Finding the “Sweet Spot” in Prescribing SGLT2 Inhibitors in Heart Failure

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MHI Grand Rounds
Disclosure

• I have no financial interest or affiliation with the manufacturer of any marketed products discussed herein.

Objectives

• Summarize the pharmacology of SGLT2 inhibitors
• Review clinical trials evaluating the use of SGLT2 inhibitors in heart failure patients
• Discuss the addition of SGLT2 inhibitors to guideline directed medical therapy for heart failure patients
• Illustrate safe prescribing and follow-up of SGLT2 inhibitors
Abbreviations

- AHF = acute heart failure
- HF = heart failure
- HFrEF = heart failure with reduced ejection fraction
- HFrEF = heart failure with preserved ejection fraction
- hHF = hospitalization for heart failure
- SGLT2 inhibitor = sodium-glucose cotransporter-2 inhibitor
- GDMT = guideline directed medical therapy
- HDL = high-density lipoprotein
- FDA = Food & Drug Administration
- PCP = primary care physician
- CKD = chronic kidney disease
- T1DM = type 1 diabetes mellitus
- T2DM = type 2 diabetes mellitus
- NYHA = New York Heart Association
- LVEF = left ventricular ejection fraction
- eGFR = estimated glomerular filtration rate
- MI = myocardial infarction
- UA = unstable angina
- TIA = transient ischemic attack
- CV = cardiovascular
- ADHF = acute decompensated heart failure
- SBP = systolic blood pressure
- IV = intravenous
- CABG = coronary artery bypass graft
- KCCQ = Kansas City Cardiomyopathy Questionnaire
- PO = oral
- AKI = acute kidney injury

Background

- **Mechanism:**
  - Inhibits SGLT2, thus reducing reabsorption of filtered glucose and promoting urinary glucose excretion
- **Drugs in class:**
  - Dapagliflozin (Farxiga)**
  - Empagliflozin (Jardiance)**
  - Canagliflozin (Invokana)**
  - Ertugliflozin (Steglatro)

** denotes ANW formulary status
Mechanisms of Cardiovascular Benefit

- Glucose lowering
- Weight loss
- Reduces blood pressure without increase in heart rate
- Decreases arterial stiffness and vascular resistance
- Increases HDL
- Reduces uric acid
- Improved renal function
- Decreases visceral adiposity
- Osmotic diuresis
- Natriuresis
Poll question

- Should cardiologists take the lead in prescribing SGLT2 inhibitors in patients with HF?

- A) Yes, for most patients who meet FDA indications for HF, regardless of the presence of diabetes mellitus
- B) Yes, for most patients WITHOUT diabetes mellitus who meet FDA indications for HF
- C) No, it should be started by the PCP or another subspecialist (endocrinology or nephrology)
Barriers to initiation

- Difficult approval process and/or cost to patient – 26%
- Lack of experience with SGLT2 inhibitors – 25%
- Overall pill burden – 5%
- Concern for hypoglycemia or needing to adjust baseline diabetic medications prescribed by other providers – 30%
- Concern for non-cardiac side-effects and having to counsel on urogenital infections – 10%
- General practice to avoid “early adoption” of newly approved therapies – 4%

<table>
<thead>
<tr>
<th>FDA Approved Indications</th>
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<tbody>
<tr>
<td><strong>Indication</strong></td>
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<tr>
<td>HFrEF</td>
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<tr>
<td>HFpEF</td>
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<tr>
<td>CKD</td>
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<td>Hyperglycemia, T2DM</td>
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</table>
# Clinical Trial Overview

<table>
<thead>
<tr>
<th></th>
<th>Farxiga® (dapagliflozin)</th>
<th>Jardiance® (empagliflozin)</th>
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<tbody>
<tr>
<td><strong>HFrEF</strong></td>
<td>DAPA-HF</td>
<td>EMPEROR-Reduced</td>
</tr>
<tr>
<td><strong>HFpEF</strong></td>
<td>PRESERVED-HF, DELIVER <em>(estimated Q1 2022)</em></td>
<td>EMPEROR-Preserved</td>
</tr>
<tr>
<td><strong>Acute HF</strong></td>
<td>DAPA ACT HF-TIMI 68 <em>(estimated Q2 2023)</em></td>
<td>EMPULSE</td>
</tr>
<tr>
<td><strong>Acute MI</strong></td>
<td>DAPA-MI <em>(estimated Q3 2023)</em></td>
<td>EMPACT-MI <em>(estimated Q1 2023)</em></td>
</tr>
<tr>
<td><strong>CKD</strong></td>
<td>DAPA CKD</td>
<td>EMPA-KIDNEY <em>(estimated Q4 2022)</em></td>
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**NOTE:** All completed trials have been positive.

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## HFrEF Trial Overview

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<th>EMPEROR-Reduced</th>
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<tr>
<td><strong>Interventions</strong></td>
<td>Dapagliflozin 10 mg daily vs placebo (1:1)</td>
<td>Empagliflozin 10 mg daily vs placebo (1:1)</td>
</tr>
<tr>
<td><strong>Key inclusion criteria</strong></td>
<td>Age ≥ 18 y.o.; NYHA Class II-IV (LVEF ≤ 40%); eGFR ≥ 30 mL/min; ~55% w/o T2DM</td>
<td>Age ≥ 18 y.o.; NYHA Class II-IV (LVEF ≤ 40%); eGFR ≥ 20 mL/min; ~50% w/o T2DM</td>
</tr>
<tr>
<td><strong>Key exclusion criteria</strong></td>
<td>MI, UA, TIA or CV procedure/surgery in previous 12 weeks; ADHF; SBP &lt; 95 mmHg or symptomatic hypotension; T1DM; recent treatment / intolerance to SGLT2 inhibitor</td>
<td>MI; CABG; other major CV surgery, stroke or TIA in previous 90 days; ADHF; SBP ≥ 180 or &lt; 100 mmHg or symptomatic hypotension; recent treatment / intolerance to SGLT2 inhibitor</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>4744 patients</td>
<td>3730 patients</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>Composite of worsening HF (hospitalization or urgent visit requiring IV therapy for HF) or CV death</td>
<td>Composite of CV death or hospitalization for worsening HF</td>
</tr>
<tr>
<td><strong>Median follow-up</strong></td>
<td>18.2 months</td>
<td>16 months</td>
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HFpEF Trial Overview

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<td>Empagliflozin 10 mg daily vs placebo (1:1)</td>
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</table>

| Patient population                  | Age ≥ 40 y.o. w/ symptomatic NYHA Class II-IV HF; LVEF > 40% & evidence of structural heart disease; eGFR ≥ 25 mL/min; off IV HF therapies for ≥ 24 hours | Age ≥ 18 y.o. w/ NYHA Class II-IV HF & stable PO diuretic dose; LVEF > 40% & evidence of structural heart disease; eGFR ≥ 20 mL/min; no episodes of ADHF w/in 1 week |

| Sample size                         | 6263 patients                                    | 5988 patients                             |
| Study duration                      | 39 months                                        | 38 months                                 |
| Primary outcome                     | Time to first occurrence of any component of the composite of CV death or HF events in patients with LVEF < 60% | Time to first occurrence of any component of the composite of CV death or hHF |
| Completion                          | Q1 2022 (estimated)                              | April 2021 (actual)                       |

Study NCT03619213. ClinicalTrials.gov website

EMPEROR-Preserved

- **Objective:** To evaluate the effects of SGLT2 inhibition with empagliflozin on major HF outcomes in patients with HFpEF
- **Inclusion criteria:**
  - 18 years of age & older
  - NYHA functional class II-IV chronic HF, LVEF >40%
- **Treatment groups:**
  - Empagliflozin (N=2,997)
  - Placebo (N=2,991)
- **Primary outcome:**
  - Composite of CV death or hospitalization for HF over 26.2 months: 13.8% vs. 17.1% (P<0.001)
- **Secondary outcomes:**
  - Hospitalization for HF: 8.6% vs. 11.8% (P<0.001)
  - Death from CV causes: 7.3% vs. 8.2% (P=NS)
- **Conclusion:** Empagliflozin reduced the combined risk of CV death or hospitalization for HF in patients with HFpEF, regardless of the presence or absence of diabetes.

