AN OVERVIEW OF SGLT-2 INHIBITORS AND THEIR ROLE IN CLINICAL PRACTICE

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DISCLOSURE INFORMATION

No financial relationships to disclose

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HealthWorks

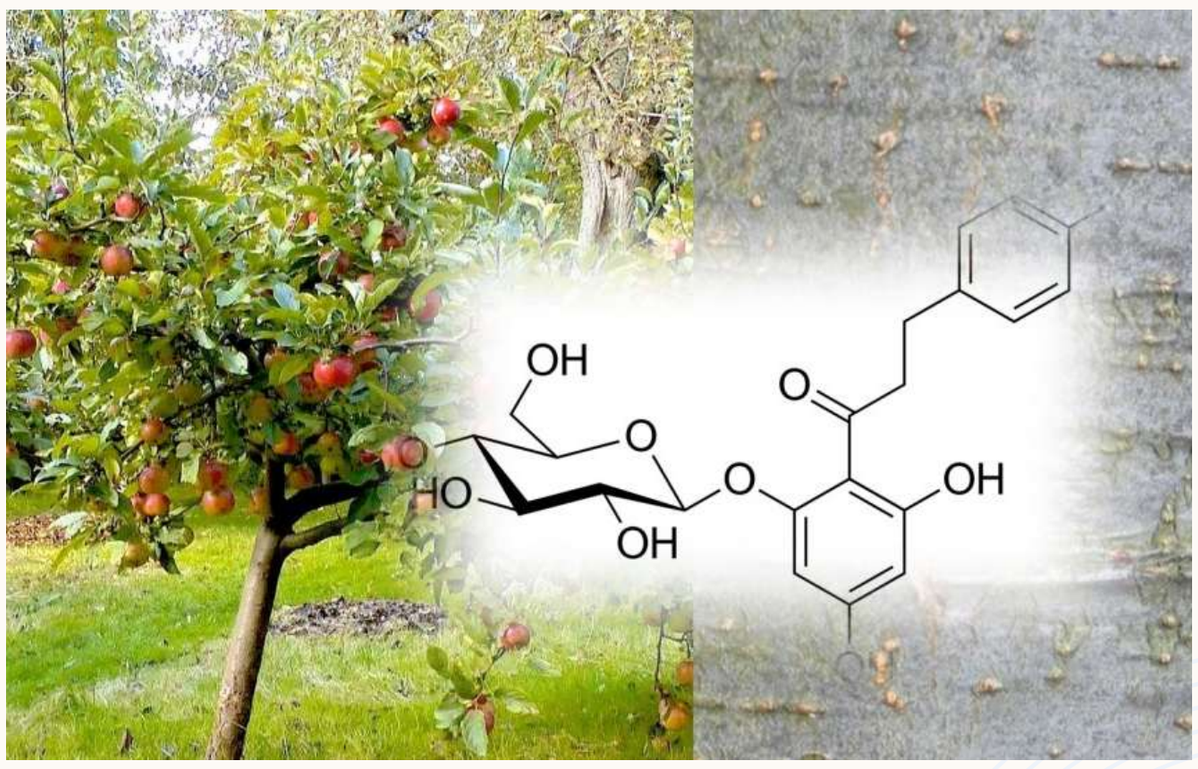
PRESENTATION OVERVIEW AND OBJECTIVES

At the end of this session participants will be able to:

- Explain the mechanism of action of SGLT-2 inhibitors and their therapeutic role in the management of diabetes and related comorbid conditions.
- Evaluate clinical considerations for the appropriate use of SGLT-2 inhibitors in practice, including benefits, risks, and patient selection.
- Demonstrate effective patient education for the appropriate use and potential adverse effects of SGLT-2 inhibitor treatment options.

HISTORY

- The molecule Phlorizin was isolated from the bark of apple trees in 1835 by French chemists.
- As a natural inhibitor of SGLT, it was proposed as an early diabetes treatment option



Valdes-Socin, 2022
McConnell, 2023

MECHANISM OF ACTION

SGLT2i work through inhibition of the sodium-glucose cotransporters (SGLT2) located within the proximal tubule of the kidney.

Inhibition of this transporter **prevents the reabsorption of glucose and sodium** from the glomerular filtrate.

Results in increased excretion of glucose and sodium in the urine.

Youssef et al., 2023

BENEFITS IN TYPE 2 DM

Increased excretion of glucose in the **urine**

Decreased glucose in the blood

Padda et al., 2025

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BENEFITS IN TYPE 2 DM

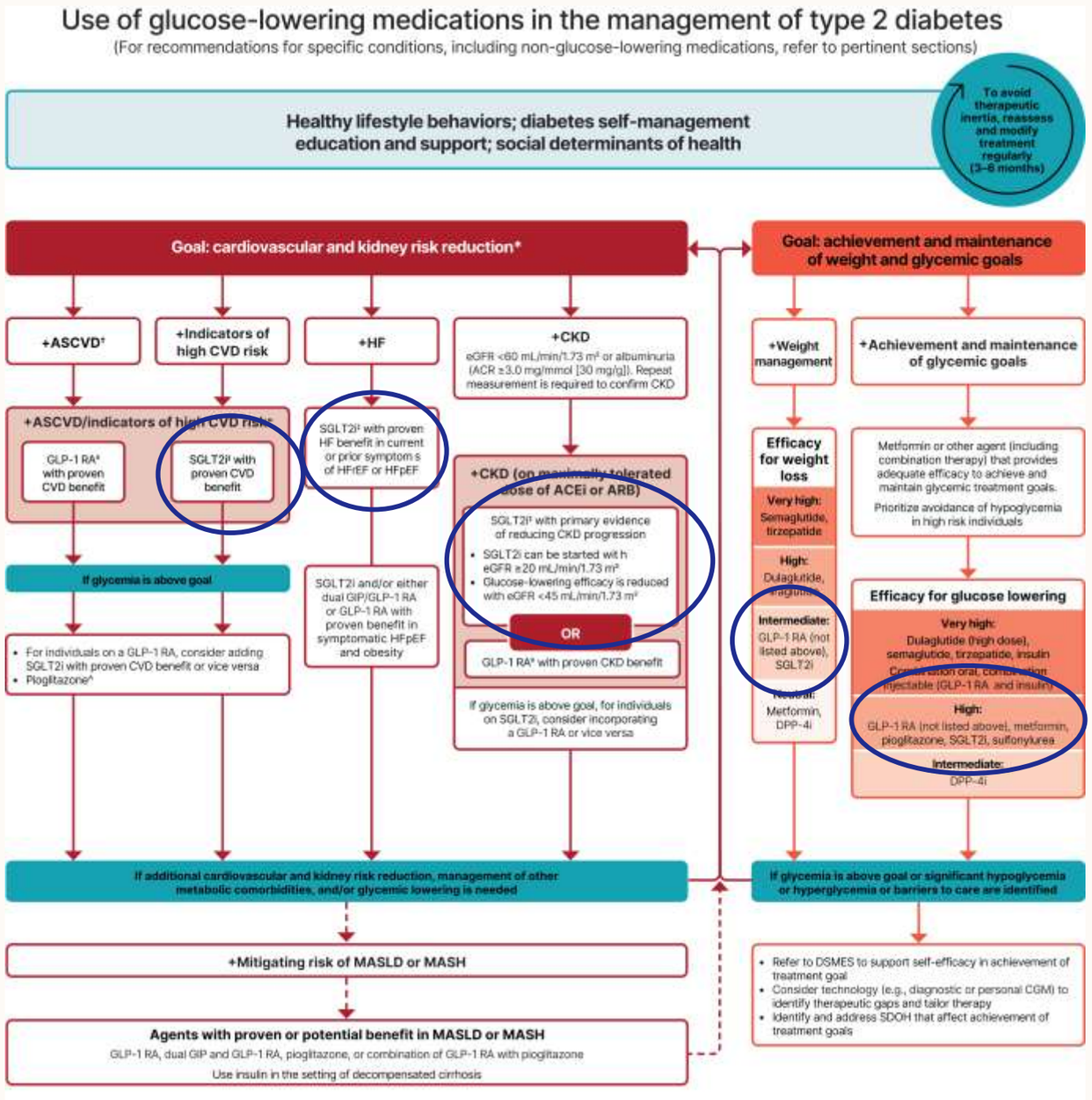
SGLT2i treatment results in an average A1C reduction of

