Journal Club - DAPA-HF trial

Emma de Louw, PGY-3
Thomas Jefferson University

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Journal Club

DAPA-HF trial

Emma de Louw, PGY-3
9/24/20
Disclosures

I have no disclosures
Outline

- Heart failure background
- Overview SGLT-2 inhibitor
- Previous evidence
- DAPA-HF trial
  - Aim
  - Methods
  - Results
  - Limitations
  - Conclusion
- Future directions
- Translate to JFMA
Heart failure

- ~6.2 million adults in the US
- High costs: $30.7 billion (‘12)
- Treatment guidelines HFrEF (2017):
  - Beta blocker + diuretic + ACEi/ARB/ARNI
<table>
<thead>
<tr>
<th>New York Heart Association classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Asymptomatic</td>
</tr>
<tr>
<td>II: Minor symptoms, symptoms with modest exertion</td>
</tr>
<tr>
<td>III: Moderate symptoms, symptoms with minor exertion</td>
</tr>
<tr>
<td>IV: Symptoms at rest</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>American College of Cardiology/American Heart Association classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: At risk of heart failure but without structural disease</td>
</tr>
<tr>
<td>B: Structural heart failure but without symptoms</td>
</tr>
<tr>
<td>C: Structural heart failure with current or prior symptoms</td>
</tr>
<tr>
<td>D: Symptoms at rest</td>
</tr>
</tbody>
</table>
SGLT-2 inhibitors

- Block glucose reabsorption in blood
- Increased urinary glucose & sodium secretion
- Side effects:
  - Increased UTI
  - Genital mycotic infections
  - Increased risk of DKA
  - Fournier’s gangrene
  - AKI
  - Hypotension, dehydration
SGLT-2 inhibitors

“Gliflozins”:

- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
- Ertugliflozin (Steglatro)
A schematic representation of the different mechanisms implicated in the cardiovascular benefits of SGLT2 inhibitors.
Previous evidence

- SGLT2 inhibitors decrease risk of first hospitalization for heart failure in patients with DM2 (25 - 35%) = prevention
- CANVAS + EMPA-REG: mechanisms CV benefit likely driven by reduced HF death
- EMPA-REG OUTCOME: reduced risk of pump failure and sudden deaths
- DECLARE-TIMI 58: no reduction in major adverse CV events, but reduction in CV death or HF hospitalization (Esp. HFrEF)

→ Can SGLT-2 inhibitors treat HFrEF?
Benefits on HF could not be explained by diuretic or anti-hyperglycemic effects.

Benefits may be mediated by the inhibition of sodium-hydrogen exchange rather than the effect on glucose reabsorption.

Reduced cardiac injury, hypertrophy, fibrosis, systolic dysfunction.

Will it work for patients without DM?

Effects of Sodium-Glucose Cotransporter 2 Inhibitors for the Treatment of Patients With Heart Failure
Proposal of a Novel Mechanism of Action

Milton Packer, MD; Stefan D. Anker, MD; Javed Butler, MD, MPH; et al

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

Aim

“To prospectively evaluate the efficacy and safety of the SGLT2 inhibitor dapagliflozin in patients with heart failure and a reduced ejection fraction, regardless of the presence or absence of diabetes”
Methods

- Trial design
- Patients
- Outcomes
- Statistical analyses
Methods – Trial design

- Phase 3, Randomized, Double-Blinded
- Placebo-controlled
  - Dapagliflozin 10 mg vs Placebo
  - + Conventional HF therapy
- 410 centers in 20 countries
- N = 4744
- Stratification: DM2 (A1c ≥ 6.5%)
- Median follow up time: 18.2 months
  - 14 days, 60 days, q4 months

- In collaboration with sponsor: AstraZeneca
  - Analyses replicated by independent academic group
Clinical Trials

Clinical Trial Phases

PHASE I
Safety
20–80 Participants
Drug approved for testing in humans

PHASE II
Safety and Dosing
100–300 Participants
Drug submitted for FDA approval

PHASE III
Safety and Efficacy
300–3000 Participants

PHASE IV
Post approval surveillance
1000+ Participants
Drug approved

Phase 1
1 month
10-20
Is it safe?
How does the body process it?
What are the side effects?

