DICTATE-AHF

Efficacy and Safety of Dapagliflozin in Acute Heart Failure

NCT04298229

Zachary Cox, PharmD

Professor, Lipscomb University College of Pharmacy, USA

Department of Pharmacy, Vanderbilt University Medical Center

On behalf of DICTATE-AHF Investigators

August 28, 2023

Background

Two Goals for Acute Heart Failure

1) Decongestion

2) GDMT Optimization

→ Improve Post-DC Outcomes

Loop + Acetazolamide	✓	⊘	No Improvement
Loop + Thiazide	✓	⊘	No Improvement
Loop + SGLT2i	?	✓	Improved Outcomes

Background

- **Concerns of very early in-hospital SGLT2 inhibitor SAFETY:**
  - Hypoglycemia
  - Ketoacidosis
  - Worsening renal function
  - Genitourinary infections
  - Questionable magnitude of diuretic and natriuretic benefit

Early addition of Dapagliflozin is a potential strategy to improve achievement of both primary AHF therapeutic goals, but **efficacy and safety** are unknown

DICTATE-AHF Design

- Investigator-initiated, multicenter, prospective, randomized, open-label study funded by AstraZeneca

  Objective efficacy outcomes and blinded assessment of safety outcomes

- 240 Patients regardless of LVEF hospitalized with hypervolemic AHF were randomized
- Beginning April 2020, only patients with Type 2 diabetes mellitus were included
  - September 2021 - protocol amended to include:
    - With or without type 2 diabetes mellitus
    - eGFR $\geq$ 25 mL/min/1.73m^2

