DAPA ACT HF – TIMI 68

Dapagliflozin in Patients Hospitalized for Heart Failure

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for the DAPA ACT HF – TIMI 68 Investigators

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Background

Patients hospitalized for HF have a high risk of death and adverse outcomes during hospital admission and in the early post-discharge period

SGLT2 inhibitors are indicated for the treatment of HF regardless of LVEF

Data are limited regarding the efficacy and safety of initiating SGLT2 inhibitors during HF hospitalization

Heidenreich PA, et al. *Circulation*. 2022;145:e895-e1032.
McDonagh TA, et al. *Eur Heart J*. 2023;44:3627-3639.

Trial Design

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Randomization (Day 0) → ***End of Study (Day 60)***

Patients Hospitalized for **Acute Heart Failure**

N=2401

1:1 Randomization (Double-blind)

- **Dapagliflozin** 10 mg daily
- **Placebo**

Primary Endpoint

Time to CV Death or Worsening HF

(Decompensation during Index Admission, Rehospitalization for HF, Urgent HF visit)

Key Entry Criteria

- S/Sx of fluid overload
- Elevated NT-proBNP or BNP
- eGFR >25 ml/min/1.73 m^2
- Any LVEF, w/ or w/o T2D
- Newly diagnosed & worsening chronic HF
- >24h but <14d after admission (early as possible)
- No intensification of IV diuretics x12h, no IV vasoactives x24h

Sample Size Assumptions

- Placebo event rate = 16%
- Relative risk reduction (RRR) = 27%
- Drop out rate (WoC, LTFU) = 0.5%
- Alpha level (2-sided) = 0.05
- Power = 80%

Berg DD, et al. *JACC Heart Fail*. 2025;13(5):829-839.

Meta-Analysis

Prespecified meta-analysis of randomized trials evaluating initiation of SGLT2i in patients hospitalized for HF

Main outcomes: (1) CV death or worsening HF; (2) all-cause death

Random effects models used to generate estimates of treatment effect

Trial Organization

DAPA ACT HF
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TIMI Study Group (Sponsor)

Marc Sabatine (Study Chair)
David Berg (Principal Investigator*)
Stephen Wiviott (Principal Investigator*)
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Christian Ruff (CEC)
Michelle O'Donoghue (Safety)

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Eileen O'Meara
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Independent Data Monitoring Committee

Gregg Fonarow (Chair)
KyungAh Im (Biostatistician)

Nancy Sweitzer
Bernard Zinman

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*Global Principal Investigator role transitioned on 28 March 2025

Enrollment & Retention

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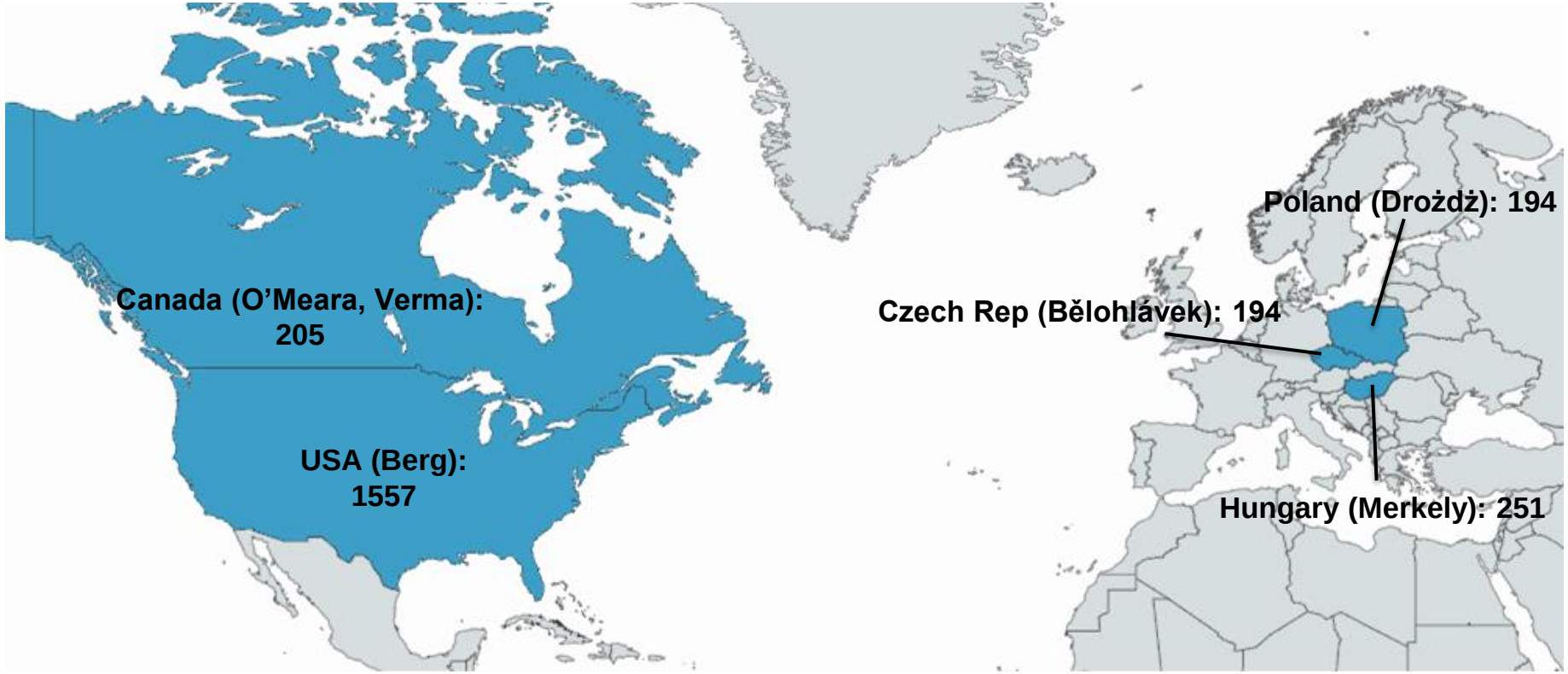
September 2020 – March 2025 | **2401** Patients | **210** Sites | **5** Countries



