The role of SGLT2 inhibitors in the treatment of heart failure

Farah Alhalabi, Pharm.D.

Christian Hospital PGY-1 Pharmacy Resident

Learning objectives

1. Classify heart failure based on left ventricular ejection fraction.
2. Compare the treatment recommendations between the 2017 and 2022 AHA/ACC/HFSA guideline
3. Summarize the data supporting the use of SGLT2 inhibitors in patients with heart failure in the 2022 AHA/ACC heart failure guidelines

Background:[1]

- Heart failure prevalence in US:
  - 6.2 million adults
  - Expected to increase to eight million in 2030
- In 2018, heart failure was mentioned on 379,800 death certificates
- 2012 estimated cost is $ 30.7 billion
  - Cost of healthcare services
  - Medicines
  - Missed days of work

Risk factors[2]

- Coronary artery disease
- Diabetes
- Hypertension
- Obesity
- Smoking tobacco
- No getting enough physical activity

Classification of heart failure by left ventricular ejection fraction (LVEF)[3]

Heart failure with reduced ejection fraction (HFrEF)	Left ventricular ejection fraction ≤ 40%
Heart failure with improved ejection fraction (HFimpEF)	Previous LVEF of ≤ 40% and follow up measurement of more than 40 %
Heart failure with mildly reduced ejection fraction (HFmrEF)	LVEF of 41% to 49%

	Plus evidence of increased left ventricular filling pressures and elevated natriuretic peptide.
Heart failure with preserved ejection fraction (HFpEF)	LVEF ≥ 50% Plus evidence of increased left ventricular filling pressures and elevated natriuretic peptide

2022 ACC/AHA heart failure guideline update:[3]

- Guideline directed medical therapy for heart failure with reduced ejection fraction includes 4 medications classes which include beta blocker, ACE-I, mineralocorticoid receptor antagonists and SGLT2 inhibitors

SGLT2 inhibitors[4,5,6,7]

Drugs	Mechanism of Action	Indications/doses	Adverse effects
Dapagliflozin	Inhibits SGLT2 in the proximal renal tubules. It reduces reabsorption of filtered glucose from tubular lumen. It also reduces sodium reabsorption	Heart failure with reduced ejection fraction: 10 mg once daily Heart failure with preserved ejection fraction (off-label): with and without diabetes 10 mg once daily Type 2 diabetes: 5 mg once daily Chronic kidney disease: 10 mg once daily	Acute kidney injury Bone fractures, Hypotension/volume depletion, Urinary tract infections Fungal infections Ketoacidosis Lower limb amputation
Empagliflozin		Heart failure reduced or preserved ejection fraction: 10 mg once daily Type 2 diabetes: 10 mg once daily Diabetes and atherosclerotic cardiovascular disease: 10 or 25 mg once daily	

		Diabetic kidney disease (off-label): 10 mg once daily	
Canagliflozin	Inhibits SGLT2 in the proximal renal tubules which reduces the reabsorption of glucose.	Type 2 Diabetes: Hyperglycemia: 100 mg once daily Atherosclerotic cardiovascular disease: 100 or 300 mg once daily Diabetic kidney disease: 100 mg once daily	
Ertugliflozin		Type 2 Diabetes: 5 mg daily	

Trials

Study 1:[8]

Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction. (The DEFINE-HF Trial 2019).

Design:

- Multicenter, double-blind, parallel-group, randomized, controlled trial conducted across 26 sites in the United States.
- N= 263 patients
- Patients randomized into 1:1 ratio to dapagliflozin 10 mg daily or placebo

Inclusion criteria	Exclusion criteria
Patients 18 years and older NYHA class II,III or IV with a LVEF ≤ 40 % Plasma NT-proBNP level of ≥ 600pg/mL OR ≥ 400pg/mL if they were hospitalized for HF within the past 12 months OR ≥ 900pg/mL if patient had atrial fibrillation/flutter on baseline ECG.	Patients on SGLT2 inhibitors or have side effects from it Type 1 diabetes SBP< 95 mmHg eGFR<30 ml/min/1.73m2 Patients hospitalized for decompensated heart failure within 30 days Patients with MI, unstable angina or TIA within 3 months before enrollment

Outcomes:

- Primary outcomes: average of 6- and12-week mean NT-proBNP and a composite of the proportion of patients that achieved a meaningful improvement in health status (≥5-point increase in average of 6- and 12-week Kansas city cardiomyopathy questionnaire or KCCQ-OS) or NT-proBNP (≥20% decrease in average of 6- and 12-week NT-proBNP)
- Secondary end points included proportion of patients with meaningful change in KCCQ, and NT-proBNP at each time point.

Results:

Primary outcomes:

No difference in biomarkers, the average 6 and 12 week adjusted mean NT-proBNP between patients treated with dapagliflozin versus placebo. P=0.43

Patients treated with dapagliflozin had a clinically meaningful improvement of ≥5 points in KCCQ-OS or at least a 20% reduction in NT-proBNP, as compared with placebo.

- No difference in NT-proBNP reduction >20% or KCCQ-OS improvement > 5 points between diabetic and non-diabetics patients. P=0.304

Conclusions:

- Dapagliflozin addition did not affect the mean NT-proBNP but significantly increased the patients' quality of life as measured by the Kansas City Cardiomyopathy Questionnaire overall summary score.

