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Finding the "Sweet Spot" in Prescribing SGLT2 Inhibitors in Heart Failure

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MHI Grand Rounds

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Disclosure

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

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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

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Abbreviations

- AHF = acute heart failure
- HF = heart failure
- HFrEF= heart failure with reduced ejection fraction
- HFpEF = 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

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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

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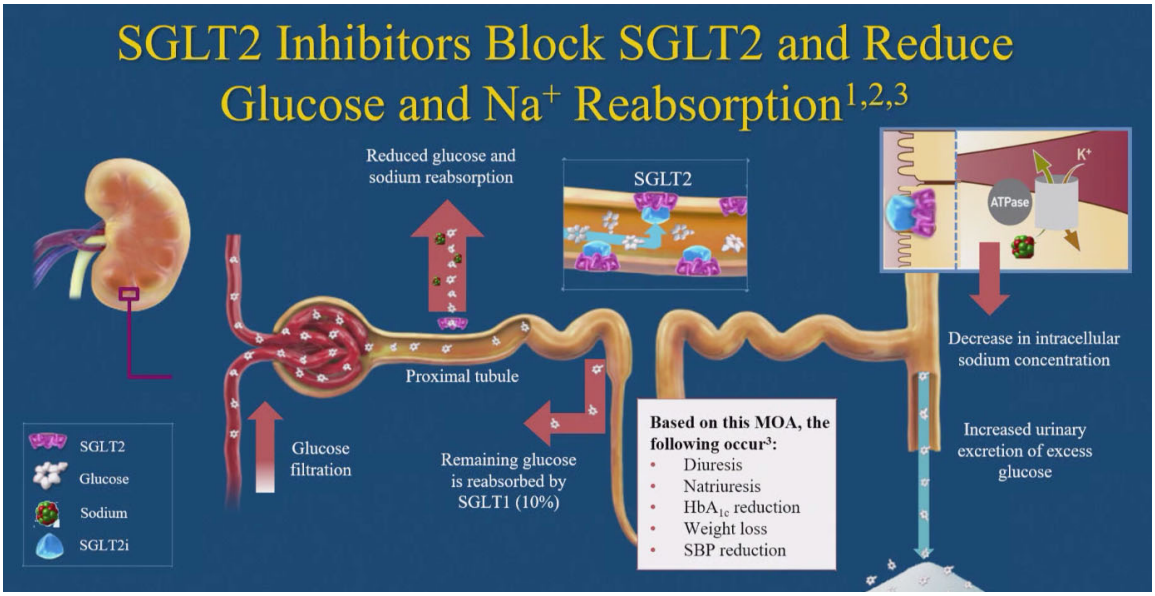

Wojcik C, Warden BA. *Current Cardiology Reports*. 2019;21:130.

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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 albuminuria
- Reduces uric acid
- Improved renal function
- Decreases visceral adiposity
- Osmotic diuresis
- Natriuresis

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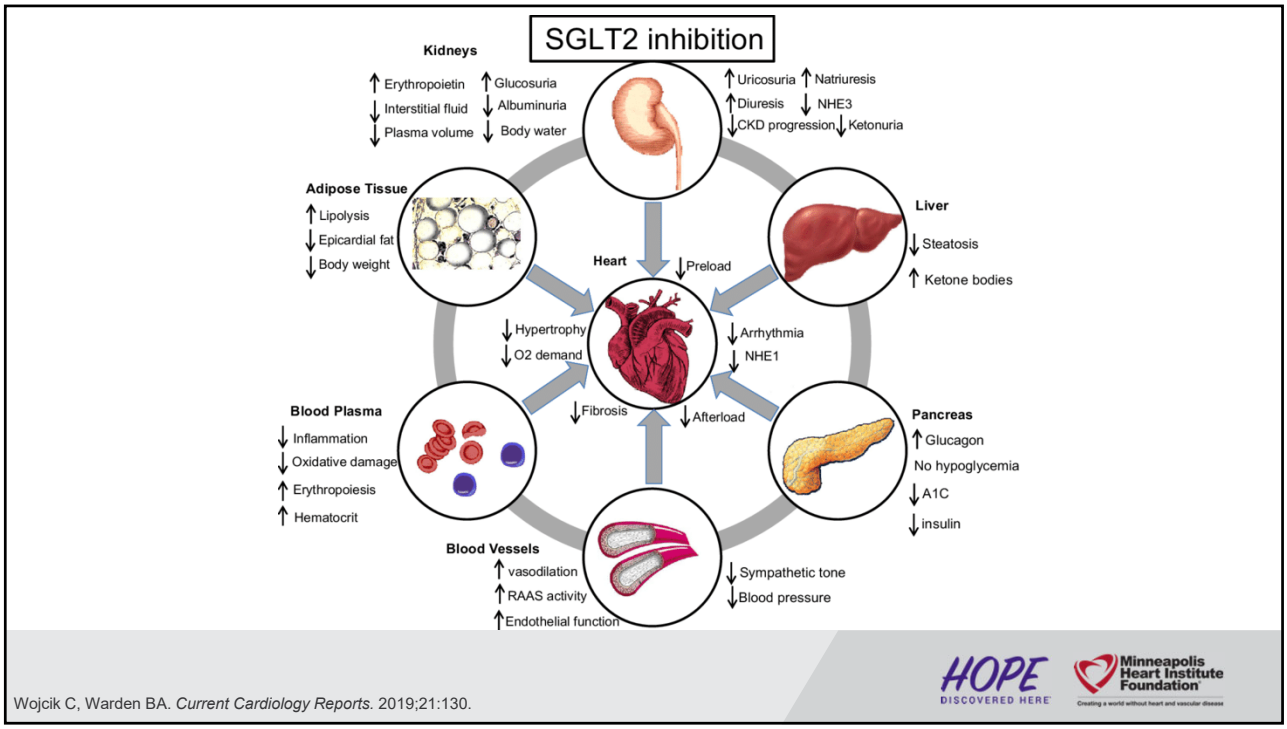