Country Start Date: USA (24 Sep 2020), Canada (07 May 2021), Hungary (08 Mar 2023), Poland (24 May 2023), Czech Republic (23 Jun 2023)

Retention Metrics

Never received or prematurely discontinued study drug:
n=274 (11.4%)

Withdrew consent:
n=13 (0.5%)

Lost to follow-up:
n=4 (0.2%)

Baseline Characteristics

Patient Characteristics	Overall N=2401
Age (yrs)	69 (58-77)
Female sex	34
Black race	19
Type 2 DM	35
LVEF ≤40%	72
Heart failure chronicity	
Newly diagnosed (*de novo*)	45
Worsening chronic HF	55
Natriuretic peptides	
NT-proBNP (pg/ml) (n=1582)	4803 (2812-8768)
BNP (pg/ml) (n=830)	1106 (717-1859)
eGFR <60 ml/min/1.73m²	45
Admission to Rando Time (d)	3.6 (2.1-5.4)

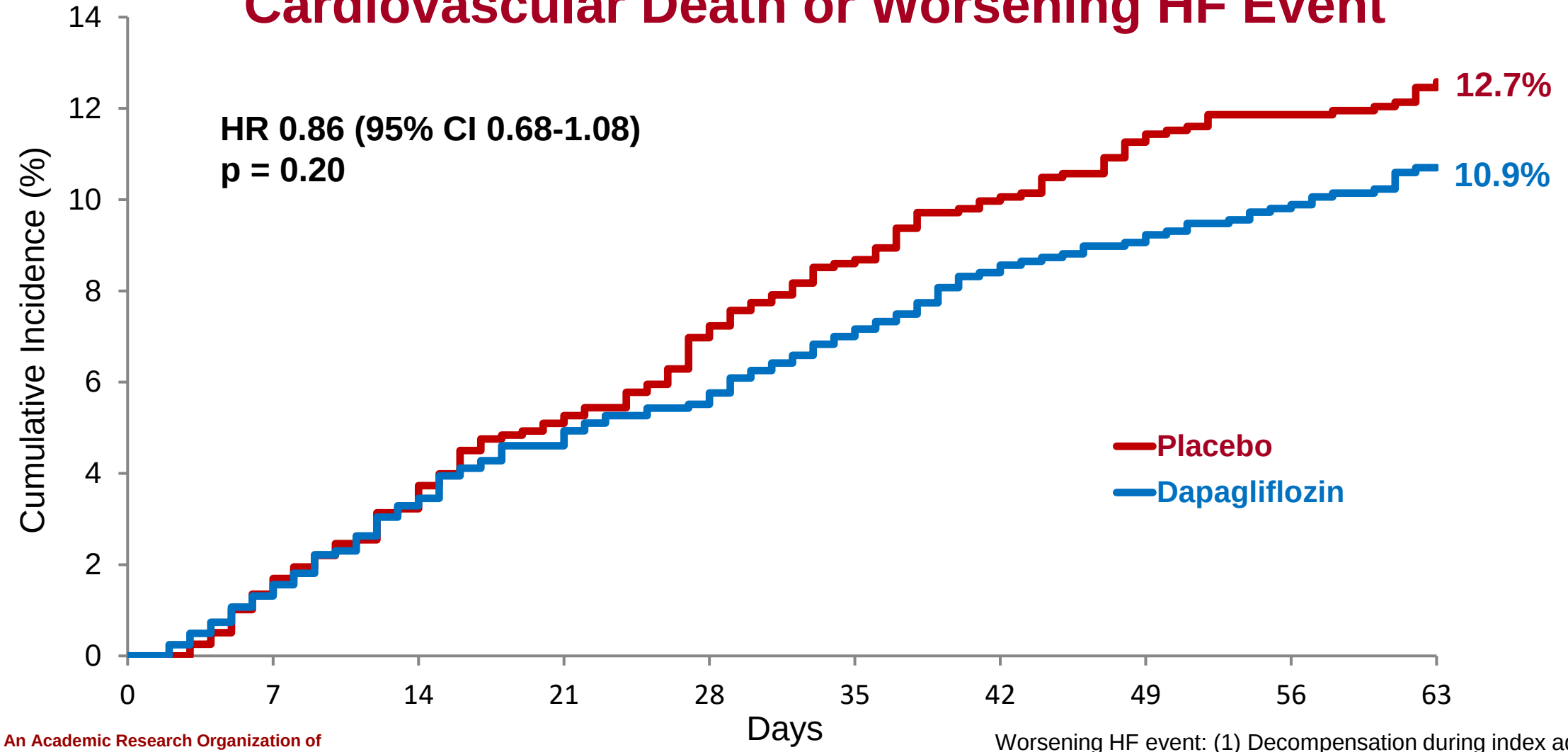
Medications	Overall N=2401
Randomization	
Beta-blocker	83
ACEI / ARB / ARNI	70
ARNI	27
MRA	49
Loop diuretic	85
Discharge	
Beta-blocker	88
ACEI / ARB / ARNI	76
ARNI	31
MRA	54
Loop diuretic	88