Phase 2
3 - 12 months
50-75
Is it safe?
How well is it working?
How much should be taken?

Phase 3
6 - 12 months
100-300
Is it safe?
How well is it working?
Does the benefit outweigh the risk?

Phase 4
3 - 12 months
100-300
Does it still appear to be safe?
Are there rare side effects?
Cost effectiveness & comparison to other similar drugs

FDA Approval
Application submitted
Application reviewed
Application Approved
Available to public

*number of participants varies based on study characteristics

15 healthy participants
15 participants with CF
Number of months of participant involvement
Methods - Patients

Inclusion criteria:

- Age ≥ 18 years
- EF ≤ 40%
- NYHA class II-IV
- NT-proBNP ≥ 600 pg/ml
  - or ≥ 400 pg/ml if HF hospitalization in previous 12 mo
  - Afib or Aflutter: NT-proBNP ≥ 900 mg/ml
- Standard treatment for heart failure
  - Device: ICD, cardiac resynchronization therapy, or both
  - Meds: ACEi, ARB, sacubitril-valsartan + beta-blocker +/- mineralocorticoid receptor antagonist
- DM: continued to take glucose-lowering therapy
  - Doses could be adjusted as required (insulin, sulfonylurea)
Methods – Patients

Exclusion criteria:

- Recent treatment with SGLT2 inhibitor
- Unacceptable side effects associated with SGLT2 inhibitor
- DM type 1
- Symptomatic hypotension or SBP < 95 mmHg
- eGFR ≤ 30
Figure 1. Enrollment and Follow-up.
All the patients who underwent randomization were included in the primary analysis. Patients who did not receive a dose of either dapagliflozin or placebo were excluded from the safety analysis.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dapagliflozin (N=2373)</th>
<th>Placebo (N=2371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>66.2±11.0</td>
<td>66.5±10.8</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>564 (23.8)</td>
<td>545 (23.0)</td>
</tr>
<tr>
<td>Body-mass index†</td>
<td>28.2±6.0</td>
<td>28.1±5.9</td>
</tr>
<tr>
<td>Race — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1662 (70.0)</td>
<td>1671 (70.5)</td>
</tr>
<tr>
<td>Black</td>
<td>122 (5.1)</td>
<td>104 (4.4)</td>
</tr>
<tr>
<td>Asian</td>
<td>552 (23.3)</td>
<td>564 (23.8)</td>
</tr>
<tr>
<td>Other</td>
<td>37 (1.6)</td>
<td>32 (1.3)</td>
</tr>
<tr>
<td>Region — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>335 (14.1)</td>
<td>342 (14.4)</td>
</tr>
<tr>
<td>South America</td>
<td>401 (16.9)</td>
<td>416 (17.5)</td>
</tr>
<tr>
<td>Europe</td>
<td>1094 (46.1)</td>
<td>1060 (44.7)</td>
</tr>
<tr>
<td>Asia–Pacific</td>
<td>543 (22.9)</td>
<td>553 (23.3)</td>
</tr>
<tr>
<td>NYHA functional classification — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1606 (67.7)</td>
<td>1597 (67.4)</td>
</tr>
<tr>
<td>III</td>
<td>747 (31.5)</td>
<td>751 (31.7)</td>
</tr>
<tr>
<td>IV</td>
<td>20 (0.8)</td>
<td>23 (1.0)</td>
</tr>
<tr>
<td>Heart rate — beats/min</td>
<td>71.5±11.6</td>
<td>71.5±11.8</td>
</tr>
<tr>
<td>Systolic blood pressure — mm Hg</td>
<td>122.0±16.3</td>
<td>121.6±16.3</td>
</tr>
<tr>
<td>Left ventricular ejection fraction — %</td>
<td>31.2±6.7</td>
<td>30.9±6.9</td>
</tr>
<tr>
<td>Median NT-proBNP (IQR) — pg/ml</td>
<td>1428 (857–2655)</td>
<td>1446 (857–2641)</td>
</tr>
<tr>
<td>Principal cause of heart failure — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>1316 (55.5)</td>
<td>1358 (57.3)</td>
</tr>
<tr>
<td>Nonischemic</td>
<td>857 (36.1)</td>
<td>830 (35.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>200 (8.4)</td>
<td>183 (7.7)</td>
</tr>
<tr>
<td>Medical history — no. (%)</td>
<td>1124 (47.4)</td>
<td>1127 (47.5)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>916 (38.6)</td>
<td>902 (38.0)</td>
</tr>
<tr>
<td>Diabetes mellitus§</td>
<td><strong>993 (41.8)</strong></td>
<td><strong>990 (41.8)</strong></td>
</tr>
<tr>
<td>Estimated GFR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean — ml/min/1.73 m²</td>
<td>66.0±19.6</td>
<td>65.5±19.3</td>
</tr>
<tr>
<td>Rate of &lt;60 ml/min/1.73 m² — no./total no. (%)</td>
<td>962/2372 (40.6)</td>
<td>964/2371 (40.7)</td>
</tr>
<tr>
<td>Device therapy — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implantable cardioverter–defibrillator¶</td>
<td>622 (26.2)</td>
<td>620 (26.1)</td>
</tr>
<tr>
<td>Cardiac resynchronization therapy¶</td>
<td>190 (8.0)</td>
<td>164 (6.9)</td>
</tr>
<tr>
<td>Heart failure medication — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic</td>
<td>2216 (93.4)</td>
<td>2217 (93.5)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>1332 (56.1)</td>
<td>1329 (56.1)</td>
</tr>
<tr>
<td>ARB</td>
<td>675 (28.4)</td>
<td>632 (26.7)</td>
</tr>
<tr>
<td>Sacubitril–valsartan</td>
<td>250 (10.5)</td>
<td>258 (10.9)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>2278 (96.0)</td>
<td>2280 (96.2)</td>
</tr>
<tr>
<td>Mineralocorticoid receptor antagonist</td>
<td>1696 (71.5)</td>
<td>1674 (70.6)</td>
</tr>
<tr>
<td>Digitalis</td>
<td>445 (18.8)</td>
<td>442 (18.6)</td>
</tr>
<tr>
<td>Glucose-lowering medication — no./total no. (%)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biguanide</td>
<td>504/993 (50.8)</td>
<td>512/990 (51.7)</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>228/993 (23.0)</td>
<td>210/990 (21.2)</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>161/993 (16.2)</td>
<td>149/990 (15.1)</td>
</tr>
<tr>
<td>GLP-1 receptor agonist</td>
<td>11/993 (1.1)</td>
<td>10/990 (1.0)</td>
</tr>
<tr>
<td>Insulin</td>
<td>274/993 (27.6)</td>
<td>266/990 (26.9)</td>
</tr>
</tbody>
</table>
Methods – Outcomes

