Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction
The DELIVER Trial

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

HARVARD MEDICAL SCHOOL

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Background and Rationale

- SGLT2 inhibitors reduce morbidity and mortality in patients with heart failure and reduced ejection fraction (left ventricular ejection fraction ≤ 40%) and their use is strongly recommended in current clinical practice guidelines.
- Few pharmacologic treatment options are available for patients with heart failure with mildly reduced or preserved ejection fraction, representing about half of all our patients with heart failure.
- The EMPEROR-Preserved trial demonstrated reduction in cardiovascular death or heart failure hospitalization with empagliflozin in this population.
- Uncertainty remains regarding efficacy in several groups:
  - Those in the highest part of the ejection fraction range, where there has been concern about attenuation of the treatment effect
  - Those initiated on treatment during or soon after hospitalization, where limited data are available
  - Those with a previously reduced ejection fraction that has improved to > 40%, a group that has been excluded from prior trials

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

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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

Endpoints and Analysis Plan

Dual Primary Endpoints – Full Population and Patients with LVEF < 60%

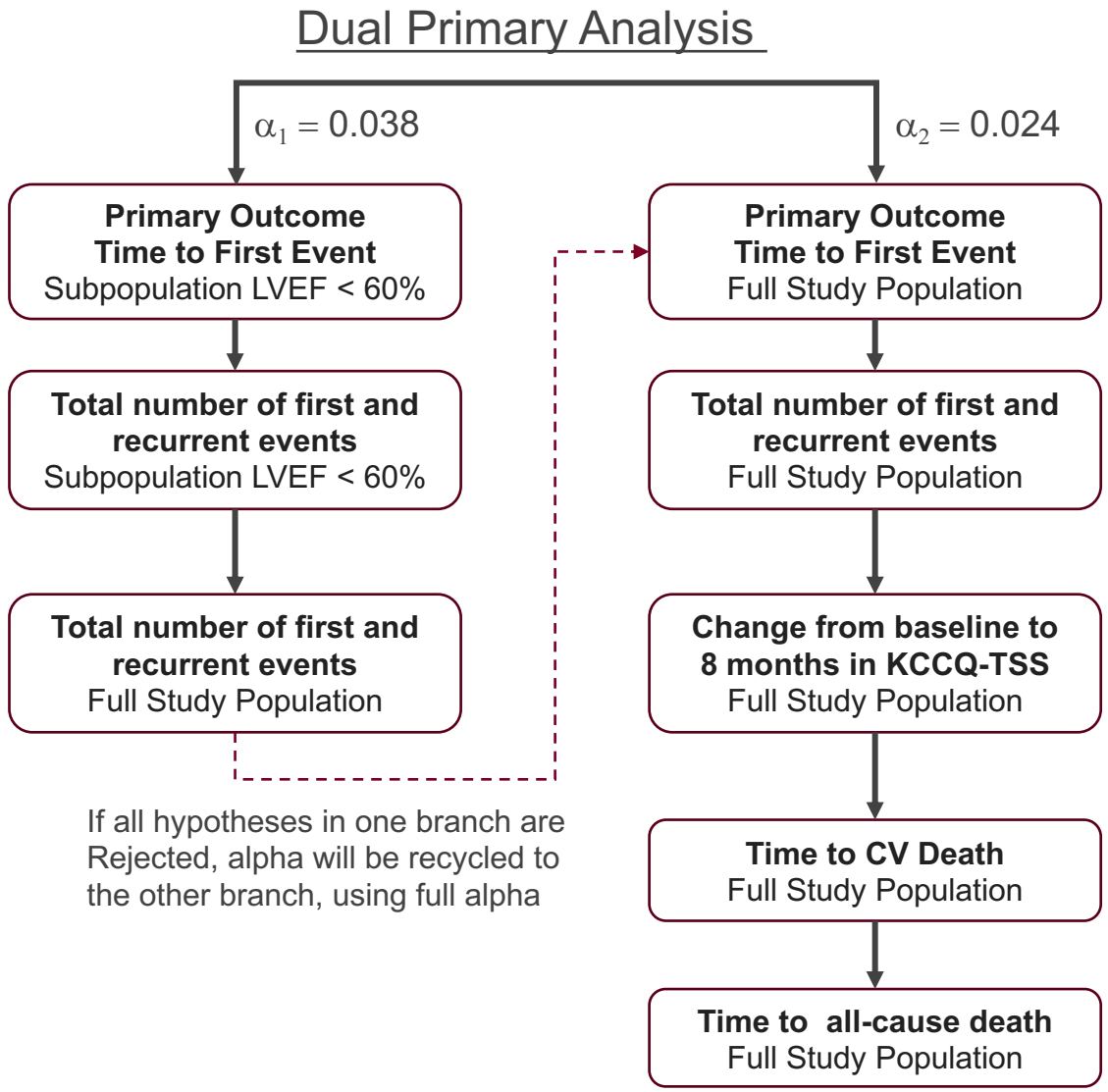
Primary Endpoint

Time to first Composite of

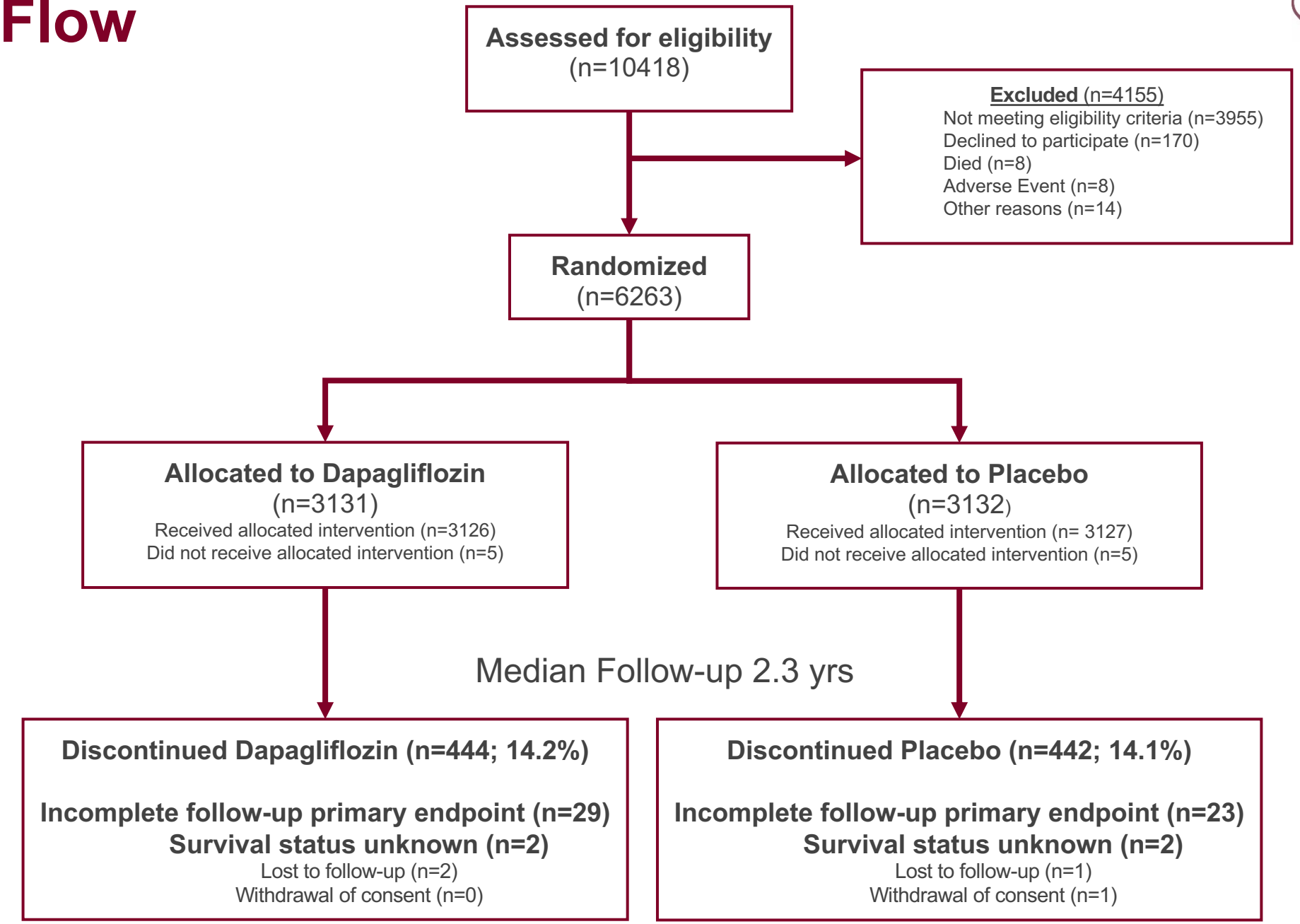
- **CV death or**
- **Worsening Heart Failure (HF Hospitalization or Urgent HF Visit)**