0.5% - 1%

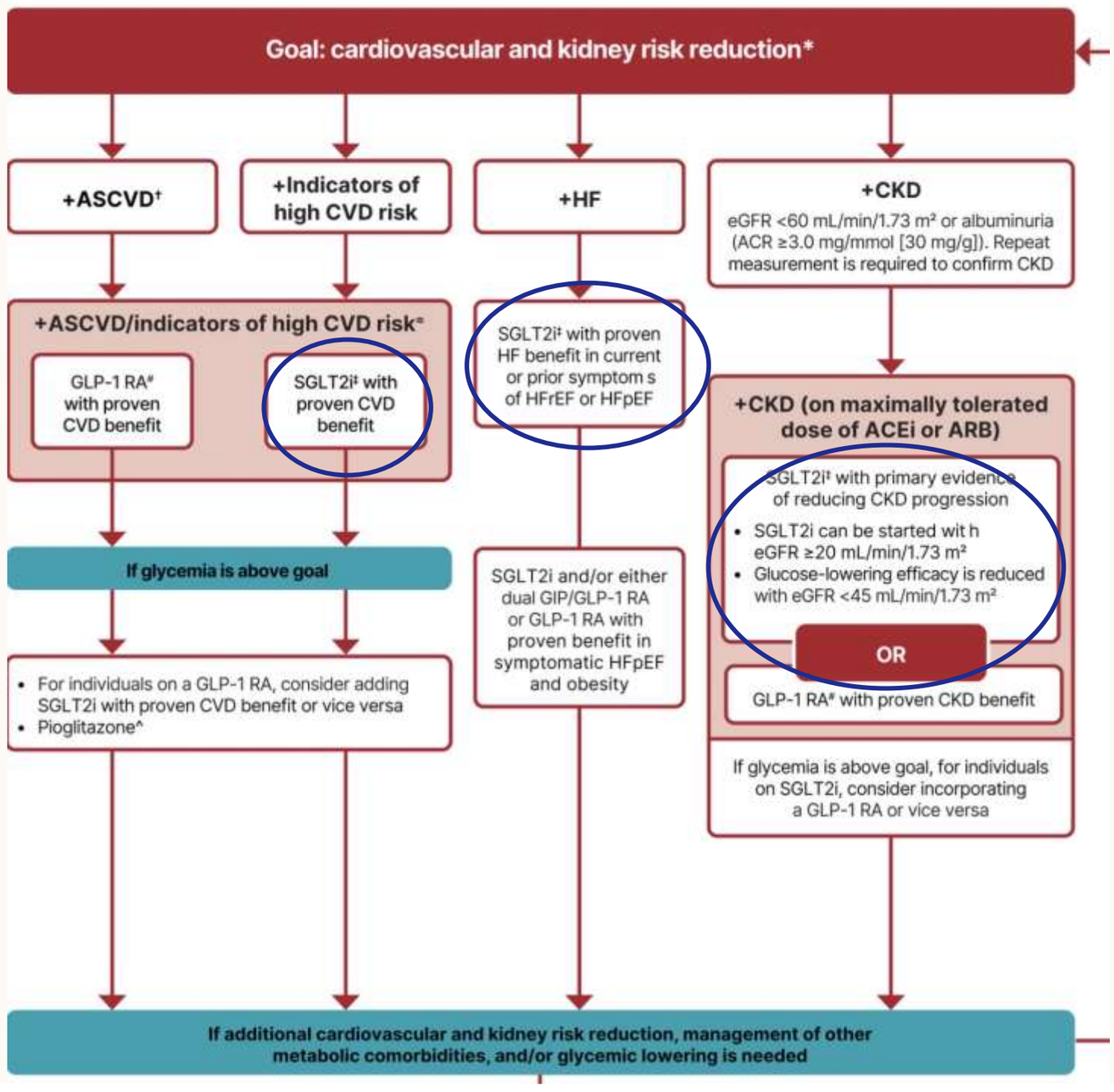
Padda et al., 2025

Use of glucose-lowering medications in the management of type 2 diabetes

(For recommendations for specific conditions, including non-glucose-lowering medications, refer to pertinent sections)



ADA Standards, 2026



ADA Standards, 2026

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ADA Standards, 2026

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ADDITIONAL BENEFICIAL EFFECTS

- Weight loss (intermediate)
- Blood pressure lowering (modest)
- **Cardiorenal Benefits (more on this later)**

Padda et al., 2025

ADA Standards of Care, 2026

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CONTRAINDICATIONS

- History of serious hypersensitivity reaction to an SGLT2i

PRECAUTIONS

- History of diabetic ketoacidosis (DKA)
- Ketogenic eating pattern
- Hypoglycemia risk
- Volume depletion risk
- Genital infection risk
- Diabetic foot ulcer risk
- Immunosuppression

Rossing et al., 2022

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ADVERSE EFFECTS

Commonly occurring adverse effects:

- Female genital mycotic infections
- Urinary tract infections (UTIs)
- Polyuria
- Nausea
- Constipation

Padda et al., 2025

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ADVERSE EFFECTS

Rare and clinically significant adverse effects:

- Urosepsis and Pyelonephritis
- Lower Limb Amputation
- Diabetic Ketoacidosis
- Euglycemic Diabetic Ketoacidosis
- Acute Kidney Injury
- Hypoglycemia
- Fournier Gangrene
- Bone Fracture

Padda et al., 2025

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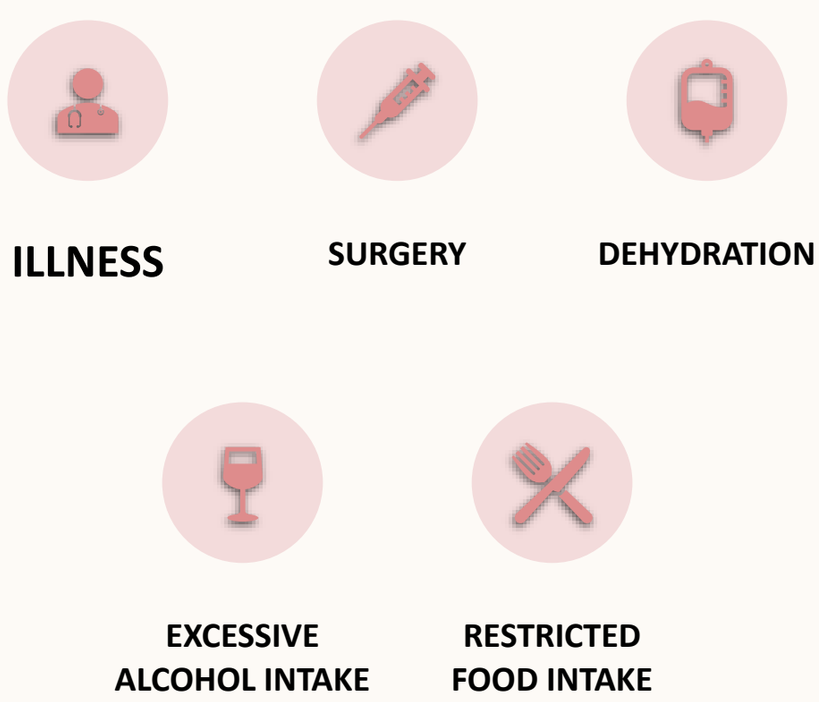
SICK-DAY RULES

Temporary discontinuation may be necessary during:



Padda et al., 2025

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DRUG INTERACTIONS

- Hypoglycemia risk may be increased with insulin or insulin secretagogues
- Concurrent use of an SGLT2 inhibitor with lithium can reduce serum lithium concentrations
- Non-selective beta-blockers may mask the hypoglycemic symptoms related to SGLT2i use

<u>Canagliflozin (Invokana) only</u>

- Increases plasma concentration of digoxin
- UGT enzyme inducers reduce canagliflozin exposure
  - Rifampin
  - Phenytoin
  - Ritonavir
  - Phenobarbital

Padda et al., 2025

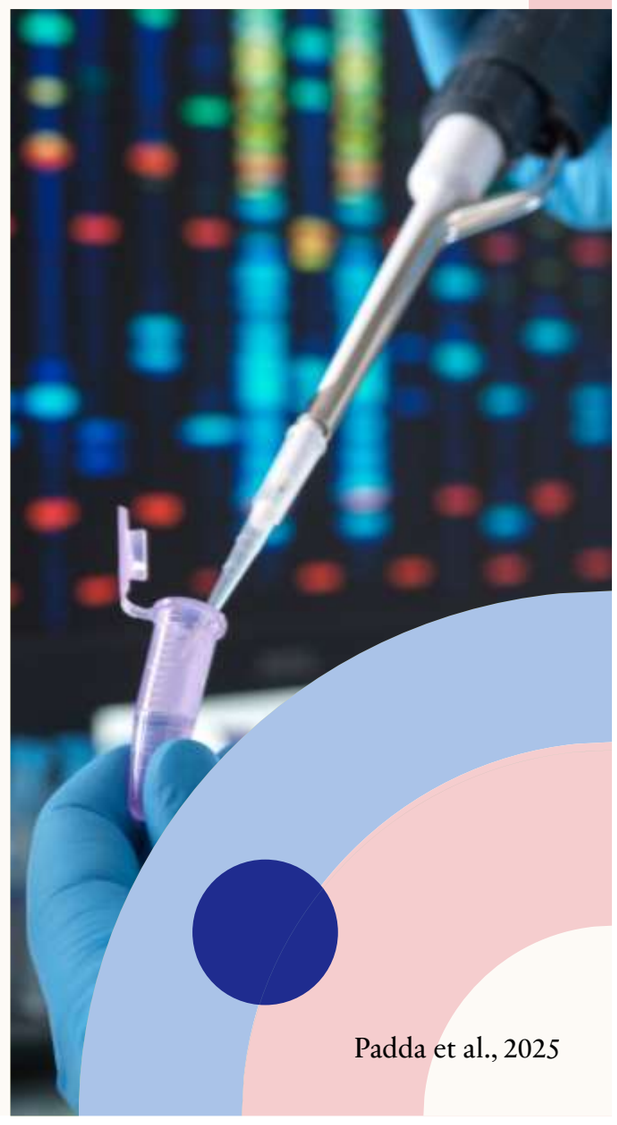
DIAGNOSTIC INTERFERENCE

Urinalysis

- Urine glucose tests will be elevated and are unreliable for assessing glycemic control inpatients receiving SGLT2 inhibitors