Primary outcome:

- Composite of worsening heart failure or death from cardiovascular causes
  - Hospitalization
  - Urgent visit resulting in IV therapy for HF
Secondary outcomes:

- Composite of hospitalization for heart failure or cardiovascular death
- Total number of hospitalizations for HF & cardiovascular deaths
- Change in symptoms
  - Kansas City Cardiomyopathy Questionnaire
- Composite of worsening renal function
  - ≥ 50% decline in eGFR, ESRD (eGFR ≤ 15 for ≥ 28 days), renal death
- Death from any cause
Methods – Outcomes

Safety analysis:

- Serious adverse events
- Adverse events associated with discontinuation of a trial treatment
- Adverse events of interest
  - Volume depletion
  - Renal events
  - Major hypoglycemic events
  - Bone fractures
  - DKA
  - Amputations
  - Fournier’s gangrene
- Abnormal lab findings of note

*Data on other adverse events not routinely collected given extensive previous collection on safety data regarding dapagliflozin (Wiviott ea 2019)*
Methods – Statistical Analysis

● Intention-to-treat analysis
● Time-to-event data: Kaplan-Meier estimates & cox proportional-hazards models
● Incidence of adverse events: Fisher’s exact test
Cox proportional hazards model

Relate several risk factors/exposures, considered simultaneously, to survival time

Effect measured: **Hazard rate** = Probability of an individual at time $t$ has event happening at that time

