The Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure Trial (DAPA-HF)

Results in Nondiabetic Patients

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On behalf of the DAPA-HF Committees and Investigators
Disclosures

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My institution has been paid by AstraZeneca for my time spent as principal investigator for DAPA-HF and for advisory boards related to dapagliflozin, diabetes and heart failure.
Sodium-glucose co-transporter 2 (SGLT2) inhibitors prevent the development of heart failure in patients with type 2 diabetes (T2D). Can they be used to treat patients with established heart failure?

The benefits of SGLT2 inhibitors may be glucose-independent. Can SGLT2 inhibitors be used to treat patients without T2D?

We tested the SGLT2 inhibitor dapagliflozin, 10 mg once daily, added to standard therapy, in patients with heart failure and reduced ejection fraction (HFrEF) both with and without T2D.
Inclusion:
• NYHA class II-IV
• LVEF ≤40%
• NT-proBNP ≥600 pg/ml*

Exclusion:
• eGFR <30 ml/min/1.73 m²
• SBP <95 mmHg
• type 1 diabetes

N=2371 Placebo
N=2373 Dapagliflozin 10 mg once daily

≥844 Primary endpoints
Composite of:
• CV death
• HF hospitalization
• Urgent HF visit

4,744 patients 20 countries

Event-driven

Visit 1 Visit 2 Visit 3 Visit 4 Visit 5 Visit 6 etc.
Day -14 Day 0 Day 14 Day 60 Day 120 Every 120 days

*≥400 pg/ml if HF hospitalization within ≤12 months; ≥900 pg/ml if atrial fibrillation/flutter
### Key baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diabetes (n=2139)*</th>
<th>No diabetes (n=2605)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>67</td>
<td>66</td>
</tr>
<tr>
<td>Male (%)</td>
<td>78</td>
<td>76</td>
</tr>
<tr>
<td>NYHA class II/III/IV (%)</td>
<td>64/35/1</td>
<td>71/29/1</td>
</tr>
<tr>
<td>Mean LVEF (%)</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Median NT-proBNP (pg/ml)</td>
<td>1484</td>
<td>1413</td>
</tr>
<tr>
<td>Mean systolic BP (mmHg)</td>
<td>123</td>
<td>121</td>
</tr>
<tr>
<td>Ischaemic aetiology (%)</td>
<td>62</td>
<td>51</td>
</tr>
<tr>
<td>Mean eGFR (ml/min/1.73m²)</td>
<td>63</td>
<td>68</td>
</tr>
<tr>
<td>eGFR &lt;60 ml/min/1.73m² (%)</td>
<td>46</td>
<td>36</td>
</tr>
<tr>
<td>Prior heart failure hospitalization (%)</td>
<td>49</td>
<td>46</td>
</tr>
</tbody>
</table>

*includes 156 patients with previously undiagnosed diabetes i.e. two HbA1c ≥6.5% (≥48 mmol/mol)
### Baseline treatment

<table>
<thead>
<tr>
<th>Treatment (%)</th>
<th>Diabetes (n=2139)</th>
<th>No diabetes (n=2605)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic</td>
<td>95</td>
<td>92</td>
</tr>
<tr>
<td>ACE-inhibitor/ARB/ARNI*</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>55</td>
<td>57</td>
</tr>
<tr>
<td>ARB</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>Sacubitril/valsartan</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>97</td>
<td>96</td>
</tr>
<tr>
<td>MRA</td>
<td>72</td>
<td>71</td>
</tr>
<tr>
<td>ICD*</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>CRT**</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

*ARNI = angiotensin receptor neprilysin inhibitor

*ICD or CRT-D  **CRT-P or CRT-D
Primary outcome
Primary composite outcome
CV Death/HF hospitalization/Urgent HF visit

Diabetes

HR 0.75 (0.63, 0.90)

Placebo
Dapagliflozin

No Diabetes

HR 0.73 (0.60, 0.88)

Placebo
Dapagliflozin

P interaction 0.80

Number at Risk
Dapagliflozin 1075 1037 994 955 876 678 500 259 88
Placebo 1064 1005 949 899 816 630 469 253 89

Number at Risk
Dapagliflozin 1298 1268 1227 1192 1126 882 646 353 122
Placebo 1307 1253 1214 1176 1101 848 627 340 121
Components of primary outcome

Cardiovascular death

Diabetes

HR 0.79 (0.63, 1.01)

No Diabetes

HR 0.85 (0.66, 1.10)

P interaction 0.70
Components of primary outcome

Worsening HF event

Diabetes

Placebo

HR 0.77 (0.61, 0.95)

Dapagliflozin

HR 0.62 (0.48, 0.80)

No Diabetes

Placebo

P interaction 0.23
Secondary outcomes
In order of hierarchical testing
CV death or HF hospitalization

Diabetes

HR 0.75 (0.63, 0.90)

Placebo

Dapagliflozin

No Diabetes

HR 0.73 (0.60, 0.89)

Placebo

Dapagliflozin

P interaction 0.83
Total HF hospitalizations and CV death
Including first and repeat hospitalizations

Diabetes
Rate Ratio 0.77 (0.63, 0.94)

P interaction 0.74

No Diabetes
Rate Ratio 0.73 (0.59, 0.91)

Placebo
Dapagliflozin
Clinically meaningful change (≥5 points) in KCCQ-TSS

**Diabetes**

- Placebo: 0.78 (0.71, 0.87)
- Dapagliflozin: 1.20 (1.09, 1.31)

