Growth Differentiation Factor-15, Clinical Outcomes, and the Effect of Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction: Insights from the DAPA-HF Trial

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BACKGROUND

• Growth differentiation factor-15 (GDF-15), a stress-induced cytokine associated with adverse cardiovascular outcomes, is an emerging therapeutic target in heart failure (HF).

• Little is known about the effect of SGLT2i on clinical outcomes in relation to GDF-15 and the effect of SGLT2i on circulating GDF-15 levels.

METHODS

• DAPA-HF was a randomized, placebo-controlled trial of the SGLT2i dapagliflozin in patients with NYHA class II-IV HF and LVEF ≤40% (median follow-up = 18 mo).

• Prespecified nested biomarker substudy of DAPA-HF: GDF-15 (Roche) measured at baseline in 3,103 patients and at 1 year in 2,464 patients.

• Primary composite endpoint was adjudicated on circulating GDF-15 levels.

• Hazard ratios for associations of GDF-15 with outcomes adjusted for age, sex, BMI, eGFR, T2DM, NYHA class, principal cause of HF, LVEF, NT-proBNP (log), hsTnT (log), and randomized treatment.

• Comparative effects of dapagliflozin vs. placebo on clinical outcomes assessed across quartiles of baseline GDF-15 using Cox regression with a randomized treatment-by-GDF-15 quartile interaction term.

• Effect of dapagliflozin on change in GDF-15 from baseline to 1 year explored using ANCOVA model.

RESULTS

• Median baseline GDF-15 = 1888 (IQR, 1323-2755) pg/ml

Table 1. Baseline characteristics by baseline GDF-15 level.

<table>
<thead>
<tr>
<th>GDF-15</th>
<th>&lt;Median</th>
<th>≥Median</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>64.1±10.6</td>
<td>70.4±9.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>75.2%</td>
<td>81.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.0±6.1</td>
<td>28.1±5.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>73.1±17.0</td>
<td>57.1±17.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>29.6%</td>
<td>53.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>31.3±6.7</td>
<td>31.6±6.8</td>
<td>0.42</td>
</tr>
<tr>
<td>NYHA III or IV</td>
<td>26.6%</td>
<td>35.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>KCCQ-TSS</td>
<td>80.6±14.5</td>
<td>75.7±9.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

• Patients with higher GDF-15 were older, and more likely to have T2DM, lower BMI, lower eGFR, and poorer health status reflected by NYHA class and KCCQ-TSS (Table 1).

Figure 1. Adjusted outcome associations by GDF-15 quartile.

- Worsening Heart Failure or CV Death

- Adjusted HR (95% CI)

Q1: 2.3 (1.7-3.2)  
Q2: 1.7 (1.2-2.3)  
Q3: 1.3 (1.01-1.8)  
Q4: Reference

- When GDF-15 and NT-proBNP were considered collectively, GDF-15 identified gradients of risk within quartiles of NT-proBNP (Figure 2).

- Although relative reduction in risk of worsening HF or CV death with dapagliflozin was consistent across quartiles (p-interaction = 0.96), absolute risk reduction was greater in patients with higher GDF-15 (p-trend < 0.01; Figure 3).

- Dapagliflozin did not significantly change GDF-15 levels over 1 year compared to placebo (relative LS mean change, +4% [95% CI, -2% to +10%]).

CONCLUSIONS

- Higher GDF-15 predicts greater risk of worsening HF or cardiovascular death and may identify patients with HF who derive greater absolute benefit from SGLT2i.

- The clinical benefits of dapagliflozin are not likely related to effects on GDF-15.