The SGLT-2 Inhibitor: Its Indication in Glycemic, Cardiovascular, and Renal Management

Disclosures

Objectives

1. Review key results from cardiovascular outcomes trials (CVOTs) with SGLT-2 inhibitors.

2. Discuss clinical indications for use of SGLT-2 inhibitors from CVOTs and more recent trials.

3. Discuss how to design treatment approaches with SGLT-2 inhibitors based on guideline updates.

T2DM Associations:

Associated with CVD, CKD, and numerous additional complications associated with increased all cause and CVD mortality

T2DM Treatment Goals:

Improve glycemic control
modify risk for complications

History of FDA CVOT trials
Timeline of CVOT trials

CVOT trials
EMPA REG OUTCOME
CANVAS
DECLARE TIMI 58
VERTIS CV TRIAL
BEST

Who are the SGLT-2i and when were they approved?

SGLT-2i – Approved FDA indications

Improvement of glycemic control in type 2 diabetes mellitus (T2DM)

Reduction of major adverse cardiovascular events (nonfatal MI, nonfatal stroke, cardiovascular death) in patients with T2DM and established cardiovascular disease

To decrease the risk of cardiovascular hospitalization and death for heart failure in patients with HFrEF- NYHA class II-IV

Reduction of the risk of eGFR decline and hospitalization in patients with chronic kidney disease at risk of progression

Improvement of cardiovascular outcomes in patients with HFpEF

Glycemic Indications

Improvement of glycemic control in T2DM

Reduction of major adverse cardiovascular events in patient with T2DM and established cardiovascular disease

SGLT-2i – MOA in glycemic management

Potential Side Effects/Adverse Reactions
- Female and male genital mycotic infections
- Urinary tract infection
- Fournier gangrene (rare)
- Diabetic ketoacidosis (rare)
- Increased urination
- Nausea
- Nasopharyngitis
- Polydipsia
- Constipation

Additional warnings and precautions
- Increased risk of hypoglycemia with insulin secretagogues or insulin
- Symptomatic hypotension
- Consider holding 3 days prior to surgery

ADA Standards of Care (SOC) Glycemic Management in T2DM Figure

ADA SOC Updates – Pharmacologic Approaches to Glycemic Treatment

Key Features of SGLT-2i in glycemic management table

Glycemic efficacy correlation with eGFR

The glycemic efficacy of SGLT-2i is dependent on glomerular filtration and is attenuated in patients with more advanced CKD.

The glucose-lowering effect of SGLT2 inhibitors is attenuated in patients with eGFR <60 ml/min per 1.73 m2 and minimal when eGFR is <30 ml/min per 1.73 m2

Keep in mind, we know SLGT-2i are safe and efficacious for management and prevention of CKD, however we do not anticipate to see similar glycemic efficacy from the SGLT-2i class in patients with lower eGFR levels.

Euglycemic DKA

Known risk associated with use of SGLT-2i class

Higher association in patients with some sort of other ongoing primary acute illness… similar to risk we see with traditional DKA

Important to assess risk factors for development of euglycemic DKA
- Prior episodes of DKA
- Ketogenic diet
- Alcohol use

Possibility of type 1 diabetes
Insulin requirements

Sick day dosing
Educate patients to hold dose if little to no PO intake
Educate your patients who are on proper insulin sick day dosing (in particular with basal insulin)

Surgery
Most guidelines recommend holding for 3 to 5 days before planned procedures

Euglycemic DKA Assessment Flowsheet

Hospitalization – SGLT-2i for glycemic management

Given rising use of SGLT-2i and changes in guidelines, hospitalists need to be comfortable caring for hospitalized patients who are on SGLT-2i.

Current guidelines from Endocrine Society and the American Diabetes Association (ADA) advised providers to stop giving SGLT-2i to acutely ill hospitalized patients and to consider an individual's risk of DKA.

The Society of Hospital Medicine also recommends discontinuation, however also offers examples of high-risk presentation (sepsis, hypovolemia) to help guide treatment.

Consensus from most surgical societies is to hold SGLT-2i for 3 to 5 days prior to planned surgical procedure.

Can be safely continued in the inpatient setting – evaluation on a case by case basis.
Emerging evidence supporting safety of continuing these medications in certain inpatient populations
Prompt discontinuation if patient becomes hemodynamically unstable, cannot tolerate enteral nutrition, or if labs show developing metabolic acidosis.

