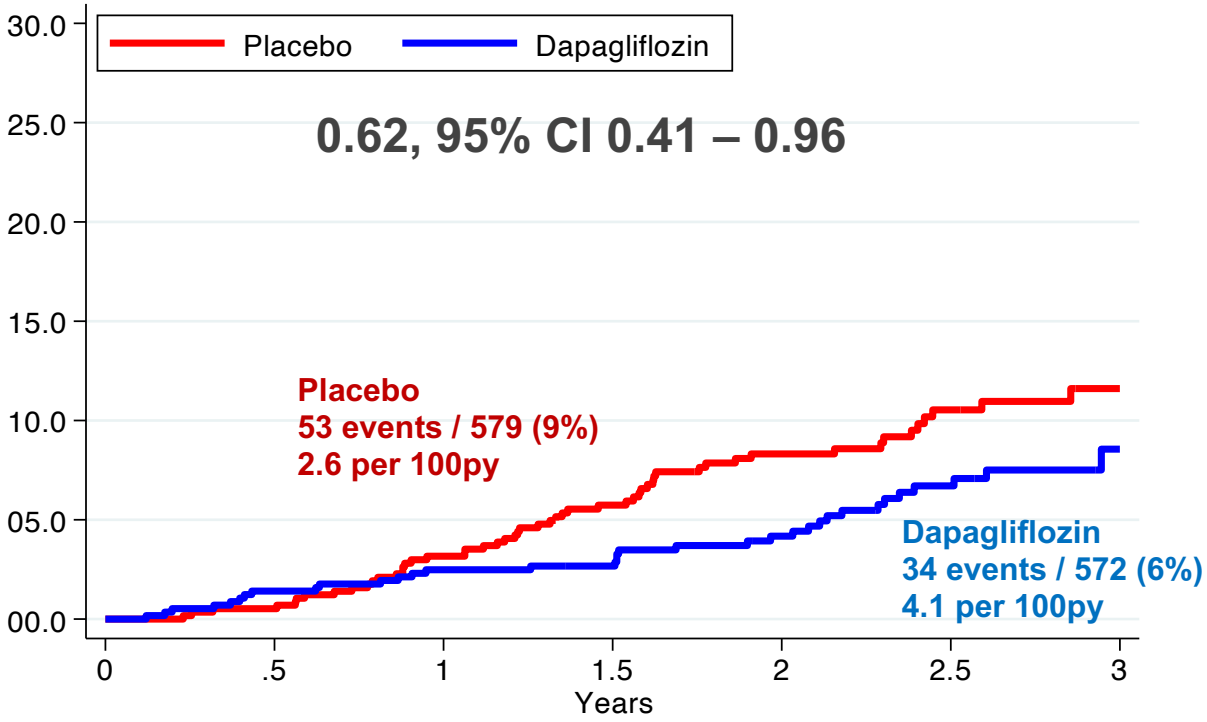
HR 0.74, 95% CI 0.56 - 0.97
NNT = 20

Components of Primary Endpoint in Patients with HFimpEF