**Hazard Ratio** = Probability of events in treatment group / probability of events in control group

Averaged over the whole follow-up period

HR ≠ RR

→ Time to event
Results

- Efficacy Outcomes
- Safety Outcomes
Primary Outcome

Composite of a First Episode of Worsening Heart Failure or Cardiovascular Death

Hazard Ratio, 0.74; 95% CI, 0.65 to 0.85; P < 0.001
Primary outcome - Worsening HF or CV death

HR 0.74

Dapa → 26% less risk of developing worsening HF or CV death, at any time

NNT = 21
Secondary outcome – HF hospitalization

B Hospitalization for Heart Failure

Hazard ratio, 0.70 (95% CI, 0.59–0.83)

No. at Risk
Placebo 2371 2264 2168 2082 1924 1483 1101 596 212
Dapagliflozin 2373 2306 2223 2153 2007 1563 1147 613 210
Secondary outcome – mortality

C Death from Cardiovascular Causes

Hazard ratio, 0.82 (95% CI, 0.69–0.98)

D Death from Any Cause

Hazard ratio, 0.83 (95% CI, 0.71–0.97)
# Efficacy outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dapagliflozin (N = 2373)</th>
<th>Placebo (N = 2371)</th>
<th>Hazard or Rate Ratio or Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>values</td>
<td>events/100 patient-yr</td>
<td>values</td>
<td>events/100 patient-yr</td>
</tr>
<tr>
<td>Primary composite outcome — no. (%) †</td>
<td>386 (16.3)</td>
<td>11.6</td>
<td>502 (21.2)</td>
<td>15.6</td>
</tr>
<tr>
<td>Hospitalization or an urgent visit for heart failure</td>
<td>237 (10.0)</td>
<td>7.1</td>
<td>326 (13.7)</td>
<td>10.1</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>231 (9.7)</td>
<td>6.9</td>
<td>318 (13.4)</td>
<td>9.8</td>
</tr>
<tr>
<td>Urgent heart-failure visit</td>
<td>10 (0.4)</td>
<td>0.3</td>
<td>23 (1.0)</td>
<td>0.7</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>227 (9.6)</td>
<td>6.5</td>
<td>273 (11.5)</td>
<td>7.9</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death or heart-failure hospitalization — no. (%)</td>
<td>382 (16.1)</td>
<td>11.4</td>
<td>495 (20.9)</td>
<td>15.3</td>
</tr>
<tr>
<td>Total no. of hospitalizations for heart failure and cardiovascular deaths</td>
<td>567</td>
<td>—</td>
<td>742</td>
<td>—</td>
</tr>
<tr>
<td>Change in KCCQ total symptom score at 8 mo ‡</td>
<td>6.1±18.6</td>
<td>—</td>
<td>3.3±19.2</td>
<td>—</td>
</tr>
<tr>
<td>Worsening renal function — no. (%) †‡</td>
<td>28 (1.2)</td>
<td>0.8</td>
<td>39 (1.6)</td>
<td>1.2</td>
</tr>
<tr>
<td>Death from any cause — no. (%)</td>
<td>276 (11.6)</td>
<td>7.9</td>
<td>329 (13.9)</td>
<td>9.5</td>
</tr>
</tbody>
</table>
### Effect by subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Dapagliflozin (N=2373)</th>
<th>Placbo (N=2377)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td>386/2373</td>
<td>502/2371</td>
<td>0.74 (0.65–0.85)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>162/1052</td>
<td>196/998</td>
<td>0.78 (0.63–0.96)</td>
</tr>
<tr>
<td>&gt;65 yr</td>
<td>224/1341</td>
<td>306/1373</td>
<td>0.72 (0.60–0.85)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>307/1809</td>
<td>406/1826</td>
<td>0.73 (0.63–0.85)</td>
</tr>
<tr>
<td>Female</td>
<td>79/564</td>
<td>96/545</td>
<td>0.79 (0.59–1.06)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>275/1662</td>
<td>348/1671</td>
<td>0.78 (0.66–0.93)</td>
