**DAPA-HF: Dapagliflozin versus Placebo in Patients with Heart Failure & Reduced EF**

**Dapagliflozin And Prevention of Adverse Outcomes in Heart Failure**

**SUMMARY**
- In **DAPA-HF**, clinically stable HF-ref patients (NYHA class II ~68%, III ~32%) on standard HF therapy (beta-blocker 96%, ACEI / ARB / ARNI 94.4% [=ACEI 56.1%, ARB 27.6%, ARNI 10.7%], diuretics 93.5%, MRA 71%) who received dapagliflozin 10mg daily (vs placebo) x 1.5 years:
  - A lower risk of worsening HF or CV death NNT 21
  - Individual composite endpoints: HF hospitalization (NNT 27), urgent HF visit requiring IV HF therapy (NNT 167), CV death (NNT 53)
  - HF hospitalization or CV death (i.e. common primary composite endpoint for HF trials) NNT 21
  - Were more likely to experience an improvement in quality of life (clinically meaningful change in Kansas City Questionnaire) NNT 14
  - NNT 4.4% [empagliflozin - 42% at screening, and an additional 3% received a new diagnosis)
  - At the time of print, dapagliflozin FORXIGA was approximately $725/100-day supply. Drug Status on the Saskatchewan Drug Plan and Prior Approval on NIH is limited to those with T2DM unable to achieve glycemic control with or are intolerant to metformin & a sulfonylurea. In addition, Health Canada has currently only approved SGLT2-I for T2DM.

**BACKGROUND**
- **Dapagliflozin** is a sodium-glucose cotransporter 2 inhibitor (SGLT2-I) approved in 2014 for the management of T2DM as either monotherapy or add-on therapy to metformin, a sulfonylurea, sitagliptin, or insulin.
- Previous trials have demonstrated a reduction in HF hospitalizations with SGLT2-I, despite the majority of patients (~85%) not having a diagnosis of HF at baseline:
  - **EMPA-REG** empagliflozin JARDIANCE 10mg or 25mg daily vs placebo in T2DM + CVD x 3 years:
    - Secondary efficacy endpoint of HF hospitalization: 2.7% vs 4.1%, HR 0.65 (95% CI 0.5-0.85), ARR 1.4%, NNT 71/3 years
    - 10% of participants had HF at baseline
  - **CANVAS** canagliflozin INVOKANA 100mg or 300mg daily vs placebo in T2DM + CVD or an elevated risk of CV disease x 3.6 years
    - Exploratory secondary endpoint HF hospitalizations: 5.5% vs 8.7%/1000 pt yrs, HR 0.67 (95% CI 0.52-0.87), ARR 3.2%, NNT 32/3.6 years
    - 14% of participants had HF at baseline
  - **DECLARE-TIMI 58** dapagliflozin FORXIGA 10mg daily vs placebo in T2DM + CVD or CV major risk factors x 4.2 years:
    - Co-primary endpoint of CV death and HF hospitalization: 4.9% vs 5.8%, HR 0.83 (95% CI 0.73-0.95), ARR 0.9%, NNT 112/4.2 years
    - This co-primary endpoint was driven by HF hospitalization (ARR 0.8%, NNT 125), as CV death was non-statistically significant on its own
    - 10% of participants had HF at baseline
- **DAPA-HF** is the first of the SGLT2-I trials to focus on a HF (HF-ref) patient population, and less than half of the participants had DM (42%). Other SGLT2-I trials in HF are currently underway (e.g. **EMPEROR-Reduced** [empagliflozin], **EMPERIAL-Reduced** [empagliflozin], **SOLOIST-WHF** [sotagliflozin in HF with EF <50%]), including studies in HF with preserved ejection fraction (e.g. **DELIVER** [dapagliflozin], **EMPEROR-Preserved** [empagliflozin], **EMPERIAL-Preserved** [empagliflozin]).

**TRIAL BACKGROUND**
- **DESIGN**: randomized, double-blind, international (20 countries), multicentre (410 centres), placebo-controlled trial. ITT analysis for efficacy endpoints; safety analyses included only those who received at least one dose of dapagliflozin or placebo. Funding: AstraZeneca (dapagliflozin). Enrollment February 2017 to August 2018.

**INTERVENTION:** Dapagliflozin 10mg once daily versus placebo, in addition to guideline recommended drug & device therapy

**INCLUSION:** NYHA class II-IV HF-ref (LVEF ≤40% within the last 12 months, HF diagnosis of ≥2 months), ≥18 years of age, NTproBNP ≥600pg/mL or ≥400pg/mL if HF hospitalization in the past 12 months or ≥900pg/mL if AF or Aflutter on baseline ECG, standard HF device (ICD and/or CRT) and drug therapy (ACEI / ARB / ARNI, beta-blocker) that had been individually optimized and stable for ≥ 4 weeks unless contraindicated or not tolerated. MRA was encouraged. DM: continued glucose-lowering therapies and doses were adjusted as needed (e.g. to minimize risk of hypoglycemia if baseline A1C <7%).