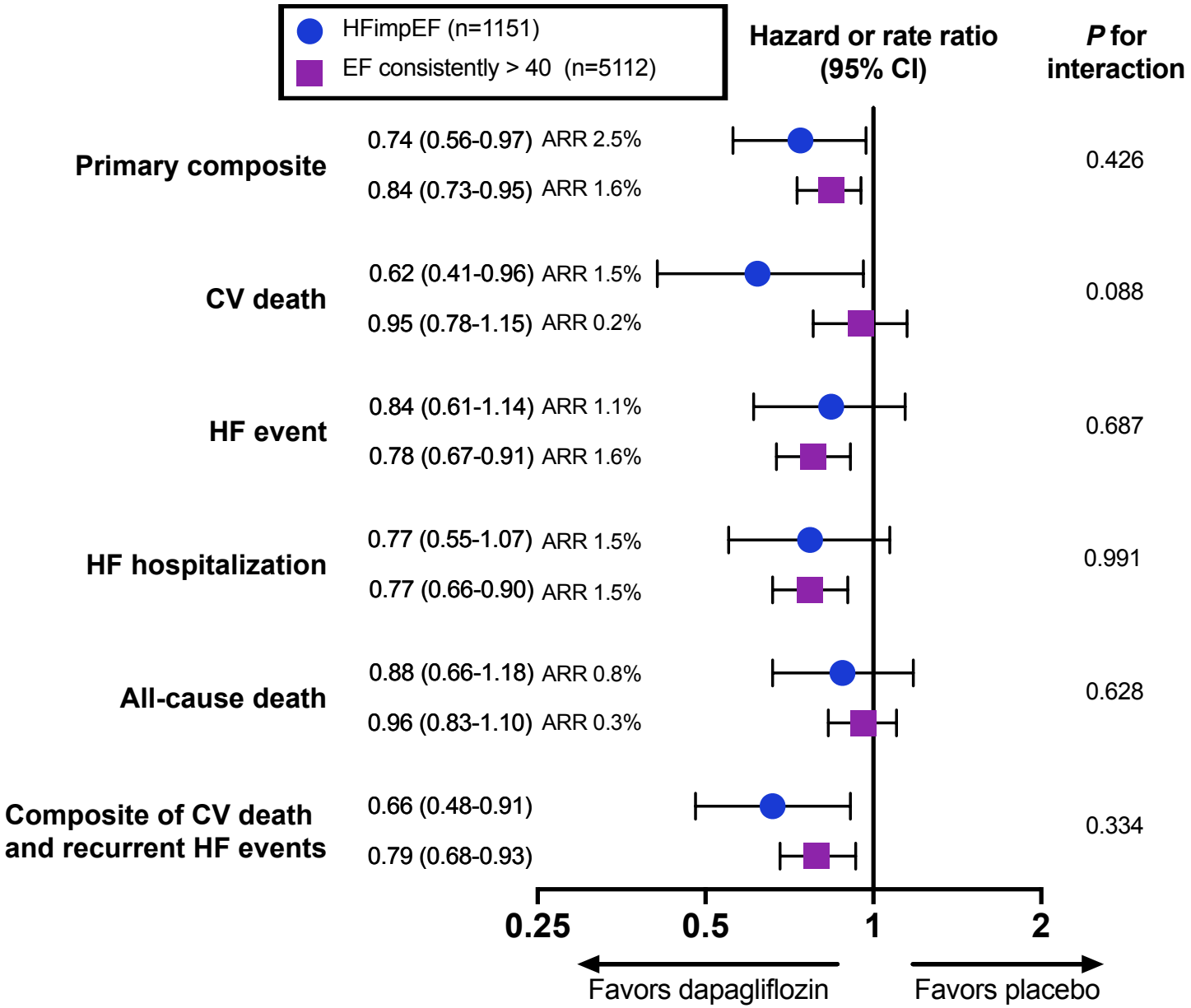
Worsening Heart Failure (HF Hospitalization + Urgent HF Visit)



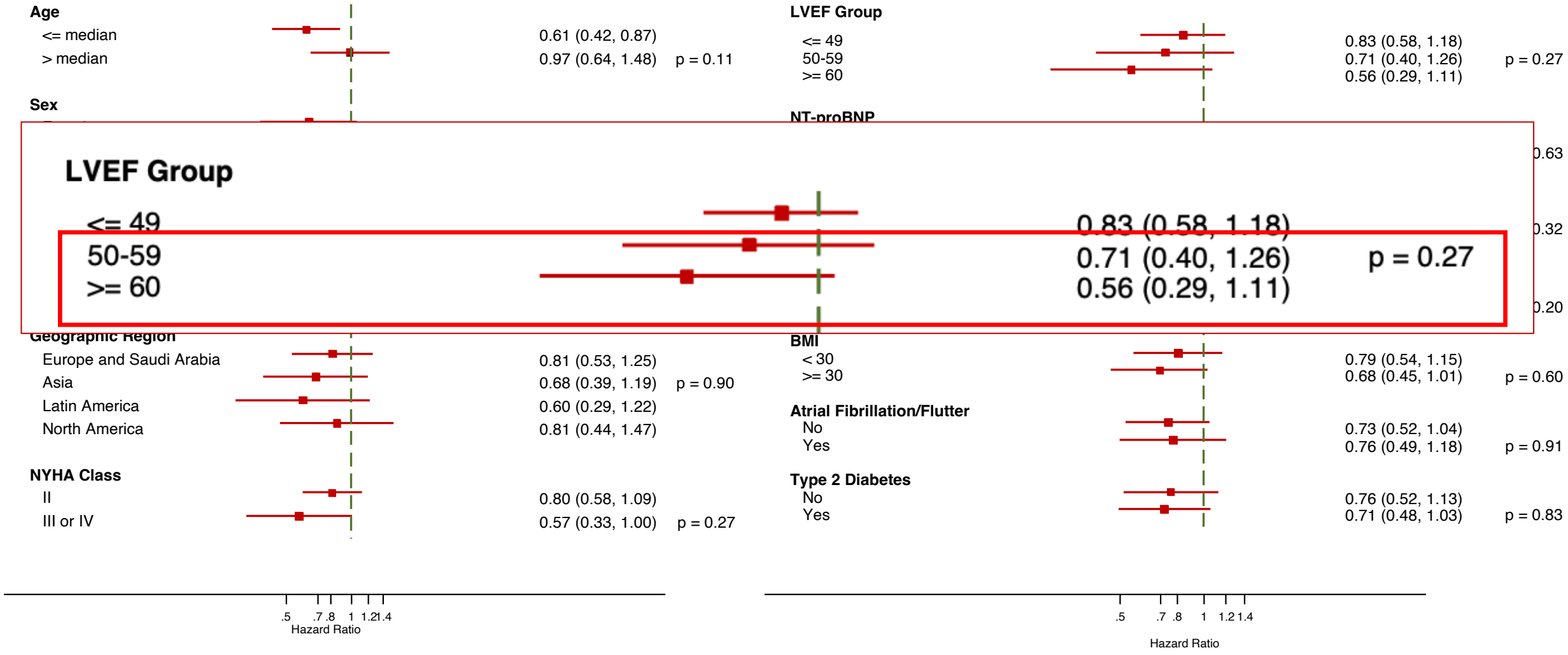
Cardiovascular death



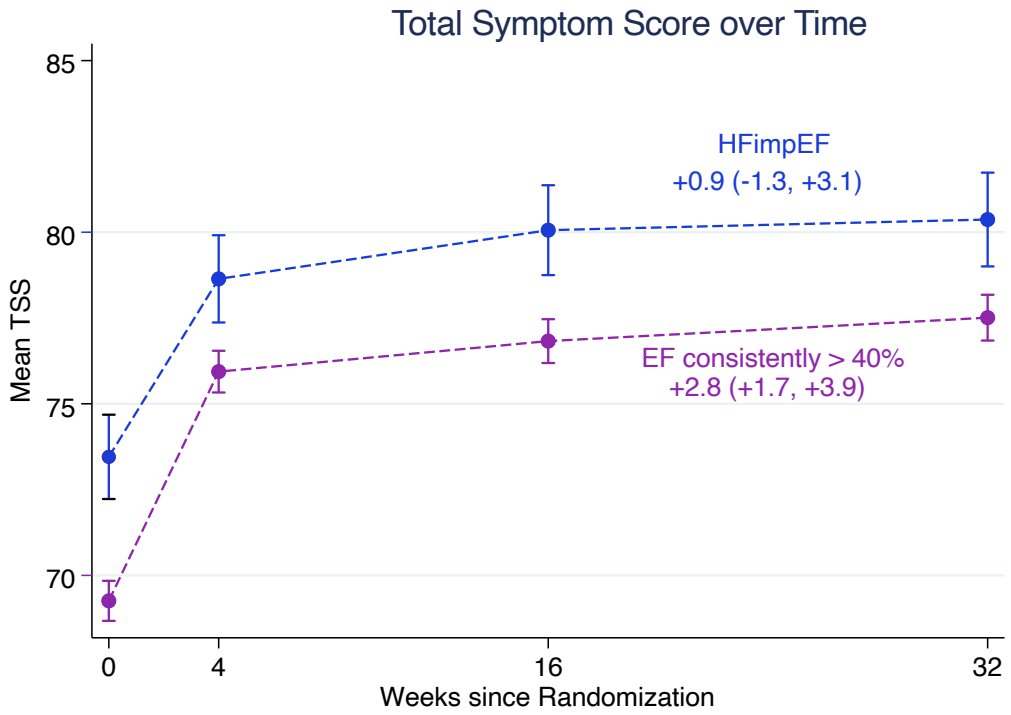
Primary and Secondary Endpoints by HFimpEF Status

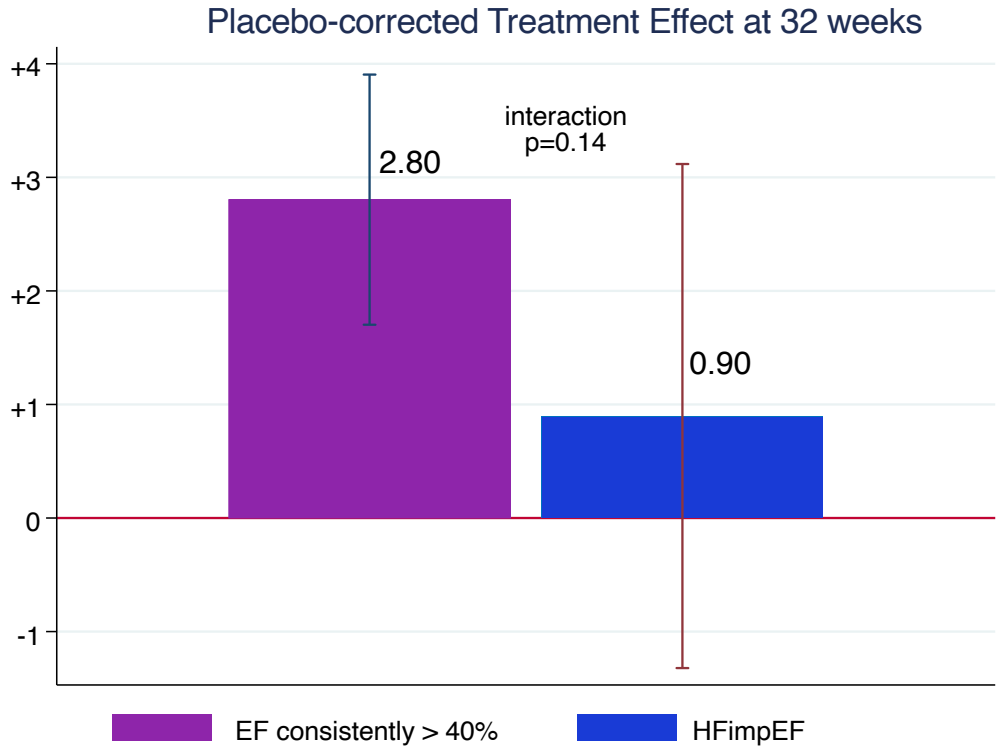


Primary Endpoint by Prespecified Subgroups in Patients with HFimpEF



Change in Total Symptom Score from Baseline to 32 Weeks in Patients with HFimpEF





Adverse Events

Safety Outcomes	HFimpEF N=1151		EF consistently > 40% N=5112	
	Dapa N=572	Placebo N=579	Dapa N=2559	Placebo N=2553
Any SAE	247 (43.2%)	273 (47.3%)	1114 (43.6%)	1150 (45.1%)
Any AE leading to treatment discontinuation	36 (6.3 %)	38 (6.6 %)	146 (5.7 %)	143 (5.6 %)
Any AE leading to treatment interruption	79 (13.8%)	92 (15.9%)	357 (14.0%)	402 (15.8%)
Any amputation	5 (0.9 %)	7 (1.2 %)	14 (0.5 %)	18 (0.7 %)
Any definite or probable diabetic ketoacidosis	0 (0.0 %)	0 (0.0 %)	2 (0.1 %)	0 (0.0 %)
Any major hypoglycemic event	1 (0.2 %)	1 (0.2 %)	5 (0.2 %)	6 (0.2 %)
Events related to volume depletion	10 (1.7 %)	8 (1.4 %)	32 (1.3 %)	24 (0.9 %)
Renal Events	14 (2.4 %)	16 (2.8 %)	59 (2.3 %)	63 (2.5 %)

Conclusions

- Despite previous improvement in LVEF, patients with HFimpEF in DELIVER encountered heightened risks of disease progression including worsening HF events and death, which were comparable to those who have had LVEF consistently over 40%.
- In patients enrolled in the DELIVER study who had HFimpEF, dapagliflozin compared with placebo reduced the composite of cardiovascular death or worsening heart failure to a similar extent as patients with LVEF consistently over 40%
- These data are the largest randomized data of this population and suggest that patients with HFimpEF who remain symptomatic may benefit from the addition of a SGLT2 inhibitor to previously instituted GDMT to further reduce morbidity and mortality

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