1,5-Anhydroglucitol (1,5 AG)

- 1,5 AG assay is unreliable for assessing glycemic control inpatients receiving SGLT2 inhibitors



Padda et al., 2025

MONITORING

At Baseline and Regular Follow up

- Blood glucose
- A1c
- Renal Function
- Volume status
- Diabetic foot exam
- Genital infection risk assessment
- Hypoglycemia risk assessment

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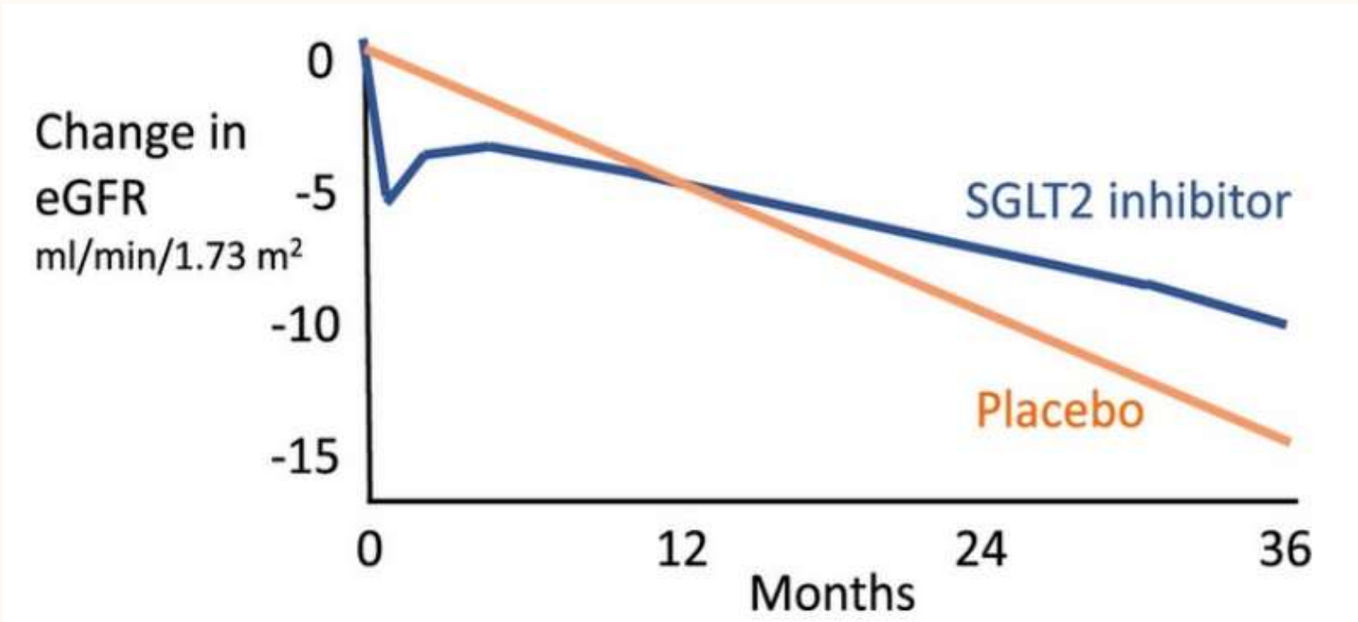
EXPECTED eGFR DECLINE

Initiation of SGLT2 inhibitor therapy is associated with an acute eGFR reduction.

This initial decline should be anticipated and is not an indication for discontinuation if the amount of reduction is less than 30%



Rossing et al., 2022

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SPECIAL POPULATIONS

- Hepatic Impairment
  - Mild to moderate: No dose adjustment necessary
- Renal Impairment
  - Effect on glycemia is reduced below eGFR of 30-45
  - SGLT2i should not be initiated at eGFR < 20
  - SGLT2i treatment should be continued even at lower eGFR for cardiovascular and renal benefits.
- Older adults
  - Increased risks related to reduced intravascular volume and hypotension
- Pregnancy
  - Contraindicated in pregnancy
- Breastfeeding
  - Not recommended

Padda et al., 2025

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INDICATION

An **ADJUNCT** to diet and exercise for improving glycemic control in patients with Type II Diabetes Mellitus

THE "-GLIFLOZINS"

CANAGLIFLOZIN (INVOKANA)

- Adults and children >10 years old with T2DM

Dosing

- 100 mg orally once daily, taken before the first meal of the day
    - Increase to 300 mg once daily for additional glycemic control

Perkovic et al., 2017

CANAGLIFLOZIN (INVOKANA)

CANVAS Program

Participants (N=10142)	Primary Endpoints	Key Findings
Patients with T2DM and high CV risk; 65.6% had a history of CV disease at baseline	• Composite of death from CV causes • Nonfatal myocardial infarction • Nonfatal stroke	• Canagliflozin reduced the risk of CV events • Increased the risk of amputation.

Perkovic et al., 2017

DAPAGLIFLOZIN (FARXIGA)

- Adults and children >10 years old with T2DM

Dosing

- 5 mg orally once daily
  - Increase to 10 mg once daily
    if additional glycemic control is required

Wiviott et al., 2019

DAPAGLIFLOZIN (FARXIGA)

DECLARE-TIMI 58

Participants (N=17,160)	Primary Endpoints	Key Findings
Patients with T2DM and established ASCVD or multiple risk factors for ASCVD	• Composite of CV death or hospitalization for HF • Major adverse CV events	• Dapagliflozin resulted in lower rates of CV death or hospitalization for HF than placebo • Did not result in a lower rate of major adverse CV events (MACE)

Wiviott et al., 2019

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EMPAGLIFLOZIN (JARDIANCE)

- Adults and children >10 years old with T2DM

Dosing

- 10 mg orally once daily in the morning
  - Increase to 25 mg orally once daily for additional glycemic control

Zinman et al., 2015

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EMPAGLIFLOZIN (JARDIANCE)

EMPA-REG OUTCOME		
Participants (N=7,020)	Primary Endpoints	Key Findings
Patients with T2D and high CV risk	• Composite of CV death, nonfatal myocardial infarction, or nonfatal stroke	• Empagliflozin, when added to standard care, reduced the risk of CV death, nonfatal myocardial infarction, or nonfatal stroke

Zinman et al., 2015

ERTUGLIFLOZIN (STEGLATRO)

- Adults with T2DM
- 5 mg orally once daily in the morning; for additional glycemic control, dose may be increased to 15 mg once daily if tolerated

BEXAGLIFLOZIN (BRENZAVVY)

- Adults with T2DM
- 20 mg orally once daily in the morning

COMBINATION PRODUCTS

Metformin

- Dapagliflozin / Metformin ER [Xigduo XR]
- Empagliflozin / Metformin (XR) [Synjardy / Synjardy XR]
- Canagliflozin / Metformin (XR) [Invokamet / Invokamet XR]
- Ertugliflozin / Metformin [Segluromet]

DPP4 Inhibitors

- Empagliflozin / Linagliptin [Glyxambi]
- Dapagliflozin / Saxagliptin [Qtern]

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U.S. FDS APPROVED INDICATIONS

Agent	T2DM Glycemic Control	CV risk reduction	Heart Failure	Chronic Kidney Disease
Canagliflozin (Invokana)	✓	✓	✗	✓
Dapagliflozin (Farxiga)	✓	✗	✓	✓
Empagliflozin (Jardiance)	✓	✓	✓	✓
Ertugliflozin (Steglatro)	✓	✗	✗	✗
Bexagliflozin (Brenzavvy)	✓	✗	✗	✗
Sotagliflozin (Inpefa)	✗	✗	✓	✗

Padda et al., 2025
Paolillo et al., 2025

SOTAGLIFLOZIN (INPEFA)

- Combination SGLT1/SGLT2 inhibitor approved to reduce the risk of cardiovascular death, HHF, and urgent heart failure visits in adults with
  - **Heart failure**
  - **T2DM, chronic kidney disease, and other cardiovascular risk factors**

- Not approved for glycemic control in T2MD
  - Studies indicate a similar glucose lowering effect as SGLT2i

- 200 mg orally once daily
  - Increase to 400 mg once daily after at least 2 weeks as tolerated

GENERIC AVAILABILITY

DRUG	Generic Available
Canagliflozin (Invokana)	✗
Dapagliflozin (Farxiga)	✓
Empagliflozin (Jardiance)	✗
Ertugliflozin (Steglatro)	✗
Bexagliflozin (Brenzavvy)	✓
Sotagliflozin (Inpefa)	✗