Median Time Rando to Discharge = 2 (1-4) days

Values shown are % or median (IQR) for pooled treatment arms
There were no significant differences across treatment arms

Primary Endpoint

Cardiovascular Death or Worsening HF Event



Worsening HF event: (1) Decompensation during index admission; (2) Rehospitalization for HF; (3) Urgent HF visit with IV diuretic Rx

Primary EP Components

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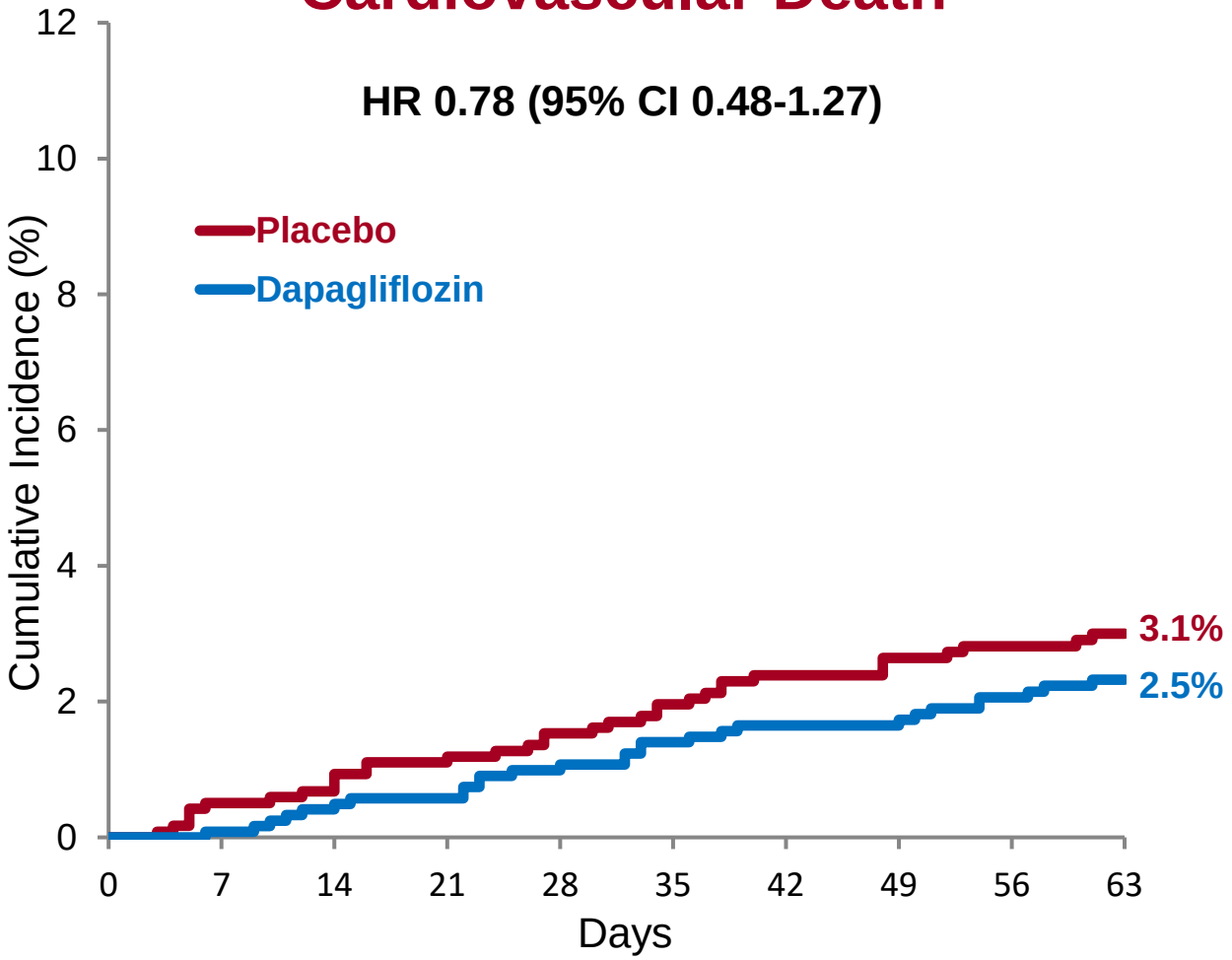
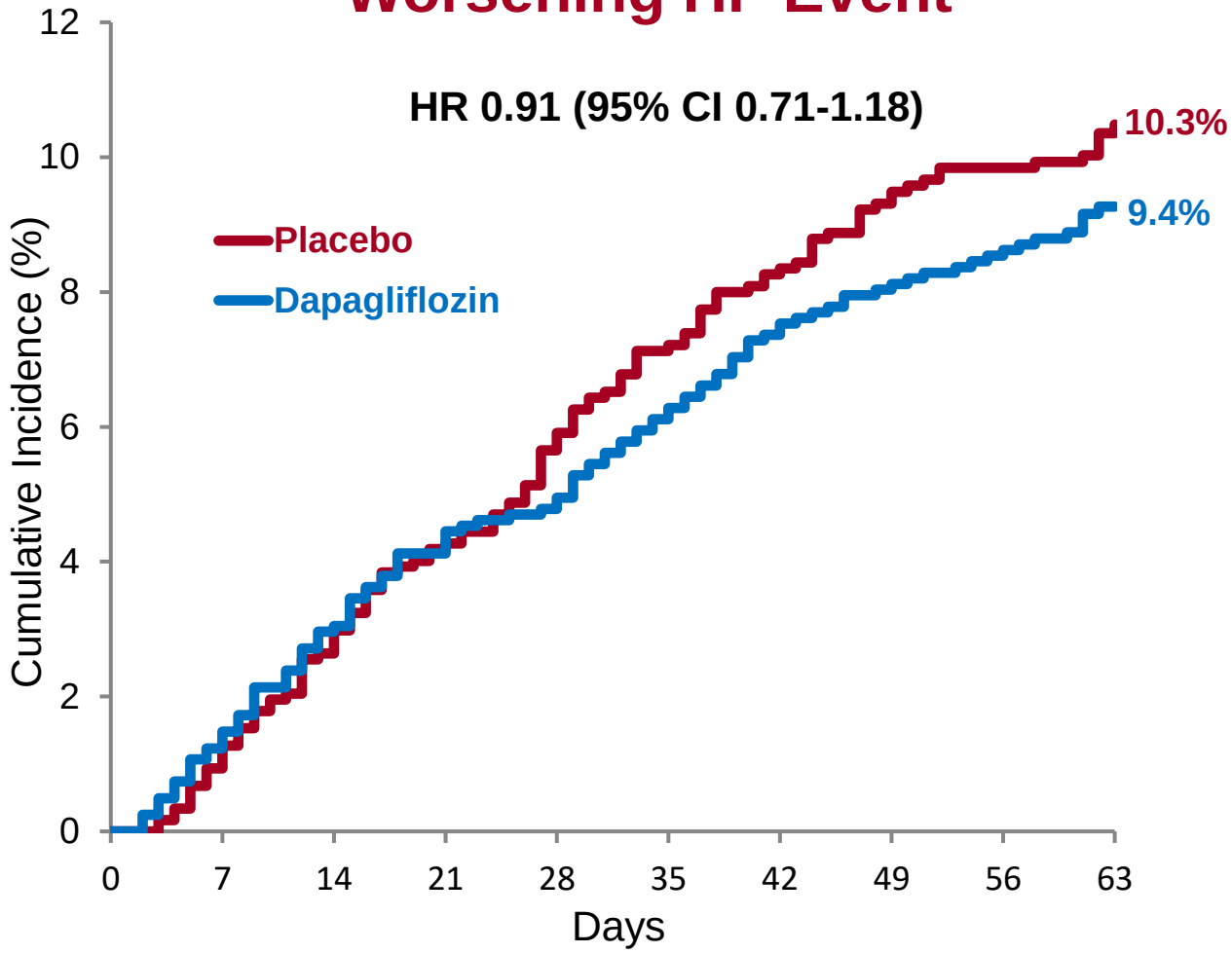
Cardiovascular Death



Worsening HF Event



Other Endpoints

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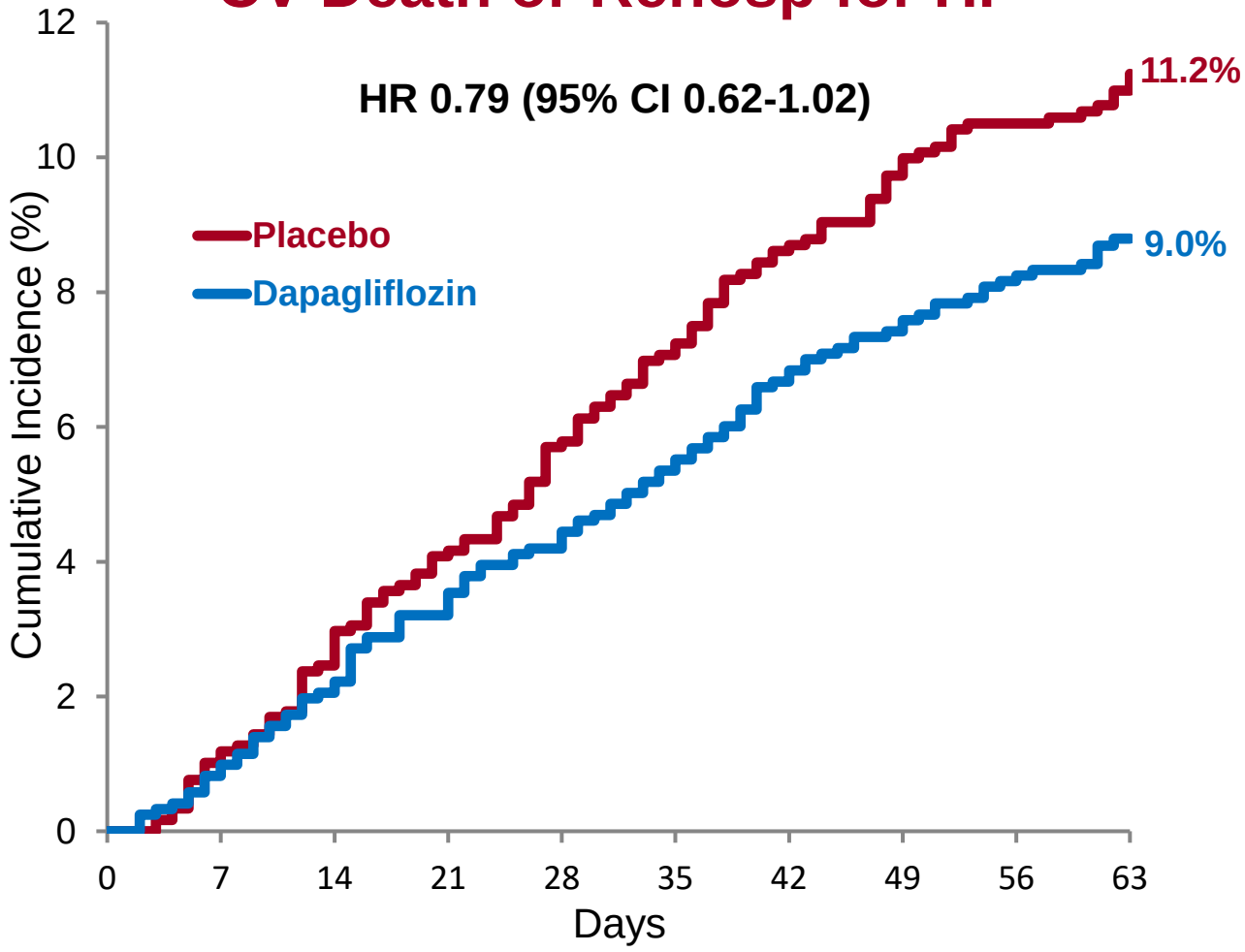
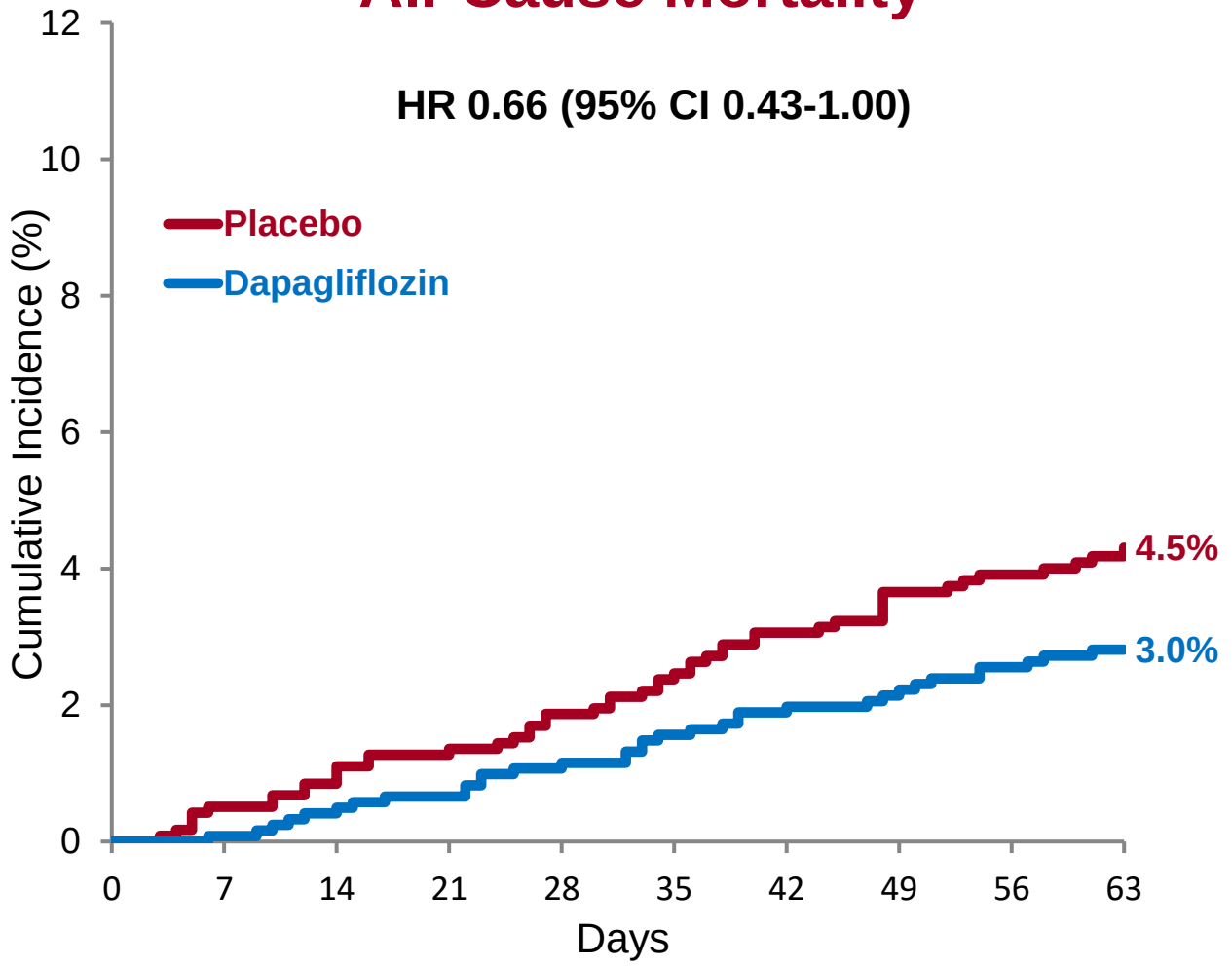
CV Death or Rehosp for HF



All-Cause Mortality



Key Subgroups

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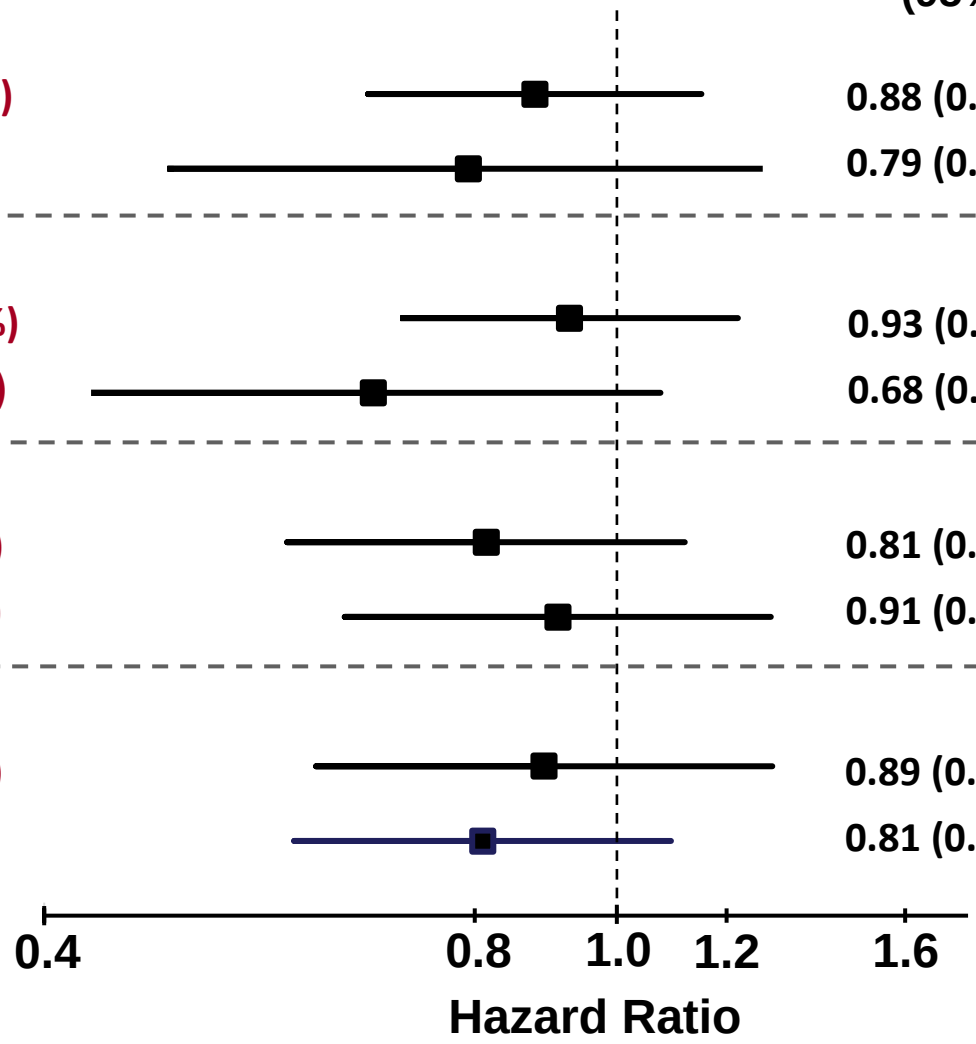
	Dapagliflozin n (%)	Placebo n (%)	Hazard Ratio (95% CI)	P-interaction
HF Chronicity				
Worsening chronic HF	101 (15.3%)	113 (17.0%)	0.88 (0.67-1.15)	0.71
Newly diagnosed HF	32 (5.8%)	37 (7.1%)	0.79 (0.49-1.27)	
LVEF				
≤ 40%	102 (11.8%)	107 (12.6%)	0.93 (0.71-1.22)	0.26
> 40%	31 (8.8%)	43 (13.0%)	0.68 (0.43-1.08)	
eGFR				
< 60 ml/min/1.73m^2	68 (12.7%)	84 (15.2%)	0.81 (0.59-1.12)	0.63
≥ 60 ml/min/1.73m^2	65 (9.5%)	66 (10.4%)	0.91 (0.65-1.29)	
NT-proBNP or BNP				
< Median	53 (9.0%)	62 (10.3%)	0.89 (0.62-1.29)	0.73
≥ Median	80 (12.8%)	88 (15.2%)	0.81 (0.60-1.10)	



Safety Endpoints

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	Dapagliflozin (N=1218)	Placebo (N=1183)
Symptomatic hypotension	43 (3.6%)	26 (2.2%)
Worsening kidney function	71 (5.9%)	55 (4.7%)
Major hypoglycemia	3 (0.2%)	3 (0.3%)
Diabetic ketoacidosis	0 (0.0%)	0 (0.0%)
AE leading to IP discontinuation	58 (4.8%)	56 (4.7%)

Symptomatic hypotension included events leading to hospitalization or study drug discontinuation
Worsening kidney function defined as resulting in at least a doubling of serum creatinine, hospitalization, study drug discontinuation, dialysis, or renal death
Major hypoglycemia defined as resulting in severe impairment in consciousness or behavior, or requiring emergency external assistance

Meta-Analysis

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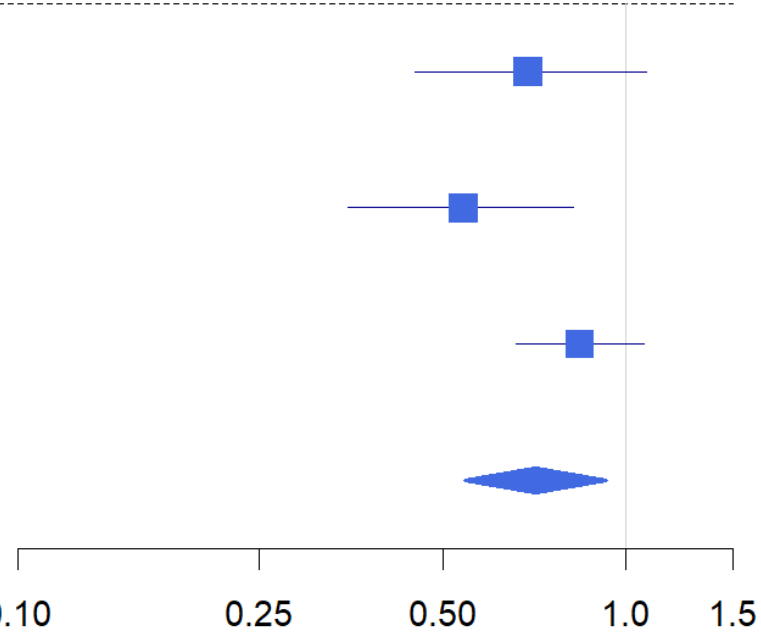
Cardiovascular Death or Worsening HF Event

