First and Repeat Episodes of Worsening Heart Failure in Patients With Heart Failure With Mildly Reduced and Preserved Ejection Fraction: An Analysis of DELIVER

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DELIVER

Disclosures

- Speakers Fees –AstraZeneca, Novartis, Alkem Metabolics, ProAdWise Communications, Sun Pharmaceuticals
- Advisory Board – AstraZeneca, Boehringer Ingelheim, Novartis
- Research Funding – AstraZeneca, Boehringer Ingelheim, Analog Devices Inc

- My employer, the University of Glasgow, has been remunerated for my time working on clinical trials by AstraZeneca, Bayer AG, Novartis and NovoNordisk

DELIVER recurrent events: Background

- When added to standard therapy, the SGLT2 inhibitor, dapagliflozin, reduced the risk of first of worsening heart failure (HF) or cardiovascular (CV) death in patients with HF and a mildly reduced or preserved ejection fraction (HFmrEF/HFpEF) in the DELIVER trial
- However, in patients with heart failure the risk of death decreases as ejection fraction increases but the risk of hospitalization for heart failure remains static
- Therefore, repeat hospitalizations account for a greater burden of disease in patients with HFmrEF/HFpEF

Aim

- In this pre-specified analysis of the DELIVER trial we examined the effect of the SGLT2 inhibitor dapagliflozin on total i.e. first and repeat heart failure events (hospitalizations for heart failure and urgent visits for heart failure) and cardiovascular death

DELIVER Study Design

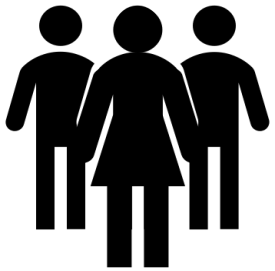
Randomized, double-blind, placebo-controlled trial testing the hypothesis that dapagliflozin would reduce cardiovascular death or worsening heart failure in patients with heart failure and mildly reduced or preserved ejection fraction

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 Either Ambulatory or Hospitalized for Heart Failure

N=6,263

Double-blind treatment period



Dapagliflozin 10mg once daily

Placebo

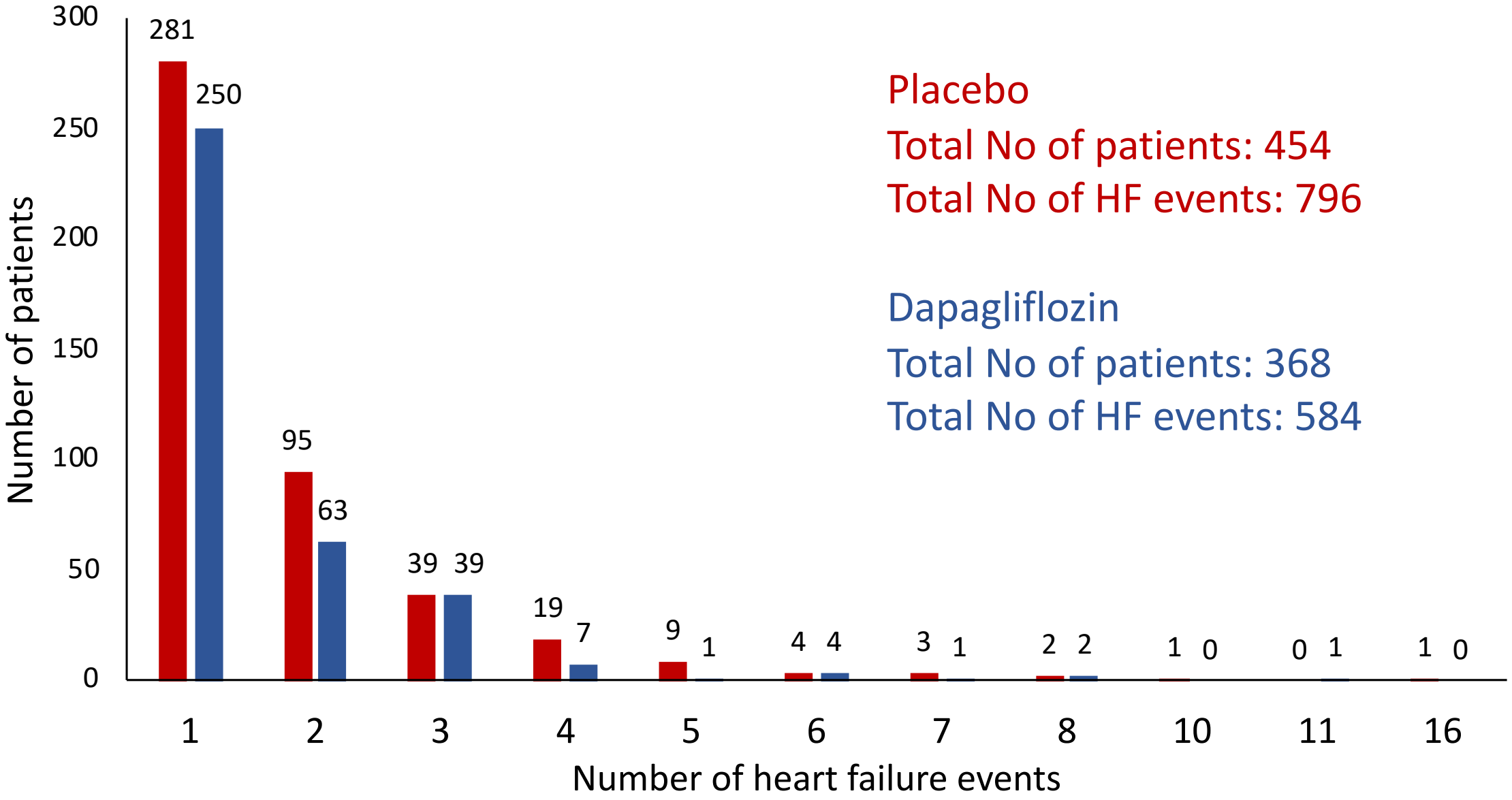
Primary outcome: Time to first Worsening HF event or CV death

Solomon et al. Eur J Heart Fail 2021

DELIVER recurrent events: Methods

- The pre-defined endpoint was total (first and repeat) worsening episodes of heart failure and CV deaths
- The first pre-specified method used was the semiparametric proportional-rates model described by Lin Wei Yang Ying (LWYY)
- The second pre-specified method used was a joint frailty model
- Total HF events were plotted over time allowing for cardiovascular death as the terminal event following the approach of Ghosh and Lin