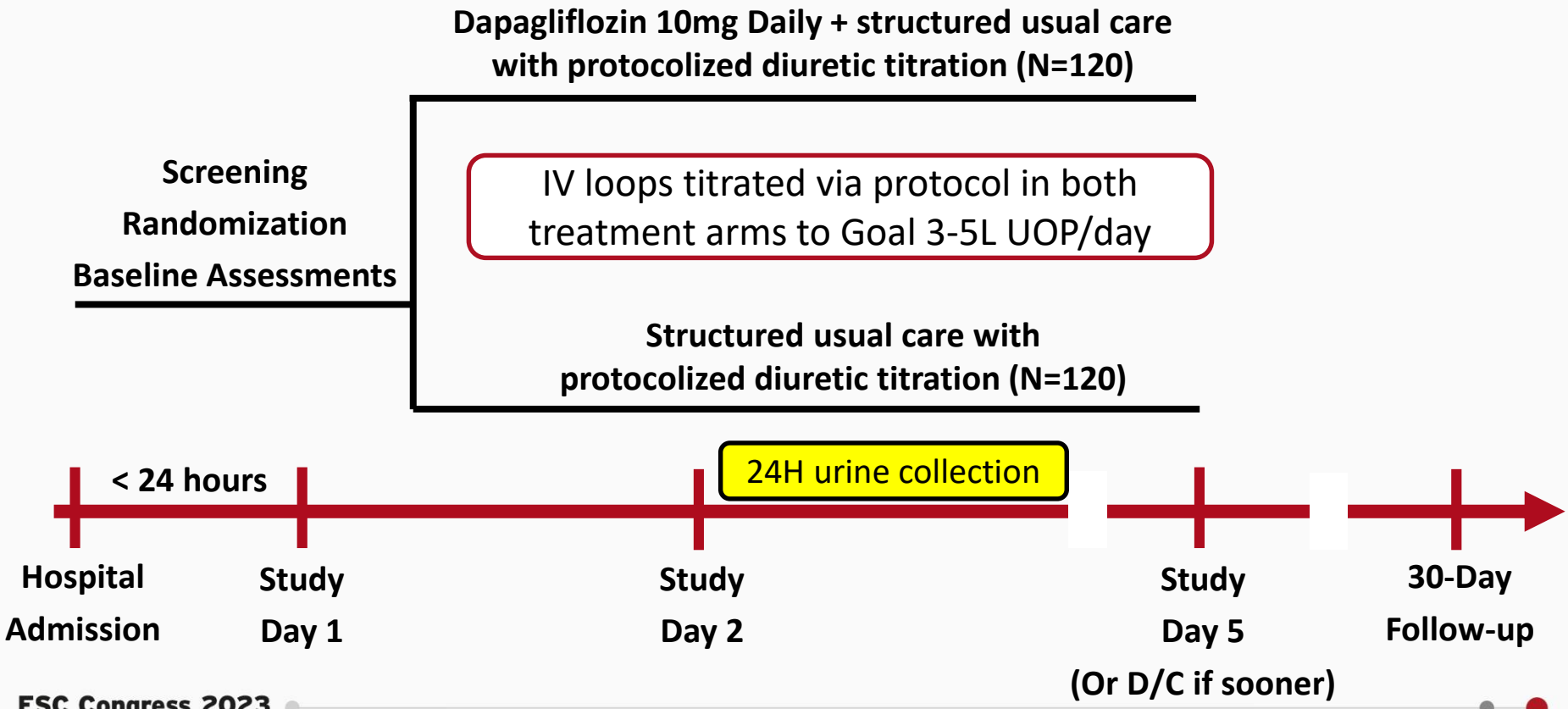
Key Inclusion Criteria

- Age of 18 years or older
- Randomized within 24 hours of presentation hypervolemic AHF:
  - ≥2 objective measures of hypervolemia
- Planned or current use of IV loop diuretic therapy
- eGFR ≥ 25 mL/min/1.73m^2

Key Exclusion Criteria

- Type 1 diabetes
- Serum glucose < 80mg/dL
- Systolic blood pressure < 90mmHg
- IV inotropic therapy
- History of diabetic ketoacidosis
- Inability to perform standing weights or measure urine output accurately

DICTATE-AHF


Dapagliflozin 10mg Daily + structured usual care with protocolized diuretic titration (N=120)
Screening
Randomization
Baseline Assessments
IV loops titrated via protocol in both treatment arms to Goal 3-5L UOP/day
Structured usual care with protocolized diuretic titration (N=120)
24H urine collection
< 24 hours
Hospital Admission
Study Day 1
Study Day 2
Study Day 5 (Or D/C if sooner)
30-Day Follow-up

Study Outcomes

Primary Outcome

$$\text{Diuretic Efficiency} = \frac{\text{Cumulative weight change (kg)}}{\text{Cumulative loop diuretic dose (mg)}}$$

- Calculated until Day-5 or hospital discharge if sooner
- Expressed as *kg/40mg IV Furosemide equivalents*
- Compared across treatment assignment using a proportional odds regression model adjusting for baseline weight

Study Outcomes

Secondary Outcomes adjudicated by blinded committee

- Incidence of worsening HF during hospital stay
- HF-related or diabetes-related 30-day readmissions

Safety Outcomes adjudicated by blinded committee

- Incidence of diabetic ketoacidosis
- Prolonged hospitalization for hypotension
- Prolonged hospitalization for hypoglycemia
- Change in eGFR from baseline to end-of-study

Select Exploratory Outcomes

- Measures of natriuresis and diuresis
- Hospital length of stay

Baseline Characteristics

Characteristic	Total Population (N=238)	Usual Care (N=119)	Dapagliflozin (N=119)
Age (yrs)	65 (56 – 73)	64 (55 – 74)	65 (56 – 73)
Male Sex	61%	56%	66%
White Race	68%	71%	66%
T2DM	71%	71%	71%
LVEF $\leq$ 40%	52%	55%	48%
SBP (mmHg)	121 (110 – 136)	120 (110 – 136)	121 (112 – 136)
eGFR (mL/min/1.73m^2)	53 (42 – 70)	54 (40 – 71)	51 (43 – 68)
IV furosemide dose prior to randomization (mg)	80 (40 – 140)	80 (80 – 120)	80 (40 - 160)

