DECLARE-TIMI 58: Dapagliflozin vs Placebo in T2DM + CVD/Major Risk Factors [1]
Dapagliflozin Effect on CardiovascuLAR Events-Thrombolysis In Myocardial Infarction 58

RESULTS SUMMARY AND DISCUSSION

Dapagliflozin 10mg daily vs. placebo as add-on therapy to standard antihyperglycemic care in patients with T2DM and clinical atherosclerotic cardiovascular disease (ASCVD) risk factors 60% or ASCVD: 40%

- **Benefits:** Dapagliflozin 10mg daily was non-inferior to placebo for the primary safety endpoint of major adverse cardiovascular events (MACE= composite endpoint of CV death, non-fatal MI and non-fatal stroke). As for the two primary efficacy endpoints, dapagliflozin was not superior to placebo for the reduction of MACE (HR 0.93; 0.84-1.03; 95% CI; p=0.17), however dapagliflozin reduced the composite endpoint of CV death or hospitalizations for heart failure (HHF) (NNT=112/4.2yrs or NNT=470/1 yr).
  - The secondary composite endpoint of CV death or HHF was found to be driven by a reduction in HHF (NNT=125/4.2 yrs), although this was an underpowered, exploratory outcome only. There was no statistically significant difference in CV death (HR 0.93; 0.82-1.04; 95% CI) between the two groups.
- **Harms:** Increased genital infections (NNH=125/4.2yrs) were more prominent in the dapagliflozin group. Diabetic ketoacidosis (DKA), although rare, was more common in the dapagliflozin group compared to the placebo group (0.3% vs 0.1%, NNH=500/4.2yrs). There was no evidence for increased rates of fracture, amputation, bladder cancer, or stroke in the dapagliflozin group. Withdrawals due to AEs were 8.1% vs 6.9% (NNH=84/4.2 yrs) for the dapagliflozin and placebo groups respectively.

Bottom Line: Dapagliflozin neither increased nor decreased the risk of MACE, as it remained neutral compared to placebo. Ongoing investigation of dapagliflozin's potential role in HHF reduction is underway in the **DAPA-HF** trial (see "uncertainties" section for more on HHF). Presently within the SGLT-2 inhibitor class, the results of the **EMPA-REG** and **CANVAS** trials seem to be more compelling showing empagliflozin and canagliflozin's CV benefits. The **DAPA-CKD** trial is currently attempting to determine the possibility of dapagliflozin therapy leading to renal benefits in CKD patients.

BACKGROUND

- **Dapagliflozin** Forxiga ☎ ✐ ~$320/100days is a sodium-glucose cotransporter 2 (SGLT-2) inhibitor approved in 2014 for the management of T2DM as either monotherapy or in combination with metformin, a sulfonylurea, sitagliptin, or insulin along with diet and exercise.
- Previous SGLT-2 inhibitor trials have demonstrated CV benefits associated with this class of medications.
  - **Empagliflozin** Jardiance ☎ ✐ ~$320/100days (**EMPA-REG OUTCOME**) lead to a reduction in MACE (NNT=63/3.1yrs or NNT=195/1yr) and all-cause mortality (NNT= 38/3.1 yrs).
  - **Canagliflozin** Invokana ☎ ✐ ~$320/100days (**CANVAS**) lead to a reduction in MACE (NNT=220/1yr), with no significant reduction in mortality.[2,3]
- Diabetes Canada (DC) 2018 guidelines do not consider the results of **DECLARE-TIMI 58** as it was completed post-publication; however, DC recommends that patients with T2DM and clinical CVD in whom A1C targets are not achieved with existing pharmacotherapy, receive an add-on antihyperglycemic agent with demonstrated CV outcome benefits (i.e. empagliflozin or canagliflozin) to reduce CV risk.[4] The 2019 American Diabetes Association Guidelines have been updated to include the data from this trial, stating that dapagliflozin is associated with reduced HHF and reduced progression of CKD.[5]

TRIAL BACKGROUND

DESIGN: Randomized, double-blind (no reported allocation concealment), multinational (882 sites, 33 countries including Canada), placebo-controlled trial (both intention-to-treat and per-protocol analyses used for primary safety and efficacy endpoints); 4-8 week single-blind placebo run-in; non-inferiority design.

INTERVENTION: Dapagliflozin 10mg once daily vs. matching placebo, added to existing antihyperglycemic therapy (except TZDs or previous SGLT-2 inhibitors)

INCLUSION: T2DM, **Age ≥40yrs**, **A1C 6.5-11.9%**, **CrCl ≥60mL/min**, multiple **risk factors for ASCVD**59.4% (♂ ≥55yrs or ♀ ≥60yrs with ≥1 of the following: hypertension, dyslipidemia, or tobacco use) or **established ASCVD**40.6% (defined as clinically evident ischemic heart disease, ischemic cerebrovascular disease, or PAD).