Number of heart failure events by randomized therapy



Baseline characteristics by number of repeat HF events

	No HF events	1 HF event	≥2 HF events	p-value
	N=5,441	N=531	N=291	
Age (years), mean (SD)	71±9	71±9	72±10	0.061
Sex, (%)				0.080
Men	56%	59%	61%	
Race, (%)				<0.001
White	70%	76%	72%	
Black or African American	2%	3%	5%	
Asian	20%	20%	23%	
Other	7%	2%	1%	
Geographic region, (%)				<0.001
Europe and Saudi Arabia	48%	50%	50%	
Asia	20%	19%	22%	
Latin America	20%	12%	6%	
North America	13%	19%	23%	

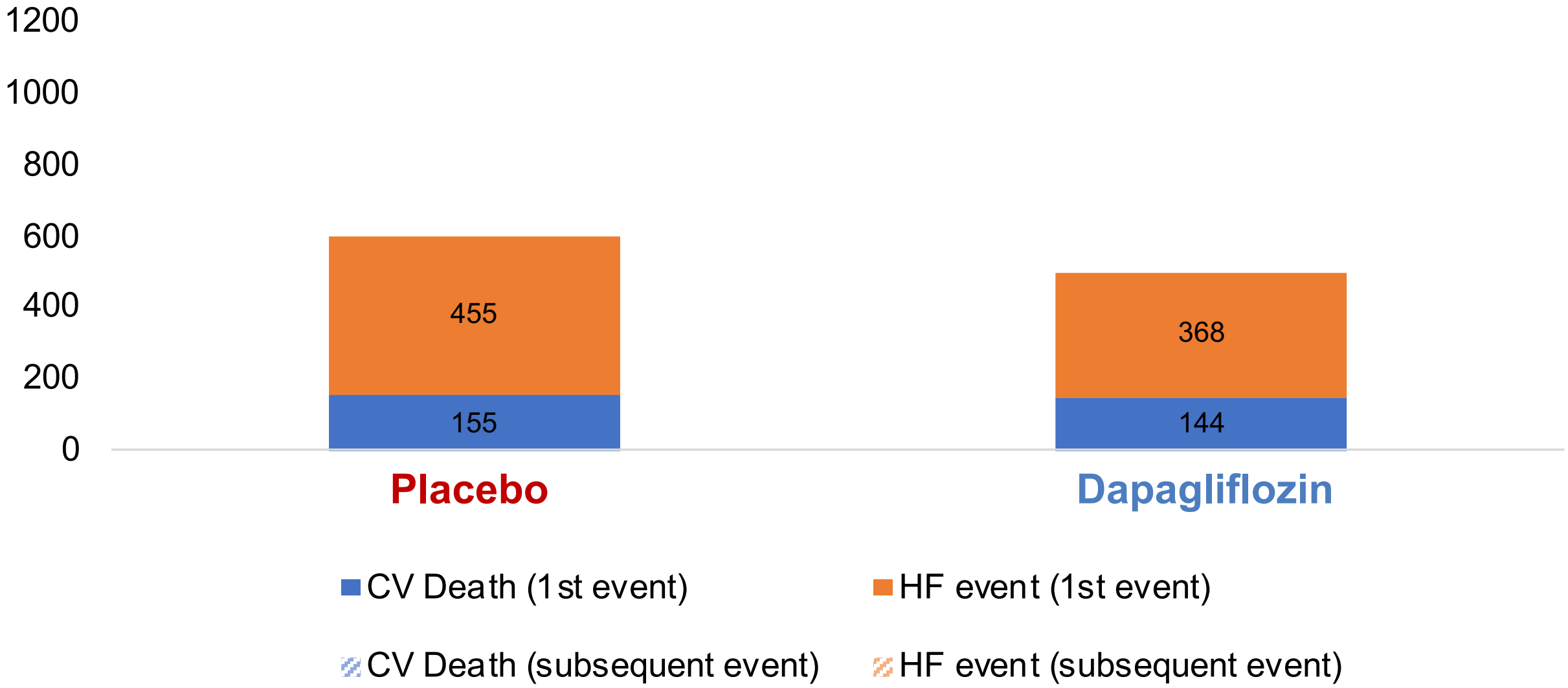
Baseline characteristics by number of repeat HF events

	No HF events	1 HF event	≥2 HF events	p-value
	N=5,441	N=531	N=291	
Systolic blood pressure (mmHg), mean (SD)	128±15	128±16	129±17	0.66
Heart rate (bpm), mean (SD)	71±12	73±12	73±12	<0.001
Body mass index, mean (SD)	30±6	30±7	31±6	<0.001
NT-proBNP (pg/mL), median (IQR)	961 (602-1644)	1433 (800-2695)	1500 (839-2618)	<0.001
eGFR (mL/min/1.73m^2), mean (SD)	62±19	58±20	54±19	<0.001
Prior LVEF Measurement ≤40%	18%	20%	19%	0.54
Randomized during or within 30 days of a heart failure hospitalization	9%	18%	21%	<0.001
LVEF (%), mean (SD)	54±9	54±9	54±8	0.26
NYHA class, (%)				<0.001
I, II	77%	67%	65%	
III, IV	23%	33%	35%	
KCCQ total symptom score, median (IQR)	72.9 (56.3-88.5)	67.7 (50.0-83.3)	66.7 (46.9-83.3)	<0.001

