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

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# Background

## Two Goals for Acute Heart Failure

1) Decongestion

2) GDMT Optimization

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<table>
<thead>
<tr>
<th>Treatment</th>
<th>Post-DC Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop + Acetazolamide</td>
<td>✔️</td>
</tr>
<tr>
<td>Loop + Thiazide</td>
<td>✔️</td>
</tr>
<tr>
<td>Loop + SGLT2i</td>
<td>?</td>
</tr>
</tbody>
</table>
Background

- Concerns of 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 hospitalized with hypervolemic AHF randomized within 24 hours of presentation
  • Regardless of LVEF
  • 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 \( \geq 25 \text{ mL/min/1.73m}^2 \)
Key Inclusion Criteria

• Age of 18 years or older
• Randomized within 24 hours of presentation hypervolemic AHF:
  o ≥2 objective measures of hypervolemia
• Planned or current use of IV loop diuretic therapy
• eGFR ≥ 25 mL/min/1.73m²
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)

< 24 hours

Hospital Admission

Study Day 1

Study Day 2

24H urine collection

Study Day 5

(Or D/C if sooner)

30-Day Follow-up

ESC Congress 2023
Amsterdam & Online
Study Outcomes

Primary Outcome

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
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Population (N=238)</th>
<th>Usual Care (N=119)</th>
<th>Dapagliflozin (N=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>65 (56 – 73)</td>
<td>64 (55 – 74)</td>
<td>65 (56 – 73)</td>
</tr>
<tr>
<td>Male Sex</td>
<td>61%</td>
<td>56%</td>
<td>66%</td>
</tr>
<tr>
<td>White Race</td>
<td>68%</td>
<td>71%</td>
<td>66%</td>
</tr>
<tr>
<td>T2DM</td>
<td>71%</td>
<td>71%</td>
<td>71%</td>
</tr>
<tr>
<td>LVEF ≤ 40%</td>
<td>52%</td>
<td>55%</td>
<td>48%</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>121 (110 – 136)</td>
<td>120 (110 – 136)</td>
<td>121 (112 – 136)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>53 (42 – 70)</td>
<td>54 (40 – 71)</td>
<td>51 (43 – 68)</td>
</tr>
<tr>
<td>IV furosemide dose prior to randomization (mg)</td>
<td>80 (40 – 140)</td>
<td>80 (80 – 120)</td>
<td>80 (40 - 160)</td>
</tr>
</tbody>
</table>
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

**Cumulative Weight Change**
- Usual Care: Median weight change
- Dapagliflozin: Median weight change
- P = 1.0

**Cumulative Loop Diuretic Dose**
- Usual Care: Median dose (IQR)
- Dapagliflozin: Median dose (IQR)
- P = 0.006

**Values**
- Usual Care: Median 800mg (IQR 380 - 1715)
- Dapagliflozin: Median 560mg (IQR 260 - 1150)
## Heterogeneity of Treatment Effect