Cardiovascular and renal benefits seen in CVOTs with SGLT-2 inhibitors are most likely explained by events beyond glucose lowering. Improved glycemic control could have been contributed to observed renal and cardiovascular benefit, however – in these trials there was small Hba1c reductions and rapid onset of cardiovascular and renal benefit

Potential MOAs of SLGT-2i in cardio-renal risk reduction

Weight loss
Anti-hypertensive effect
Glycosuria accompanied osmotic diuresis decreased intravascular volume
SGLT-2 inhibitors decrease sodium re-absorption in the proximal tubal

⇩ oxidative stress
⇩ fibrosis induction

⇩ local inflammation
⇩ tubular senescence
⇩ glomerular damage

Cardiovascular Indications

Reduction of major adverse cardiovascular events (nonfatal MI, nonfatal stroke, cardiovascular death) in patients with T2DM and established cardiovascular disease

To decrease the risk of cardiovascular hospitalization and death for heart failure in patients with HFrEF- NYHA class II-IV

Improvement of cardiovascular outcomes in patients with HFpEF

2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure Table

Stage A, at risk for Heart Failure

Patients with T2DM who have or are at high risk for CVD – class 1 recommendation to prevent HF-related complications

Recommendations based on results from CANVAS, DECLARE-TIMI 58, and EMPA-REG OUTCOME clinical trials

Heart Failure with Reduced Ejection Fraction – Pillars

DAPA HF

4744 patients
NYHA II, III, IV HF with EF 40% or lower
Dapagliflozin 10mg vs placebo

EMPORER REDUCED trial

3730 patients
NYHA II, III, IV HF with EF 40% or lower
Empagliflozin 10mg vs placebo
Primary outcome: composite of CV death or hospitalization for worsening HF

Adding SGLT-2i as part of GDMT in HF reduced EF

Initiation and titration of GDMT should be individualized and optimized as frequently as every 1 to 2 weeks based on patient specific factors (symptoms, tolerance, VS, labs)

patients with HFrEF, decisions regarding simultaneous initiation or sequencing of GDMT usually are individualized and they do not necessarily need to follow the sequencing of trial publications

Remember to adhere to listed contraindications and precautions

eGFR $\geq$ 20

In patients with T2DM on insulin or sulfonylureas, consider reducing dose when SGLT-2i are initiating; consideration for glycemic effect given eGFR.

Heart Failure with Preserved EF and mildly reduced EF

Class 2A recommendation

Based off of results from EMPORER-PRESERVED and the DELIVER trials

EMPORER-PRESERVED trial

5988 patients

HFpEF – LVEF > 40% - patients with or without T2DM

Empagliflozin 10mg PO daily vs placebo (in addition to SOC)

Primary endpoint: time to first event analysis of the combined risk for cardiovascular death and hospitalization for heart failure

DELIVER trial

6263 patients

Pts age > 40 years

HFpEF (LVEF > 40% + evidence of structural heart disease, and NYHA class II-IV; elevated pro BNP levels; with or without T2DM

Both outpatient and inpatients hospitalized for heart failure off IV HF therapy for 24h

dapagliflozin 10mg daily or placebo (+ SOC)

Primary outcome: composite of CV death and heart failure events (HHF or urgent HF visits)

2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee – May 2023

SGLT-2i significantly reduce the risk of hospitalization for heart failure and cardiovascular death across all EF subgroups.

SGLT-2i should be initiated in all individuals with HFpEF with no contradictions.

Notes that in-hospital initiation of HF GDMT is associated with greater long-term adherence and prescription persistence, it is reassuring to note that the use of SGLT-2i appears to be safe and effective when initiated in the context of hospitalization for acutely decompensated HF, once clinically stable.

SGLT-2i use in hospitalized patients with HF

Known positive and rapid effects of SGLT-2i on cardiorenal outcomes indicates potential for benefit in hospitalized patients

Concept of SGLT-2i use inpatient has evolved greatly over the past few years

Evidence has shown SGLT-2i are well tolerated, safe, and effective in hospitalized patients

Incidence of DKA low

Potential for future research to evaluate if benefit for patients with non-cardiometabolic disorders including sepsis, cirrhotic ascites, and malignancy.

Translating clinical trial data into real world clinical practice remains a challenge.