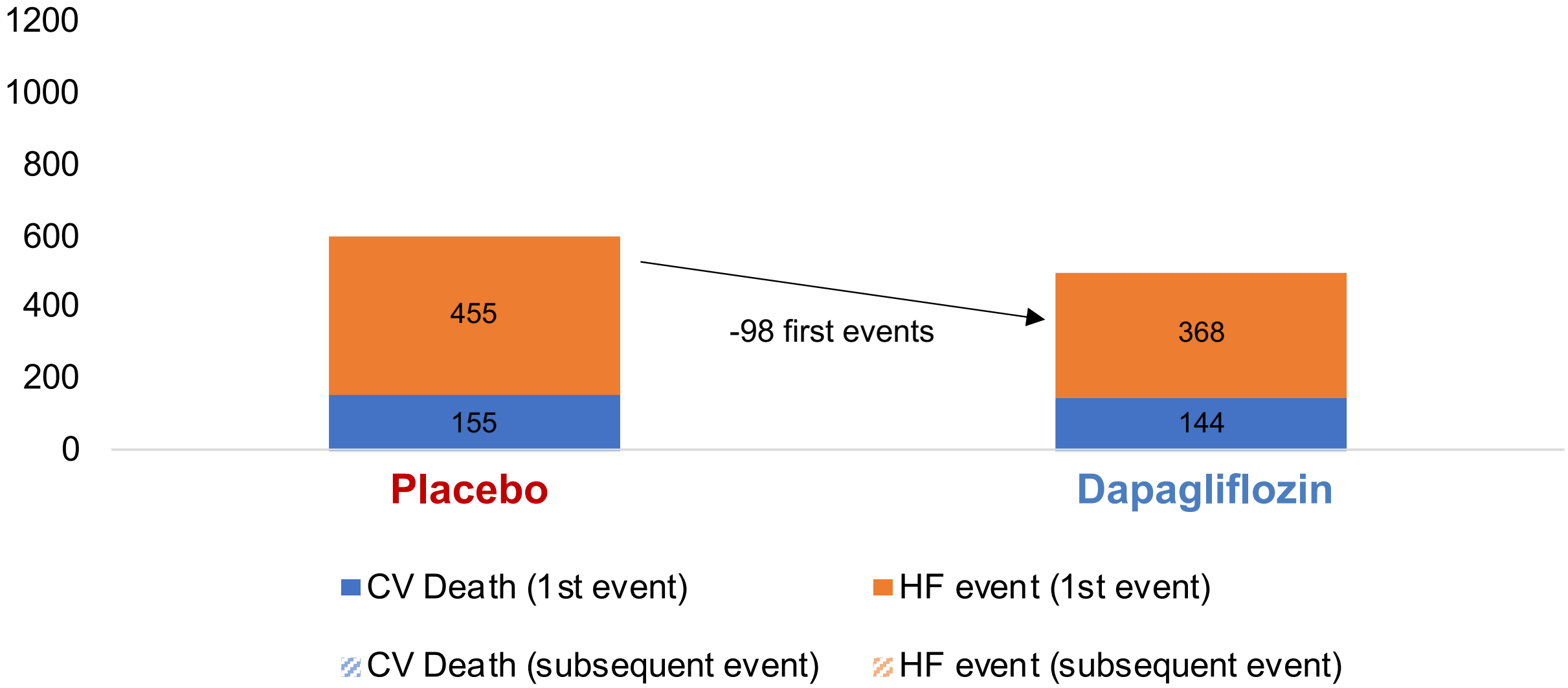
Baseline characteristics by number of repeat HF events

	No HF events	1 HF event	≥2 HF events	p-value
	N=5,441	N=531	N=291	
Hospitalization for HF	38%	55%	62%	<0.001
Atrial fibrillation/flutter	56%	64%	65%	<0.001
Myocardial infarction	26%	27%	28%	0.75
Type 2 diabetes mellitus	44%	52%	55%	<0.001
Loop diuretic	75%	88%	89%	<0.001
ACEI/ARB	73%	72%	65%	0.005
ARNI	5%	6%	8%	0.052
Beta-blocker	83%	79%	81%	0.063
MRA	43%	44%	39%	0.46
Anticoagulant	53%	61%	61%	<0.001
Pacemaker	10%	11%	18%	<0.001
CRT-P/CRT-D	2%	1%	3%	0.028
ICD/CRT-D	3%	4%	4%	0.069

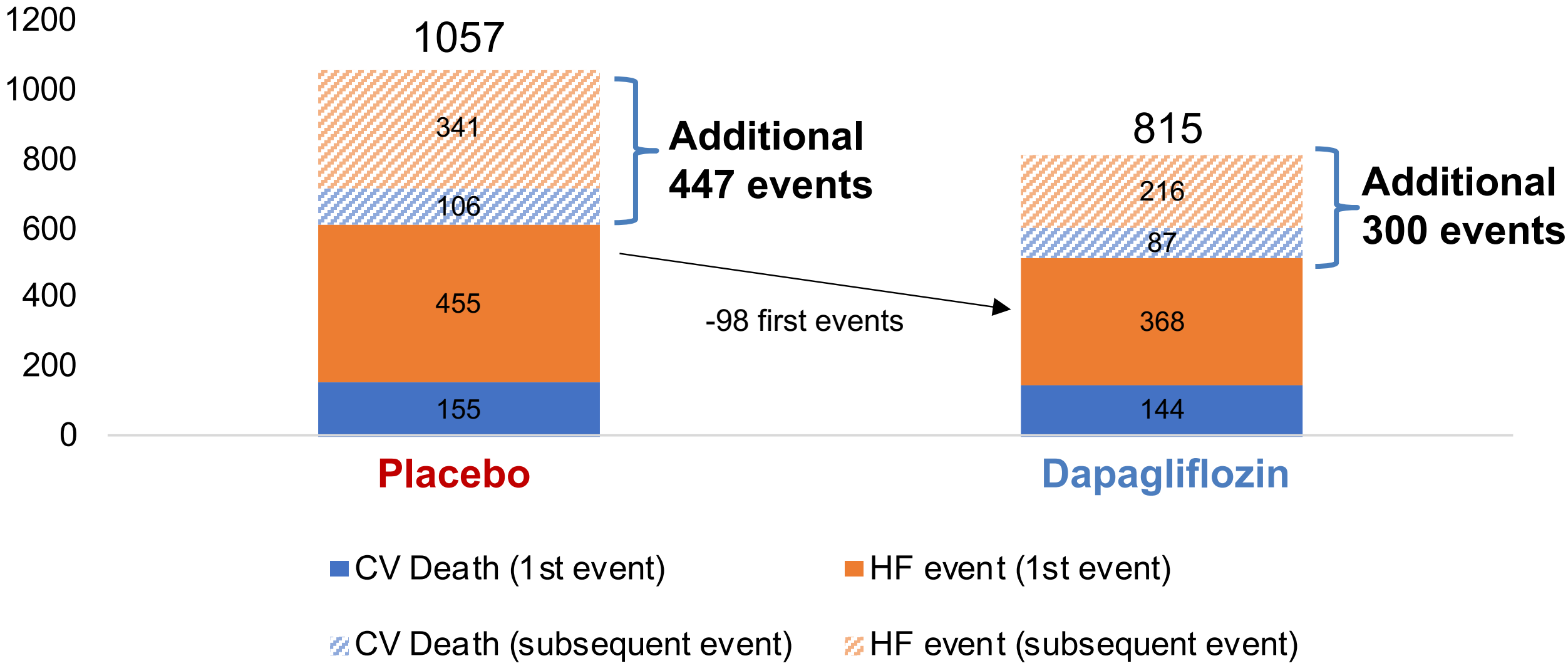
Number of first and subsequent HF events and CV deaths



