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Sodium Glucose Co-Transporter 2 Inhibitors (SGLT2 inhibitors) The Gliflozins

SGLT2 Inhibitors are a new class of oral antihyperglycemic agents indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus. The Canadian Diabetes Association recently updated the guidelines for pharmacotherapy in type 2 diabetes and added SGLT2 inhibitors as an add-on to metformin or when metformin is not tolerated. SGLT2 Inhibitors can be prescribed in monotherapy or combination with other oral antihyperglycemic agents and Insulin. Table 1 reviews the common combinations.

SGLT2 Inhibitors: Indications (Not Indicated for Type 1 Diabetes)

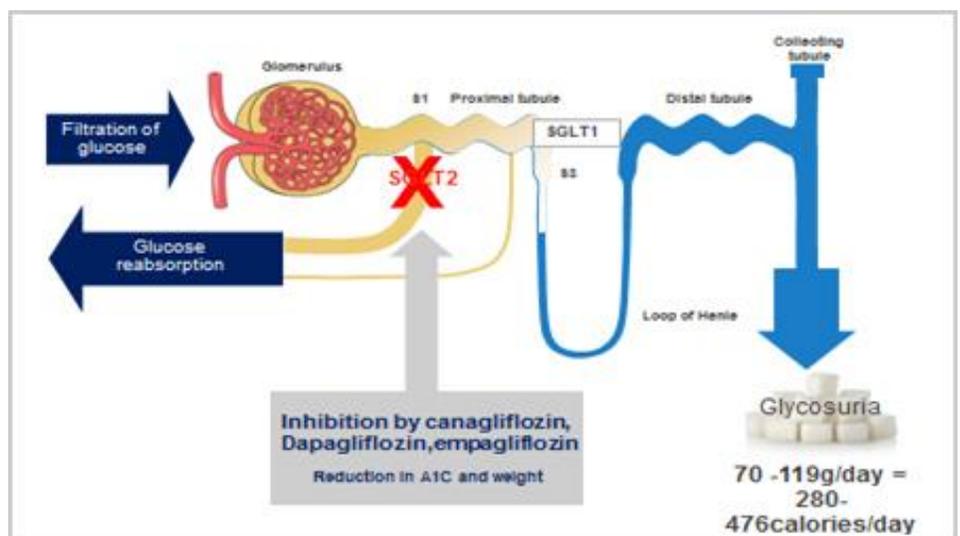
SGLT2 Inhibitor	Monotherapy	Dual Combination			Triple Combination			Add-On to Insulin
	If Metphormin inappropriate	Add-On MET	Add-On SU	Add-On SITA	Add-On MET+SU	Add-On MET+PIO	Add-On MET-SITA	
Canagliflozin	☺	☺	☺		☺	☺		☺
Dapagliflozin	☺	☺	☺	☺	☺		☺	☺
Empagliflozin	☺	☺			☺	☺		☺

SU=sulfonylureas: glyburide, glipizide, glimepiride / SITA= sitagliptin / PIO= pioglitazone / MET = metformin

Mechanism of Action: SGLT2 Inhibitors

The Sodium Glucose Co-Transporter 2 is expressed in the proximal tubule and mediates reabsorption of approximately 90% of the filtered glucose load. SGLT2 Inhibitors promote the renal excretion of glucose and thereby modestly lower elevated blood glucose levels in patients with type 2 diabetes.

Glycosuria carries a loss of 280 to 476 calories daily which may result in a weight loss of 2-3 kg which appears to be sustained over time. In a meta-analysis of three longer-term trials (48 to 52 weeks) comparing dapagliflozin (10 mg daily) versus placebo, there was a significant reduction in weight in the dapagliflozin group (mean difference - 2.36 kg, 95% CI -2.85 to -1.88)





Adverse Effects

The most common AEs were genital, mycotic infection, urinary tract infection (UTIs) and pollakiuria (defined as frequent urination which does not include polyuria, i.e., large volume)

Patients 65 years of age and older also had a higher incidence of AEs related to reduced intravascular volume including hypotension, postural dizziness, orthostatic hypotension, syncope and dehydration compared with younger patients.

Dosage According to eGFR

Currently, all three agents that are approved in Canada, require eGFR ≥ 60 ml/min to be initiated. Dapagliflozin should be discontinued if eGFR falls below 60 ml/min. Canagliflozin and Empagliflozin should be discontinued if eGFR falls below 45 ml/min. Due to the mechanism of action, these drugs tend to decline in their ability to lower glucose as the eGFR becomes lower and cause worsening of kidney function.

	eGFR		
Stage	<45	45 to 60	>60
Canagliflozin	Contraindicated	100 mg	100-300 mg
Empagliflozin	Contraindicated	10-25 mg	10-25 mg
Dapagliflozin	Contraindicated	Contraindicated	5-10 mg

Approximately 80% of the efficacy is achieved at lower dosage. Start at lower dose and increase to a maximum dosage to get the best benefit according to eGFR.

Drug Interactions

Patients receiving digoxin should have levels monitored appropriately while taking canagliflozin 300mg.

Rifampin and Phenytoin (inducers of UGT enzymes/drug transporters) and canagliflozin (Invokana): Consider increasing the dose to 300 mg once daily if patients are currently tolerating Invokana 100 mg once daily.

Diuretics: SGLT2 Inhibitors should be used with caution in patients taking diuretics, particularly loop diuretics, due to the increased risk of adverse events due to volume depletion during coadministration.

Summary

SGLT2 Inhibitors have been shown to reduce A1C by up to 1.2% depending on the starting A1C. They also lower SBP, reduce body weight, and have an impact on HDL-c and triglycerides levels

The rates of genital mycotic infections, osmotic diuresis, and volume-depletion related to SGLT2 Inhibitors may limit its utility in the elderly and in long-term care facility residents.

Basic Verifications Before Starting SGLT2 Inhibitors

eGFR	<ul style="list-style-type: none">eGFR must be > 60ml / min to initiate
A1C	<ul style="list-style-type: none">If A1C close to normalReduction/withdrawal of SU or insulin might be required
BP	<ul style="list-style-type: none">If optimal BP under antihypertensives:Reduction/withdrawal of other antihypertensive agents might be required

References

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