# Acute HF Trial Overview

<table>
<thead>
<tr>
<th>Interventions</th>
<th>DAPA ACT HF-TIMI 68: Dapagliflozin 10 mg daily vs placebo (1:1)</th>
<th>EMPULSE: Empagliflozin 10 mg daily vs placebo (1:1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment timing</td>
<td>From ≥ 24 hours to day 7 of admission until 60 days</td>
<td>From within 24 hours to day 5 of admission until 90 days</td>
</tr>
<tr>
<td>Patient population</td>
<td>Age ≥ 18 y.o.; currently hospitalized for AHF &amp; stabilized; LVEF ≤ 40% within last 12 months; eGFR ≥ 30 mL/min</td>
<td>Age ≥ 18 y.o.; hospitalized for AHF (any LVEF) &amp; stabilized; dyspnea w/ ≥ 2 sx of HF; ≥ 40 mg IV furosemide or equivalent; eGFR ≥ 20 mL/min</td>
</tr>
<tr>
<td>Sample size</td>
<td>2400 patients (estimated)</td>
<td>530 patients (actual)</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Time to first occurrence of CV death or worsening HF</td>
<td>Clinical benefit at 90 days (composite of time to all-cause death, # of HF events, time to first HF event &amp; increase in KCCQ score)</td>
</tr>
<tr>
<td>Completion</td>
<td>Q1 2023 (estimated)</td>
<td>May 2021 (actual)</td>
</tr>
</tbody>
</table>

Study NCT04363697. ClinicalTrials.gov website.
DAPA ACT HF-TIMI 68. TIMI Study Group website.

![Guidelines Diagram](image_url)
Dosing

- **Dosing:**
  - Dapagliflozin (Farxiga)
    - Starting dose: 10 mg PO daily
    - Goal dose: 10 mg PO daily
    - Caution if eGFR <25 mL/min
  - Empagliflozin (Jardiance)
    - Starting dose: 10 mg PO daily
    - Goal dose: 10 mg PO daily
    - Caution if eGFR <20 mL/min

- **Administration:**
  - With or without food

- **Adjusting diuretics:**
  - Mild diuretic effect
  - Monitor for hypovolemia and potential need to reduce diuretic doses to prevent dizziness / lightheadedness

- **Adjusting diabetes medications:**
  - Basal insulin
    - Reduce dose ~20%
  - Sulfonylureas
    - Glipizide, gimepiride, glyburide
    - Reduce dose by ~50%

Monitoring

- **Adverse effects:**
  - Polyuria
  - Dehydration
  - AKI
  - Genitourinary infections
  - Increased risk of genital mycotic infections
    - Women > uncircumcised male > circumcised male
    - Usually mild to moderate
    - Responds well to fluconazole 150 mg PO x1 dose
  - Lower limb amputation (canagliflozin)

- **Monitoring:**
  - Renal function
  - Hypovolemia
  - Euglycemic diabetic ketoacidosis
  - Foot care

- **Contraindications:**
  - T1DM
  - Lactation (no data)
  - On hemodialysis

- **Cautions:**
  - Pregnancy
  - Ketoacidosis in patients with diabetes
  - AKI with reduced oral intake or fluid loss
  - Urosepsis and pyelonephritis
Additional Tips to Remember