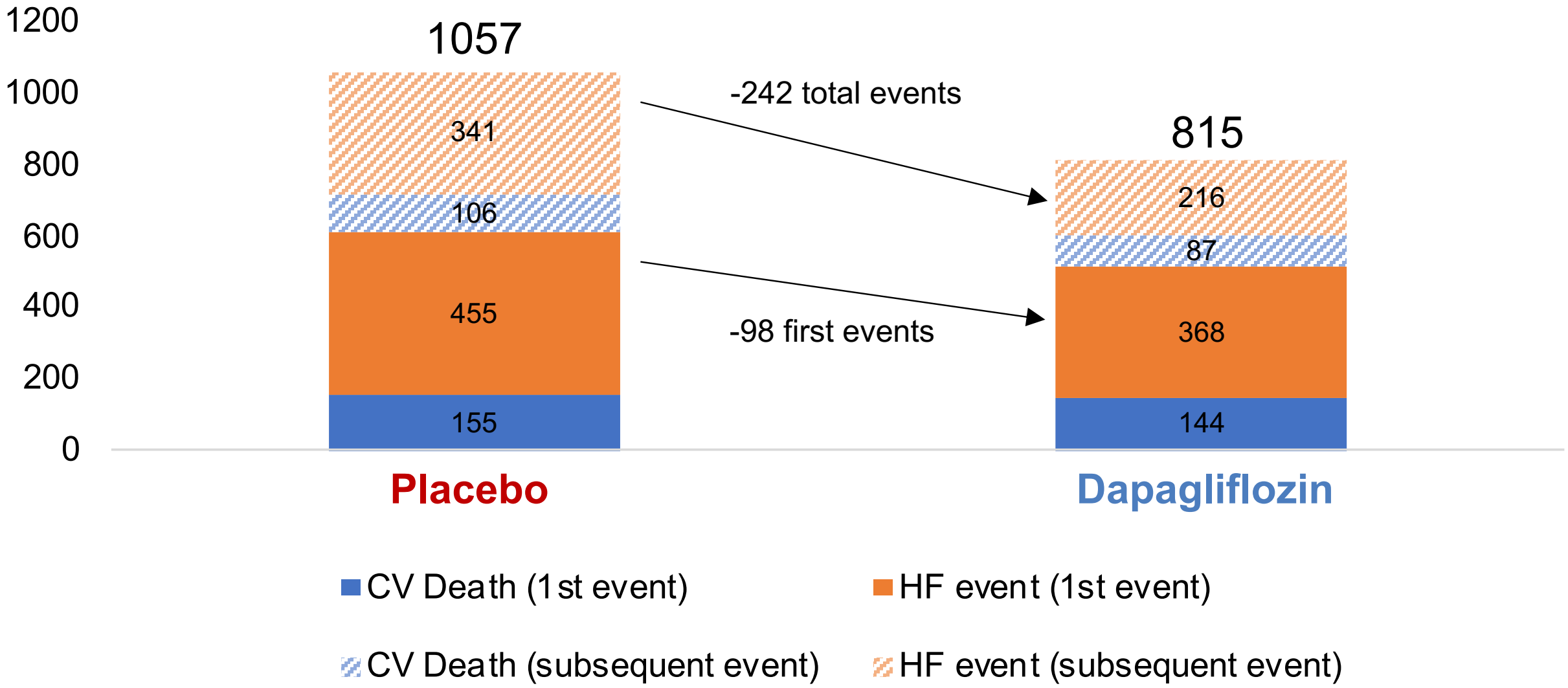
Number of first and subsequent HF events and CV deaths



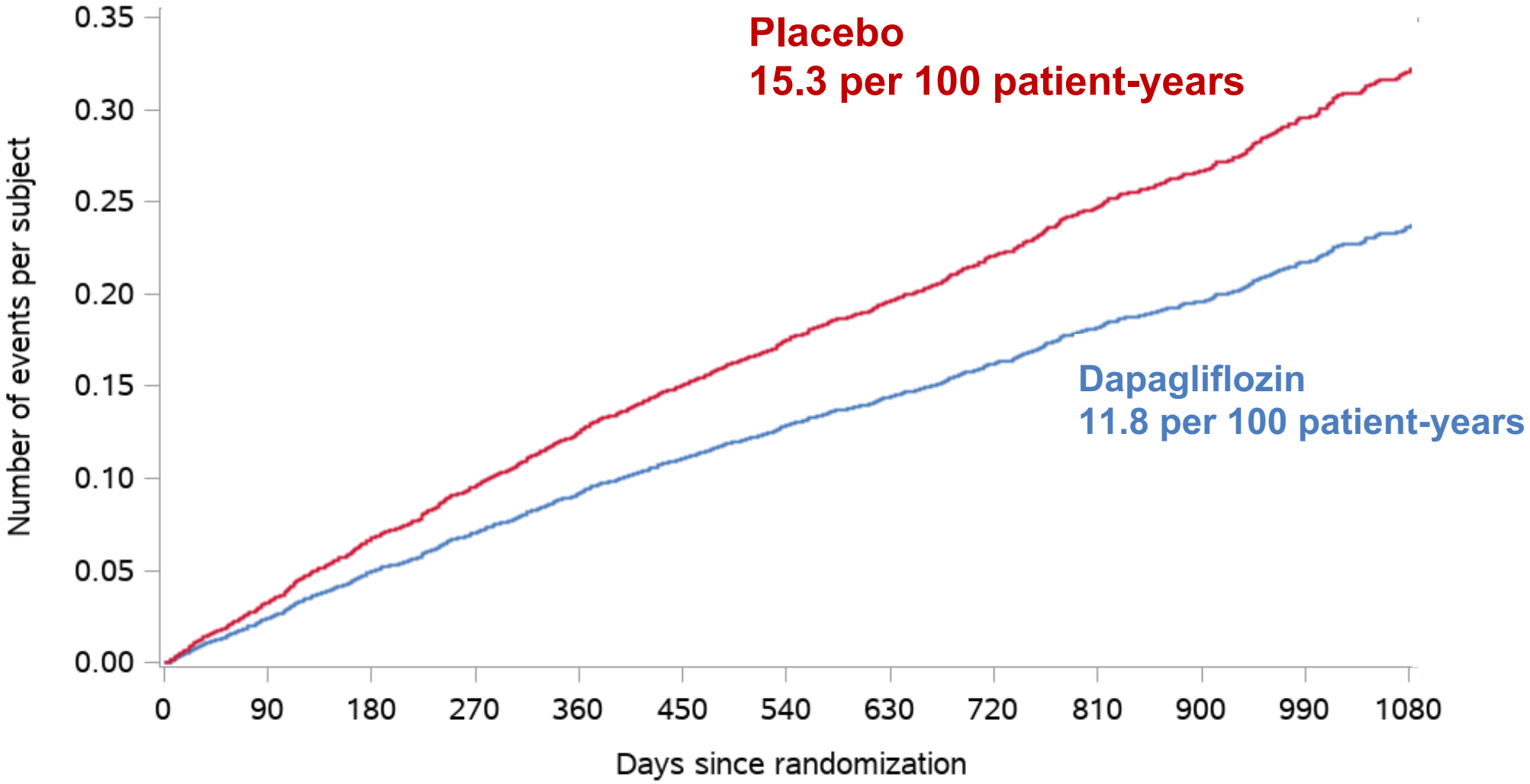
Number of first and subsequent HF events and CV deaths



