

EXECUTIVE SUMMARY: SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS (SGLT2i)

A. BASIC PHARMACOLOGY

SGLT2i:

- Increase urinary glucose excretion by lowering renal glucose reabsorption (Grade A, EL1).
- Improve glycemic parameters (fasting, postprandial) with low risk of hypoglycemia (the risk may increase with concomitant insulin / insulin secretagogues) (Grade A, EL1).
- Reduce A1c with simultaneous reduction in weight and blood pressure (Grade A, EL1).

B. NOVEL MECHANISMS

SGLT2i:

- Work as calorie restriction mimetics / nutrient offloaders (Grade C, EL4), thus reducing stress on β -cells and hyperinsulinemia (Grade B, EL2).
- Promote adaptive ketogenesis (Grade B, EL2), providing a superfuel for tissues, including myocardium (Grade D, EL4).
- Increase hematocrit and myocardial oxygen supply, without increasing the heart-rate, thus improving cardiac efficiency (Grade D, EL4).

C. VASCULAR OUTCOMES

SGLT2i:

- Reduce risk factors associated with macrovascular disease (Grade A, EL1)
- Decrease death due to CV causes, and all-cause mortality (Grade A, EL1), and hospitalization for heart failure (Grade B, EL1).*
- Slow progression of nephropathy, thereby improving renal outcomes (Grade B, EL1).**

D. CLINICAL PHARMACOLOGY

SGLT2i may be used as:

- Dual or triple combination, in patients inadequately controlled on metformin or other AHAs (Grade A, EL1).
- Combination therapy with insulin, and may reduce insulin requirement*** (Grade A, EL1).
- Monotherapy in patients with contraindication to, or intolerance to, metformin (Grade B, EL1).

E. POSOLOGY

SGLT2i:

- Are prescribed as once daily oral tablets (Grade A, EL1).
- Require minimal dose titration (Grade A, EL1).
- Have minimal drug interactions (Grade C, EL4).

F. PRAGMATIC USAGE

SGLT2i use:

- Requires adequate fluid intake to prevent volume depletion. Cautious use recommended in frail elderly patients, and with concomitant use of diuretics (Grade A, EL1).
- Requires maintenance of perineal hygiene to prevent GTI. Avoid use in patients with h/o recurrent GTI (>4/year), or h/o recent upper UTI. During an episode of severe UTI, temporary discontinuation is recommended (Grade A, EL1).
- Requires appropriate patient selection, medication counseling and monitoring (Grade A, EL2).

G. CONTRAINDICATIONS

SGLT2i are contraindicated in:

- Patients with an eGFR <45 mL/min/1.73 m² (Grade A, EL1).
- Patients with extreme insulinopenia or type-1 diabetes, on fluid/carbohydrate restricted diet, or with decompensated medical/surgical illness (Grade A, EL1).
- Pregnancy, lactation, children, pre-diabetics, or for weight-loss in non-diabetic patients (Grade A, EL1).

: In the EMPA-REG-OUTCOME trial, empagliflozin demonstrated reduction in death due to CV causes and all-cause mortality (Grade A, EL1), and in hospitalizations for heart failure (Grade B, EL1). Other SGLT2-i agents are likely to demonstrate these benefits, which would be confirmed in the ongoing trials (Grade B, EL4).

***: In the EMPA-REG-OUTCOME trial, empagliflozin demonstrated reduction in new onset or worsening of nephropathy, preservation of renal function, and regression of macroalbuminuria (Grade B, EL1). In the CANTATA SU trial, canagliflozin demonstrated improvement in UACR and eGFR; long-term preservation of renal function remains to be confirmed (Grade B, EL1). Dapagliflozin demonstrated a reduction in proteinuria in a retrospective analysis; evidence from prospective trials is awaited (Grade B, EL2). Cases of acute kidney injury have been reported with canagliflozin and dapagliflozin; while the long-term renal safety of SGLT2-i therapy is reassuring based on the EMPA-REG-OUTCOME trial, these signals underline the importance of appropriate patient selection.

***: If an SGLT2-i is added to an insulin-based regimen, gradual down-titration of insulin dose is recommended.

BP: blood pressure

CV: cardiovascular

eGFR: estimated glomerular filtration rate

GTI: genital tract infections

UTI: urinary tract infection