**EXCLUSION:** recent (within 8 weeks) of hypotension or SBP <95mmHg; current acute compensated HF or HF hospitalization <4 weeks prior to enrolment; MI, unstable angina, stroke or TIA within 12 weeks of enrolment; implantation of a CRT within 12 weeks or intent to implant a CRT device; cardiac transplantation or implantation of a ventricular assistance device; symptomatic bradycardia or second or third-degree heart block without a pacemaker; HF due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic (obstructive) cardiomyopathy or uncorrected primary valvular disease; PCI, CABG, or valvular repair/replacement within 12 weeks prior to enrolment or planned to undergo procedure after randomization; active malignancy; eGFR <30mL/min or rapidly declining renal function; hepatic impairment.

**POPULATION at baseline:**

- **Age:** ~66.5 years (±11 years), 65-74 years (36.2%, n=1717), 55-64 years (26.2%, n=1242), ≥75 years (24.2%, n=1149), <55 years (13.4%, n=636)
- **Race/ethnicity:** White 70%; Asian ~24%; African-American/Black ~3%; Other ~1.5%
- **Geographical region:** Europe ~46%; Asia-Pacific ~23%; South America 17%; North America ~14%
- **HF:** NYHA class II ~68%, III ~32%, IV ~1%; mean LVEF 31% (±6.8%); median NTproBNP 1437 pg/mL (857-2648); principle cause of HF: ischemic 56%, non-ischemic 35.5%, unknown ~8%; prior HF hospitalization 47.5%; **device therapy:** ICD 26%, CRT 7.5%; **drug therapy:** beta-blocker 96%, ACEI / ARB / ARNI 94.4% (=ACEI 56.1%, ARB 27.6%, ARNI 10.7%), diuretics 93.5%, MRA 71%, digoxin 18.7%
- **CV:** mean SBP 122mmHg (±16.3mmHg); mean HR 71.5bpm (±11.7bpm); AF ~38%
- **DM:** DM 41.8%; additional 3% diagnosed with DM after screening; mean eGFR 66mL/min/1.73m² (±19.5); eGFR <60mL/min 40.7%; **DM therapy:** metformin 51%, insulin 27%, sulfonylurea 22%, DPP4 inhibitor 15.5%, GLP4 receptor agonist 1%
Worsening renal function

KCCQ

Significant deterioration in

months

points from baseline to 8 months

Chan

Questionnaire

All

CV death

recurrent) & CV death

Total HF hospitalizations (first &

HF hospitalizations or CV death

Urgent HF visit (IV HF therapy)

HF hospitalization

or an urgent visit resulting in IV

SECON

or an urgent visit resulting in IV

PRIMARY ENDPOINTS

Worsening HF (hospitalization

or an urgent visit resulting in IV

HF therapy) or CV death

16.3% (n=386) 21.2% (n=502) 0.74 (0.65-0.85) <0.001 4.9% 21

- Kaplan-Meier curves separated soon after randomization for worsening HF
- Subgroup analyses: NYHA class III to IV appeared to have less benefit than class II
- Statistically significant difference for the following surrogate endpoints (in favour of dapagliflozin): between group difference from baseline to 8 months:
  - A1C 0.24%
  - NTproBNP -303pg/mL
  - Weight -0.87kg
  - SBP -1.27mmHg
  - 2039 (98.1%) of the patients still taking dapagliflozin at the last assessment were on 10mg daily

SECONDARY ENDPOINTS

Worsening HF (hospitalization

or an urgent visit resulting in IV

HF therapy)

10% (n=237) 13.7% (n=326) 0.7 (0.59-0.83) - 3.7% 27

HF hospitalization

9.7% (n=231) 13.4% (n=318) 0.7 (0.59-0.83) - 3.7% 27

Urgent HF visit (IV HF therapy)

0.4% (n=10) 1% (n=23) 0.43 (0.2-0.9) - 0.6% 167

HF hospitalizations or CV death

16.1% (n=382) 20.9% (n=495) 0.75 (0.65-0.85) <0.001 4.8% 21

Total HF hospitalizations (first &

recurrent) & CV death

567 742 0.75 (0.65-0.88) <0.001 - -

CV death

9.6% (n=227) 11.5% (n=273) 0.82 (0.69-0.98) - 1.9% 53

All-cause mortality

11.6% (n=276) 13.9% (n=329) 0.83 (0.71-0.97) - 2.3% 44

Kansas City Cardiomyopathy

Questionnaire (KCCQ) change

from baseline to 8 months *

6.1 ± 18.6 3.3 ± 19.2 1.18 (1.11-1.26) <0.001 - -

Change in KCCQ by at least 5

points from baseline to 8

months (clinically meaningful)*

58.3% 50.9% 1.15 (1.08-1.23) <0.001 7.4% 14

Significant deterioration in

KCCQ

25.3% 32.9% 0.84 (0.78-0.9) <0.001 7.6% 14

Worsening renal function ‡

1.2% (n=28) 1.6% (n=39) 0.71 (0.44-1.16) NS - -

* Kansas City Cardiomyopathy Questionnaire: scale from 0 to 100, with a higher score indicating fewer symptoms and a change of 5 or more points considered clinically meaningful.