Number of first and subsequent HF events and CV deaths

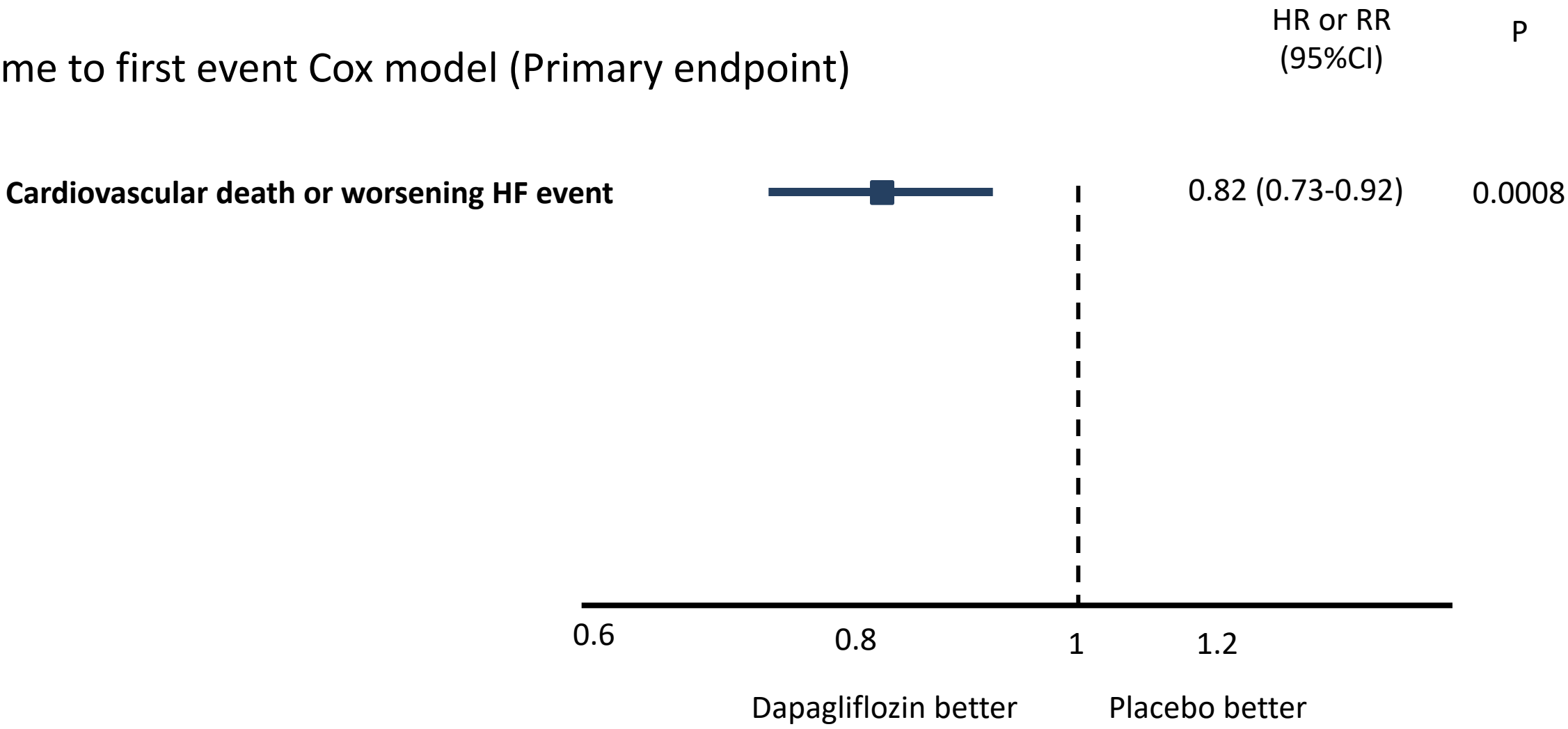


Cumulative incidence of total heart failure events with CV death as a competing risk – Ghosh and Lin method

