High-Sensitivity Cardiac Troponin and the Efficacy of Dapagliflozin in Patients with Heart Failure with Reduced Ejection Fraction: An Analysis of the DAPA-HF Trial

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DAPA-HF Trial

Dapagliflozin (SGLT2 inhibitor) ↓ CV death, HF hospitalization, and urgent HF visits in ambulatory patients with HFrEF (LVEF ≤40%)

HR 0.74 (95% CI, 0.65-0.85)
p=0.00001

Background

• Circulating cardiac troponin T measured with high sensitivity assay (hsTnT), reflecting myocardial injury, is elevated in many patients with chronic HFrEF

• Higher levels of troponin are associated with a higher risk of adverse outcomes in patients with chronic HFrEF

• Concerns have been raised about possible attenuated treatment effect of SGLT2 inhibitors in patients with more advanced HFrEF

Objectives

• Assess the prognostic significance of hsTnT in patients with HFrEF

• Assess the benefit of dapagliflozin in HFrEF as a function of baseline hsTnT
Methods

Ambulatory patients with:
- NYHA class II-IV
- LVEF ≤ 40%
- Elevated NT-proBNP
- With or without T2DM
- Optimized GDMT

Placebo

- Median follow-up = 18 mo
- Primary composite outcome:
  - Cardiovascular death
  - HF hospitalization
  - Urgent HF visit

Dapagliflozin
(10 mg daily)

- Other secondary outcome:
  - All-cause mortality

N = 4,744
n = 3,138 (66%)

➢ Prespecified nested biomarker substudy of DAPA-HF
➢ hsTnT (Roche Diagnostics) measured (TIMI Biomarker Laboratory)
Troponin Distribution

Median (25\textsuperscript{th}-75\textsuperscript{th}):
20.0 (13.7-30.2) ng/L

99\textsuperscript{th} percentile URL (14 ng/L)

Limit of quantitation (6 ng/L)

Frequency

Percentage of Patients with hsTnT ≥ 6 ng/L
98.2%

Percentage of Patients with hsTnT ≥ 14 ng/L
73.7%
### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>hsTnT &lt; Median (&lt;20.0 ng/L)</th>
<th>hsTnT ≥ Median (≥20.0 ng/L)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>65 ± 10</td>
<td>69 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>72</td>
<td>85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type 2 diabetes (%)</td>
<td>34</td>
<td>49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic etiology (%)</td>
<td>57</td>
<td>62</td>
<td>0.008</td>
</tr>
<tr>
<td>NYHA class III or IV (%)</td>
<td>26</td>
<td>36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml), median (IQR)</td>
<td>1,162 (722-1,917)</td>
<td>1,831 (1,075-3,440)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF, mean ± SD</td>
<td>32 ± 7</td>
<td>31 ± 7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²), mean ± SD</td>
<td>71 ± 18</td>
<td>60 ± 18</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Primary Outcome by Baseline hsTnT

Cardiovascular Death, HF Hospitalization, or Urgent HF Visit

### Baseline hsTnT
- Quartile 4 (≥30.2 ng/L)
- Quartile 3 (20.0-30.2 ng/L)
- Quartile 2 (13.7-20.0 ng/L)
- Quartile 1 (≤13.7 ng/L)

### Event Rate (n/N)
- Quartile 4: 31.2%
- Quartile 3: 22.4%
- Quartile 2: 13.9%
- Quartile 1: 6.3%

### Adjusted HR (95% CI)*
- Quartile 4: 5.10 (3.67, 7.08)
- Quartile 3: 3.60 (2.60, 5.01)
- Quartile 2: 2.20 (1.56, 3.11)

**ARD = 24.9%**

*Adjusted HR (95% CI)*

* Adjusted HR is derived from Cox proportional hazards models stratified by DM status and adjusted for randomized treatment, age, sex, eGFR, history of HF hospitalization, principal cause of HF (ischemic vs non-ischemic).
Secondary Outcomes by Baseline hsTnT

Hospitalization for Heart Failure
- Quartile 1: 6.1
- Quartile 2: 11.0
- Quartile 3: 16.9
- Quartile 4: 24.8

Cardiovascular Death
- Quartile 1: 2.2
- Quartile 2: 7.8
- Quartile 3: 14.3
- Quartile 4: 17.2

All-cause Mortality
- Quartile 1: 3.3
- Quartile 2: 9.3
- Quartile 3: 16.9
- Quartile 4: 20.6

* Cox proportional hazards models stratified by DM status and adjusted for randomized treatment, age, sex, eGFR, history of HF hospitalization, principal cause of HF (ischemic vs non-ischemic)
Primary Outcome by Baseline hsTnT and NT-proBNP

Cardiovascular Death, HF Hospitalization, or Urgent HF Visit

**hsTnT**
- Q1: ≤13.7 ng/L
- Q2: 13.7-20.0 ng/L
- Q3: 20.0-30.2 ng/L
- Q4: ≥30.2 ng/L

**NT-proBNP**
- Q1: <857 pg/mL
- Q2: 857-1,437 pg/mL
- Q3: 1,438-2,649 pg/mL
- Q4: ≥2,650 pg/mL

Event Rate (n/N) (%)
Dapagliflozin Effect by Baseline hsTnT

Primary Outcome

Cumulative Event Rate (n/N) (%)

Q1 Q2 Q3 Q4
0 10 20 30
5.9 11.1 20.8 27.6

HR 0.89
(0.51 - 1.57)

HR 0.61
(0.41 - 0.89)

HR 0.85
(0.63 - 1.15)

HR 0.73
(0.57 - 0.95)

p-interaction = 0.55

hsTnT Quartile 4
ARR = 7.5% (95% CI, 1.0% - 14.0%)
Dapagliflozin Effect on Secondary Outcomes

Consistent treatment effect across quartiles of baseline hsTnT concentration for all secondary EPs

Hospitalization for Heart Failure
- HR 0.74 (0.54-1.02)
- HR 0.49 (0.29-0.82)
- HR 0.86 (0.59-1.25)
- HR 0.81 (0.42-1.56)

Cardiovascular Death
- HR 0.79 (0.56-1.11)
- HR 0.91 (0.63-1.32)
- HR 0.63 (0.38-1.05)
- HR 0.91 (0.35-2.37)

All-cause Mortality
- HR 0.82 (0.60-1.11)
- HR 0.65 (0.41-1.04)
- HR 1.03 (0.48-2.23)

Placebo
Dapagliflozin

p-interaction = 0.41
p-interaction = 0.47
p-interaction = 0.67

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Summary

- Patients with HFrEF in DAPA-HF had evidence of chronic myocardial injury (~75% had hsTnT value above 99th percentile URL)

- Higher baseline concentration of hsTnT associated with up to 5-fold higher risk of HF events and death

- Highest risk of worsening HF or CV death (up to 10-fold) observed in patients with elevations in both hsTnT and NT-proBNP

- Cardiovascular benefits of dapagliflozin in patients with HFrEF were consistent irrespective of baseline hsTnT concentration

- Patients in top hsTnT quartile enjoyed numerically largest ARR