DAPA-HF: Dapagliflozin versus Placebo in Patients with Heart Failure & Reduced EF [1]

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:
  - Had 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
  - Without increasing the risk of adverse events (e.g. volume depletion, renal impairment, hypoglycemia)
- Only ~45% of the participants had a **diagnosis of T2DM** (42% at screening, and an additional 3% received a new diagnosis)
- At the time of print, dapagliflozin **FORXIGA** ☎ ✆ is approximately $325 / 100-day supply. Exception Drug Status on the Saskatchewan Drug Plan and Prior Approval on NIHB 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**:[2] 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**:[3] 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**:[4] dapagliflozin **FORXIGA** 10mg daily vs placebo in T2DM + CVD or CVD 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 [1,5,6,7]

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 therapy (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 use 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) treatment with, or unacceptable side effects associated with, an SGLT2-I; T1DM; symptoms of hypotension or SBP <95mmHg; current acute decompensated 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: ..... N=4744, 77% males

- **Age:**.....mean 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 ~5%; 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/1.73m^2 (±19.5); eGFR <60mL/min 40.7%; **DM therapy**: metformin 51%, insulin 27%, sulfonylurea 22%, DPP4 inhibitor 15.5%, GLP4 receptor agonist 1%

RESULTS

Follow-up: Median 18.2 months (1.5 years; range 0 to 28.7 months)

TABLE 1: EFFICACY

CLINICAL ENDPOINTS	DAPAGLIFLOZIN 10MG N=2373	PLACEBO N=2371	HR (95% CI)	P VALUE	ARR/ARI	NNT / 1.5YRS	COMMENTS
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

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

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

- AstraZeneca collaborated in the study design, conduct and analysis

UNCERTAINTIES:

- Benefit and/or harm in NYHA III to IV. Subgroup analysis suggested less benefit in this patient population, and the majority (~2/3) of participants were NYHA II at baseline.
- Only 10% were on an ARNI. What are the benefits and/or harms when dapagliflozin is used concurrently with **ENTRESTO** (sacubitril / valsartan)? Post-hoc subgroup analysis of the primary outcome for those on **ENTRESTO** was HR 0.75 (95% CI 0.5 to 1.13, p=NS) versus 0.74 (95% CI 0.65 to 0.86) for those not on **ENTRESTO**.
- Would optimizing target doses of standard HF therapy result in less or even no benefit from dapagliflozin?
- What is the mechanism of benefit (appears to be independent of blood glucose lowering)?

RxFILES RELATED LINKS

- **Diabetes Agents Outcome Table:** https://www-rxfiles-ca.cyber.usask.ca/RxFiles/uploads/documents/Diabetes-Agents-Outcomes-Comparison-Summary-Table.pdf
- **DECLARE-TIMI 58 Trial Summary:** https://www-rxfiles-ca.cyber.usask.ca/RxFiles/uploads/documents/DECLARE-trial%20summary-%20Dapagliflozin-%20FORXIGA.pdf
- **EMPA-REG Trial Summary:** https://www-rxfiles-ca.cyber.usask.ca/RxFiles/uploads/documents/EMPA-REG%20Trial%20Summary.pdf

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 **ARI**=absolute risk increase **ARR**=absolute risk reduction **bpm**=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 **GLP1**=glucagon-like peptide 1 **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**=mineralocorticoid receptor antagonist **NNH**=number needed to harm **NNT**=number needed to treat **NYHA**=New York Heart Association **NTproBNP**=N-terminal pro b-type natriuretic peptide **NS**=non-statistically significant **SBP**=systolic blood pressure **SGLT2-I**= sodium-glucose transporter 2 inhibitor **T1DM**=type 1 diabetes mellitus **T2DM**=type 2 diabetes mellitus **TIA**=transient ischemic attack

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