Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF)

Background: Recently, several large clinical trials (CANVAS, DECLARE-TIMI 58, and EMPA-REG) examined the effects of sodium-glucose cotransporter 2 (SGLT2) inhibitors on cardiovascular outcomes. CANVAS and EMPA-R

EG showed that in patients with type 2 diabetes mellitus (T2DM) there were reductions in composite primary outcomes of cardiovascular (CV) mortality, non-fatal myocardial infarction, or non-fatal stroke as well as reductions in heart failure (HF) hospitalizations. DECLARE-TIMI 58 failed to show a statistically significant reduction in the primary outcome of major adverse events but did show a reduction in the composite outcome of CV death or hospitalization for HF. These studies weren't powered to examine the effects of SGLT2 inhibitors in HF patients. This trial was conducted to study whether the addition of SGLT2 inhibitor dapagliflozin could benefit patients who have heart failure with reduced ejection fraction (HFrEF) with or without T2DM.

What They Did: Phase 3, multi-centered, double-blinded, placebo-controlled trial that randomly assigned 4744 patients with New York Heart Association (NYHA) class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either dapagliflozin (at a dose of 10 mg daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of worsening heart failure or cardiovascular death.

Inclusion Criteria:

- 18+ years
- Ejection fraction of $\leq$ 40%
- NYHA Class II, III, or IV symptoms
- Plasma NT-proBNP level of:
    - $\geq$ 600 pg/mL OR
    - $\geq$ 400 pg/mL if they were hospitalized for HF within the past 12 months OR
    - $\geq$ 900 pg/mL if patient had atrial fibrillation or flutter on baseline ECG
- All patients were required to receive started heart failure device therapy
    - ICD, CRT or both
- All patients were required to receive standard drug therapy
    - ACE-inhibitor/ARB/ARNI plus beta blocker unless contraindicated
- Mineralocorticoid receptor antagonist use was encouraged, but not required
- All drug doses were individually tailored and dosing of anti-hyperglycemic medications, including insulin, were titratable as seen fit by prescriber

Exclusion Criteria:

- Recent treatment with or unacceptable side effects of SGLT2 inhibitors
- Type 1 Diabetes Mellitus
- Hypotension or a systolic blood pressure < 95 mmHg
- Estimated glomerular filtration rate (eGFR) $\leq$ 30 mL/min/1.73 m^2 or rapid decline of renal function
- Current decompensated HF or HF hospitalization < 4 weeks prior
- MI, unstable angina, stroke, or TIA within 3 months to enrollment

Outcomes:

Primary Outcomes:

- Composite of worsening HF or CV mortality
    - Worsening HF was defined as either an unplanned hospitalization or an urgent visit resulting in IV therapy for HF

Secondary Outcomes:

- Composite of CV death or HF hospitalization
- Total number of hospitalizations for HF (including repeat admissions) and CV death
- Changes from baseline in Kansas City Cardiomyopathy Questionnaire total symptom score at 8 months
- Worsening renal function defined as a decline in eGFR of 50% or greater, ESRD, or renal death
- All-cause mortality

Results:

Primary Outcomes:

- Composite of worsening HF or CV mortality: 16.3% vs 21.1% (HR 0.74; 95% CI 0.65-0.85; P<0.001)
    - Hospitalization or urgent visit for HF: 10.0% vs 13.7% (HR 0.70; 95% CI 0.59-0.83; P not given)
    - CV mortality: 9.6% vs 11.5% (HR 0.82; 95% CI 0.69-0.98; P not given)

Secondary Outcomes:

- Composite of CV death or HF hospitalization: 16.1% vs 20.9% (HR 0.75; 95% CI 0.65-0.85; P<0.001)
- Total number of hospitalizations of HF (including repeat admissions) and CV death: 567 vs 742 (HR 0.75; 95% CI 0.65-0.88; P<0.001)
- Changes from baseline in KCCQ total symptom score at 8 months: 6.1+18.6 vs 3.3+19.2 (HR 1.18; 95% CI 1.11-1.26; P<0.001)
- Worsening renal function: 1.2% vs 1.6% (HR 0.71; 95% CI 0.44-.16; P not given)
- All-cause mortality: 11.6% vs 13.9% (HR 0.83; 95% CI 0.71-0.97; P not given)

Adverse Events: there were no statistically significant differences between the two groups

- Discontinuation due to adverse event: 4.7% vs 4.9% (P = 0.79)
- Renal adverse event: 6.5% vs 7.2% (P = 0.36)
- Fracture: 2.1% vs 2.1% (P = 0.36)
- Amputation: 0.5% vs 0.5% (P = 1.00)
- Major hypoglycemia: 0.2% vs 0.2% (only occurred in patients with pre-existing DM)
- DKA: 0.1% vs 0% (only occurred in patients with pre-existing DM)
- Fournier's Gangrene: 0 vs < 0.1 (only occurred in 1 patient in placebo group)

Strengths:

- Large, multicenter, placebo-controlled, double blinded study
- 58.2% of patients in each group did not have pre-existing T2DM
- Majority of patients were on GDMT for HF before start of trial

Limitations:

- Use of the inclusion/exclusion criteria may have limited the generalizability of the findings
- P values were not given for some of the outcomes
- Rates of genitourinary infections were not reported
- Less than 5% of the patients were African American
- Few were elderly with multiple coexisting illnesses
- Most patients included were NYHA functional class II: 67.7% vs 67.4%
    - Further studies in patients with more severe HF are necessary

Discussion: Dapagliflozin was effective in 55% in reducing the risk of worsening heart failure or cardiovascular deaths in patients without T2DM. This demonstrates that in addition to the glucose lowering effects in diabetes patients SGLT2 inhibitors provide cardiovascular benefits, like reduction in mortality. Event rates for all three components of the primary composite outcome favored dapagliflozin with no difference in adverse safety events.

Study Author Conclusion: "Among patients with heart failure and a reduced ejection fraction, those who received the SGLT2 inhibitor dapagliflozin had a lower risk of worsening heart failure or death from cardiovascular causes and better symptom scores than those who received placebo, regardless of the presence or absence of diabetes."

Clinical Take Home Point: Overall, the results of this trial prove the benefit of SGLT2 inhibition, such as dapagliflozin, in patients with HFrEF and T2DM. This study also provides initial evidence of their efficacy in patients with HFrEF but without T2DM. In May of 2020, the FDA approved dapagliflozin for the indication to reduce the risk of CV death or hospitalization in patients with HFrEF with or without T2DM.

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