Secondary Endpoints

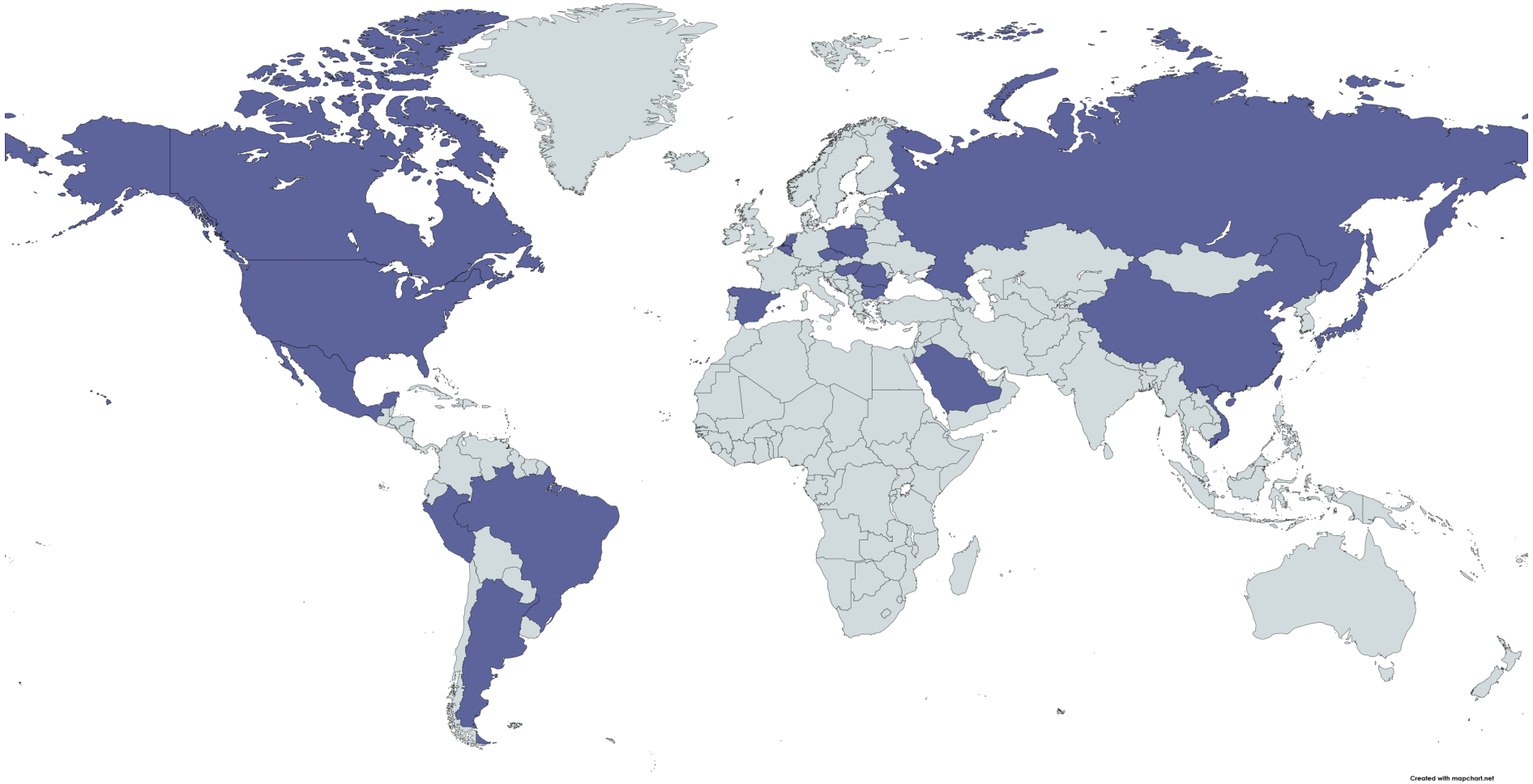
- **Total HF Events + CV Death (both populations)**
- **Change in KCCQ TSS at 8 months (full)**
- **CV Death (full)**
- **All-Cause Death (full)**



Patient Flow



Global Randomization Across 350 Sites in 20 Countries



Country	Enrollment (# of Patients)
Poland	572
USA	552
Bulgaria	493
Hungary	466
Japan	422
Brazil	405
Russia	401
Argentina	320
Taiwan	318
China	310
Spain	308
Canada	299
Czech Republic	274
Peru	240
Mexico	216
Saudi Arabia	190
Netherlands	176
Vietnam	176
Belgium	64
Romania	61

DELIVER Baseline Characteristics

Well Balanced Between Treatment Groups

	Dapagliflozin N=3131	Placebo N=3132
Age (years)	71.8 ± 9.6	71.5 ± 9.5
Female Sex	43.6%	44.2%
Baseline LVEF (%)	54.0 ± 8.6	54.3 ± 8.9
LVEF < 60%	70.3%	69.3%
HF with Improved EF (Prior LVEF ≤ 40%)	18.3%	18.5%
Race		
White	70.7%	71.0%
Black	2.6%	2.5%
Asian	20.1%	20.6%
Other	6.6%	5.9%
Geographic Region		
Europe and Saudi Arabia	47.7%	48.2%
Asia	19.4%	19.8%
Latin America	19.2%	18.5%
North America	13.7%	13.5%
NYHA Class at Baseline		
II	73.9%	76.6%
III/IV	26.1%	23.4%
KCCQ Total Symptom Score	70 ± 23	70 ± 22

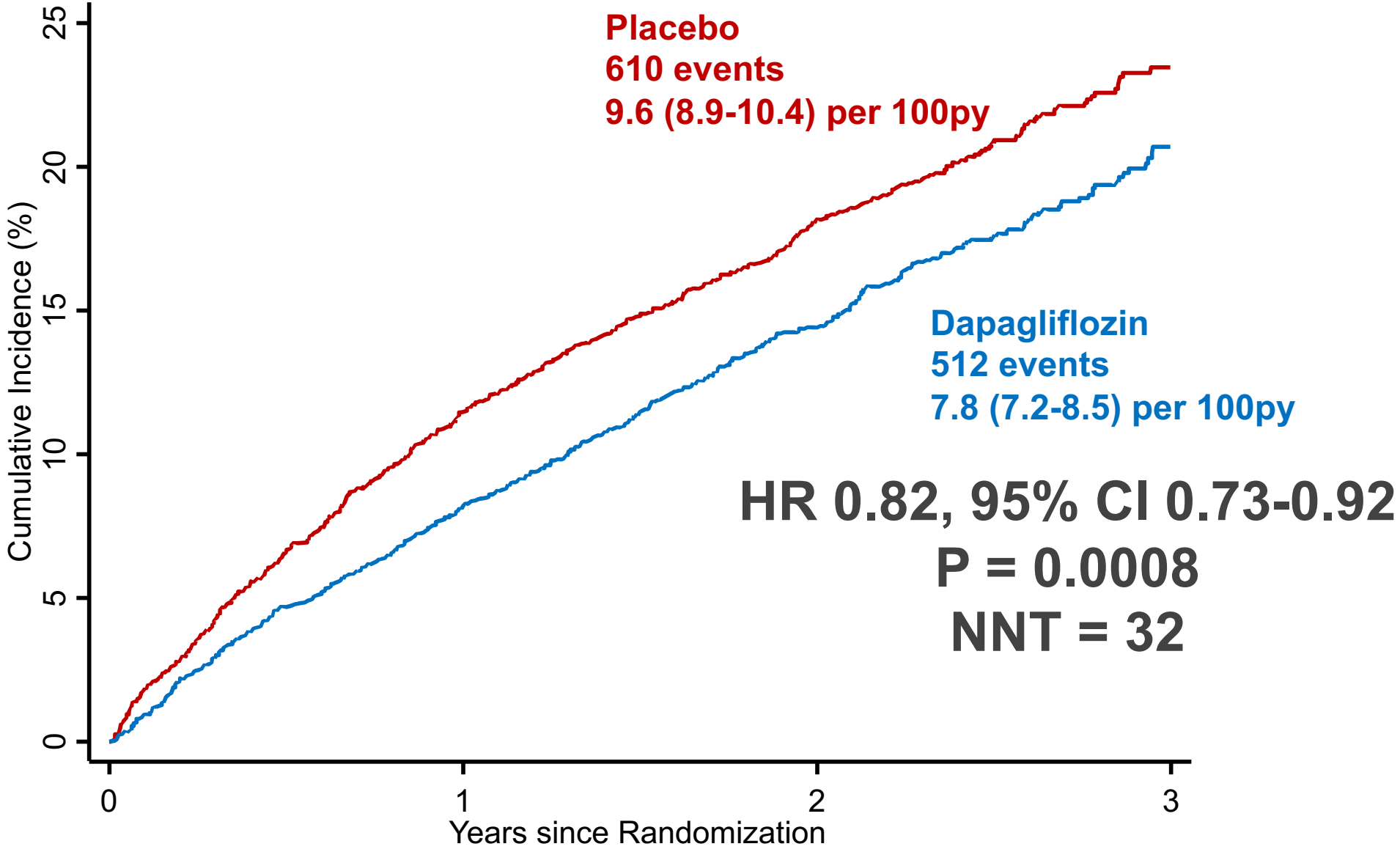
DELIVER Baseline Characteristics (2)