‡ Worsening renal function = sustained decline in eGFR of 50% or greater, end-stage renal disease (sustained ≥28 days), eGFR <15mL/min, sustained dialysis, renal transplant) or renal death.

TABLE 2: SAFETY

<table>
<thead>
<tr>
<th>CLINICAL ENDPOINTS</th>
<th>DAPAGLIFLOZIN 10MG N=2368</th>
<th>PLACEBO N=2368</th>
<th>HR (95% CI)</th>
<th>P VALUE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation due to AE</td>
<td>4.7% (n=111)</td>
<td>4.9% (n=116)</td>
<td>-</td>
<td>-</td>
<td>- 8 patients (5 dapagliflozin, 3 placebo) were excluded from the safety analyses as they didn’t receive their assigned study medication.</td>
</tr>
<tr>
<td>Discontinuation rates</td>
<td>10.5% (n=249)</td>
<td>10.9% (n=258)</td>
<td>-</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Volume depletion</td>
<td>7.5% (n=178)</td>
<td>6.8% (n=162)</td>
<td>-</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Renal adverse event</td>
<td>6.5% (n=153)</td>
<td>7.2% (n=170)</td>
<td>-</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Fracture</td>
<td>2.1% (n=49)</td>
<td>2.1% (n=50)</td>
<td>-</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Amputation</td>
<td>0.5% (n=13)</td>
<td>0.5% (n=12)</td>
<td>-</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Major hypoglycemia</td>
<td>0.2% (n=4)</td>
<td>0.2% (n=4)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>0.1% (n=3)</td>
<td>0%</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Fournier’s gangrene</td>
<td>0%</td>
<td>&lt;0.1% (n=1)</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:
- First published SGLT2-I trial focusing on HF patients, over half of which did not have DM
- Majority of patients were on an ACEI / ARB / ARNI and beta-blocker at baseline for standard HF therapy; ~70% on an MRA
- ~25% of patients were ≥75 years; the results appear to be consistent across all age groups
- Only 2 patients in the placebo group had an unknown vital status at the end of the trial (& none in the dapagliflozin group)
- Analyses conducted by the sponsor, AstraZeneca, were replicated by an independent academic group (University of Glasgow)
- Concealed allocation and blinded adjudication of clinical events

LIMITATIONS:
- 41.7% (=3390/8134) of screening participants were excluded during the screening period. 40.3% (=3279/8134) were excluded as they did not meet eligibility criteria. In other words, it may be challenging in the real-world to find similar patients who meet the inclusion criteria. A breakdown of why patients did not meet eligibility criteria was not published; generalizability is uncertain.
- Only 14% of the study participants were from North America
- The type of beta-blocker was not reported (i.e. was it a trial proven HF beta-blocker)
- Doses were not reported for HF standard therapy (i.e. target or maximally tolerated doses). The mean SBP was 122mmHg (±16.3mmHg) & mean HR was 71.5bpm (±11.7bpm; AF 38%) suggesting there was room to optimize HF medication doses.
- At the time of print, SGLT2-I only have an approved Health Canada indication and drug plan coverage for T2DM
- Testing of NT-pro-BNP may not be readily available to all prescribers (dependent on local lab)
- Short study duration of 1.5 years
A1C=hemoglobin A1C
ACEI=angiotensin converting enzyme inhibitor
AE=adverse effect
AF=atrial fibrillation
Aflutter=atrial flutter
ARB=angiotensin receptor blocker
ARNI=angiotensin receptor neprilysin inhibitor
ARR=absolute risk increase
ARN=angiotensin receptor
bpms=beats per minute
CRT=cardiac resynchronization therapy
CV=cardiovascular
DM=diabetes mellitus
DPP4=dipeptidyl peptidase-4
ECG=electrocardiogram
EF=ejection fraction
eGFR=estimated glomerular filtration rate
GLP=glucagon-like peptide
HF=heart failure
HF-REF=heart failure with reduced ejection fraction
HR=heart rate
ICD=implantable cardioverter-defibrillator
ITT=intention to treat
IV=intravenous
KCCQ=Kansas City Cardiomyopathy Questionnaire
LVEF=left ventricular ejection fraction
MI=myocardial infarction
MRA=miceralcolitocoid
NNH=number needed to harm
NNT=number needed to treat
NTproBNP=thestinal pro b-type natriuretic peptide
NTproBNP=thestinal pro
Systolic blood pressure
SGLT2=sodium-glucose transporter 2 inhibitor
T1DM=type 1 diabetes mellitus
T2DM=type 2 diabetes mellitus
TIA=transient ischemic attack

REFERENCES:


