DICTATE-AHF
Efficacy and Safety of Dapagliflozin in Acute Heart Failure
NCT04298229

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On behalf of DICTATE-AHF Investigators

August 28, 2023
## Background

### Two Goals for Acute Heart Failure

1) Decongestion

2) GDMT Optimization

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<table>
<thead>
<tr>
<th>Two Goals for Acute Heart Failure</th>
<th>Improve Post-DC Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop + Acetazolamide</td>
<td>No Improvement</td>
</tr>
<tr>
<td>Loop + Thiazide</td>
<td>No Improvement</td>
</tr>
<tr>
<td>Loop + SGLT2i</td>
<td>Improved Outcomes</td>
</tr>
</tbody>
</table>

**1) Decongestion**

- Loop + Acetazolamide: ✅
- Loop + Thiazide: ✅
- Loop + SGLT2i: ❓

**2) GDMT Optimization**

- Loop + Acetazolamide: ✗
- Loop + Thiazide: ✗
- Loop + SGLT2i: ✓

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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 $\geq 25 \text{ mL/min/1.73m}^2$
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)

Structured usual care with protocolized diuretic titration (N=120)

IV loops titrated via protocol in both treatment arms to Goal 3-5L UOP/day

Screening
Randomization
Baseline Assessments

< 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

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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
## Baseline Characteristics

<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/1.73m^2)</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
- Dapagliflozin

Cumulative Loop Diuretic Dose

- Median 800mg (IQR 380 - 1715)
- Median 560mg (IQR 260 - 1150)

P = 1.0

P = 0.006
# Heterogeneity of Treatment Effect

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Treatment</th>
<th>Usual Care</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></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>
</tr>
<tr>
<td>Female</td>
<td>93</td>
<td>-0.36 (-0.50, -0.22)</td>
<td>-0.29 (-0.40, -0.19)</td>
</tr>
<tr>
<td><strong>Edema score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/Mild</td>
<td>66</td>
<td>-0.27 (-0.39, -0.15)</td>
<td>-0.34 (-0.49, -0.19)</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>
</tr>
<tr>
<td>Severe</td>
<td>65</td>
<td>-0.50 (-0.68, -0.33)</td>
<td>-0.29 (-0.42, -0.16)</td>
</tr>
<tr>
<td><strong>NT-proBNP</strong></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>
</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>
</tr>
<tr>
<td><strong>BMI</strong></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>
</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>
</tr>
<tr>
<td><strong>eGFR</strong></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>
</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>
</tr>
<tr>
<td><strong>Weight</strong></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>
</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>
</tr>
<tr>
<td><strong>Type 2 Diabetes</strong></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>
</tr>
<tr>
<td>Yes</td>
<td>169</td>
<td>-0.39 (-0.50, -0.29)</td>
<td>-0.30 (-0.38, -0.21)</td>
</tr>
<tr>
<td><strong>Ejection Fraction</strong></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>
</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>
</tr>
</tbody>
</table>

**Overall**          | 238            | -0.42 (-0.52, -0.32) | -0.31 (-0.39, -0.23) |
Improved 24-Hour Natriuresis with Dapagliflozin

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

P = 0.025

P = 0.005

Δ 80mg IV Furosemide

Median 24-H IV Furosemide dose (mg)

Usual Care

Dapagliflozin

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Improved 24-Hour Diuresis with Dapagliflozin

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

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

P = 0.005

24-hour urine output (mL/40mg IV Furosemide)
Shorter Time to discontinue IV Diuretics and to Discharge

- **52%**
- **33%**

**p = 0.006**

**p = 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

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
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Co-Investigator: Sean Collins

Site Investigators:
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