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Treatment</th>
<th>Usual Care</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Estimated mean weight change per 40mg Furosemide-equivalents (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>145</td>
<td>-0.45 (-0.57, -0.33)</td>
<td>-0.32 (-0.43, -0.22)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>93</td>
<td>-0.36 (-0.50, -0.22)</td>
<td>-0.29 (-0.40, -0.19)</td>
<td></td>
</tr>
<tr>
<td><strong>Edema score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/Mild</td>
<td>68</td>
<td>-0.27 (-0.39, -0.15)</td>
<td>-0.34 (-0.49, -0.19)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>92</td>
<td>-0.51 (-0.67, -0.34)</td>
<td>-0.29 (-0.40, -0.19)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>65</td>
<td>-0.50 (-0.68, -0.33)</td>
<td>-0.29 (-0.42, -0.16)</td>
<td></td>
</tr>
<tr>
<td><strong>NT-proBNP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below median</td>
<td>115</td>
<td>-0.36 (-0.48, -0.25)</td>
<td>-0.25 (-0.35, -0.15)</td>
<td></td>
</tr>
<tr>
<td>Above median</td>
<td>115</td>
<td>-0.49 (-0.64, -0.34)</td>
<td>-0.36 (-0.48, -0.25)</td>
<td></td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below median</td>
<td>121</td>
<td>-0.50 (-0.64, -0.36)</td>
<td>-0.34 (-0.46, -0.22)</td>
<td></td>
</tr>
<tr>
<td>Above median</td>
<td>117</td>
<td>-0.33 (-0.45, -0.22)</td>
<td>-0.28 (-0.38, -0.19)</td>
<td></td>
</tr>
<tr>
<td><strong>eGFR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below median</td>
<td>120</td>
<td>-0.30 (-0.40, -0.20)</td>
<td>-0.28 (-0.38, -0.18)</td>
<td></td>
</tr>
<tr>
<td>Above median</td>
<td>118</td>
<td>-0.57 (-0.72, -0.41)</td>
<td>-0.32 (-0.43, -0.22)</td>
<td></td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below median</td>
<td>123</td>
<td>-0.47 (-0.60, -0.34)</td>
<td>-0.32 (-0.44, -0.21)</td>
<td></td>
</tr>
<tr>
<td>Above median</td>
<td>115</td>
<td>-0.36 (-0.48, -0.24)</td>
<td>-0.30 (-0.39, -0.20)</td>
<td></td>
</tr>
<tr>
<td><strong>Type 2 Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>69</td>
<td>-0.48 (-0.66, -0.30)</td>
<td>-0.35 (-0.49, -0.20)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>169</td>
<td>-0.39 (-0.50, -0.29)</td>
<td>-0.30 (-0.38, -0.21)</td>
<td></td>
</tr>
<tr>
<td><strong>Ejection Fraction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= 40</td>
<td>115</td>
<td>-0.49 (-0.64, -0.35)</td>
<td>-0.33 (-0.43, -0.22)</td>
<td></td>
</tr>
<tr>
<td>&gt; 40</td>
<td>108</td>
<td>-0.35 (-0.46, -0.24)</td>
<td>-0.29 (-0.39, -0.18)</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>238</td>
<td>-0.42 (-0.52, -0.32)</td>
<td>-0.31 (-0.39, -0.23)</td>
<td></td>
</tr>
</tbody>
</table>
Improved 24-Hour Natriuresis with Dapagliflozin

**Box Plot**

- **Usual Care**
  - Median 35 mmol/40mg IV Furosemide (IQR 19-63)
  - Median 50 mmol/40mg IV Furosemide (IQR 24-102)

- **Dapagliflozin**

**Bar Chart**

- **Usual Care**
  - Median 24-H IV Furosemide dose (mg): 280

- **Dapagliflozin**
  - Median 24-H IV Furosemide dose (mg): 240

**P-values**

- Median 35 vs. Median 50: $P = 0.025$
- Usual Care vs. Dapagliflozin: $P = 0.005$

**Legend**

- $\Delta$ 80mg IV Furosemide
Improved 24-Hour Diuresis with Dapagliflozin

- Median 403 mL/40mg IV Furosemide (IQR 249 - 750)
- Median 634 mL/40mg IV Furosemide (IQR 333 - 1275)

P = 0.005
Faster Time to Oral Diuretic Transition and Discharge

- **Left Graph:** Cumulative incidence of receiving last loop diuretic over days. The graph shows the progression over time with Usual Care and Dapagliflozin (Dapagliflozin is marked in red). The p-value is 0.006.

- **Right Graph:** Cumulative incidence of hospital discharge over days. The graph shows the progression over time with Usual Care and Dapagliflozin. The p-value is 0.007.
### Secondary Outcomes

<table>
<thead>
<tr>
<th>Secondary Outcomes, N</th>
<th>Usual Care</th>
<th>Dapagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening heart failure</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>30-day hospital readmission for ADHF or diabetes-related reasons</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>ADHF-related readmission</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Diabetes-related readmission</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
## Safety Outcomes and Adverse Events

<table>
<thead>
<tr>
<th>Safety Outcomes</th>
<th>Usual Care</th>
<th>Dapagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoacidosis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Symptomatic hypotension</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Prolonged hospitalization for hypotension</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Prolonged hospitalization for hypoglycemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Genitourinary tract infections</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Change in eGFR (mL/min/1.73m²)</td>
<td>-3.0 (-9 to 2)</td>
<td>-2.0 (-10 to 4)</td>
</tr>
</tbody>
</table>
Conclusions

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