</tr>
<tr>
<td>Black</td>
<td>26/122</td>
<td>32/104</td>
<td>0.62 (0.37–1.04)</td>
</tr>
<tr>
<td>Asian</td>
<td>78/552</td>
<td>118/564</td>
<td>0.64 (0.48–0.86)</td>
</tr>
<tr>
<td>Other</td>
<td>7/37</td>
<td>4/32</td>
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<tr>
<td>Geographic region</td>
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<tr>
<td>Asia</td>
<td>77/345</td>
<td>114/553</td>
<td>0.65 (0.49–0.87)</td>
</tr>
<tr>
<td>Europe</td>
<td>131/1094</td>
<td>218/1060</td>
<td>0.84 (0.69–1.01)</td>
</tr>
<tr>
<td>North America</td>
<td>54/335</td>
<td>73/342</td>
<td>0.71 (0.51–1.03)</td>
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<tr>
<td>South America</td>
<td>62/401</td>
<td>97/416</td>
<td>0.64 (0.47–0.88)</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>199/1606</td>
<td>289/1597</td>
<td>0.63 (0.52–0.75)</td>
</tr>
<tr>
<td>III or IV</td>
<td>196/767</td>
<td>213/774</td>
<td>0.90 (0.74–1.09)</td>
</tr>
<tr>
<td>LVEF</td>
<td></td>
<td></td>
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<tr>
<td>≤Median</td>
<td>222/1230</td>
<td>307/1239</td>
<td>0.70 (0.59–0.84)</td>
</tr>
<tr>
<td>&gt;Median</td>
<td>164/1143</td>
<td>195/1132</td>
<td>0.81 (0.65–0.99)</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤Median</td>
<td>100/1193</td>
<td>155/1179</td>
<td>0.61 (0.49–0.80)</td>
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<tr>
<td>&gt;Median</td>
<td>286/1179</td>
<td>347/1191</td>
<td>0.79 (0.68–0.92)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>195/1124</td>
<td>279/1127</td>
<td>0.67 (0.56–0.80)</td>
</tr>
<tr>
<td>No</td>
<td>191/1249</td>
<td>223/1244</td>
<td>0.84 (0.69–1.01)</td>
</tr>
<tr>
<td>MRA at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>281/1696</td>
<td>361/1674</td>
<td>0.74 (0.63–0.87)</td>
</tr>
<tr>
<td>No</td>
<td>105/677</td>
<td>141/697</td>
<td>0.74 (0.57–0.95)</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>Atrial fibrillation or flutter on enrollment ECG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>109/569</td>
<td>126/559</td>
<td>0.82 (0.63–1.06)</td>
</tr>
<tr>
<td>No</td>
<td>277/1804</td>
<td>376/1812</td>
<td>0.72 (0.61–0.84)</td>
</tr>
<tr>
<td>Main cause of heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>223/1316</td>
<td>289/1358</td>
<td>0.77 (0.65–0.92)</td>
</tr>
<tr>
<td>Nonischemic or unknown</td>
<td>163/1057</td>
<td>213/1033</td>
<td>0.71 (0.58–0.87)</td>
</tr>
<tr>
<td>Body-mass index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>259/1537</td>
<td>320/1533</td>
<td>0.78 (0.66–0.92)</td>
</tr>
<tr>
<td>≥30</td>
<td>127/834</td>
<td>182/838</td>
<td>0.69 (0.55–0.86)</td>
</tr>
<tr>
<td>Baseline eGFR (ml/min/1.73m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>191/962</td>
<td>254/964</td>
<td>0.72 (0.59–0.86)</td>
</tr>
<tr>
<td>≥60</td>
<td>195/1410</td>
<td>248/1406</td>
<td>0.76 (0.63–0.92)</td>
</tr>
</tbody>
</table>
Primary outcome - subgroup analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>FARXIGA 10 mg (n=2373)</th>
<th>Placebo (n=2371)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td>386/2373</td>
<td>502/2371</td>
<td>0.74 (0.65-0.85)</td>
</tr>
</tbody>
</table>

