Heart failure risk stratification and efficacy of dapagliflozin in patients with type 2 diabetes mellitus

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Topic(s):
Diabetes and the Heart: Pharmacotherapy

Citation:
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SAVOR-TIMI 53 and DECLARE-TIMI 58 were sponsored by AstraZeneca.

Background: Patients with type 2 diabetes mellitus (T2DM) are at increased risk of developing heart failure (HF). Treatment with sodium-glucose cotransporter-2 (SGLT2) inhibitors reduces the risk of hospitalization for HF (HHF) in patients with T2DM.

Purpose: To develop and validate a practical, multivariable clinical risk score for HHF in patients with T2DM and assess whether this score can identify high-risk patients with T2DM who have the greatest reduction in risk for HHF with an SGLT2 inhibitor.

Methods: We developed a clinical risk score for centrally-adjudicated HHF using independent clinical risk indicators of HHF in 8212 patients with T2DM in the placebo arm of SAVOR-TIMI 53. Candidate variables were assessed using multivariable Cox regression and independent clinical risk indicators achieving statistical significance of p<0.001 were included in the risk score and given weights proportional to the regression coefficients. We externally validated the score in 8578 patients with T2DM in the placebo arm of DECLARE-TIMI 58. Discrimination was assessed using Harrell's c-index. The relative and absolute risk reductions in HHF with the SGLT2 inhibitor dapagliflozin were assessed by baseline HHF risk.

Results: The 5 independent clinical risk indicators were prior heart failure, atrial fibrillation, coronary artery disease, estimated glomerular filtration rate (eGFR), and urine albumin/creatinine ratio (UACR). (Fig-left). A simple integer-based scheme using these predictors identified a strong >16-fold gradient of HHF risk (p-trend <0.001) in both the derivation and validation cohorts, with c-indices of 0.81 and 0.78, respectively. Whereas relative risk reductions were similar across the risk score (25-34%), absolute risk reductions were greater in those at higher baseline risk (interaction p-value for absolute risk reduction <0.01), with high-risk (2 points) and very high-risk patients (=3 points) having 1.5% and 2.7% absolute risk reductions in HHF at 4 years with dapagliflozin, translating into NNTs of only 65 and 36, respectively (Fig-right).

Conclusion(s): Risk stratification using a novel clinical risk score for HHF in patients with T2DM identifies patients at higher risk for HHF who derive greater benefit from treatment with the SGLT2 inhibitor dapagliflozin.
Abstract: Heart failure risk stratification and efficacy of dapagliflozin in patients with type 2 diabetes mellitus

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Methods: We developed a clinical risk score for centrally adjudicated HHF using independent clinical risk indicators of HHF in 8,212 patients with T2DM in the placebo arm of SAVOR-TIMI 53. Candidate variables were assessed using multivariable Cox regression and independent clinical risk indicators achieving statistical significance of p<0.001 were included in the risk score and given weights proportional to the regression coefficients. We externally validated the score in 8,578 patients with T2DM in the placebo arm of DECLARE-TIMI 58. Discrimination was assessed using Harrell’s c-index. The relative and absolute risk reductions in HHF with the SGLT2 inhibitor dapagliflozin were assessed by baseline HHF risk.

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<table>
<thead>
<tr>
<th>Risk Indicator</th>
<th>Adjusted HR (95% CI)</th>
<th>P-value</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Heart Failure</td>
<td>4.22 (3.18 - 5.59)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>2.26 (1.62 - 3.14)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>2.06 (1.45 - 2.93)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Urine ACR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;300 (mg/g)</td>
<td>4.39 (3.10 - 6.23)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>30-300 (mg/g)</td>
<td>2.00 (1.44 - 2.76)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Estimated GFR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 (ml/min<em>1.73</em>m^-2)</td>
<td>1.85 (1.40 - 2.46)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
</tbody>
</table>

C-index (derivation) = 0.81  C-index (validation) = 0.78

Effect of Dapagliflozin on HHF by Risk Score

**Table:**

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>N (%)</th>
<th>Event Rates [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0)</td>
<td>6,953 (41%)</td>
<td>0.9, 0.6</td>
</tr>
<tr>
<td>Intermediate (1)</td>
<td>5,325 (32%)</td>
<td>1.8, 1.2</td>
</tr>
<tr>
<td>High (2)</td>
<td>2,488 (15%)</td>
<td>5.1, 3.6</td>
</tr>
<tr>
<td>Very High (3)</td>
<td>2,076 (12%)</td>
<td>14.1, 11.4</td>
</tr>
</tbody>
</table>

**Graph:**

- HR 0.67 (0.45-0.99)
  - ARR = 1.5%
  - NNT = 65
- HR 0.74 (0.47-1.15)
  - ARR = 0.6%
  - NNT = 172
- HR 0.66 (0.39-1.13)
  - ARR = 0.3%
  - NNT = 303

**Legend:**

- Placebo
- Dapagliflozin

**Notes:**

- HR = Hazard Ratio
- ARR = Absolute Risk Reduction
- NNT = Number Needed to Treat