Well Balanced Between Treatment Groups

	Dapagliflozin N=3131	Placebo N=3132
NT-proBNP when no AFF (ECG) (pg/ml)	729 [472, 1299]	704 [467, 1265]
NT-proBNP in AFF (ECG) (pg/ml)	1408 [956, 2256]	1387 [966, 2180]
Prior HF Hospitalization	40.6%	40.5%
Atrial Fibrillation/Flutter at Enrollment	42.4%	42.1%
Type 2 Diabetes	44.7%	44.9%
eGFR (mL/min/1.73m^2)	61.2 ± 19.0	60.9 ± 19.3
eGFR < 60 mL/min/1.73m^2	48.4%	49.6%
Medications		
Loop diuretics	76.7%	76.9%
Angiotensin converting enzyme inhibitors (ACEi)	36.5%	36.7%
Angiotensin receptor blocker (ARB)	36.2%	36.4%
Sacubitril-valsartan	5.3%	4.3%
β-blocker	82.8%	82.5%
Mineralocorticoid receptor antagonist (MRA)	42.8%	42.4%

Primary Endpoint: CV Death or Worsening HF

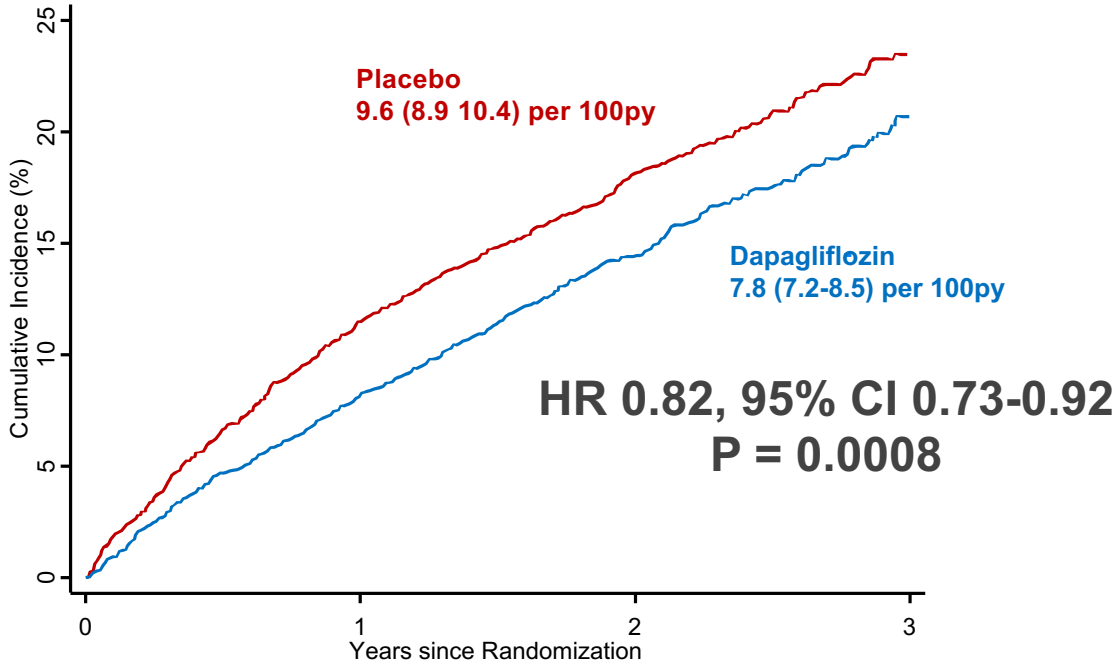
Full Population



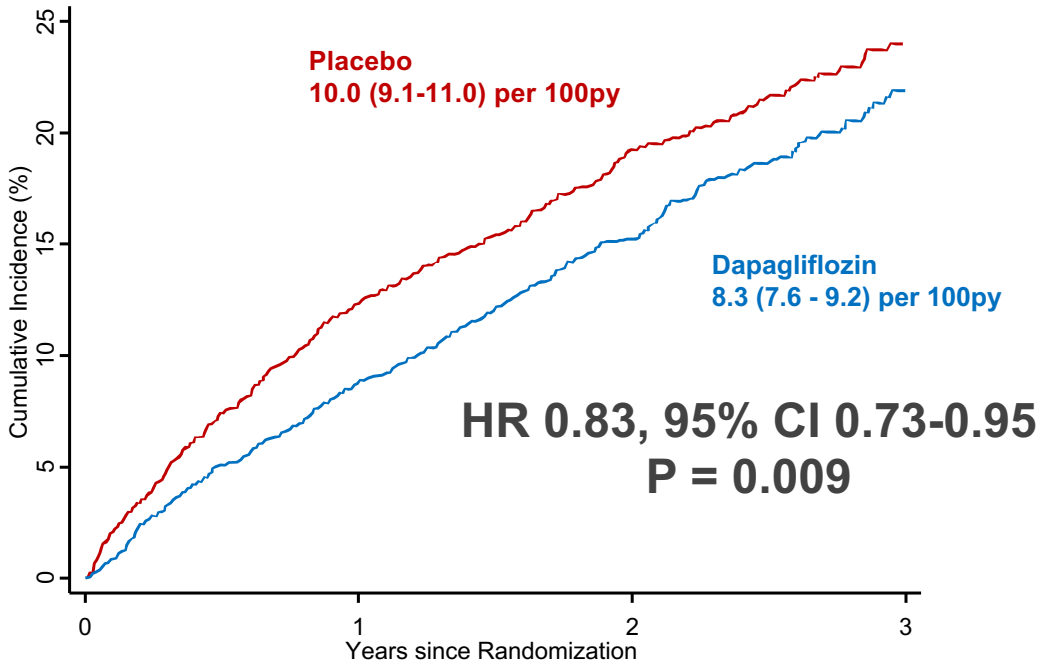
Primary Endpoint in Full Population and LVEF < 60%

Dual Primary Analyses

Full Population
N = 6263



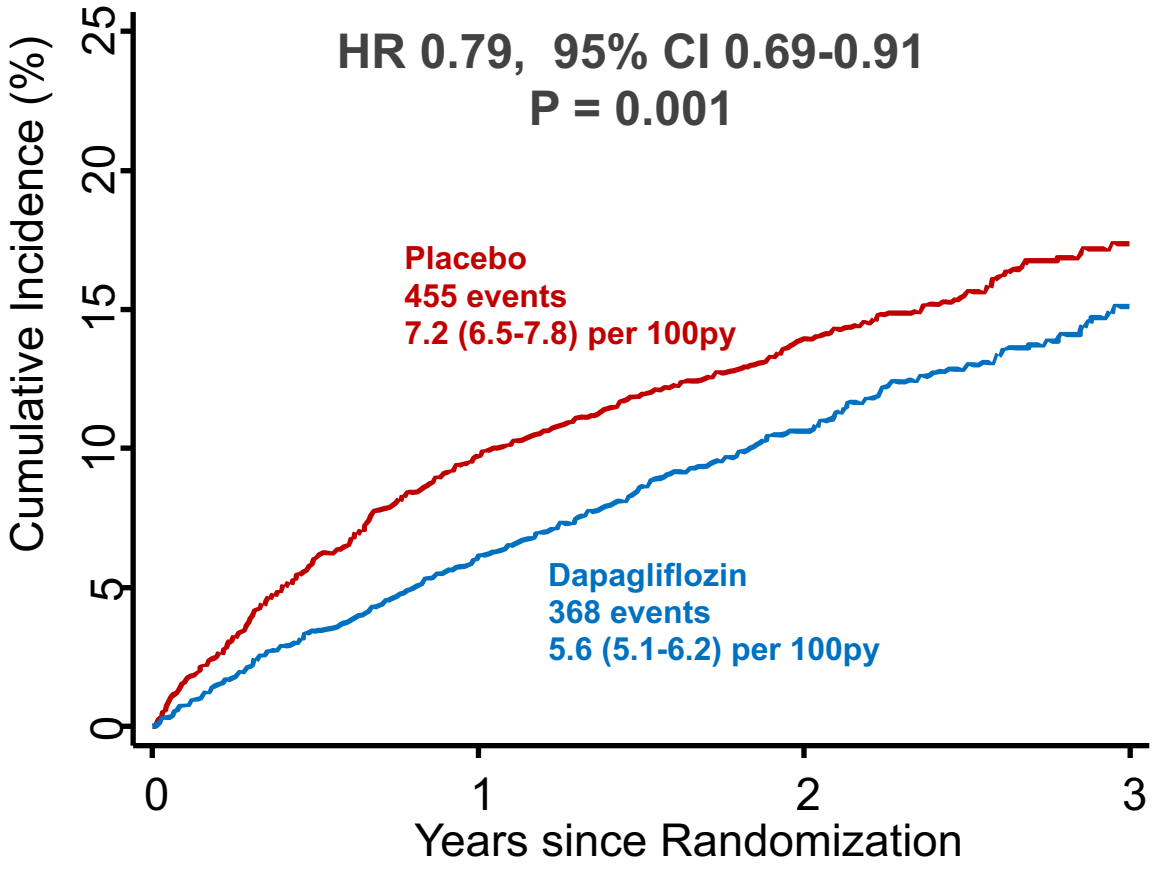
LVEF < 60%
N = 4372



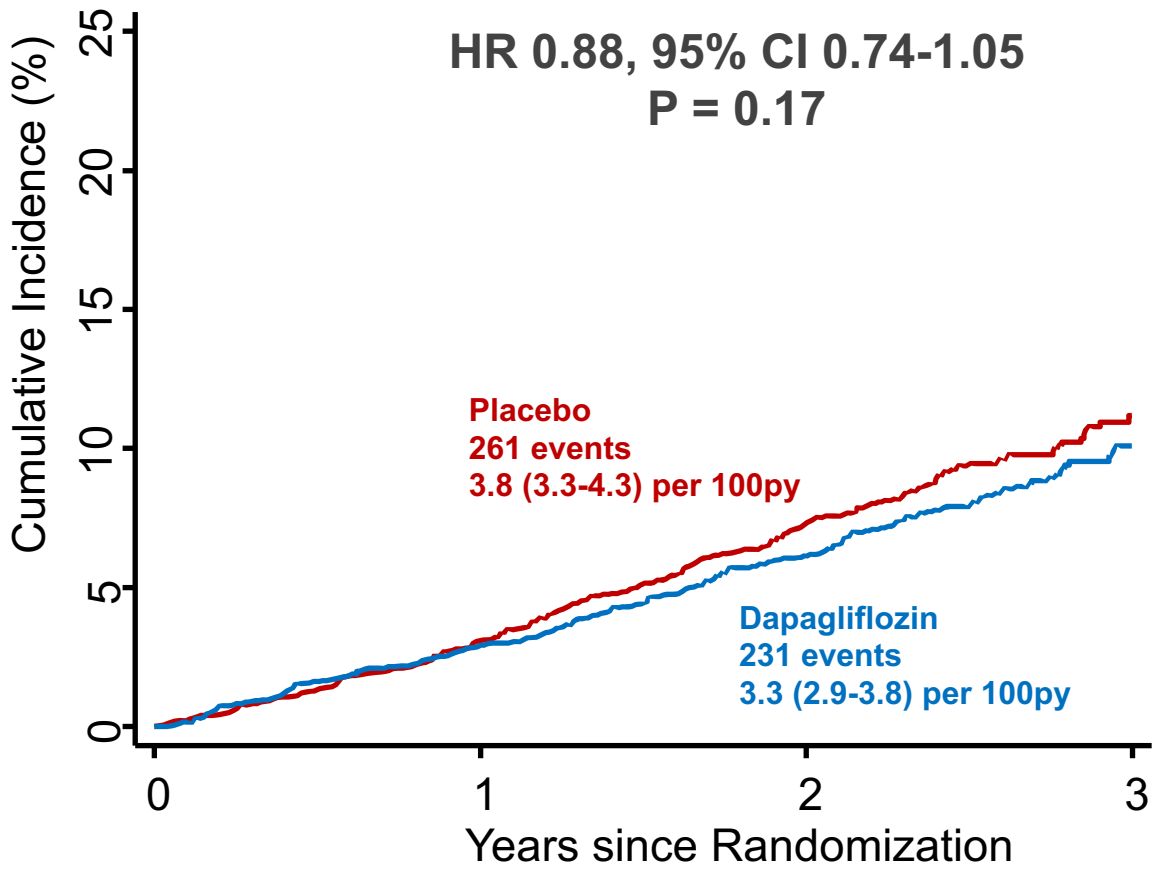
Components of Primary Endpoint

Full Population

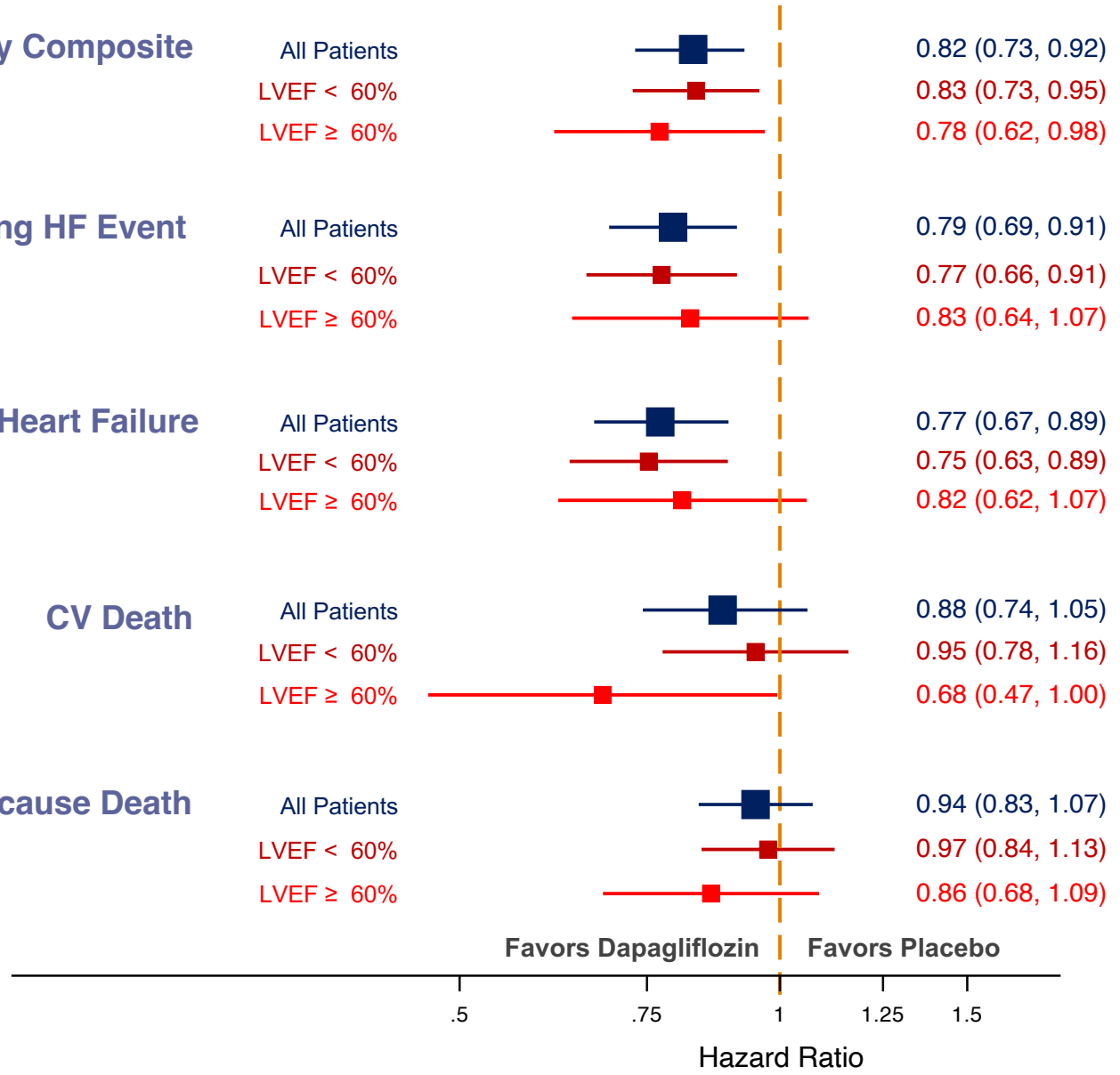
Worsening Heart Failure (HF Hospitalization + Urgent HF Visit)