Study 2:[9]

Cardiovascular and renal outcomes with Empagliflozin in heart failure. (The EMPEROR-Reduced Trial 2020)

Design:

- Multicenter, double-blind, randomized, controlled trial performed at 520 centers in 20 countries
- N= 3,730
- Patients randomized into 1:1 ratio to receive empagliflozin 10 mg or placebo daily
- Patient enrolled between April 2017 and November 2019

Inclusion criteria	Exclusion criteria
Patients 18 years and older NYHA class II,III or IV with a LVEF ≤ 40 %	Myocardial infarction, coronary artery bypass graft surgery, or other major

If LVEF 31-40%, requires history of hospitalization for heart failure for the previous 12 months 30% or less ejection fraction: 600 pg/ml NT-proBNP 31-35% ejection fraction: High level N-terminal prohormone of brain natriuretic peptide at least 1000 pg/ml 36-40% ejection fraction: at least 2600 pg/ml of NT-proBNP	cardiovascular surgery, stroke or TIA in past 90 days Acute decompensated HF SBP ≥ 180 mmHg at second visit Symptomatic hypotension and/or a SBP < 100 mmHg Impaired renal function (eGFR < 20 mL/min/1.73 m2 or dialysis patient) Current use or prior use of a SGLT-2 inhibitor Women who are pregnant

Outcomes:

- Primary outcomes: composite of cardiovascular death and first hospitalization for heart failure
- Secondary outcomes: total number of hospitalizations for heart failure and decline in eGFR

Results:

	Empagliflozin	Placebo	
Primary outcomes	19.4%	24.7%	P<0.001
Primary outcomes for patients without diabetes	17.2%	21%	HR 0.78 (95% CI, 0.64-0.97)
Secondary outcomes			
Total number of hospitalizations	388	533	0.70 (0.58-0.85) P<0.001
Mean slope of change in eGFR (ml/min/1.73 m2 per year)	- 0.55 ± 0.4	- 2.28 ± 0.23	1.73 (1.10 – 2.37) P< 0.001

Conclusion:

- Empagliflozin reduced the risk of cardiovascular events and slowed the progression of kidney disease in patients with heart failure and reduced ejection fraction regardless of the presence or absence of diabetes.

Study 3: [10]

Dapagliflozin in patients with heart failure and reduced ejection fraction. (DAPA-HF trial 2019)

Design:

- Multicenter, double-blind, randomized, controlled trial performed in 410 centers in 20 countries
- N= 4744
- Patients randomized into 1:1 ratio to dapagliflozin 10 mg daily or placebo
- Patients enrolled between February 2017 and August 2018.

Population: similar inclusion and exclusion criteria to DEFINE-HF trial.

Outcomes:

- Primary outcome is a composite of worsening heart failure or death from cardiovascular causes
- Secondary end point is a composite of hospitalization for heart failure or cardiovascular death

Results:

	Dapagliflozin	Placebo	
Primary outcomes	16.3%	21.2%	P<0.001
Primary outcomes for patients with diabetes	20%	25.4 %	HR 0.75, 95% CI 0.63-0.90
Primary outcomes for patients without diabetes	13.1%	17.6%	HR 0.73, 95% CI 0.60-0.88
Secondary outcomes	16.1%	20.9%	P< 0.001

Conclusions:

- Dapagliflozin reduced the risk of worsening heart failure or death from cardiovascular causes in patients with heart failure and reduced ejection fraction regardless of the presence or absence of diabetes.

Assessment questions:

1- **According to the 2022 guideline for heart failure, a patient that had a left ventricular ejection fraction of 38%, but 6 months later has an EF of 55% can be classify to which of the following:**

A. Heart failure reduced ejection fraction (HFrEF)

B. Heart failure preserved ejection fraction improved (HFpEF improved)

C. Heart failure improved ejection fraction (HFimpEF)

D. Heart failure with mildly reduced ejection fraction (HFmrEF)

2- **According to the 2022 ACC/AHA guidelines, which of the following can be used as treatment for patients with heart failure and EF < 40%:**

A. Verapamil

B. Liraglutide

C. Empagliflozin

D. Amiodarone

3- **The data presented in DAPA-HF trial suggest which of the following:**

A. Dapagliflozin has showed to decrease the risk of hospitalization for HF and death in patients with HFrEF and type 2 diabetes only.

B. Dapagliflozin has showed to decrease the risk of hospitalization for HF and death from CV causes in patients with HFrEF irrespective of the presence of diabetes.

C. Dapagliflozin has showed to lower the risk of hospitalization for HF but has no effect on death from CV cause in patients with HFrEF with diabetes

D. Dapagliflozin has showed to lower the risk of hospitalization for HF but has no effect on death from cardiovascular cause in patients with HFrEF irrespective of the presence diabetes.

References:

1- Centers for disease control and prevention. Heart failure. CDC. Updated October 14,2022. Accessed October 25,2022.
2- Mayo Clinic. Heart failure-complications. Mayo Clinic. Published July 21,2021. Accessed October 20, 2022. Heart failure - Symptoms and causes - Mayo Clinic
3- Heidenreich PA, Bozkurt B, Aguilar D et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. *Circulation.* 2022;145:e895-e1032
4- Empagliflozin. In: Lexi-Comp, Inc. Updated October 22,2022. Accessed November 1, 2022.
5- Dapagliflozin. In: Lexi-Comp, Inc. Updated October 22,2022. Accessed November 1, 2022.
6- Canagliflozin. In: Lexi-Comp, Inc. Updated October 22, 2022. Accessed November 1, 2022.
7- Ertugliflozin. In: Lexi-Comp, Inc. Updated October 22, 2022. Accessed November 1, 2022.
8- Nassif ME, Windsor SL, Tang F et al. Dapagliflozin effects on biomarkers, symptoms and functional status in patients with heart failure with reduced ejection fraction: The DEFINE-HF trial. *Circulation*. 2019;140(18):1463-1476.
9- Packer M, Anker SD, Butler J et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N. Engl. J Med.* 2020;383(15):1413-1424.
10- McMurray JJV, Solomon SD, Inzucchi SE et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N. Engl. J. Med. 2019;381(21):1995-2008.