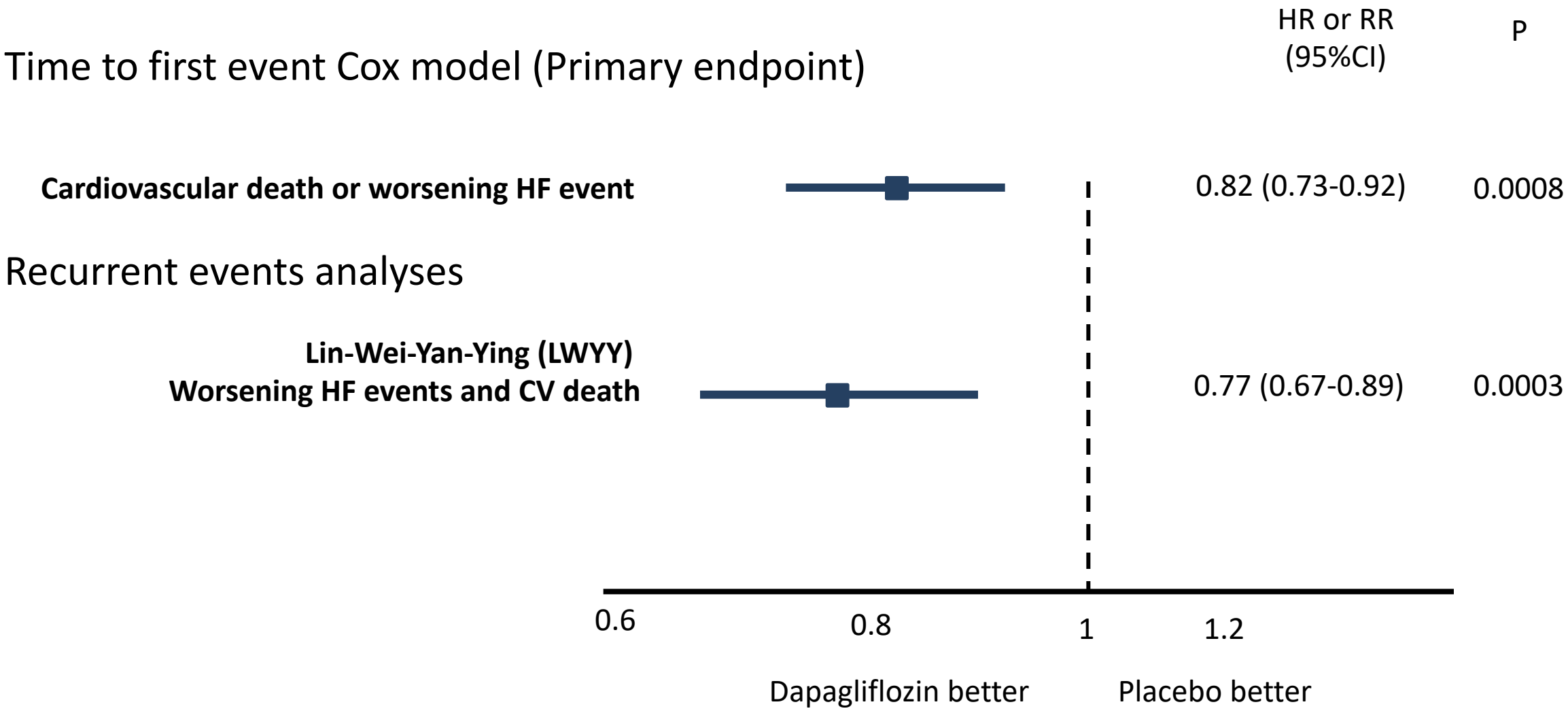


Effect of dapagliflozin on total HF events and CV death

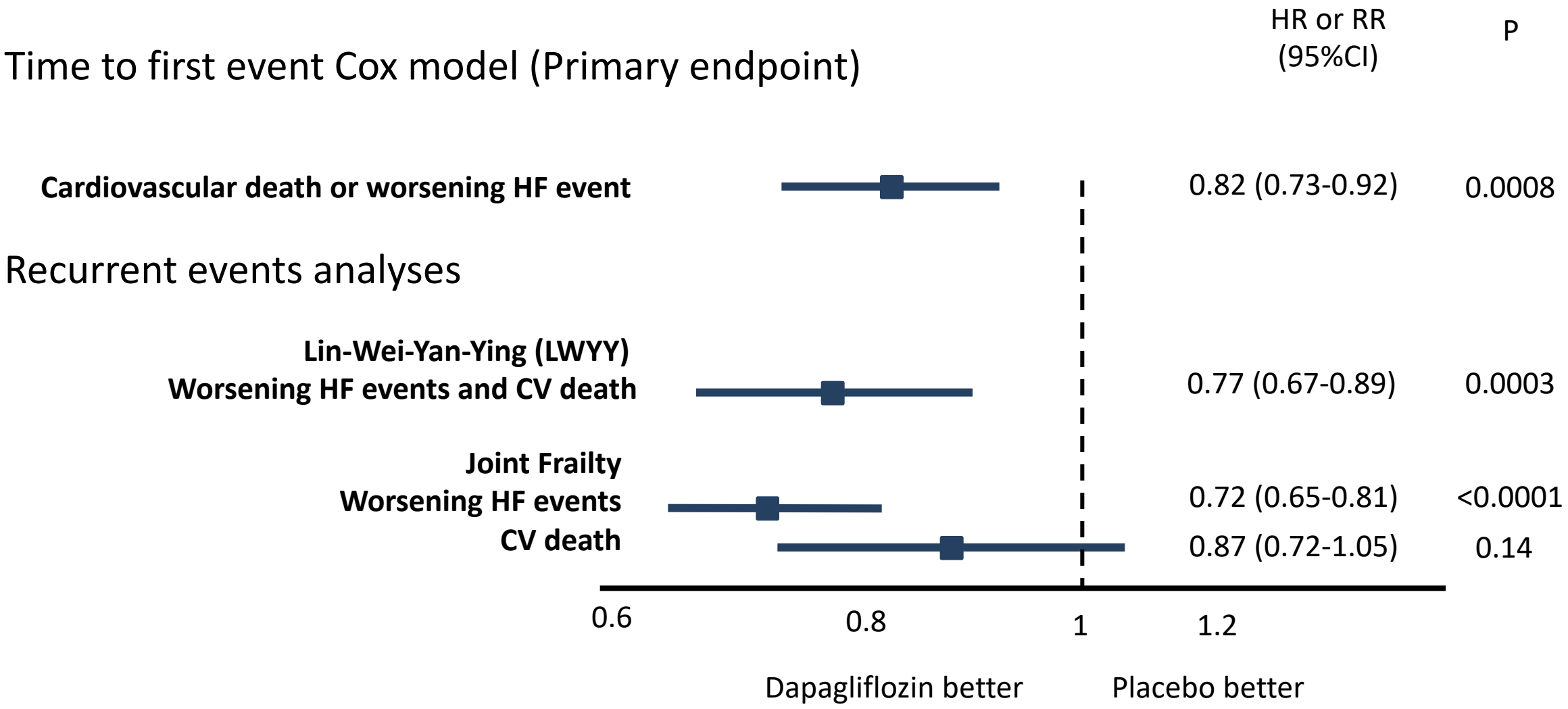
Time to first event Cox model (Primary endpoint)