Type 2 diabetes at baseline

<table>
<thead>
<tr>
<th></th>
<th>FARXIGA 10 mg</th>
<th>Placebo</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yes</strong></td>
<td>215/1075</td>
<td>271/1064</td>
<td>0.75 (0.63-0.90)</td>
</tr>
<tr>
<td><strong>No</strong></td>
<td>171/1298</td>
<td>231/1307</td>
<td>0.73 (0.60-0.88)</td>
</tr>
</tbody>
</table>
## Effect by subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Dapagliflozin (N=2373)</th>
<th>Placebo (N=2371)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 2 diabetes at baseline</strong></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><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>307/1809</td>
<td>406/1826</td>
<td>0.73 (0.63–0.85)</td>
</tr>
<tr>
<td>Female</td>
<td>79/564</td>
<td>96/545</td>
<td>0.79 (0.59–1.06)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>275/1662</td>
<td>348/1671</td>
<td>0.78 (0.66–0.91)</td>
</tr>
<tr>
<td>Black</td>
<td>26/122</td>
<td>32/104</td>
<td>0.62 (0.37–1.04)</td>
</tr>
<tr>
<td>Asian</td>
<td>78/552</td>
<td>118/564</td>
<td>0.64 (0.48–0.86)</td>
</tr>
<tr>
<td>Other</td>
<td>7/37</td>
<td>4/32</td>
<td></td>
</tr>
<tr>
<td><strong>NYHA class</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>190/1606</td>
<td>289/1597</td>
<td>0.63 (0.52–0.75)</td>
</tr>
<tr>
<td>III or IV</td>
<td>196/767</td>
<td>213/774</td>
<td>0.90 (0.74–1.09)</td>
</tr>
</tbody>
</table>
Subgroup analysis – DM vs no DM

Patients without DM2 (n=2605)

- Placebo (n=1307)
- FARXIGA 10 mg (n=1298)

Event Rates
Placebo and SoC: 17.7%
FARXIGA and SoC: 13.2%

Patients with DM2 (n=2139)

- Placebo (n=1064)
- FARXIGA 10 mg (n=1075)

Event Rates
Placebo and SoC: 25.5%
FARXIGA and SoC: 20.0%

NNT=23
↓4.5% ARR

NNT=19
↓5.5% ARR
<table>
<thead>
<tr>
<th>Variable</th>
<th>Dapagliflozin (N=2373)</th>
<th>Placebo (N=2371)</th>
<th>Hazard or Rate Ratio or Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to adverse event — no./total no. (%)</td>
<td>111/2368 (4.7)</td>
<td>116/2368 (4.9)</td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>Adverse events of interest — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume depletion</td>
<td>178/2368 (7.5)</td>
<td>162/2368 (6.8)</td>
<td></td>
<td>0.40</td>
</tr>
<tr>
<td>Renal adverse event</td>
<td>153/2368 (6.5)</td>
<td>170/2368 (7.2)</td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>Fracture</td>
<td>49/2368 (2.1)</td>
<td>50/2368 (2.1)</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Amputation</td>
<td>13/2368 (0.5)</td>
<td>12/2368 (0.5)</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Major hypoglycemia**</td>
<td>4/2368 (0.2)</td>
<td>4/2368 (0.2)</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Diabetic ketoacidosis††</td>
<td>3/2368 (0.1)</td>
<td>0</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Fournier's gangrene</td>
<td>0</td>
<td>1/2368 (&lt;0.1)</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Laboratory and other measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline to 8 mo‡‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycated hemoglobin — %§§</td>
<td>-0.21±1.14</td>
<td>0.04±1.29</td>
<td>-0.24 (-0.34 to -0.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine — mg/dl</td>
<td>0.07±0.24</td>
<td>0.04±0.25</td>
<td>0.02 (0.01 to 0.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hematocrit — %</td>
<td>2.31±3.90</td>
<td>-0.19±3.81</td>
<td>2.41 (2.21 to 2.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP — pg/ml</td>
<td>-196±2387</td>
<td>101±2944</td>
<td>-303 (-457 to -150)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight — kg</td>
<td>-0.88±3.86</td>
<td>0.10±4.09</td>
<td>-0.87 (-1.11 to -0.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure — mm Hg</td>
<td>-1.92±14.92</td>
<td>-0.38±15.27</td>
<td>-1.27 (-2.09 to -0.45)</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Safety Outcome

Rates of Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume depletion</td>
<td>7.5% (N=178)</td>
<td>6.8% (N=162)</td>
<td>0.40</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>6.5% (N=153)</td>
<td>7.2% (N=170)</td>
<td>0.36</td>
</tr>
</tbody>
</table>
Discussion