EXCLUSION: Acute CV event in prior 8 weeks (ACS, TIA, stroke, decompensated HF, any revascularization, sustained ventricular tachycardia); current/recent treatment with either pioglitazone (within 24 months or use for >2yrs) or rosiglitazone (within 12 months); previous treatment with any SGLT-2 inhibitor; chronic oral steroid (>30 days); BP>180/100mmHg; T1DM or secondary DM; hx of bladder cancer or radiation therapy to lower abdomen; hx of any other malignancy (aside from successfully treated non-melanoma skin cancers); **chronic cystitis and/or recurrent UTIs (≥3 in past year)**; pregnancy or breastfeeding patients; individuals with poor medication adherence during run-in period (<80%); AST or ALT >3x UNL or total bilirubin >2.5x UNL; hematuria.

POPULATION at baseline (mean values unless specified):
- Total; Age: ....n=17,160; age 64 ± 6.8yrs {≥65yrs (46.1%), >75yrs (6.4%)}
- Median duration of T2DM; A1C: ....11yrs (IQR 6-16yrs); 8.3 ± 1.2%
- Sex; BMI:..~63% ♂; 32.1 ± 6
- eGFR; SBP:..eGFR ~85.2mL/min/1.73m^2; 134.9 ± 15.4mmHg
- Race/ethnicity: ....White ~79.5%; Asian ~13.4%; African-American/Black ~3.5%; Other ~3.5%
- Geographical region: ....Europe ~44.4%; North America ~31.8%; Asia-Pacific ~12.7%; Latin America ~10.9%;
- Other Antihyperglycemics: ....Metformin ~82%; Sulfonylurea ~42.7%; Insulin ~40.9%; DPP-4 inhibitor~16.8%; GLP-1 agonist ~4.4%
- CVD; HF: ....Established ASCVD ~40.7% (hx of CAD ~33%, hx of cerebrovascular disease ~7.6%, hx of PAD ~6%); hx of HF~10%
- Cardiovascular Therapies: ....ACEI/ARB 81.3%; Statin or ezetimibe 74.9%; Antiplatelet 61.1%; β-blocker 52.6%; Diuretics 40.6%

RESULTS

Follow-up: Median 4.2yrs/Mean 4 yrs

TABLE 1: EFFICACY `NON-INFERIORITY`   `SUPERIORITY`

CLINICAL ENDPOINTS (over 4.2yrs)	DAPAGLIFLOZIN 10MG n=8582	PLACEBO n=8578	HR (95% CI)	P VALUE	ARR/ARI	NNT/4.2YRS	COMMENTS
CO-PRIMARY EFFICACY ENDPOINTS							
MACE (CV death, non-fatal MI, or non-fatal stroke)*	8.8% (n=756)	9.4% (n=803)	0.93 (0.84-1.03)	0.17	-	-	**Because dapagliflozin showed significance for only one of the primary efficacy outcomes, **analyses of secondary outcomes are hypothesis-generating.**
Composite of CV death and HHF	4.9% (n=417)	5.8% (n=496)	0.83 (0.73-0.95)	0.005	↓0.9%	112	
CO-SECONARY ENDPOINTS							
Death from any cause	6.2% (n=529)	6.6% (n=570)	0.93 (0.82-1.04)	-	-	-	
CV Death†	2.9% (n=245)	2.9% (249)	0.98 (0.82-1.17)	-	-	-	Dapagliflozin vs placebo, mean difference:
HHF	2.5% (n=212)	3.3% (n=286)	0.73 (0.61-0.88)	-	↓0.8%	125**	
Renal Composite (sustained ↓eGFR ≥40% to <60mL/min/1.73m², ‡ new ESRD, or death from renal/CV cause)	4.3% (n=370)	5.6% (n=480)	0.76 (0.67-0.87)	-	↓1.3%	77**	SBP ↓2.7mmHg DBP ↓0.7mmHg Weight ↓1.8Kg A1C ↓0.42%

* Dapagliflozin was non-inferior to placebo for the primary safety endpoint of MACE (P<0.001); † No difference for CV death between dapagliflozin and placebo; ‡ Calculated using CKD-EPI
Other non-significant secondary efficacy outcomes: MI, ischemic stroke, death from non-CV cause, ≥40% ↓eGFR to <60mL/min/1.73m², ESRD or death from renal cause. Results were consistent across all subgroups.