BEYOND DIABETES

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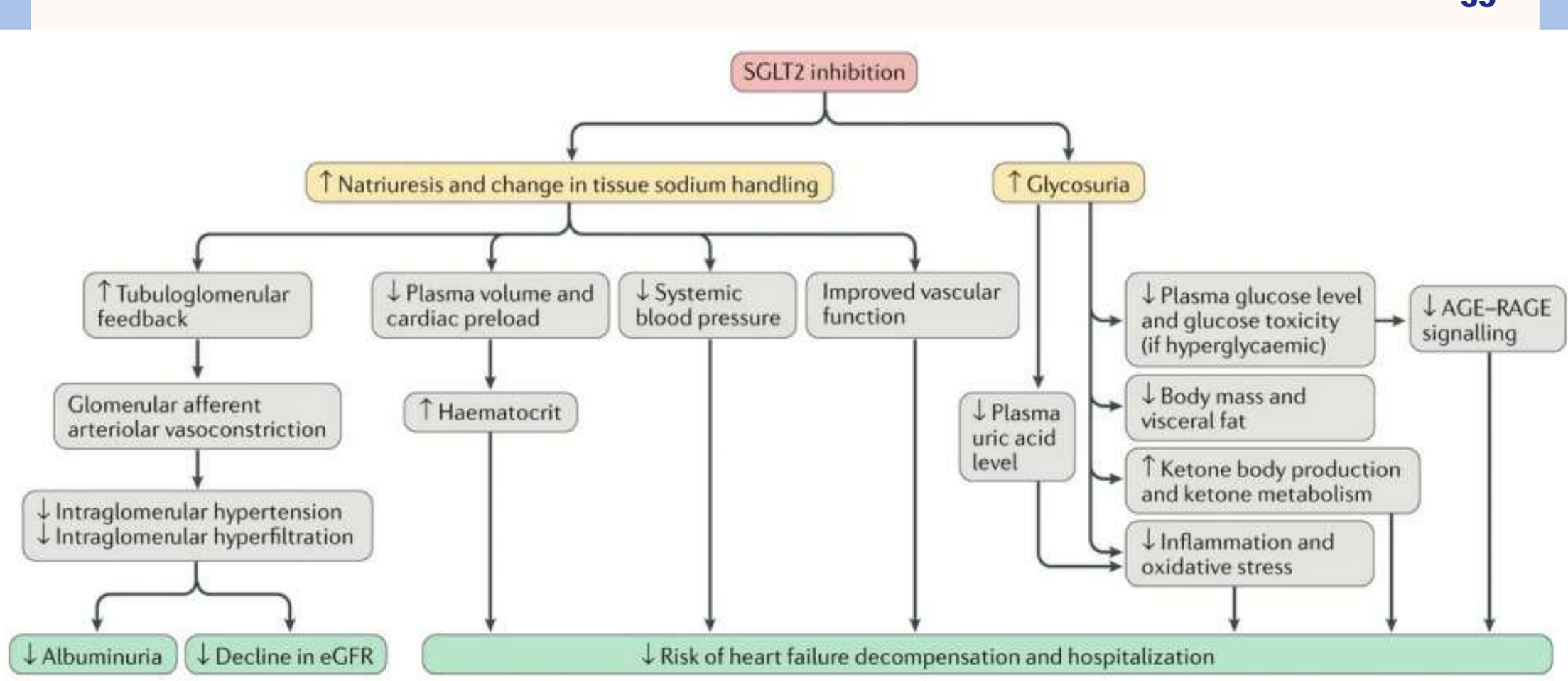