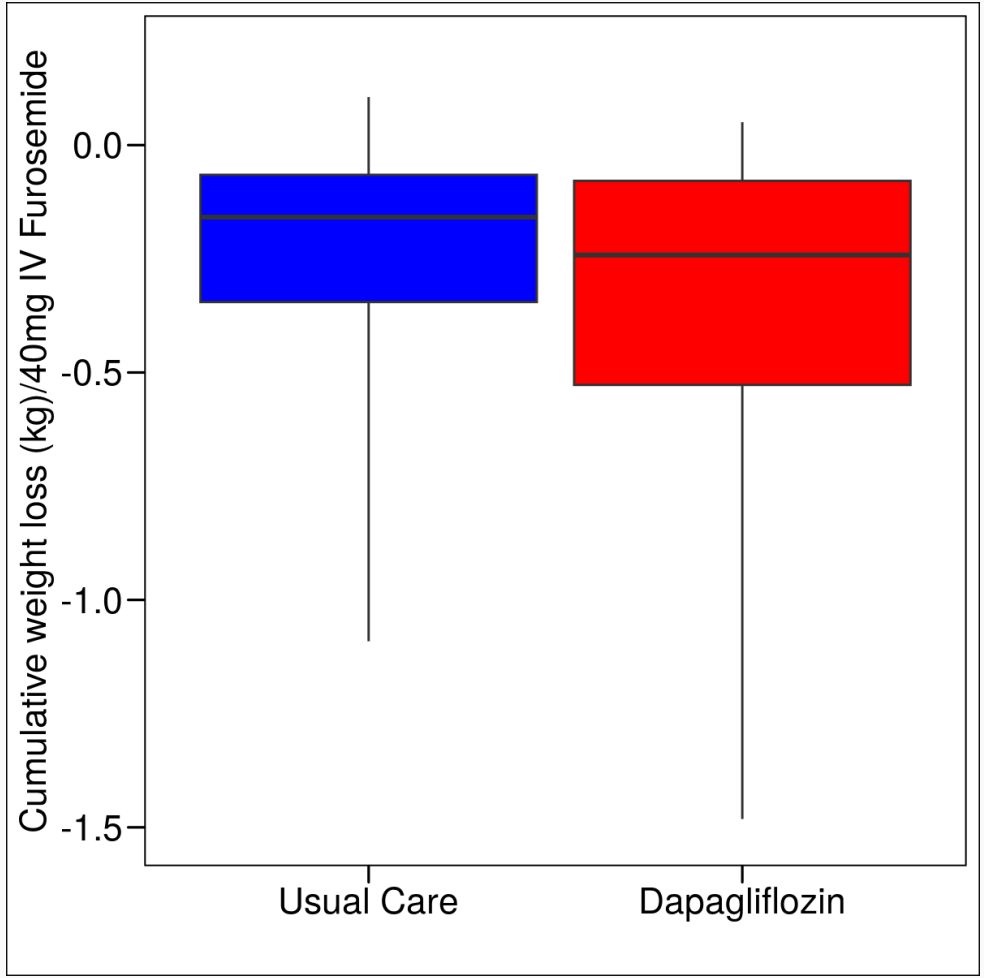
Primary Outcome

Adjusted Odds Ratio 0.65

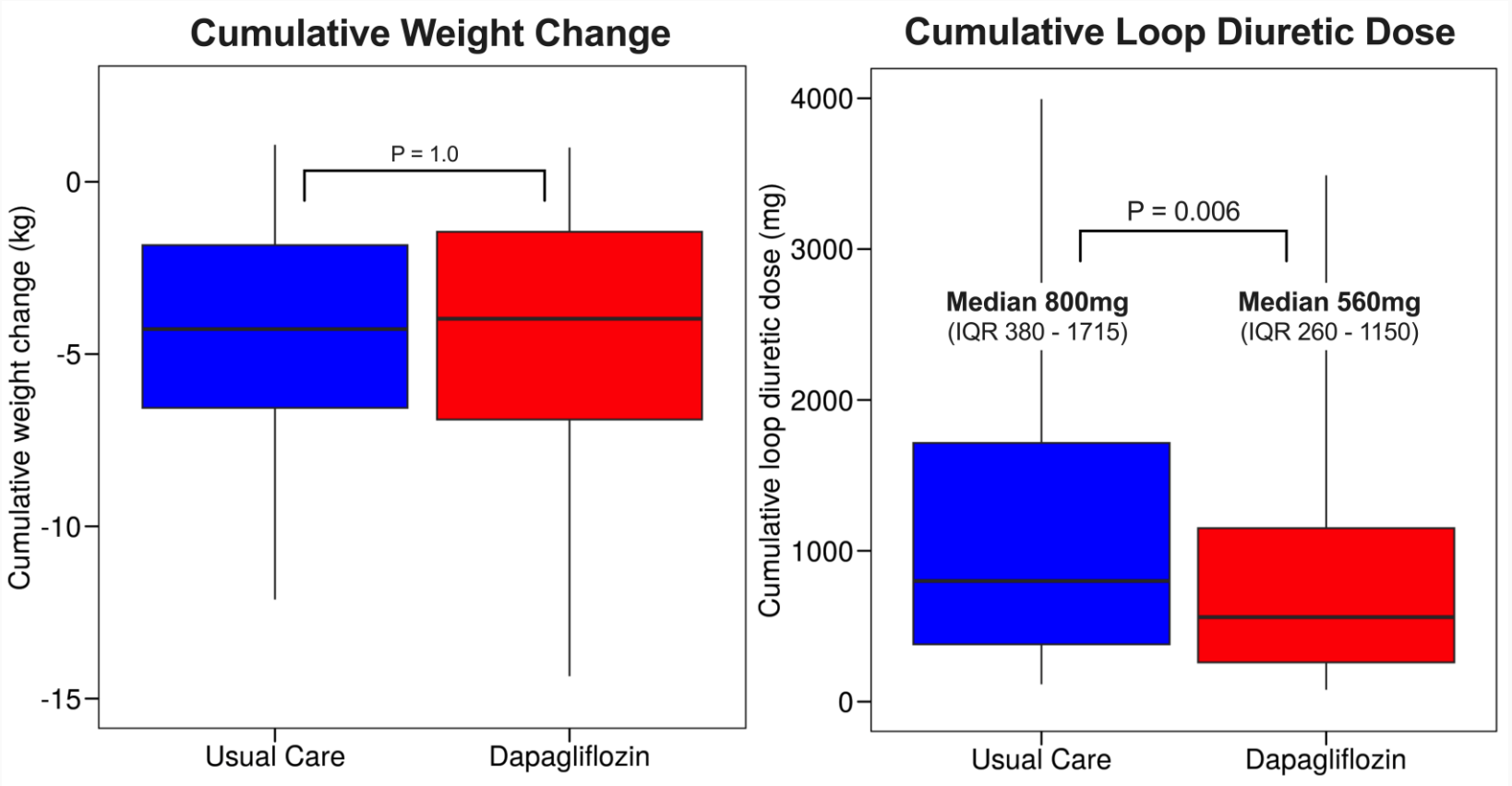
(95% CI 0.41 – 1.01); P=0.06

Unadjusted Odds Ratio 0.64

(95% CI 0.41 – 1.00)