FIGURE 1: PRIMARY EFFICACY OUTCOMES

TABLE 2: Adverse Events (AE)

CLINICAL ENDPOINTS	DAPAGLIFLOZIN 10MG n=8574	PLACEBO n=8569	HR (95% CI)	P VALUE	ARR/ARI	NNT/NNH /4.2YRS	COMMENTS
DKA	0.3% (n=27)	0.1% (n=12)	2.18 (1.1-4.3)	0.02	↑0.2%	500	Note that >80% of patients with DKA were using insulin at baseline
Major hypoglycemic event	0.7% (n=58)	1% (n=83)	0.68 (0.49-0.95)	0.02	↓0.3%	334	Other non-significant AE: sx of volume depletion, UTI, breast cancer, hypersensitivity reactions, hepatic events, amputation, and fracture.
Genital infection	0.9% (n=76)	0.1% (n=9)	8.36 (4.19-16.68)	<0.001	↑0.8%	125	
Bladder cancer	0.3% (n=26)	0.5% (n=45)	0.57 (0.35-0.93)	0.02	↓0.2%	500	
AKI	1.5% (n=125)	2% (n=175)	0.69 (0.55-0.87)	0.002	↓0.5%	200	
Serious AE	34.1% (n=2925)	36.2% (n=3100)	0.91 (0.87-0.96)	<0.001	↓2.1%	48	
AE leading to D/C of trial	8.1% (n=693)	6.9% (n=592)	1.15 (1.03-1.28)	0.01	↑1.2%	84	
D/C rates	21.1% (n=1811)	25.1% (n=2151)	-	-	-	-	

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:
- Designed to assess whether potential benefits with dapagliflozin are comparable to empagliflozin and canagliflozin (all trials were active SGLT-2 inhibitor vs placebo).
- Trial included largest percentage (~60%) of primary prevention patients (i.e. no established cardiovascular disease). This is unique compared to other SGLT-2 inhibitor studies (i.e. **EMPA-REG OUTCOME**: 100% ASCVD, **CANVAS**: 66% ASCVD).
- Large, well-designed trial.
- Low loss-to-follow up (n=30, <0.1%/yr).
- Both ITT and PP analyses were performed, which is often preferred in non-inferiority trials in order to decrease bias.[6]

LIMITATIONS:
- Investigators and participants were informed about the positive CV results from the **EMPA-REG OUTCOME** trial, upon which two additional primary <u>efficacy</u> outcomes were added to the trial protocol, rather than having one primary <u>safety</u> endpoint as originally planned. This could increase the chance of surveillance/detection bias.
- The addition of the new primary outcomes could have led to the trial being underpowered, as the sample size was not increased.
- Findings may only be relevant in patients with longstanding T2DM (mean duration ~11yrs).
- Use of open-label SGLT-2 inhibitors (3.4% in dapagliflozin group, 6.1% in placebo group).

UNCERTAINITIES:
- There are no head-to-head trials comparing dapagliflozin, canagliflozin, and empagliflozin. If they were compared, would dapagliflozin have inferior CV outcomes?
- Does the lack of MACE reduction correlate with the higher CrCl inclusion criteria (≥60mL/min/1.73m²) in **DECLARE-TIMI 58** as opposed to the lower eGFR inclusion criteria seen in **EMPA-REG OUTCOME** (>30mL/min/1.73m²)?[2] Or is it because the majority (~60%) of participants did not have established ASCVD? Or is it because of dapagliflozin's individual drug characteristics?
- Does dapagliflozin have a role in preventing the progression of CKD? Dapagliflozin significantly decreased AKI (NNT= 200/4.2 yrs). Renal outcome trial currently ongoing: **DAPA-CKD** – estimated completion 11/2020.[7] Are the renal benefits signaling a SGLT-2 inhibitor class effect?
- Does the hypothesized reduction in HHF seen with dapagliflozin correlate to EF? Further investigation is required as only ~10% of participants had established HF in this trial. HF outcome trial currently ongoing: **DAPA-HF** - estimated completion 12/2019.[8]
- Does dapagliflozin have a role in primary prevention of CV events? (subgroup analysis for 1º prevention suggests not: HR 1.01; 0.86-1.2; 95% CI).
- The statistically significant CV benefits shown in this trial are **mostly due to the participants (~40%) with established ASCVD** (secondary prevention). This is an important distinction from the population studied in the **EMPA-REG OUTCOME** trial, which solely studied participants with established ASCVD.
- SGLT-2 inhibitors are still new drugs, and their mechanisms aren't fully understood.[9] Real world data collection is important to determine the effects of these medications, as some benefits and harms may be a class effect, while others may be individual to only one drug.
- ~23.1% of participants discontinued the trial regimen early (21.1% dapagliflozin vs 25.1% placebo), but this is a reasonable representation of real-world adherence.
- There was no reported allocation concealment or mention of blinded adjudication of outcomes.

RxFILES RELATED LINKS

- RxFiles Diabetes Agents Outcome Table: https://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Agents-Outcomes-Comparison-Summary-Table.pdf
- **DECLARE-TIMI 58** Article: https://www.nejm.org/doi/full/10.1056/NEJMoa1812389
- RxFiles **EMPA-OUTCOME** Trial Summary: https://www.rxfiles.ca/rxfiles/uploads/documents/EMPA-REG%20Trial%20Summary.pdf

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