Cowie et al., 2020

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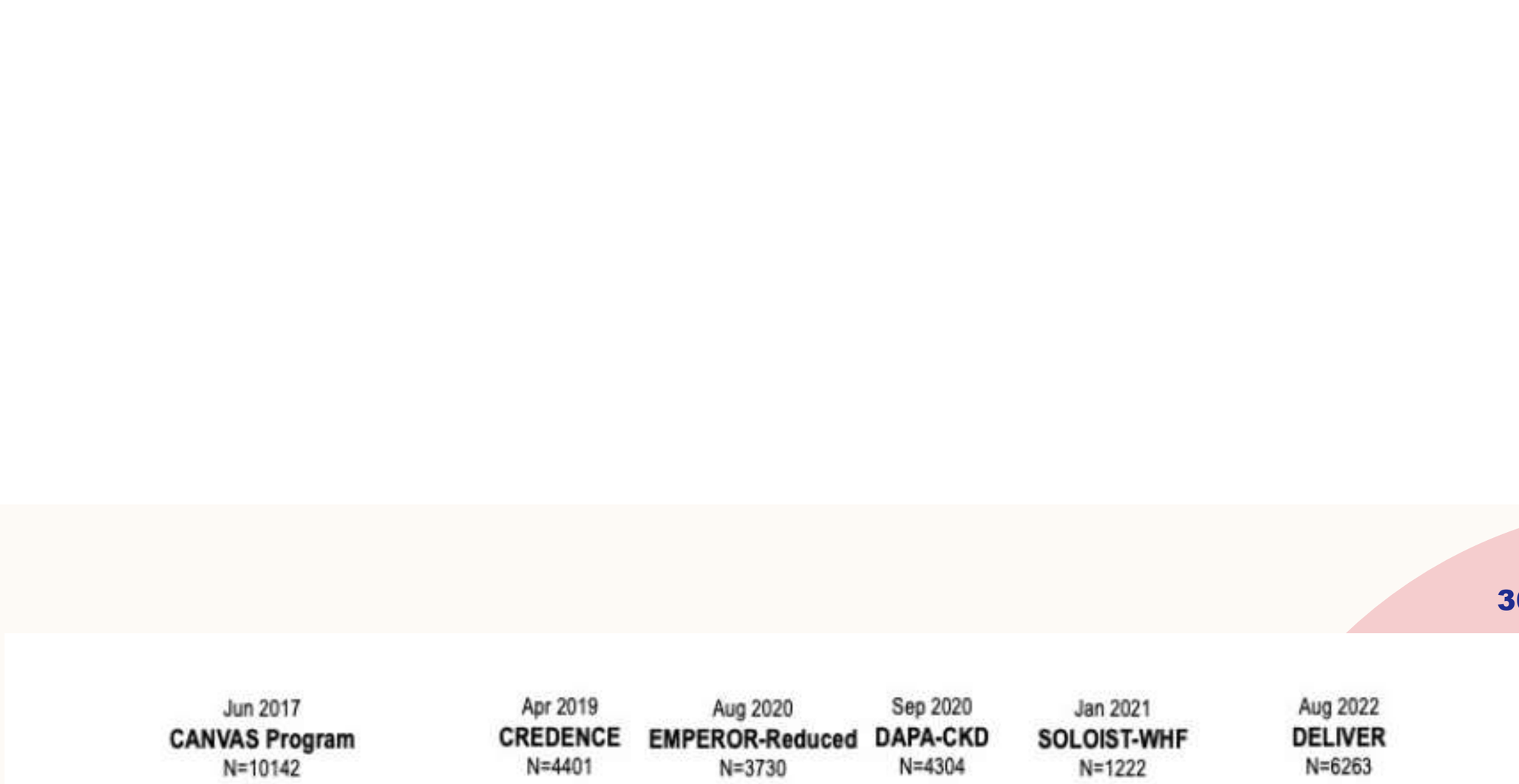

BCRenal, 2023

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KIDNEY		HEART	
increase	Diuresis, natriuresis and glycosuria	Preload and afterload	decrease
decrease	Hyperfiltration	Myocardial contractility	increase
increase	Glomerular afferent arteriole vasoconstriction and efferent arteriole vasodilatation	Endothelial inflammation and oxidative stress	decrease
decrease	Tubular energy consumption, apoptosis, oxidative stress, tubulointerstitial inflammation and fibrosis	FFA oxydation, ketogenesis, mitocondrial function, cardiomyocytes energy efficiency	increase
increase	HIF-2α, erythropoiesis and renal oxygenation	Arrhythmias, myocardial hypertrophy, HF progression	decrease
↓ CHRONIC KIDNEY DISEASE PROGRESSION		CARDIAC AND CORONARY ENDOTHELIAL FUNCTION ↑	

Di Costanzoet al., 2023

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OFF-LABEL AND INVESTIGATIONAL USES

- Acute myocardial infarction, patients without diabetes or heart failure
- Gout
- Metabolic dysfunction-associated steatotic liver disease (MASLD)
- Type 1 diabetes mellitus; Adjunct

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SGLT2 INHIBITORS IN TYPE 1 DM

Patients who may benefit:

- Overweight or insulin-resistant individuals
- Microalbuminuria with preserved eGFR
- High cardiovascular risk

Studies show a 3–4x higher DKA risk

Haider, 2025

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SGLT2 INHIBITORS IN TYPE1 DM

SGLT2i use in T1D should remain specialist-guided, patient-specific, and tightly monitored.

- Use the lowest available dose
- Educate patients on ketone testing and sick day rules
- Consider real-time or daily ketone monitoring
- Discontinue during illness, surgery, or fasting
- Avoid in underweight patients, restrictive eaters, or those with history of DKA

Looking Ahead:

Continuous Ketone Monitoring?

Haider, 2025

ROLE OF THE DIABETES EDUCATOR

- Advise patients on the benefits of SGLT2i medications in the treatment of T2DM, including additional cardiorenal benefits
- Instruct patients on ways to mitigate risks of SLGT2i therapy, including:
  - Sick-day rules
  - Prompt treatment of any genital or urinary tract infection
  - Education on proper foot care and monitoring

QUESTIONS

DISCUSSION

THANK YOU

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