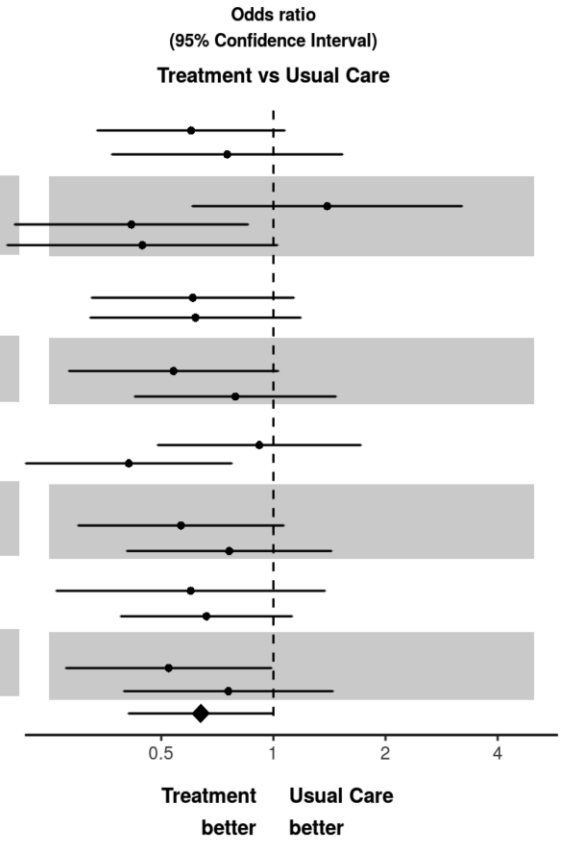


Primary Outcome Components

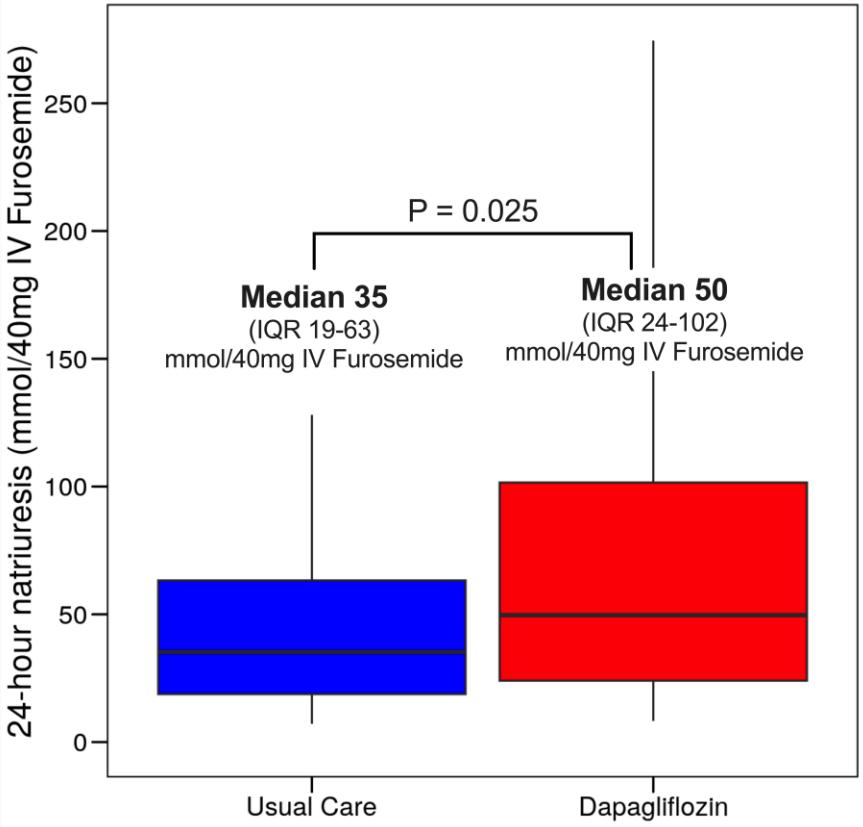


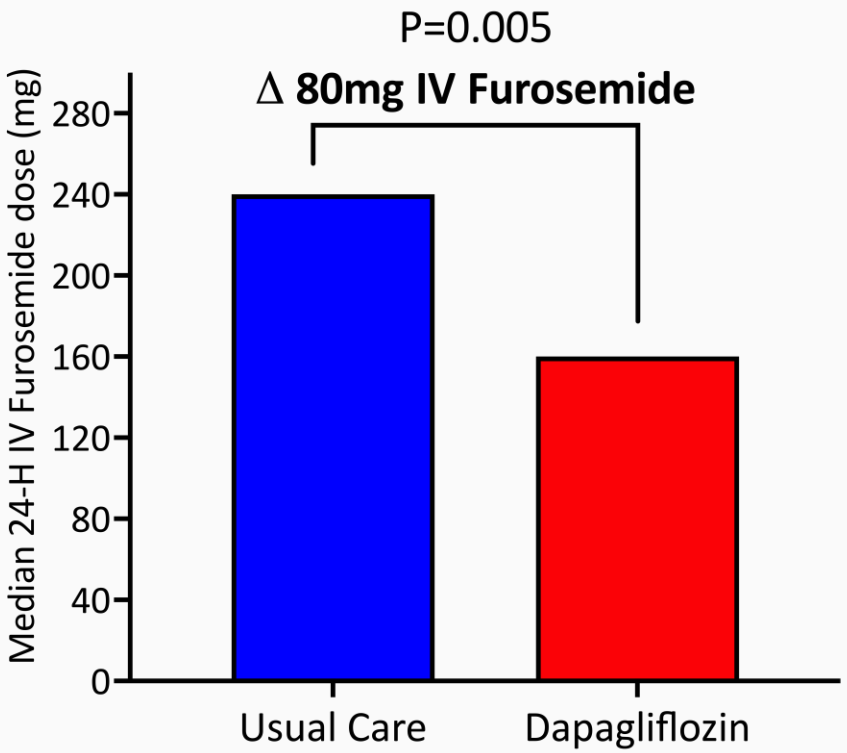
Heterogeneity of Treatment Effect

Subgroup	No. of Patients	Treatment	Usual Care
		Estimated mean weight change per 40mg Furosemide-equivalents (95% CI)	
Sex			
Male	145	-0.45 (-0.57, -0.33)	-0.32 (-0.43, -0.22)
Female	93	-0.36 (-0.50, -0.22)	-0.29 (-0.40, -0.19)
Edema score			
No/Mild	68	-0.27 (-0.39, -0.15)	-0.34 (-0.49, -0.19)
Moderate	92	-0.51 (-0.67, -0.34)	-0.29 (-0.40, -0.19)
Severe	65	-0.50 (-0.68, -0.33)	-0.29 (-0.42, -0.16)
NT-proBNP			
Below median	115	-0.36 (-0.48, -0.25)	-0.25 (-0.35, -0.15)
At/above median	115	-0.49 (-0.64, -0.34)	-0.36 (-0.48, -0.25)
BMI			
Below median	121	-0.50 (-0.64, -0.36)	-0.34 (-0.46, -0.22)
At/above median	117	-0.33 (-0.45, -0.22)	-0.28 (-0.38, -0.19)
eGFR			
Below median	120	-0.30 (-0.40, -0.20)	-0.28 (-0.38, -0.18)
At/above median	118	-0.57 (-0.72, -0.41)	-0.32 (-0.43, -0.22)
Weight			
Below median	123	-0.47 (-0.60, -0.34)	-0.32 (-0.44, -0.21)
At/above median	115	-0.36 (-0.48, -0.24)	-0.30 (-0.39, -0.20)
Type 2 Diabetes			
No	69	-0.48 (-0.66, -0.30)	-0.35 (-0.49, -0.20)
Yes	169	-0.39 (-0.50, -0.29)	-0.30 (-0.38, -0.21)
Ejection Fraction			
<= 40	115	-0.49 (-0.64, -0.35)	-0.33 (-0.43, -0.22)
> 40	108	-0.35 (-0.46, -0.24)	-0.29 (-0.39, -0.18)
Overall	***238***	***-0.42 (-0.52, -0.32)***	***-0.31 (-0.39, -0.23)***