**No diabetes**

- Placebo: 0.88 (0.81, 0.97)
- Dapagliflozin: 1.12 (1.03, 1.22)

Odds ratio: 1.20 (1.09, 1.31) for diabetes, 1.12 (1.03, 1.22) for no diabetes

P interaction: 0.74
Worsening renal function endpoint

Composite of: Sustained* ≥50% reduction in eGFR, end-stage renal disease (ESRD) or death from renal causes

<table>
<thead>
<tr>
<th></th>
<th>Placebo No. (%)</th>
<th>Dapagliflozin No. (%)</th>
<th>Hazard ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes (n=2139)</td>
<td>24 (2.3)</td>
<td>18 (1.7)</td>
<td>0.73 (0.39, 1.34)</td>
</tr>
<tr>
<td>No diabetes (n=2605)</td>
<td>15 (1.2)</td>
<td>10 (0.8)</td>
<td>0.67 (0.30, 1.49)</td>
</tr>
</tbody>
</table>

ESRD consisted of sustained eGFR below 15 ml/min/1.73m², sustained dialysis or kidney transplantation *Sustained = 28 days or more

P interaction 0.86
All-cause death

Diabetes

HR 0.78 (0.63, 0.97)

No Diabetes

HR 0.88 (0.70, 1.12)

P interaction 0.45
Treatment effect according to baseline HbA1c
## Treatment effect by diabetes status and HbA1c

### Primary endpoint

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin (n=2373)</th>
<th>Placebo (n=2371)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>386/2373</td>
<td>502/2371</td>
<td>0.74 (0.65, 0.85)</td>
</tr>
<tr>
<td>Type 2 diabetes at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>215/1075</td>
<td>271/1064</td>
<td>0.75 (0.63, 0.90)</td>
</tr>
<tr>
<td>No</td>
<td>171/1298</td>
<td>231/1307</td>
<td>0.73 (0.60, 0.88)</td>
</tr>
<tr>
<td>HbA1c tertiles in patients without T2D at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5.6%</td>
<td>65/521</td>
<td>77/485</td>
<td>0.74 (0.53, 1.04)</td>
</tr>
<tr>
<td>5.7-5.9%</td>
<td>44/365</td>
<td>66/388</td>
<td>0.71 (0.48, 1.04)</td>
</tr>
<tr>
<td>≥6.0%</td>
<td>62/408</td>
<td>87/432</td>
<td>0.72 (0.52, 1.00)</td>
</tr>
</tbody>
</table>
Treatment effect according to baseline HbA1c (All patients)

Primary endpoint

Cardiovascular death

HR=1 (unity)

Placebo better

Dapa better

Continuous HR

95%CI

Baseline HbA1c (%)
Safety and tolerability
## Safety/adverse events (AEs)

<table>
<thead>
<tr>
<th>Patients exposed to at least one dose of study drug*</th>
<th>Diabetes</th>
<th>No diabetes</th>
<th>P-value</th>
<th>Diabetes</th>
<th>No diabetes</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Dapa</td>
<td></td>
<td>Placebo</td>
<td>Dapa</td>
<td></td>
</tr>
<tr>
<td>AE of interest (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume depletion</td>
<td>7.8</td>
<td>7.8</td>
<td>1.00</td>
<td>6.1</td>
<td>7.3</td>
<td>0.24</td>
</tr>
<tr>
<td>Renal AE</td>
<td>8.7</td>
<td>8.5</td>
<td>0.94</td>
<td>6.0</td>
<td>4.8</td>
<td>0.19</td>
</tr>
<tr>
<td>Fracture</td>
<td>2.4</td>
<td>2.1</td>
<td>0.66</td>
<td>1.9</td>
<td>2.1</td>
<td>0.78</td>
</tr>
<tr>
<td>Amputation</td>
<td>0.8</td>
<td>1.1</td>
<td>0.66</td>
<td>0.2</td>
<td>0.1</td>
<td>N/A</td>
</tr>
<tr>
<td>Major hypoglycaemia+</td>
<td>0.4</td>
<td>0.4</td>
<td>N/A</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>0</td>
<td>0.3</td>
<td>N/A</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>AE leading to treatment discontinuation (%)</td>
<td>5.4</td>
<td>4.0</td>
<td>0.15</td>
<td>4.5</td>
<td>5.3</td>
<td>0.41</td>
</tr>
<tr>
<td>Any serious AE (incl. death) (%)</td>
<td>48.3</td>
<td>41.7</td>
<td>0.002</td>
<td>36.9</td>
<td>34.6</td>
<td>0.24</td>
</tr>
</tbody>
</table>

*The safety population included patients receiving ≥1 dose of trial medication: dapagliflozin n= 2368 and placebo n=2368. *Major hypoglycemia defined as hypoglycemia requiring the assistance of another person to actively administer carbohydrates, glucagon, or take other corrective action.
Summary and conclusions

• When added to standard therapy, dapagliflozin reduced the risk of worsening heart failure events and cardiovascular death, and improved symptoms, in patients with HFrEF, both with and without T2D.

• The relative and absolute risk reductions in death and hospitalization were substantial, clinically important, and consistent in patients with and without T2D.

• Dapagliflozin was well tolerated and the rate of treatment discontinuation was low in patients with and without T2D.

• Dapagliflozin offers a new approach to the treatment of HFrEF in patients with and without T2D.