- Summary of findings
- Strengths
- Limitations
Discussion

- When added to standard therapy, dapagliflozin reduced the risk of worsening HF events and CV death, and improved symptoms in patients with HFrEF, both with and without DM
- Benefits occurred early after randomization
- Dapagliflozin was well tolerated
  - <8% volume depletion or worsening kidney function
- Rate of treatment discontinuation due to adverse event was low (<5%)

→ Dapagliflozin offers new approach to treatment of HFrEF in patients with and without DM
• Heart failure
• Reduced ejection fraction

Dapagliflozin
10 mg Daily
Reduced the risk of:
• Worsening heart failure
• Cardiovascular death

Even in patients without diabetes

& Appears to be safe
Discussion – Strengths

- RCT
- Large patient population
- Multicenter trial across different countries
  - Increased external validity
- Independent analyses from sponsor
- Follow up time 24 months
Discussion - Limitations

- Limited generalizability due to specific inclusion and exclusion criteria
- <5% black patients
- Few very elderly patients with multiple coexisting illnesses
- Few NYHA III or IV
- Women ~ 25%
- Mean BMI ~ 28
- Not included in AE: UTI’s, yeast infx
Mechanism of action?

Hypotheses:

- SGLT2 inhibitors mitigate glycemia-related cardiotoxicity
- Enhanced ketogenesis contributes to the benefit of heart failure
- Renal sodium excretion
- Increase in hematocrit favorable for CAD
  - Increase in hematocrit did not affect clinical course of pts with HF

DAPA-HF did not support the above hypotheses
FDA approves new treatment for a type of heart failure

- May 5 2020
- Dapagliflozin approved specifically for the treatment of patients with heart failure and a reduced ejection fraction

**MEDICATION GUIDE**

**FARXIGA® (FAR-SEE-GUH)**
(dapagliflozin) tablets, for oral use

**What is FARXIGA?**
FARXIGA is a prescription medicine used in adults with:

- Type 2 diabetes to:
  - improve blood sugar (glucose) control along with diet and exercise
  - reduce the risk of hospitalization for heart failure in people who also have known cardiovascular disease or multiple cardiovascular risk factors
- Heart failure when the heart is weak and cannot pump enough blood to the rest of your body to:
  - reduce the risk of cardiovascular death, hospitalization for heart failure

FARXIGA is not for people with type 1 diabetes.
FARXIGA is not for people with diabetic ketoacidosis (increased ketones in your blood or urine).
It is not known if FARXIGA is safe and effective in children younger than 18 years of age.
New Guidelines

Canadian Journal of Cardiology 36 (2020) 159–169
Society Guidelines

CCS/CHFS Heart Failure Guidelines: Clinical Trial Update on Functional Mitral Regurgitation, SGLT2 Inhibitors, ARNI in HFpEF, and Tafamidis in Amyloidosis

8. **New.** We recommend SGLT2 inhibitors, such as dapagliflozin be used in patients with mild to moderate HF due to reduced LVEF (≤ 40%) and concomitant type 2 diabetes, to improve symptoms and quality of life and to reduce the risk of hospitalization and cardiovascular mortality (Strong Recommendation, High-Quality Evidence).

9. **New.** We recommend SGLT2 inhibitors, such as dapagliflozin be used in patients with mild to moderate HF due to reduced LVEF (≤ 40%) and without concomitant diabetes, to improve symptoms and quality of life and to reduce the risk of hospitalization and cardiovascular mortality (Conditional Recommendation, High-Quality Evidence).
Future directions

● EMPEROR-Reduced trial (NEJM, Aug 2020): empagliflozin, more severe HF
  ○ Similar results

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

Milton Packer, M.D., Stefan D. Anker, M.D., Ph.D., Javed Butler, M.D., Gerasimos Filippatos, M.D., Stuart J. Pocock, Ph.D., Peter Carson, M.D., James Januzzi, M.D., Subodh Verma, M.D., Ph.D., Hiroyuki Tsutsui, M.D., Martina Brueckmann, M.D., Waheed Jamal, M.D., Karen Kimura, Ph.D., et al., for the EMPEROR-Reduced Trial Investigators

● RCT dapagliflozin vs empagliflozin
● Most effective dosage
● Mechanism of action