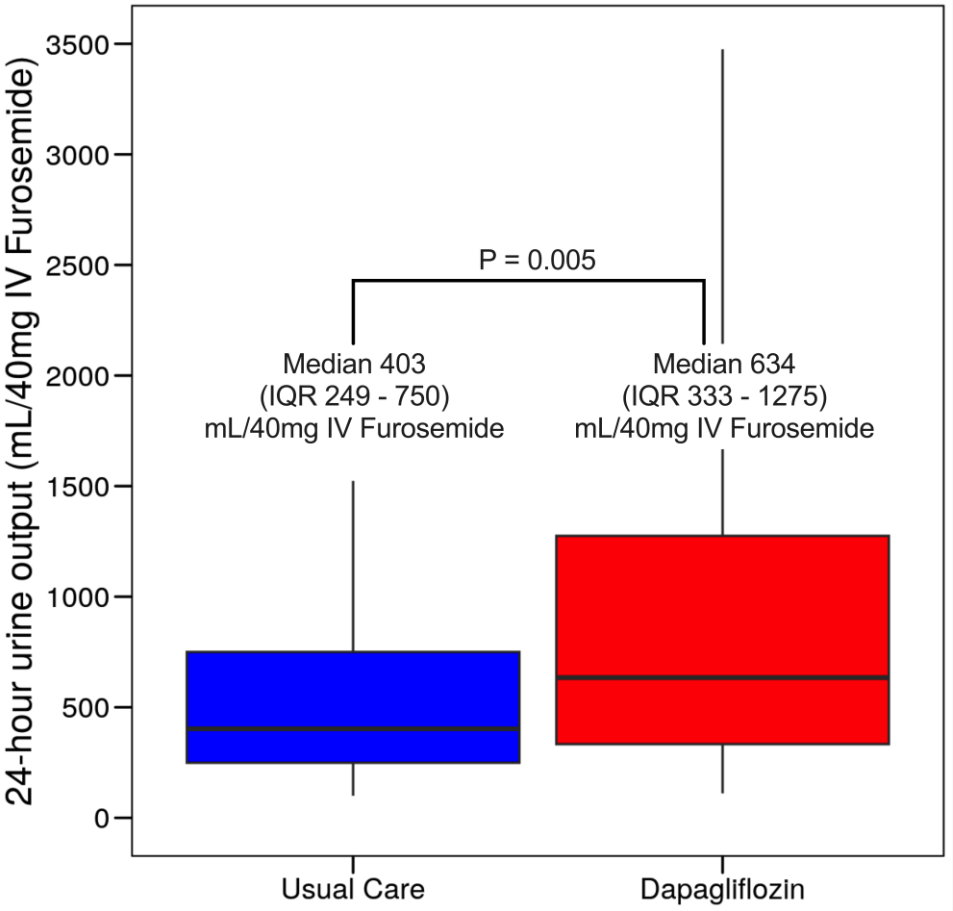


Improved 24-Hour Natriuresis with Dapagliflozin

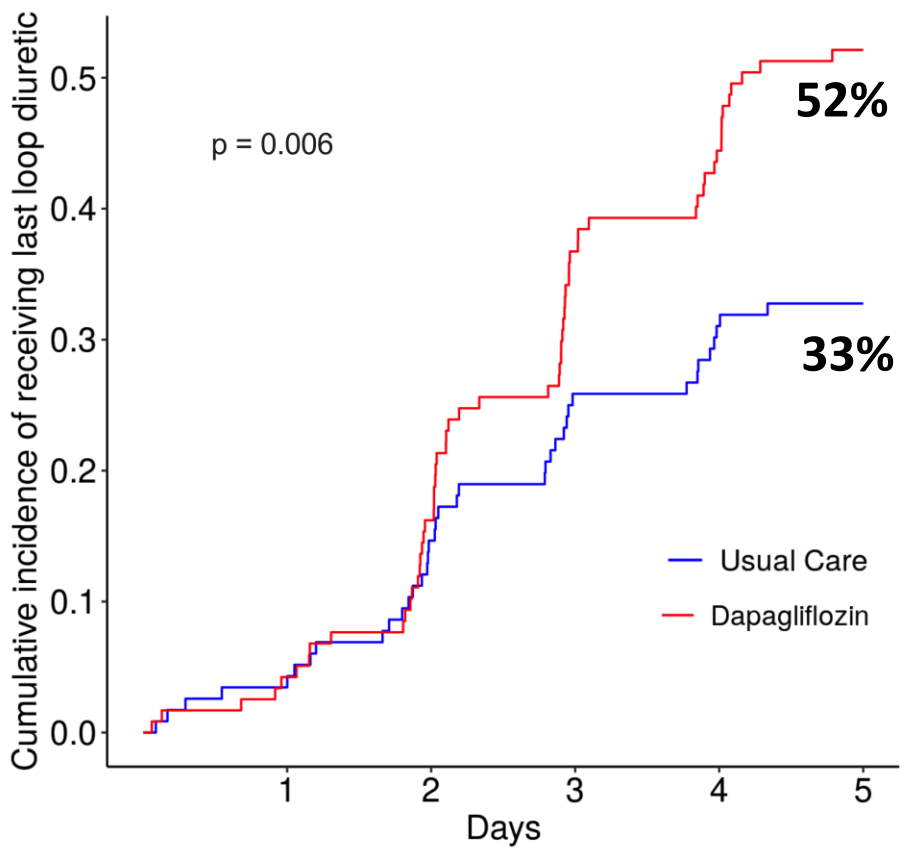


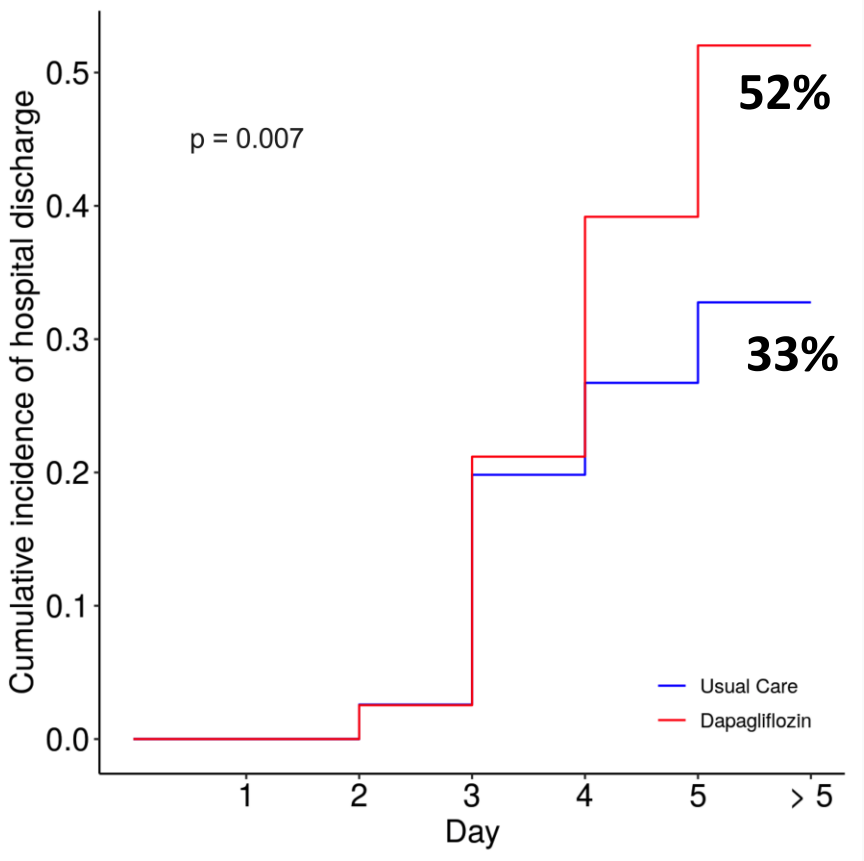


Improved 24-Hour Diuresis with Dapagliflozin



Shorter Time to discontinue IV Diuretics and to Discharge





Secondary Outcomes

Secondary Outcomes, N	Usual Care	Dapagliflozin
Worsening heart failure	3	4
30-day hospital readmission for ADHF or diabetes-related reasons	8	7
ADHF-related readmission	8	6
Diabetes-related readmission	0	1

Safety Outcomes and Adverse Events

Safety Outcomes	Usual Care	Dapagliflozin
Ketoacidosis	0	0
Symptomatic hypotension	4	2
Prolonged hospitalization for hypotension	1	1
Hypoglycemia	9	7
Prolonged hospitalization for hypoglycemia	0	0
Genitourinary tract infections	1	0
Change in eGFR (mL/min/1.73m^2)	-3.0 (-9 to 2)	-2.0 (-10 to 4)

Conclusions

Despite standardized, high-dose IV loop diuretics:

1. Dapagliflozin had a strong signal to improve diuretic efficiency supported by:
   - Increased natriuresis and diuresis per 40mg of IV furosemide
   - Decreased total dose and duration of loop diuretics required
   - Decreased time to hospital discharge
2. Early dapagliflozin initiation was safe across all diabetic and cardiorenal outcomes

Totality of DICTATE-AHF data supports the early initiation of dapagliflozin in AHF to safely facilitate decongestion and GDMT optimization

DICTATE-AHF Study Team

Principal Investigator: JoAnn Lindenfeld
Co- PI: Zachary Cox
Co- Investigator: Sean Collins

Site Investigators:
Zachary Cox, Pharm.D. – Vanderbilt University
Gabriel Hernandez, M.D. – University of Mississippi
Kirkwood Adams, M.D. – University of North Carolina
A. Tom McRae, M.D. – Centennial Hospital
Mark Aaron, M.D. - St Thomas Hospital System
Luke Cunningham, M.D. – Integris Medical Center

Clinical Coordinating Center:
Sean Collins, Christy Kampe, Karen Miller

Data Coordinating Center:
Chris Lindsell, Frank Harrell, Cathy Jenkins