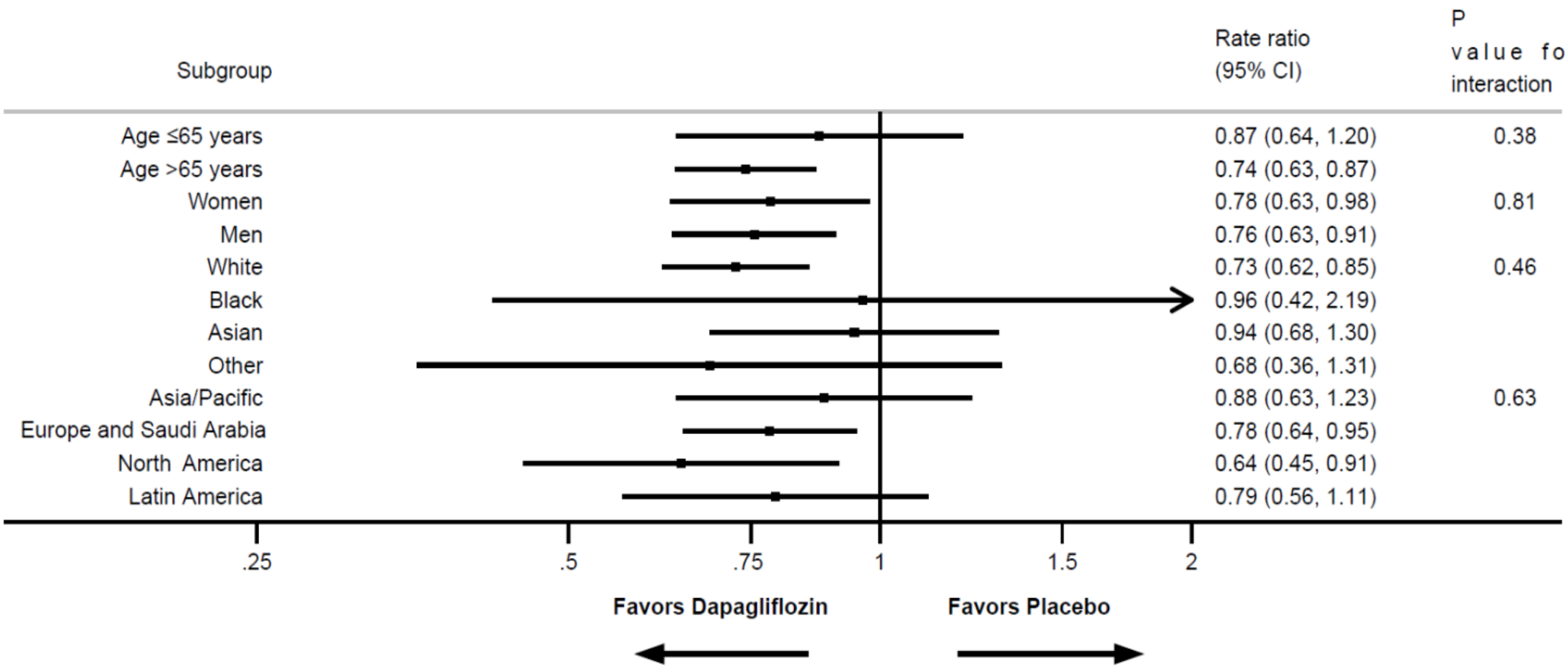
Effect of dapagliflozin on total HF events and CV death