Evaluation of the effects of sodium–glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved Trial
Practice implications for JFMA

- Dapagliflozin 10mg seems to be effective & safe for patients with mild-mod HFrEF in reducing worsening HF and death
- Additional data needed
  - More severe HF
  - More diverse patient population
  - Higher BMI
  - More comorbidities
- How to explain to our patients?
- High costs
  - Discount not for Medicare/Medicaid
References


Questions?
ELIGIBILITY CRITERIA

- ≥18 years of age
- Diagnosis of symptomatic HFrEF (NYHA class II-IV)
- LVEF ≤40%
- Elevated NT-proBNP ≥600 pg/mL (or ≥400 pg/mL if hospitalized for heart failure within the past 12 months)
- eGFR ≥30 mL/min/1.73 m²

1:1 Randomization

FARXIGA 10 mg and standard of care (n=2373)
Placibo and standard of care (n=2371)

MEDIAN FOLLOW-UP: 18.2 MONTHS
Methods - Procedures

- 14 day screening period: baseline criteria, in- and exclusion criteria
- Random assignment to treatment vs placebo group
  - Dapagliflozin 10mg once daily
- Randomization: sequestered, fixed-randomization schedule; use of balanced blocks → 1:1 ratio
Methods - Procedures

14 days
Assessment of heart failure & volume status, adverse events, evaluation of renal function and potassium levels.

4 months
8 months
12 months
16-24 months
Reassess
Reassess
Reassess

- Dapagliflozin or placebo discontinued if pregnancy, DKA
- Dose reduction or temporary discontinuation: if acute unexpected decline in eGFR, volume depletion or hypotension
SGLT2 Inhibitor

↑ Natriuresis
↑ Diuresis
↑ Glycosuria
↓ Intraglomerular pressure

↓ Cardiac preload

↑ Metabolic efficiency
↑ Oxygen supply
↓ Oxidative stress
↓ Fibrosis
↓ Epicardial fat
↓ Neurohormonal stimulation

↑ LV diastolic function
↓ LV mass

↓ Cardiac afterload

↑ Endothelial function
↓ Arterial wall stiffness
↓ Vascular resistance
CENTRAL ILLUSTRATION: Sodium-Glucose Cotransporter 2 Inhibitor Cardiorenal Protection Mechanistic Overview

Recent results in non-diabetic experimental chronic kidney disease models

- Sodium-glucose cotransporter 2 (SGLT2) Inhibitors
  - Natriuresis
  - Glucosuria
  - Tubulo-glomerular feedback
    - Blood pressure lowering
    - Amelioration of volume overload
      - Intraglomerular pressure reduction
        - Renal protection
        - Cardiovascular protection

Possible direct renal protection

**SGLT2i** Pathway

**Possible cardio-renal benefits**
- Arrhythmia
- Cardiac function/output
- Arterial wall integrity
- Glomerular pressure
- Albuminuria

**CV/renal outcomes observed in EMPA-REG OUTCOME®**
- CV death
- HHF
- Renal events
- Sudden death
- Fatal
- HF/MI/stroke
**Time to event**

**Hazard** = instantaneous event rate

Probability of an individual at time $t$ has event happening at that time

**Hazard Ratio**

Probability of events in treatment group / probability of events in control group

- $HR = 1$ (at any time, event rates similar in both arms)
- $HR 0.5$ (at any time, half as many patients in treatment group are having an event proportionally to comparison group)

$HR \neq RR$
Relative Risk (Risk Ratio) =

Risk (cumulative incidence) treatment group / risk placebo group

Relative Risk Reduction (efficacy) = 1 - RR

Relative decrease in risk of event in exposed group compared to unexposed group

Absolute Risk Reduction

Disease risk in placebo group - disease risk in treatment group

NNT = 1/ARR

How many patients need treatment before 1 patient benefits
(HR, 0.74; 95% CI, 0.65-0.85)  
Placebo (n=2371)  
FARXIGA 10 mg (n=2373)  
P<0.0001

Event Rates:
Placebo and SoC: 21.2%  
FARXIGA and SoC: 16.3%

Curves separated early and continued to diverge over time

26% RRR  
4.9% ARR  
NNT=21