Study	SGLT2 Inhibitor *Ev. (per 100 pt-mos)*	Placebo *Ev. (per 100 pt-mos)*	HR (95%CI)
EMPULSE (N=530)	34 (4.3)	49 (6.2)	0.69 (0.45-1.08)
SOLOIST-WHF (in-hospital) (N=596)	31 (3.6)	60 (6.5)	0.54 (0.35-0.82)
DAPA ACT HF-TIMI 68 (N=2401)	127 (5.2)	146 (6.2)	0.84 (0.66-1.07)
Overall			**0.71 (0.54, 0.93)**



Test for heterogeneity: I^2=0; Q=3.26 (p=0.20)

Hazard ratio (SGLT2i vs placebo): 0.71 (95% CI 0.54-0.93); p=0.012

Meta-Analysis

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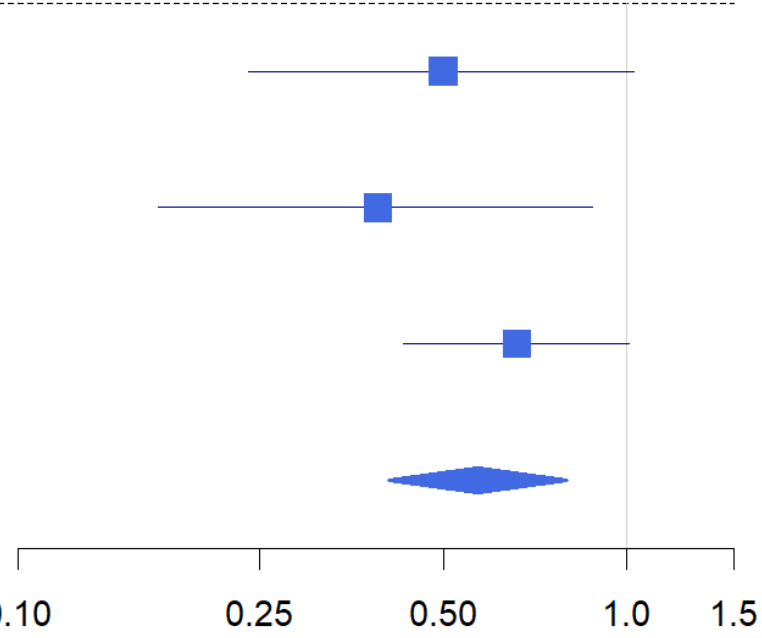
All-Cause Mortality

Study	SGLT2 Inhibitor *Ev. (per 100 pt-mos)*	Placebo *Ev. (per 100 pt-mos)*	HR (95%CI)
EMPULSE (N=530)	11 (1.4)	22 (2.8)	0.50 (0.24-1.03)
SOLOIST-WHF (in-hospital) (N=596)	9 (1.0)	22 (2.4)	0.39 (0.17-0.88)
DAPA ACT HF-TIMI 68 (N=2401)	36 (1.5)	53 (2.2)	0.66 (0.43-1.00)
Overall			**0.57 (0.41, 0.80)**



Test for heterogeneity: I^2=0; Q=1.40 (p=0.50)

Hazard ratio (SGLT2i vs placebo): 0.57 (95% CI 0.41-0.80); p=0.001

Limitations

Several factors may have contributed to non-significant treatment difference for primary EP in DAPA ACT HF – TIMI 68

- Only 2-month follow-up duration
- Lower than anticipated event rate → total primary EP events: 283 vs. 320
- Underpowered (~75% for 27% RRR, <50% for 20% RRR)

Meta-Analysis

- Modest sample sizes and lack of CEC adjudication in EMPULSE and SOLOIST-WHF in-hospital cohort
- Differences in study designs, study populations, and follow-up duration

Conclusions

In-hospital initiation of dapagliflozin did not significantly reduce the risk of CV death or worsening HF through two months in hospitalized HF patients in the DAPA ACT HF – TIMI 68 trial

However, totality of RCT data suggests that in-hospital initiation of SGLT2i reduces high risk of adverse outcomes, including CV death or worsening HF and all-cause mortality, in the early post-discharge period

Dapagliflozin was safe and well-tolerated in hospitalized HF patients, consistent with known safety profile of SGLT2i medication class

Circulation

Dapagliflozin in Patients Hospitalized for Heart Failure: Primary Results of the DAPA ACT HF-TIMI 68 Randomized Clinical Trial and Meta-Analysis of Sodium-Glucose Cotransporter-2 Inhibitors in Patients Hospitalized for Heart Failure

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