Sotagliflozin

Dual SGLT-2 and SGLT-1 inhibitor

FDA approved May 26, 2023; 200mg or 400mg PO daily

Indication: indicated to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with:

- Heart failure (across the EF spectrum)
- Type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors

Sotagliflozin is not indicated for glycemic control

Renal dosing:

- eGFR > 90: no adjustment
- eGFR 25-90: not defined, cautions advised***
- eGFR <25: not defined
- Contraindicated with dialysis

Side effect profile similar to that seen with SGLT-2i class, same contraindications

SOLOIST-WHF

SCORED - Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease

10,584 patients

Pts with T2DM, CKD (eGFR 25 to 60) , and risk for CVD

primary endpoint: composite of the total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure.

In patients with diabetes and chronic kidney disease, with or without albuminuria, sotagliflozin resulted in a lower risk of the composite of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure than placebo but was associated with adverse events.

SGLT-2i Inpatient Use with HFrEF

JACC Nov 2021 – "In Hospital Initiation of SGLT-2i for Heart Failure with Reduced Ejection Fraction:

Rationale for Routine In-hospital Initiation of SGLT-2i for HFrEF

Patient-centered Benefits

- Early clinical benefits within days to weeks of initiation
- Deferred in-hospital initiation of GDMT is associated with never initiating
- Potential improved tolerance to other evidence-based therapies

Safety and Tolerability

- Favorable blood pressure and kidney profile
- Favorable glucose safety profile
- Well-tolerated and safe, including among high-risk subgroups

DEFINE-HF - Dapagliflozin Effects on Biomarkers, Symptoms and Functional Status in Patients with HF with Reduced Ejection Fraction

263 patients – dapagliflozin 10mg vs placebo , 12 weeks

Inclusion criteria:

LVEF ≤ 40%
NYHA class II-III
eGFR ≥ 30
Elevated proBNP

Dual primary outcome:

1) mean NT-proBNP
2) proportion of patients with ≥ 5 point increase in HF disease-specific health status on the Kansas City Cardiomyopathy Questionnaire overall summary score, or a ≥ 20% decrease in NT-proBNP

Found that a greater proportion of patients with symptomatic HFrEF who were treated with dapagliflozin experienced clinically meaningful improvements in HF-related symptoms, functional status, and quality of life than did those given placebo

Observed benefits were consistent regardless of T2DM

CHIEF HF – A Study on Impact of Canagliflozin on Health Status, Quality of Life, and Functional Status in Heart Failure

EMPULSE trial - Impact of empagliflozin on decongestion in acute heart failure: the EMPULSE trial

530 patients
Hospitalized with acute heart failure
47% patients with diabetes
Randomized to empagliflozin 10mg vs placebo in addition to standard treatment

90 days of follow up improved experience with clinical benefit (hierarchal composite of death, number of HF events, and time to first HF event, or change from symptomatic baseline (KCC Questionnaire) in empagliflozin group compared to placebo

Renal Indications

Reduction of the risk of eGFR decline and hospitalization in patients with chronic kidney disease at risk of progression

DKD with albuminuria
Nondiabetic CKD with albuminuria

ADA Standards of Care 2024 – CKD progression and prevention figure

Kidney outcomes from the CVOTS

CVOTs including EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI-58, VERTIS CV, and SCORED revealed the benefit of SGLT-2i in improving cardiovascular outcomes in patients with T2DM and varying risks for ASCVD

Secondary analysis of renal outcomes from CVOTs was the first to suggest potential benefit in patients with kidney disease.

KDIGO statement(s)

CREDENCE- Canagliflozin and Renal Outcomes in T2DM with nephropathy

DAPA CKD – dapagliflozin in patients with chronic kidney disease

ADA SOC Updates – SGLT-2i

EMPA KIDNEY – Empagliflozin in Patients with Chronic Kidney Disease

6609 patients

Enrolled patients with CKD who had an eGFR of at least 20 but less than 45 OR who had an eGFR of at least 45 but less than 90 with a urinary albumin-to-creatinine ratio of at least 200

Primary outcome: composite of progression of kidney disease (defined as ESRD, a sustained decrease in eGFR $\geq$ 40% from baseline, or death from renal causes) or death from cardiovascular causes.

Current indications for SGLT2 inhibitors – renal

Diabetic vs nondiabetic indications – table

Practical Guidelines for the use of SGLT-2i in T2DM and CKD – flow chart

SGLT-2i Glycemic indications and renal parameters
SGLT-2i Cardiovascular Indications and renal parameters
SGLT-2i Renal Indications and renal parameters