Effect of dapagliflozin on total HF events and CV death

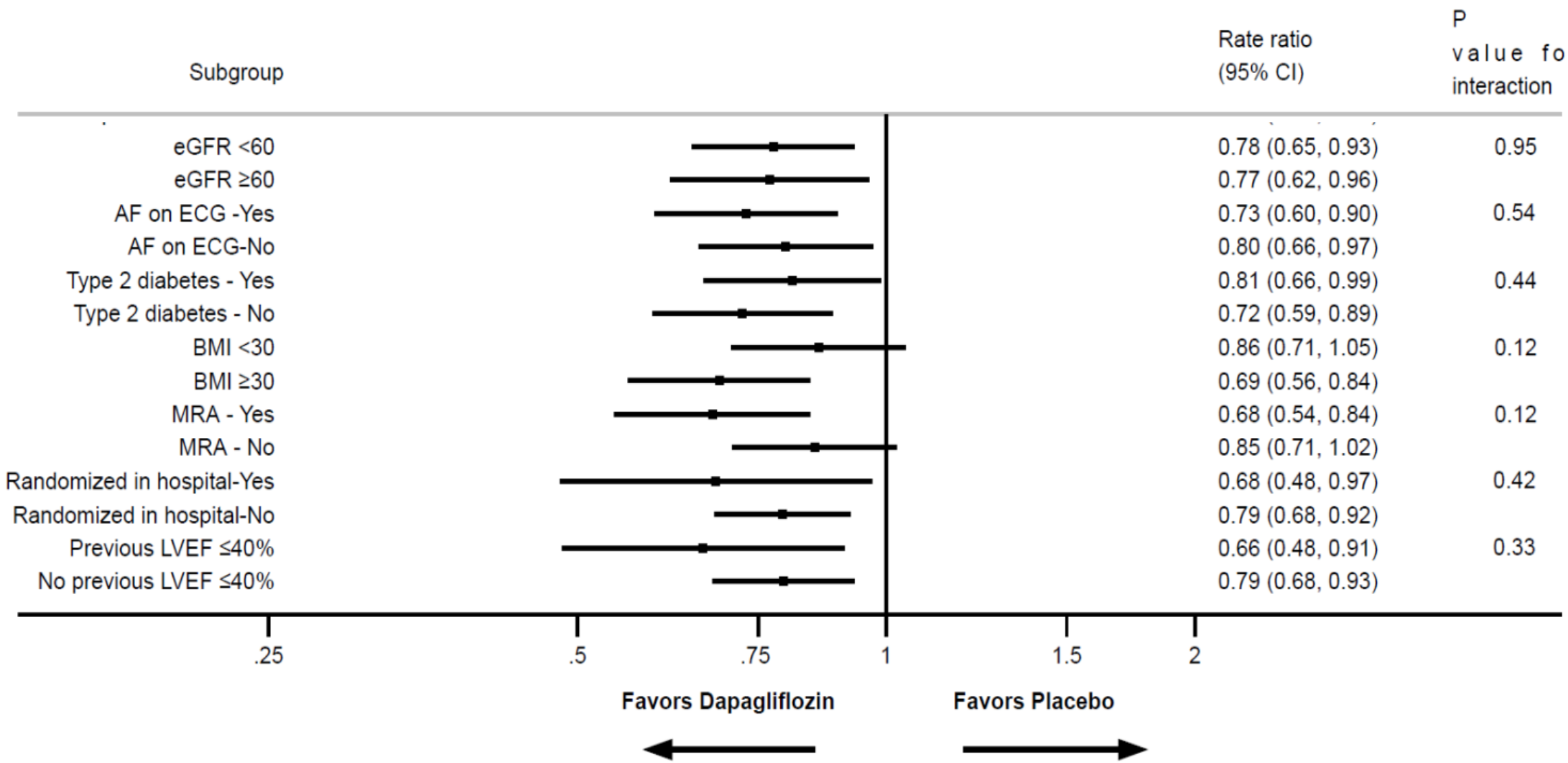


Effect of dapagliflozin on total HF events and CV death by subgroups*



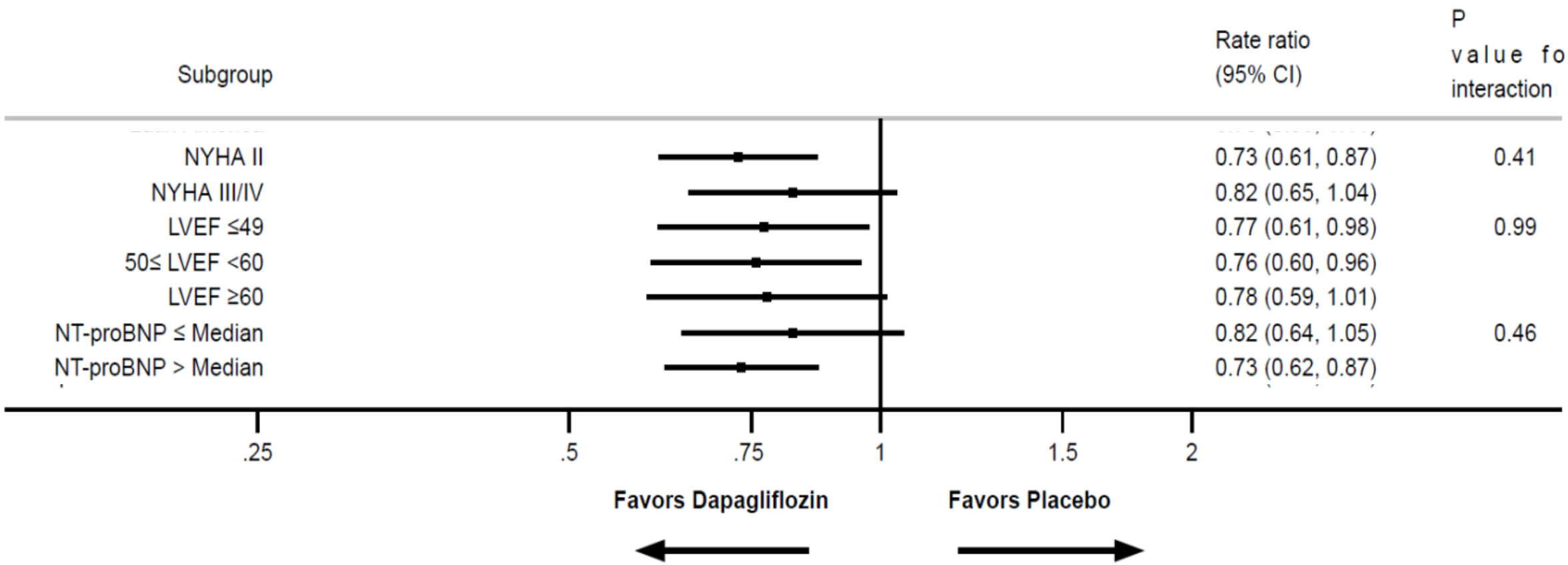
*LWYY model

Effect of dapagliflozin on total HF events and CV death by subgroups*



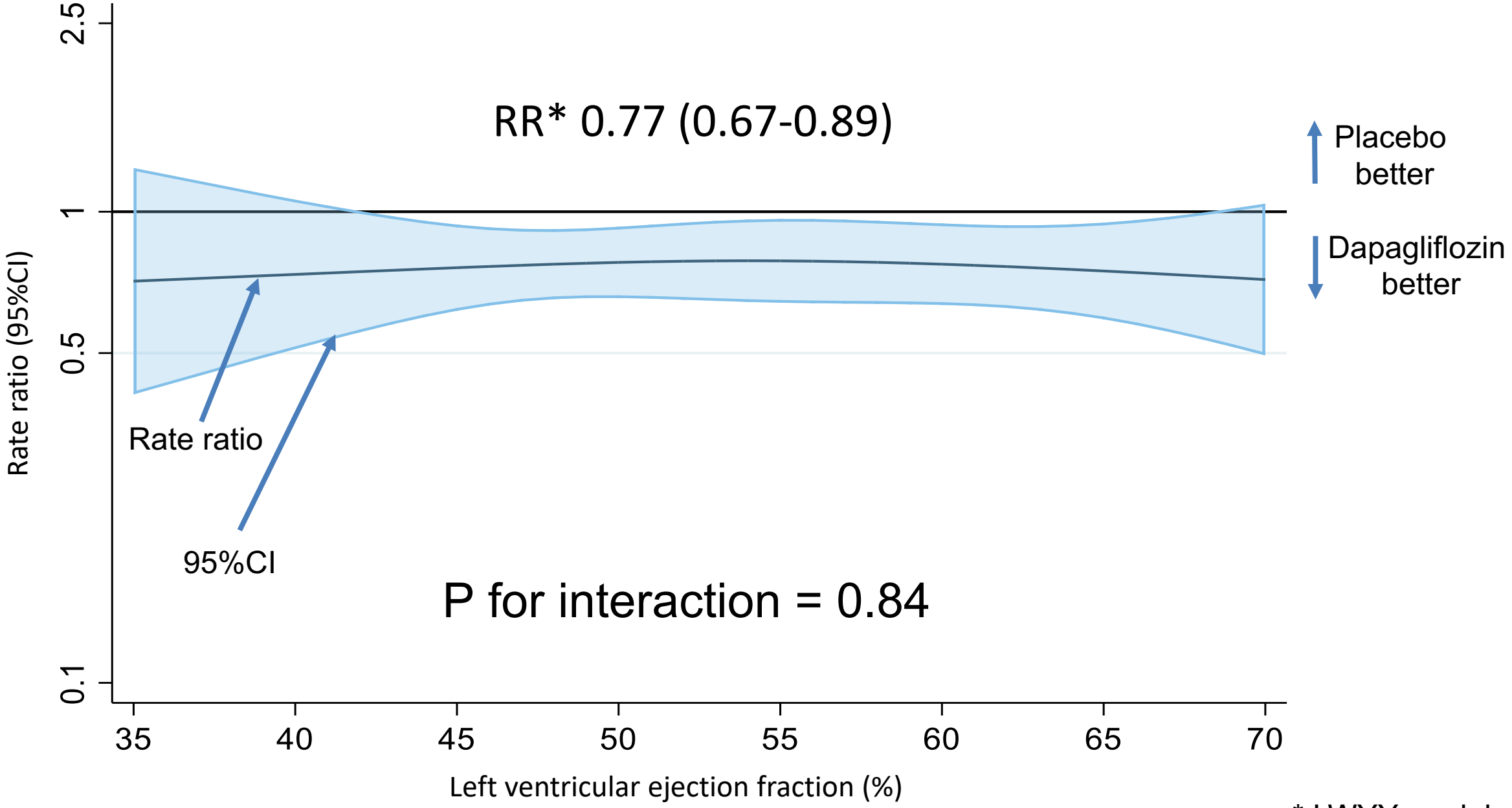
*LWYY model

Effect of dapagliflozin on total HF events and CV death by HF characteristics*



*LWYY model

Effect of dapagliflozin on total HF events and CV death by LVEF



* LWYY model

DELIVER recurrent events: Summary

- Recurrent HF events are common and preventable
- Dapagliflozin reduced the risk of total HF events and CV death in patients with HFmrEF/HFpEF in the DELIVER trial
- The efficacy of dapagliflozin in reducing the number of HF events was consistent across a broad range of subgroups and across the spectrum of ejection fraction