The 6th SGLT-Inhibitor Works at BOTH SGLT2 and SGLT1: sotagliflozin (Inpefa®)

Another addition to the Sodium Glucose Co-Transport Inhibitors (SGLT2i) drug class has been FDA approved and is available. Data from clinical trials has led to the use of drugs in the class beyond their efficacy for glycemic control, and now recognizes the benefits of decreased ASCVD risk factors via decreasing blood pressure and body weight, decreases in heart failure hospitalizations and acute heart failure, and decreases in the progression of kidney disease, which led to FDA approvals for these indications for specific agents. (See table below)

Mechanism of Action: SGLT2i drugs work renally to promote glucosuria. The SGLT co-transporters are membrane proteins in the proximal renal tubules (SGLT2) and *intestinal epithelium (SGLT1)* that transport glucose, amino acids, vitamins, ions, and osmolytes across the membrane. The renal SGLT2 co-transporters are responsible for 90% of glucose reabsorption, which promotes glucose excretion in the urine, decreasing blood glucose levels. The intestinal SGLT1 co-transporters reduce post-prandial glucose level by delaying intestinal glucose absorption.[1]

Place in Therapy:[2] 2024 ADA and EASD/ADA Standards of Care recommend the use of specific agents in this class with proven indications, independently of baseline A1C for persons with:

- ASCVD or Indicators of HIGH risk
- Heart Failure
- CKD, DKD and albuminuria
- Compelling need to minimize hypoglycemia or weight gain

What we know about the new agent "Inpefa":

- **Indicated to:**
  - Reduce the risk of *CV death, hospitalization for heart failure, and urgent heart failure* in adults with:
    - Heart Failure -OR- T2DM, CKD, and other CV risk factors
- **Efficacy:** FDA approval was based on the SOLOIST and SCORED randomized, double-blind, placebo-controlled trials with the composite outcome of CV death/hospitalization for heart failure/urgent heart failure in adults.
  - SOLOIST (T2DM and HF): composite Hazard Ratio (HR) **0.67** (0.53-0.85), 95% CI, p =0.001
  - SCORED (T2DM and CKD): HR 0.75 (0.63-0.88), 95% CI, p=0.001
  - Can be used as monotherapy or combined with all other classes
- **Tolerability:** Similar to other SGLT2i (with a low discontinuation rate in trials)
  - Risk for genital mycotic infections, UTIs, and polyuria – monitor for signs and symptoms, then treat
  - Hypoglycemia in combination with insulin/secretagogues
  - **Due to the SGLT- 1 inhibition**, *diarrhea* is an additional potential adverse reaction
- **Safety:** Risks similar to other SGLT2i, and considerations should be made before initiating:
  - Euglycemic DKA
    - Risk is higher during acute illness, infections, fasting or ketogenic diet, pancreatitis, alcohol abuse, steroid therapy, rapid progression to insulin, LADA, Pregnancy
    - Consider ketone *monitoring* and educate on symptoms (N/V/abd pain/fatigue/SOB)
    - HOLD the medication in temporary situations (acute illness) that can predispose to KA
  - Volume depletion: In order to prevent acute kidney injury, correct volume status.
    - *Monitor* for hypotension
  - Lower limb amputation due to infection: increased incidence in trials (8.3 vs 5.1 events per 1000 pt years), but not statistically significant.
    - Caution with low bone mineral density, osteoporosis, history of fractures, frailness, hx of PAD
    - *Monitor* bone mineral density, promote weight bearing exercise, Calcium/Vit D as indicated
  - Necrotizing Fasciitis of the Perineum
    - Caution in persons with history of frequent or severe genital infections, urinary incontinence
    - *Monitor* for pain, tenderness, erythema or swelling in the area
  - NOT recommended in pregnancy or when breastfeeding (due to lack of data)

Comparison of Current Available Agents[3–7]

			FDA Approved Indications			
Drug	**Dosing: once daily in the AM:**	**Renal: eGFR limits**	**Type 2 DM**	**CV Risk reduction**	**Reduce risk of HF hospitalization**	**Kidneys: Reduce risk of ESKD**
Bexagliflozin (Brenzavvy®)	20 mg	Not recommended for < 30 ml/min	Yes	-	-	-
Canagliflozin (Invokana®)	100–300 mg before AM meal	30-60 ml/min = 100 mg If < 30 ml/min *may continue* to use to reduce risk of ESKD, CV death and hHF	Yes	Yes: MACE reduction in established ASCVD	Yes: In adults w/T2DM	Yes: In adults w/T2DM
Dapagliflozin (Farxiga®)	5 – 10 mg	> 25ml/min: 5-10 mg daily < 25 ml/min: not effective for glycemic control, but continue to use to reduce risk of eGRF decline, ESKD, CV death and hHF	Yes	Yes: Risk of CV death in est. w/multiple ASCVD risk factors	Yes: In adults *with or without T2DM*	Yes: In adults *with or without* T2DM
Empagliflozin (Jardiance®)	10 – 25 mg	< 30 ml/min: not effective for glycemic control, but can use down to 20 ml/min	Yes	Yes: risk of CV death in adults w/ASCVD	Yes: In adults *with or without* T2DM	Yes: In adults *with or without* T2DM
Ertugliflozin (Steglatro®)	5 -15 mg	45-60 ml/min = 5 mg Avoid < 45 ml/min	Yes	-	-	-
Sotagliflozin (Inpefa®)	200- 400 mg before AM meal	< 30 ml/min: not effective for glycemic control, but can use down to 15 ml/min	Yes	Yes: risk of CV death, hospitalization from HF and urgent HF in adults *with or without* T2 DM		No approval to date

1. Bhatt D, et al. SOLOIST-WHF:Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med 2021; 384:117-128. DOI: 10.1056/NEJMoa2030183

2. American Diabetes Association Professional Practice Committee. Summary of Revisions: Standards of Care in Diabetes—2024. *Diabetes Care*. 2023;47(Supplement_1). doi:10.2337/dc24-SREV

3. Brenzavvy [prescribing information]. Accessed April 4, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214373s000lbl.pdf

4. Invokana (canagliflozin) [prescribing information]. Accessed April 4, 2024. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVOKANA-pi.pdf

5. Farxiga highlights of prescribing information. Accessed April 7, 2024 https://den8dhaj6zs0e.cloudfront.net/50fd68b9-106b-4550-b5d0-12b045f8b184/0be9cb1b-3b33-41c7-bfc2-04c9f718e442/0be9cb1b-3b33-41c7-bfc2-04c9f718e442_viewable_rendition__v.pdf

6. Jardiance (empagliflozin) [prescribing information]. Accessed April 4, 2024. https://content.boehringer-ingelheim.com/DAM/7d9c411c-ec33-4f82-886f-af1e011f35bb/jardiance-us-pi.pdf

7. Steglatro_pi.pdf. Accessed April 4, 2024 https://www.merck.com/product/usa/pi_circulars/s/steglatro/steglatro_pi.pdf

8. Inpefa-US-PI.pdf. Accessed April 7, 2024. https://www.lexpharma.com/inpefa-US-PI.pdf