Wojcik C, Warden BA. *Current Cardiology Reports.* 2019;21:130.

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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)

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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%**

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FDA Approved Indications

Indication	Farxiga® (dapagliflozin)	Jardiance® (empagliflozin)	Invokana® (canagliflozin)	Steglatro® (ertugliflozin)
HFrEF	★	★		
HFpEF		★		
CKD	★			
Hyperglycemia, T2DM	★	★	★	★

Farxiga ® [prescribing information]. AstraZeneca. October 2021.
Jardiance ® [prescribing information]. Boehringer-Ingelheim. October 2021.
Invokana ® [prescribing information]. Janssen Pharmaceuticals. October 2021.
Steglatro ® [prescribing information]. Merck & Co. October 2021.

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Clinical Trial Overview

	Farxiga® (dapagliflozin)	Jardiance® (empagliflozin)
HFrEF	DAPA-HF	EMPEROR-Reduced
HFpEF	PRESERVED-HF, DELIVER *(estimated Q1 2022)*	EMPEROR-Preserved
Acute HF	DAPA ACT HF-TIMI 68 *(estimated Q2 2023)*	EMPULSE
Acute MI	DAPA-MI *(estimated Q3 2023)*	EMPACT-MI *(estimated Q1 2023)*
CKD	DAPA CKD	EMPA-KIDNEY *(estimated Q4 2022)*

NOTE: All completed trials have been positive

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HFrEF Trial Overview

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

McMurray JJV et al. Article and study protocol. N Engl J Med. 2019;381:1995-2008.
Packer M et al. Eur J Heart Fail. 2019;21:1270-1278.
Packer M et al. N Engl J Med. 2020;383:1413-1424.

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HFpEF Trial Overview

	DELIVER	EMPEROR-Preserved
Interventions	Dapagliflozin 10 mg daily vs placebo (1:1)	Empagliflozin 10 mg daily vs placebo (1:1)
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)

Solomon SD et al. Online ahead of print. *Eur J Heart Fail*. 2021;10.1002/ejhf.2249
Study NCT03619213. ClinicalTrials.gov website
Anker SD et al. Online ahead of print. *N Engl J Med*. 2021.

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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.

Anker SD et al. Online ahead of print. *N Engl J Med*. 2021.

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Acute HF Trial Overview

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

Study NCT04363697. ClinicalTrials.gov website.
DAPA ACT HF-TIMI 68. TIMI Study Group website.
Tromp J et al. *Eur J Heart Fail*. 2021;23:826-834.