1. Renal Dose Adjustments

- **Farxiga® (dapagliflozin)**
  - eGFR > 25 mL/min: 10 mg orally daily
  - eGFR < 25 mL/min:
    - Do not start
    - If patient is already receiving, may continue until initiation of dialysis
  - Dialysis: contraindicated

- **Jardiance® (empagliflozin)**
  - eGFR > 20 mL/min: 10 mg orally daily
  - eGFR < 20 mL/min:
    - Do not start (no dosing data)
    - Dialysis: contraindicated

2. Diuretic Adjustments

- **General HF population:**
  - Euvolemic or dry → reduce diuretic dose by ~25%
  - Hypervolemic → no diuretic dose adjustment

- **LVADs:**
  - More sensitive to volume changes!

3. Euglycemic DKA

- **Definition** = euglycemia (blood glucose < 250 mg/dL) with severe metabolic acidosis (arterial pH < 7.3, serum bicarbonate < 18 mEq/L) & ketonemia

- **Clinical features:**
  - N/V/D, abdominal pain
  - Hyperventilation
  - Signs of hyperglycemia: polyuria & polydipsia

- **Laboratory assessment:**
  - BMP (glucose, SCr, BUN, electrolytes, bicarbonate, anion gap)
  - Urine ketones (+serum ketones if urine ketones present)
  - Arterial blood gas (if serum bicarbonate reduced or hypoxic)

- **Treatment:**
  - Start EndoTool
  - Use fluids containing D5W
• J – Just
• A – Always
• R – Remember
• D – Diuretics
• I – Insulin
• A – And
• N – Nephrology
• C – Clearance
• E – EASY!!!

May need to reduce loop diuretic dose to prevent hypovolemia (dizziness, lightheadedness)

May need to reduce basal insulin dose by ~20% to prevent hypoglycemia. If on a sulfonylurea, may need to reduce dose by ~50%.

Check eGFR to ensure safe use! Avoid Jardiance if eGFR <20 mL/min & Farxiga if eGFR <25 mL/min

Patient Assistance Programs

Dapagliflozin (Farxiga)
• ALL patients eligible for first 30 days free
• Commercial / private insurance patients eligible for copay card that could bring copay as low as $0/month
• Covered on MN Medicaid’s formulary with no prior authorization required
• Cash out of pocket cost of Farxiga is $532.84/month
• Visit www.azandmeapp.com to see if your patient qualifies for free Farxiga from AstraZeneca

Empagliflozin (Jardiance)
• Commercial / private insurance patients eligible for $10/month copay card
• Covered on MN Medicaid’s formulary with no prior authorization required
• Cash out of pocket cost of Jardiance is $582.89/month
• Visit www.bipatientassistance.com to see if your patient qualifies for free Jardiance from Boehringer Ingelheim
Summary

- GDMT has changed! Consider all therapies when treating HFrEF patients:
  - ACEI / ARB / ARNI → preference for ARNI (sacubitril-valsartan)!
  - Beta blocker (metoprolol XL, carvedilol, or bisoprolol)
  - Aldosterone antagonist (spironolactone or eplerenone)
  - SGLT2i (dapagliflozin or empagliflozin)

- When starting a SGLT2i:
  - Consider adjusting diuretic dose
  - Consider adjusting sulfonlurea / basal insulin dose
  - Assess renal function
  - Counsel on the importance of genital hygiene

- Consider the use of empagliflozin for HFpEF patients with the EMPEROR-Preserved trial results

- Assess insurance coverage for ARNI & SGLT2 inhibitors prior to starting therapy

References

4) Invokana ® [prescribing information]. Janssen Pharmaceuticals. October 2021
10) Study NCT03619213. ClinicalTrials.gov website
12) Study NCT04363697. ClinicalTrials.gov website.
13) DAPA ACT HF-TIMI 68. TIMI Study Group website.
Questions?

• Email: Paige.skelton@allina.com
• EPIC in-basket message
• EPIC secure chat
• Microsoft Teams chat