Cardiovascular Death



Outcomes by LVEF < 60% or LVEF ≥ 60%

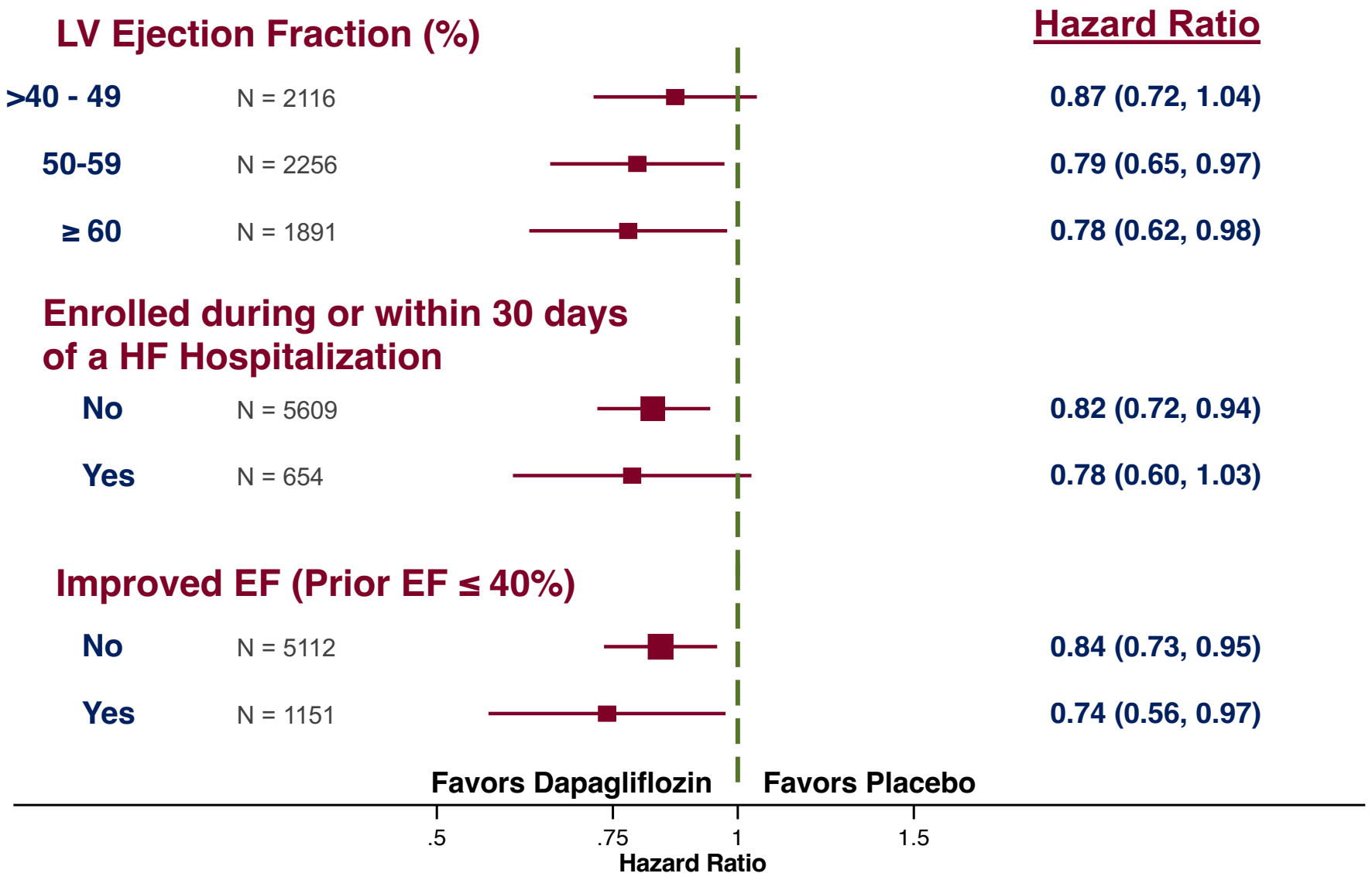


All Patients N = 6263

LVEF < 60% N = 4372 (70%)

LVEF ≥ 60% N = 1891 (30%)