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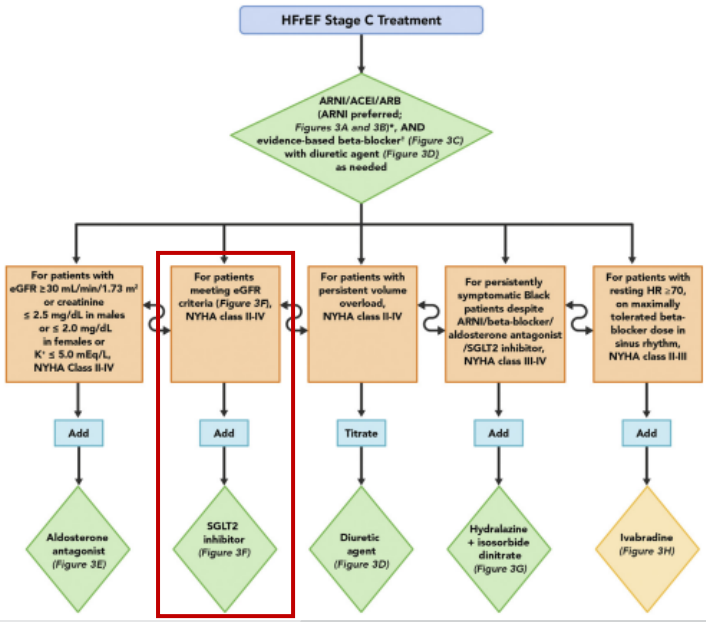
Guidelines



Maddox *et al*. 2021 Update to 2017 ECDP for Optimization of Heart Failure Treatment. JACC 2021.

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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, glimepiride, glyburide
    - Reduce dose by ~50%

Farxiga ® [prescribing information]. AstraZeneca. October 2021.
Jardiance ® [prescribing information]. Boehringer-Ingelheim. October 2021.
Maddox *et al.* 2021 Update to 2017 ECDP for Optimization of Heart Failure Treatment. JACC 2021.

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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

Farxiga ® [prescribing information]. AstraZeneca. October 2021.
Jardiance ® [prescribing information]. Boehringer-Ingelheim. October 2021.
Maddox *et al.* 2021 Update to 2017 ECDP for Optimization of Heart Failure Treatment. JACC 2021.

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Additional Tips to Remember

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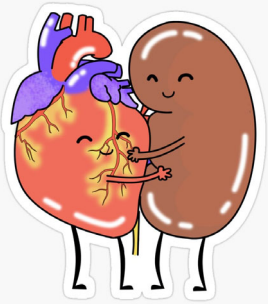
1. Renal Dose Adjustments

- **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



Farxiga ® [prescribing information]. AstraZeneca. October 2021.
Jardiance ® [prescribing information]. Boehringer-Ingelheim. October 2021.
Maddox *et al.* 2021 Update to 2017 ECDP for Optimization of Heart Failure Treatment. JACC 2021.

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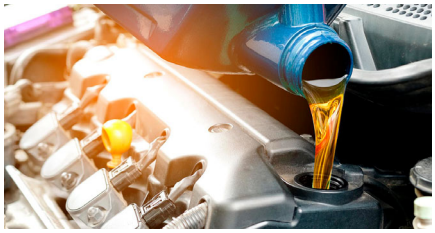
2. Diuretic Adjustments

- **General HF population:**
  - Euvolemic or dry → reduce diuretic dose by ~25%
  - Hypervolemic → no diuretic dose adjustment
- **LVADs:**
  - More sensitive to volume changes!



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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

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- **J** – Just
- **A** – Always
- **R** – Remember
- **D** – Diuretics
- **I** – Insulin
- **A** – And
- **N** – Nephrology
- **C** – Clearance
- **E** – EASY!!!

Pneumonic applies to Farxiga as well

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

Farxiga ® [prescribing information]. AstraZeneca. October 2021.
Jardiance ® [prescribing information]. Boehringer-Ingelheim. October 2021.
Maddox *et al.* 2021 Update to 2017 ECDP for Optimization of Heart Failure Treatment. JACC 2021.

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Patient Assistance Programs

Dapaglifloxin (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

Farxiga ® [prescribing information]. AstraZeneca. October 2021.
Jardiance ® [prescribing information]. Boehringer-Ingelheim. October 2021.

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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 sulfonylurea / 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

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References

1) Wojcik C, Warden BA. *Current Cardiology Reports.* 2019;21:130.
2) Farxiga ® [prescribing information]. AstraZeneca. October 2021.
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5) Steglatro ® [prescribing information]. Merck & Co. October 2021.
6) McMurray JJV et al. Article and study protocol. N Engl J Med. 2019;381:1995-2008.
7) Packer M et al. Eur J Heart Fail. 2019;21:1270-1278.
8) Packer M et al. N Engl J Med. 2020;383:1413-1424.
9) Solomon SD et al. Online ahead of print. *Eur J Heart Fail*. 2021;10.1002/ejhf.2249
10) Study NCT03619213. ClinicalTrials.gov website
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12) Study NCT04363697. ClinicalTrials.gov website.
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14) Tromp J et al. *Eur J Heart Fail*. 2021;23:826-834.
15) Maddox *et al*. 2021 Update to 2017 ECDP for Optimization of Heart Failure Treatment. JACC 2021.

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Questions?

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

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