Clinical Resource Guide:
SGLT2 Inhibitors (JARDIANCE, INVOKANA, FARXIGA)

INTRODUCTION TO SGLT2 Inhibitors

JARDIANCE, INVOKANA, and FARXIGA belong to the class of drugs known as sodium glucose co-transporter 2 inhibitors (SGLT2-i) and the class of drugs were initially approved to treat type 2 diabetes. They have since gained FDA approval to treat heart failure and chronic kidney disease. This guidance document will educate on the role of SGLT2-I in the setting of palliative care and hospice, provide patient-specific clinical considerations and serve as a guide to navigate the appropriateness of deprescribing medications with this pharmacologic class.

Pharmacist Corner Objectives

1.) Describe the clinical significance and mechanism of action of SGLT2 Inhibitors.
2.) Evaluate the risks involved with continuing SGLT2 Inhibitors in palliative care and end of life patients.
3.) Understand the rationale for deprescribing SGLT2 Inhibitors.

MECHANISM OF ACTION

The mechanism of action for the current medications in the SGLT2 inhibitor class inovles the inhibition of the SGLT2 protein found in the proximal convoluted tubules of the kidneys. These proteins are responsible for reabsorbing filtered glucose and sodium back into the bloodstream. SGLT2 inhibitors work by blocking the SGLT2 protein, reducing the amount of glucose and sodium reabsorbed into the blood stream, while also promoting osmotic diuresis. These effects subsequently positively impact the following disease states:

- **Type 2 Diabetes Mellitus:** decreases blood glucose concentrations, weight loss, reduction in blood pressure, reduction in albuminuria and slowed progression of diabetic kidney disease
    - ***Efficacy:*** *compared with placebo SGLT2-I's reduce A1c levels by an average of 0.5%-0.8% when used as monotherapy or add-on therapy.*
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- **Heart Failure (all ejection fraction subtypes):** decreased blood pressure, decreased plasma volume, heart muscle functional improvement
    - ***Efficacy:*** *JARDIANCE and INVOKANA - significant decline in specific MACEs and HF hospitalization was seen in patients with HF and/or CVD with T2D*
    - ***Efficacy:*** *significantly decreased CV death and hospitalizations for HF in patients with HFrEF regardless of presence or absence of T2DM.*

- **Chronic Kidney Disease:** slows disease progression, decreases albuminuria, and prevents death by renal or CV causes.
    - ***Efficacy:*** *Compared with placebo SLGT2-I agents reduced the risk of kidney disease progression by 37% irrespective of diabetes status and underlying kidney disease.*

Despite these benefits noted with long-term use, the absence activity to reduce symptom burden at the end-of-life, the following side effects

SGLT2-I Mechanisms, Risks, and Recommendations

The benefits seen with SGLT2 Inhibitors are typically not applicable to the goals of the hospice patient as they provide no symptom management or relief.

Mechanism to Consider	Risk to Patient	Recommendation
Decrease blood glucose by increasing glucose excretion in the urine	*Increased risk of*: • UTI • yeast infection • Fournier's Gangrene • Hypoglycemia	Recommended alternatives for blood glucose management if concerns for symptomatic hyperglycemia during end-of-life care: **deprescribe**
Promote weight loss by inducing lipolysis	Increased risk of euglycemic diabetic ketoacidosis (EDKA) in the elderly patients or those with low oral intake, and/or patients with a low BMI	Weight loss not a focal point of hospice care: **deprescribe**
Decrease serum sodium concentrations and plasma volume	*Increased risk of*: • Volume depletion and symptomatic hypotension in the elderly • AKI	Consider loop diuretic to treat edema; Not recommended in patients with an eGFR <20 mL/min/1.73 m^2: **deprescribe**

SUMMARY

SGLT2 Inhibitors are becoming more and more popular in the ambulatory care space for disease states such as Type 2 Diabetes, heart failure, and chronic kidney disease. While these drugs do have notable clinical efficacy, they often do not align with the goals of care for palliative care and hospice patients. The mechanisms of the drug class should be considered and evaluated to determine if the risk to the patient outweighs the benefit.

REFERENCES:

1. Kowalska K, Walczak J, Femlak J, Młynarska E, Franczyk B, Rysz J. Empagliflozin-A New Chance for Patients with Chronic Heart Failure. *Pharmaceuticals (Basel)*. 2021;15(1):47. Published 2021 Dec 30
2. Yau K, Dharia A, Alrowiyti I, Cherney DZI. Prescribing SGLT2 Inhibitors in Patients With CKD: Expanding Indications and Practical Considerations. *Kidney Int Rep*. 2022;7(7):1463-1476. Published 2022 May 5
3. Padda IS, Mahtani AU, Parmar M. Sodium-Glucose Transport Protein 2 (SGLT2) Inhibitors. [Updated 2023 Jun 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. https://www.ncbi.nlm.nih.gov/books/NBK576405/
4. Commissioner O of the. FDA Approves Treatment for Wider Range of Patients with Heart Failure. FDA. Published March 2, 2022. https://www.fda.gov/news-events/press-announcements/fda-approves-treatment-wider-range-patients-heart-failure
5. Zurek AM, Yendapally R, Urteaga EM. A Review of the Efficacy and Safety of Sodium-Glucose Cotransporter 2 Inhibitors: A Focus on Diabetic Ketoacidosis. *Diabetes Spectr*. 2017;30(2):137-142. doi:10.2337/ds16-0030
6. Lenahan, Christy McDonald DNP, FNP-BC, ENP-C, CNE; Harrington, Deedra DNP, MSN, ACNP-BC; Stueben, Frances DNP, RN, CHSE. SGLT2 inhibitors: What role do they play in heart failure with reduced ejection fraction?. The Nurse Practitioner 46(7):p 30-37, July 2021. | DOI: 10.1097/01.NPR.0000753832.85114.65
7. Kimberly E. Ng, et al.. Management of Euglycemic Diabetic Ketoacidosis. www.uspharmacist.com
8. National Kidney Foundation. SGLT2 inhibitors. National Kidney Foundation. Published January 14, 2022. https://www.kidney.org/atoz/content/sglt2-inhibitor
9. Zurek AM, Yendapally R, Urteaga EM. A Review of the Efficacy and Safety of Sodium-Glucose Cotransporter 2 Inhibitors: A Focus on Diabetic Ketoacidosis. *Diabetes Spectr*. 2017;30(2):137-142. doi:10.2337/ds16-0030
10. Lenahan, Christy McDonald DNP, FNP-BC, ENP-C, CNE; Harrington, Deedra DNP, MSN, ACNP-BC; Stueben, Frances DNP, RN, CHSE. SGLT2 inhibitors: What role do they play in heart failure with reduced ejection fraction?. The Nurse Practitioner 46(7):p 30-37, July 2021. | DOI: 10.1097/01.NPR.0000753832.85114.65
11. Palmer BF, Clegg DJ. Euglycemic Ketoacidosis as a Complication of SGLT2 Inhibitor Therapy. *Clin J Am Soc Nephrol*. 2021;16(8):1284-1291. doi:10.2215/CJN.17621120
12. Joshi SS, Singh T, Newby DE*, et al*Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure*Heart* 2021;107:1032-1038.