Primary Endpoint in Prespecified Subgroups



Primary Endpoint in Prespecified Subgroups

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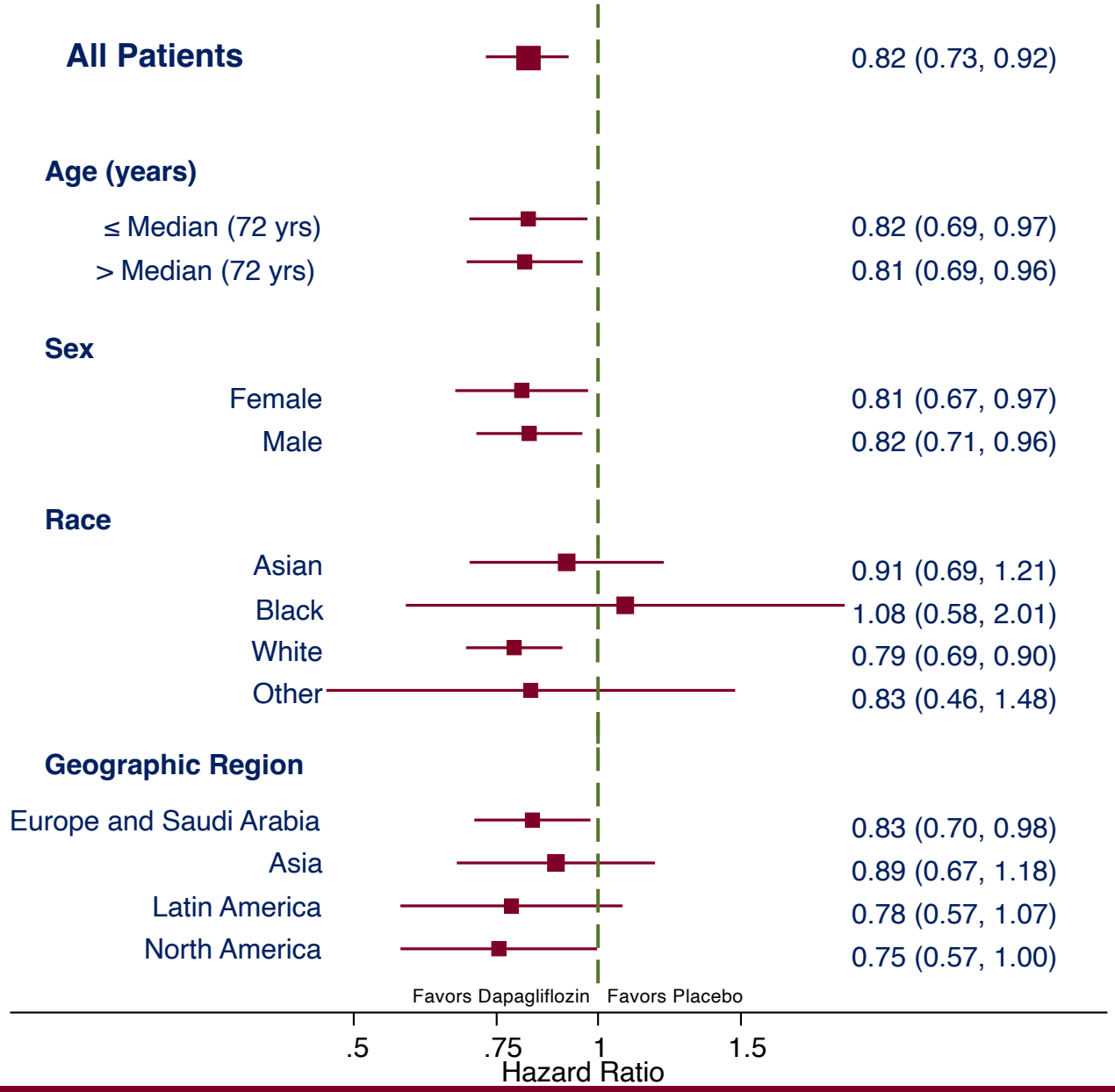
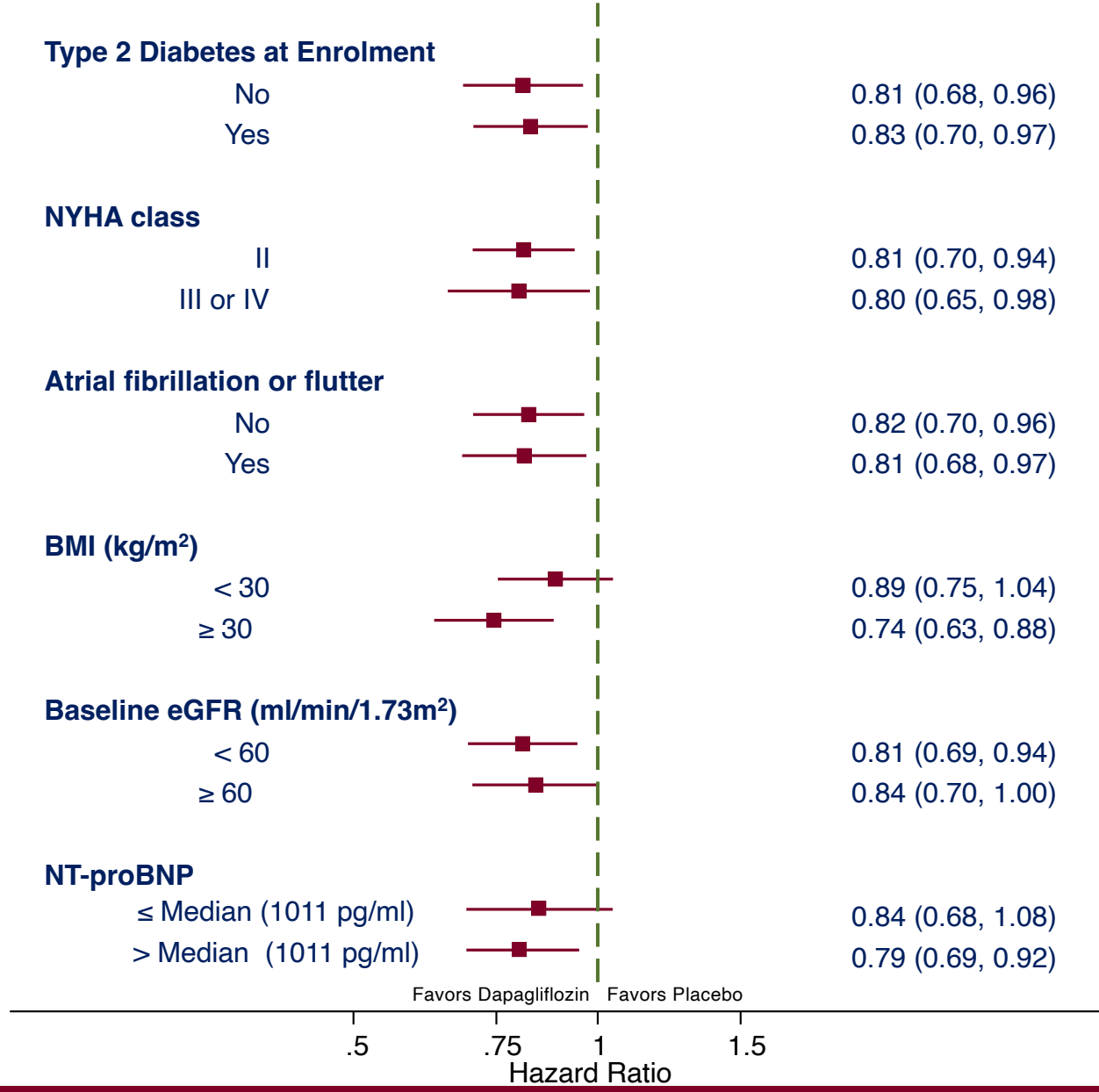
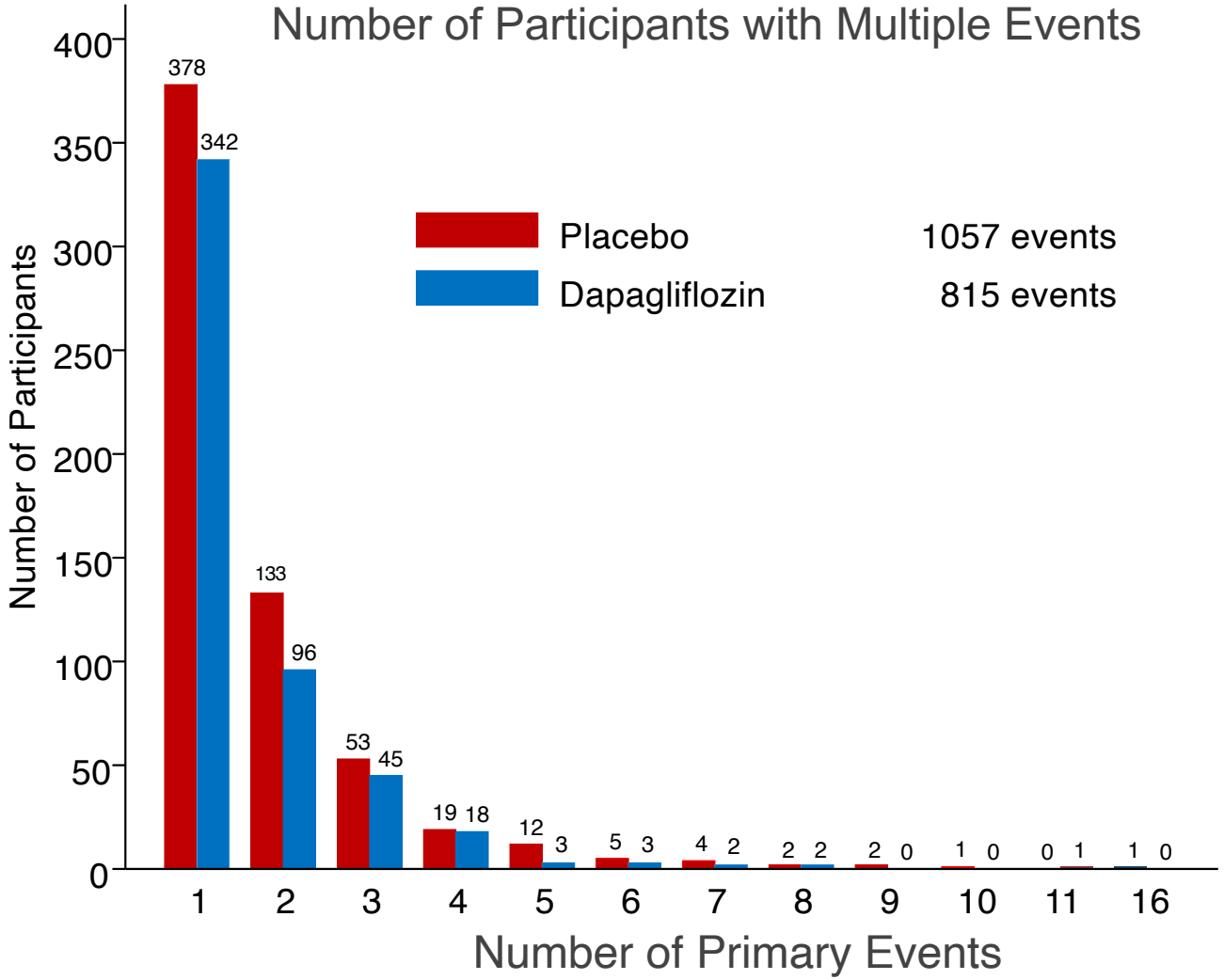
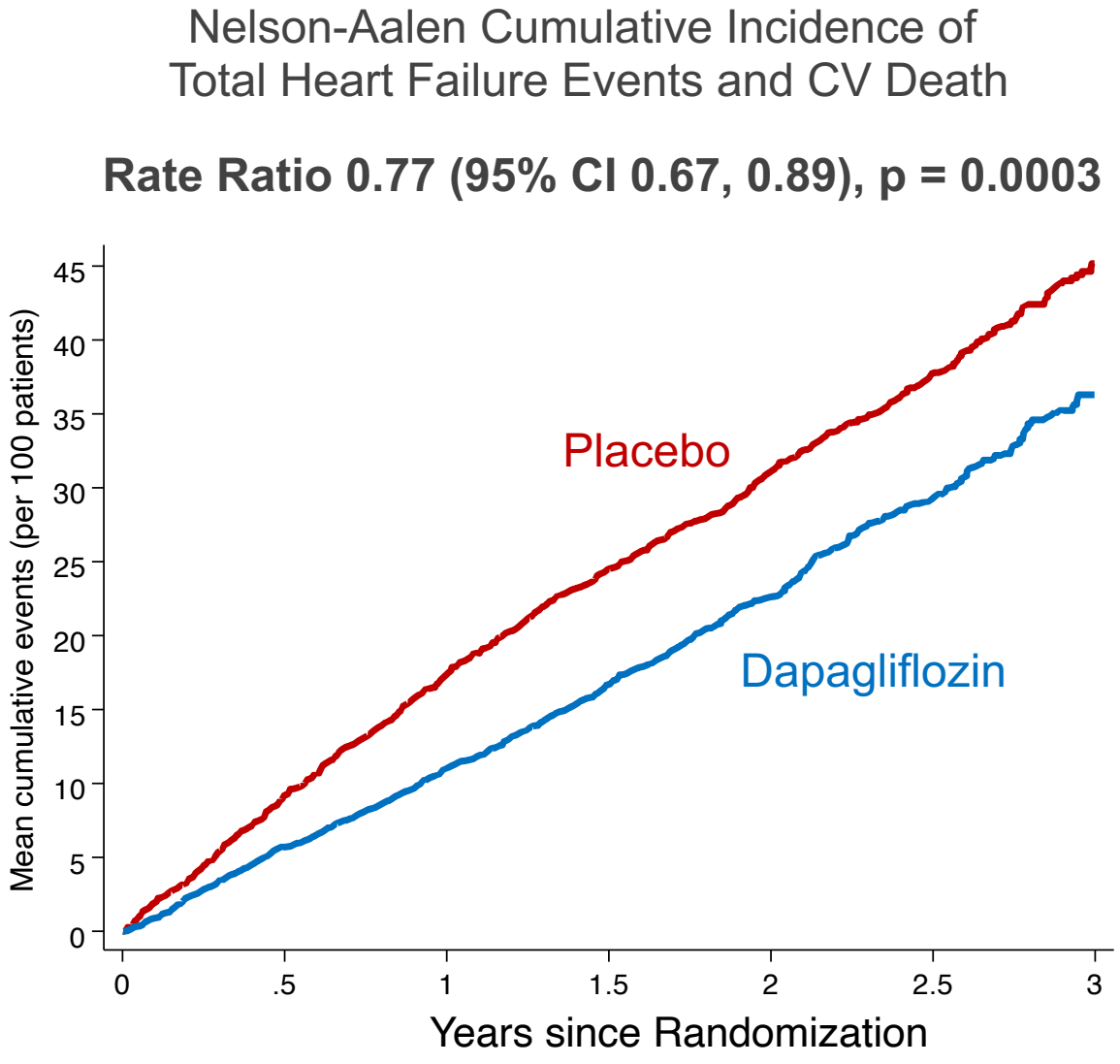




Secondary Endpoint: Total Heart Failure Events and Cardiovascular Death

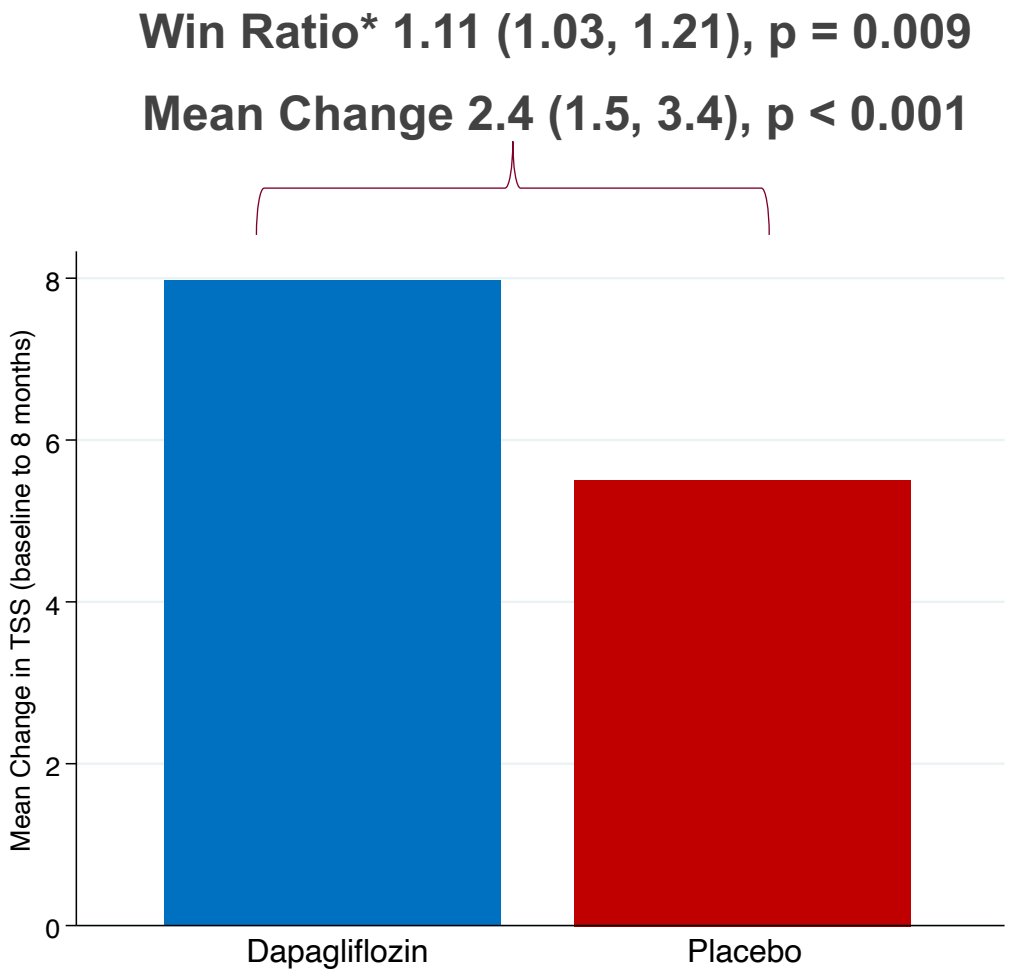
Full Population

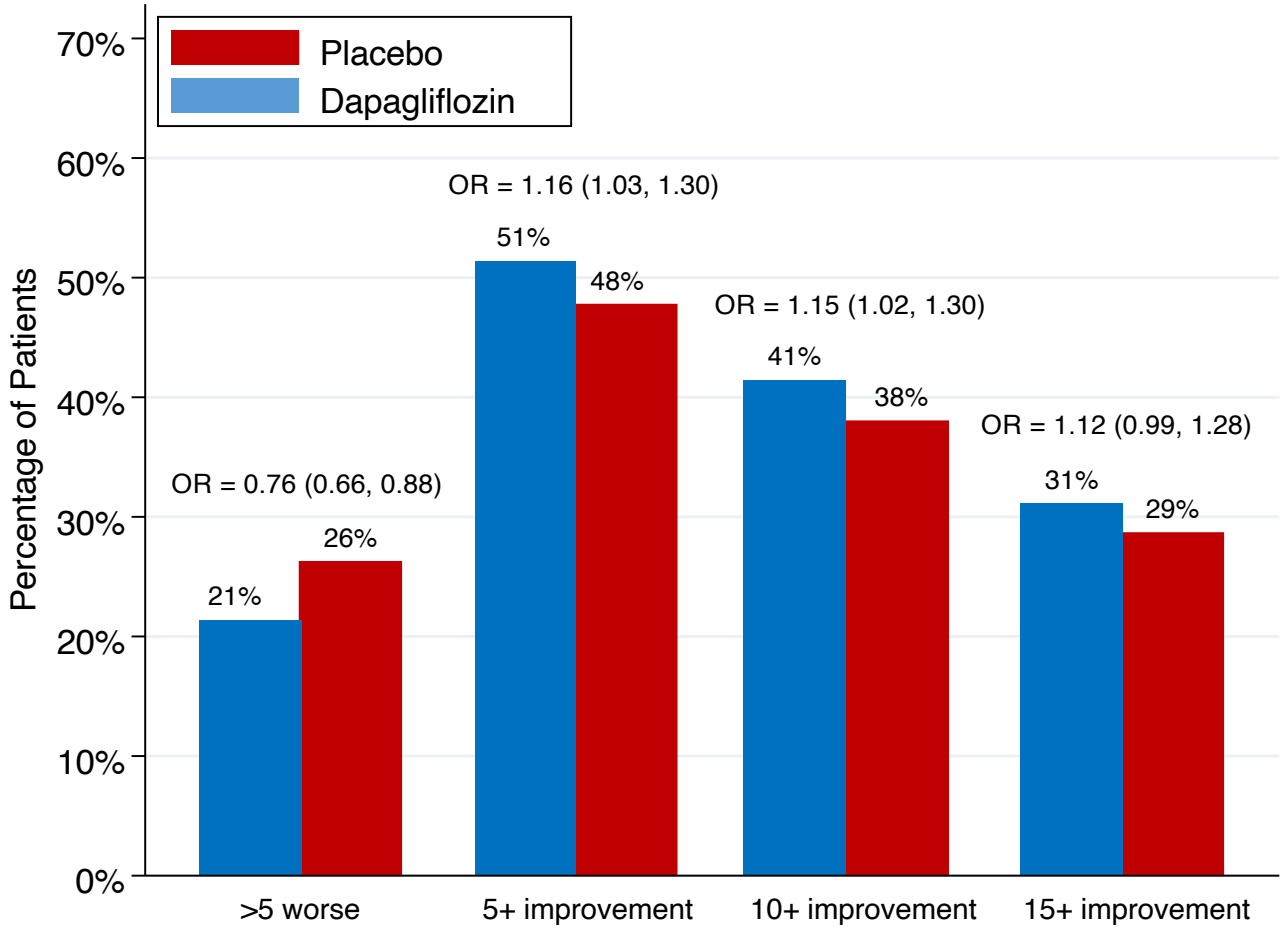




Secondary Endpoint: Improvement in KCCQ Total Symptom Score

Baseline to 8 months

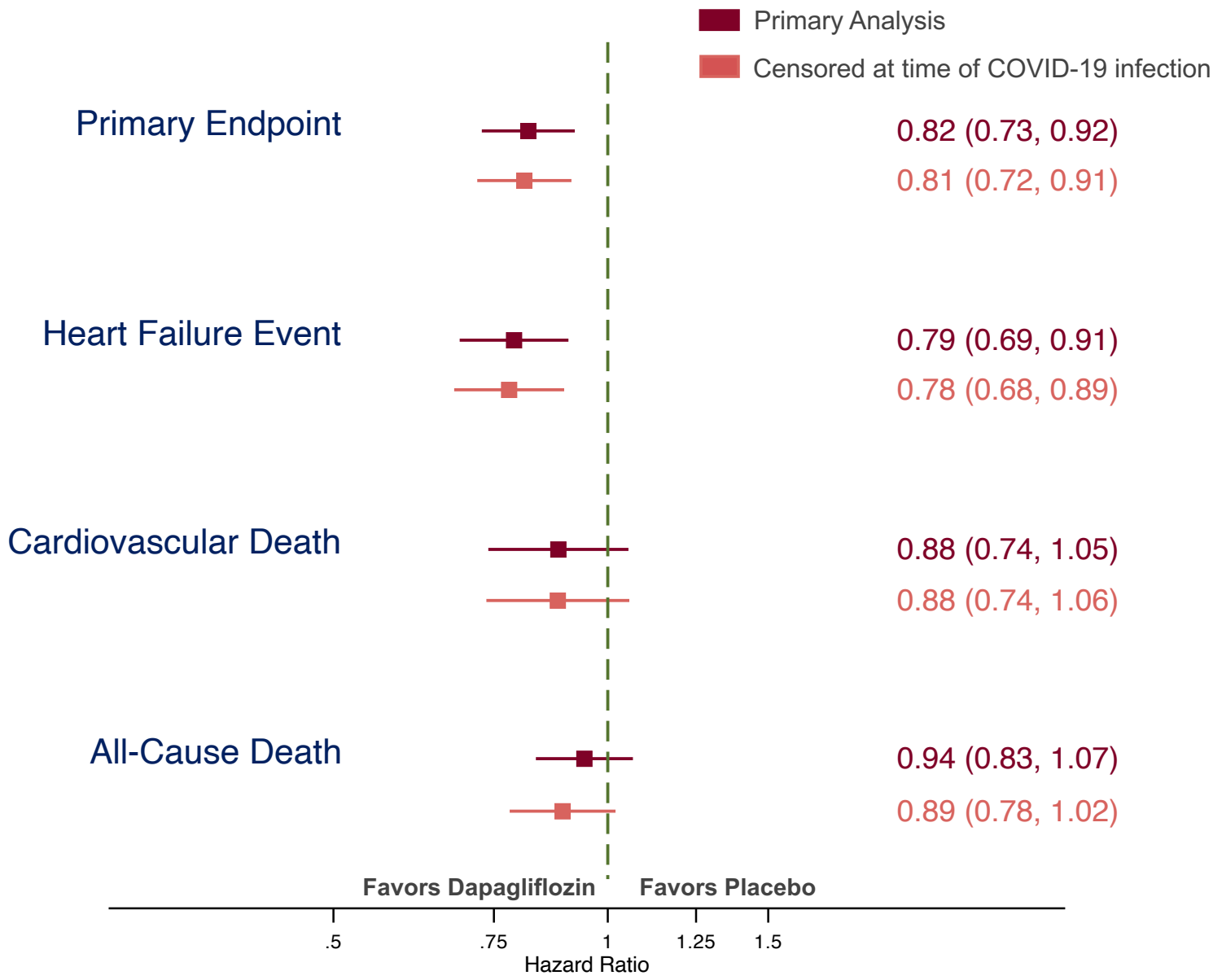




*Primary Analysis Method in patients who reached 8 months prior to COVID-19 Pandemic

COVID-19 Sensitivity Analysis

589 patients diagnosed with COVID-19, 155 COVID-19 Deaths



Adverse Events*

AE data collection of Serious Adverse Events, Adverse Events leading to treatment discontinuation and other selected adverse events

	Dapagliflozin* n=3126	Placebo* n=3127
Any SAE (including death)	1361 (43.5%)	1423 (45.5%)
Any AE leading to treatment discontinuation	182 (5.8%)	181 (5.8%)
Any AE leading to treatment interruption	436 (13.9%)	494 (15.8%)
Any amputation	19 (0.6%)	25 (0.8%)
Any definite or probable diabetic ketoacidosis	2 (0.1%)	0 (0.0%)
Any major hypoglycemic event	6 (0.2%)	7 (0.2%)
Events related to volume depletion	42 (1.3%)	32 (1.0%)
Renal Events	73 (2.3%)	79 (2.5%)

*On treatment (in patients receiving at least one dose and up to 30 days following last dose of IP)

Conclusions

- In the largest and most inclusive trial of patients with heart failure and mildly reduced or preserved ejection fraction, treatment with dapagliflozin reduced the risk of the primary composite outcome of cardiovascular death or worsening heart failure.
- Dapagliflozin reduced all components of the composite, total heart failure events, and resulted in improvement in symptom burden as measured by KCCQ-total symptom score.
- These findings were consistent across prespecified subgroups, including those defined according to left ventricular ejection fraction, with no attenuation in the highest LVEF group.
- Dapagliflozin was as effective in patients with recent HF hospitalization, and in those with prior reduced ejection fraction that had improved to over 40%.
- Serious adverse events and adverse events leading to discontinuation were similar between dapagliflozin and placebo.

These data provide further evidence to support the use of an SGLT2 inhibitor as foundational therapy in patients with heart failure, regardless of care setting or ejection fraction

Steering Committee

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ORIGINAL ARTICLE

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