DECLARE-TIMI 58: Dapagliflozin vs Placebo in T2DM + CVD/Major Risk Factors

Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction

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) (NNH=112/4.2yrs or NNT=470/1yr).
  - 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** 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** (EMPA-DANCE) lead to a reduction in MACE (NNH=63/3.1yrs or NNT=195/1yr) and all-cause mortality (NNT= 38/3.1 yrs).
  - **Canagliflozin** (CANVAS) lead to a reduction in MACE (NNH=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 ASCVD59.4% (≥55yrs or ≥60yrs with ≥1 of the following: hypertension, dyslipidemia, or tobacco use) or established ASCVD40.6% (defined as clinically evident ischemic heart disease, ischemic cerebrovascular disease, or PAD).

**EXCLUSION:** Acute CV event in prior 8 weeks (ACS, TIA, stroke, decompenated HF, any revascularization, sustained ventricular tachycardia); current/recent treatment with any pioglitazone (within 24 months or use for >2yrs) or rosiglitazone (within 12 months); previous/recent 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: 66.6 ± 3.6yrs \(n=17,160\); age 64 ± 6.8yrs \(\geq 65\) yrs (46.1%), >75yrs (6.4%)
- Median duration of T2DM: A1C: 111yrs (IQR 6-16yrs); 8.3 ± 1.2%
- Sex; BMI: 46% \(\geq 65\) yrs, 54% \(\geq 60\) yrs
- eGFR, SBP: 85.2mL/min/1.73m², 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

**TABLE 1: Efficacy**

<table>
<thead>
<tr>
<th>Clinical Endpoints</th>
<th>Dapagliflozin 10mg (n=8532)</th>
<th>Placebo (n=8578)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
<th>ARR/ARI</th>
<th>NNT/4.2 yrs</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Co-primary Endpoints</strong></td>
<td></td>
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<tr>
<td>MACE (CV death, non-fatal MI, or non-fatal stroke*)</td>
<td>8.8% (n=756)</td>
<td>9.4% (n=803)</td>
<td>0.93 (0.84-1.03)</td>
<td>0.17</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Composite of CV death and HfH</td>
<td>4.9% (n=417)</td>
<td>5.8% (n=496)</td>
<td>0.83 (0.73-0.95)</td>
<td>0.005</td>
<td>↓ 0.9%</td>
<td>112</td>
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</tr>
<tr>
<td><strong>Secondary Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>6.2% (n=529)</td>
<td>6.6% (n=570)</td>
<td>0.93 (0.82-1.04)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>CV Death*</td>
<td>2.9% (n=245)</td>
<td>2.9% (n=249)</td>
<td>0.98 (0.82-1.17)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>HfH</td>
<td>2.5% (n=212)</td>
<td>3.3% (n=286)</td>
<td>0.73 (0.61-0.88)</td>
<td>-</td>
<td>↓ 0.8%</td>
<td>125**</td>
<td></td>
</tr>
<tr>
<td>Renal Composite (sustained ↓ eGFR ≤40% to &lt;60mL/min/1.73m², ↓ new ESRD, or death from renal/CV cause)</td>
<td>4.3% (n=370)</td>
<td>5.6% (n=480)</td>
<td>0.76 (0.67-0.87)</td>
<td>-</td>
<td>↓ 1.3%</td>
<td>77**</td>
<td></td>
</tr>
</tbody>
</table>

* 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>
<thead>
<tr>
<th>Clinical Endpoints</th>
<th>Dapagliflozin 10mg (n=8532)</th>
<th>Placebo (n=8578)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
<th>ARR/ARI</th>
<th>NNT/4.2 yrs</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>DKA</td>
<td>0.3% (n=27)</td>
<td>0.1% (n=12)</td>
<td>2.18 (1.1-4.3)</td>
<td>0.02</td>
<td>↑ 0.2%</td>
<td>500</td>
<td>Note that &gt;80% of patients with DKA were using insulin at baseline Other non-significant AE: sx of volume depletion, UTI, breast cancer, hypersensitivity reactions, hepatic events, amputation, and fracture.</td>
</tr>
<tr>
<td>Major hypoglycemic event</td>
<td>0.7% (n=58)</td>
<td>1% (n=83)</td>
<td>0.68 (0.49-0.95)</td>
<td>0.02</td>
<td>↓ 0.3%</td>
<td>334</td>
<td></td>
</tr>
<tr>
<td>Genital infection</td>
<td>0.9% (n=76)</td>
<td>0.1% (n=9)</td>
<td>8.36 (4.19-16.68)</td>
<td>&lt;0.001</td>
<td>↑ 0.8%</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>0.3% (n=26)</td>
<td>0.5% (n=45)</td>
<td>0.57 (0.35-0.93)</td>
<td>0.02</td>
<td>↓ 0.2%</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td>AKI</td>
<td>1.5% (n=125)</td>
<td>2% (n=175)</td>
<td>0.69 (0.55-0.87)</td>
<td>0.002</td>
<td>↓ 0.5%</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>Serious AE</td>
<td>34.1% (n=2925)</td>
<td>36.2% (n=3100)</td>
<td>0.91 (0.87-0.96)</td>
<td>&lt;0.001</td>
<td>↓ 2.1%</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>AE leading to D/C of trial</td>
<td>8.1% (n=693)</td>
<td>6.9% (n=592)</td>
<td>1.15 (1.03-1.28)</td>
<td>0.01</td>
<td>↑ 1.2%</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>D/C rates</td>
<td>21.1% (n=1811)</td>
<td>25.1% (n=2151)</td>
<td></td>
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</tbody>
</table>

**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.

**LIMITATIONS:**
- Investigators and participants were informed about the positive CV results from the EMPA-REG OUTCOME trial, upon which two additional primary efficacy outcomes were added to the trial protocol, rather than having one primary safety 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).

**UNCERTAINTIES:**
- 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 (~260mL/min/1.73m²) in DECLARE-TIMI 58 as opposed to the lower eGFR inclusion criteria seen in EMPA-REG OUTCOME (>30mL/min/1.73m²)? Is 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-CVD – estimated completion 11/2020. Are the renal benefits signaling a SGLT-2 inhibitor class effect?
- Does the hypothesized reduction in HfH seen with dapagliflozin correlate to EF? Further investigation is required as only ~10% of patients had established HF in this trial. HF outcome trial currently ongoing: DAPA-HF - estimated completion 12/2019.
- Does dapagliflozin have a role in primary prevention of CV events? (subgroup analysis for 1° 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. 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 TRIAL SUMMARY
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RxFiles RELATED LINKS
- RxFiles Diabetes Agents Outcome Table: https://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Agents-Outcomes-Comparison-Summary-Table.pdf

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References: