ECHO Diabetes

SGLT2 inhibitors

Increasing Confidence in Prescribing

January 12, 2023

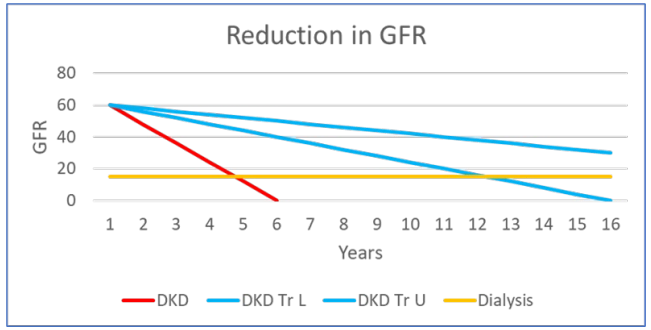
Carol Greenlee MD MACP

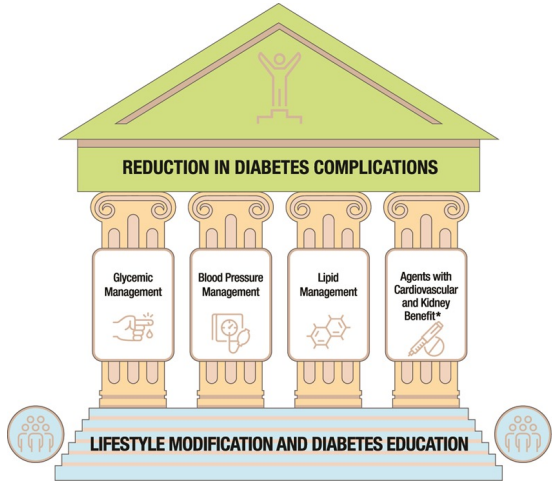
Pre-Question – which statement is accurate

- SGLT2i medications
  - Increase the risk of gout
  - Increase the risk of acute kidney injury (AKI)
  - Have evidence of “non-glycemic” benefit for CKD, ASCVD and Heart Failure (HF)
  - Should only be used as a third-line treatment option in diabetes management

Primary Care Clinicians need to be Confident in Prescribing SGLT2i Medications

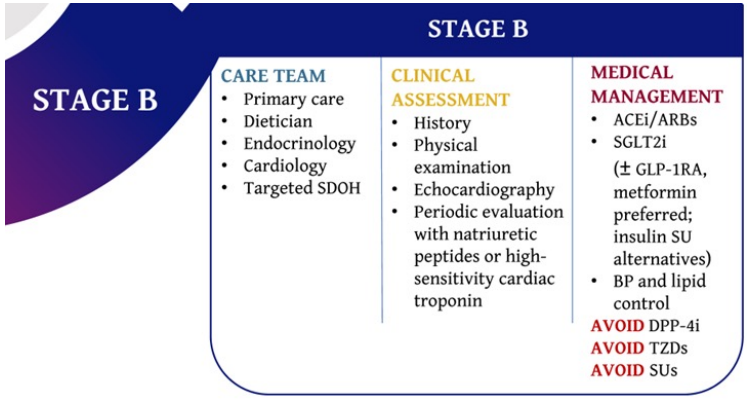
- Guidelines/Standards of Care
  - recommend SGLT2i medications for both glycemic & non-glycemic benefits for people with diabetes
- Use of SGLT2i medications early in a disease state can improve outcomes, e.g.:
  - Prevent or delay ESKD





When possible, select meds that do "double (or more) duty"

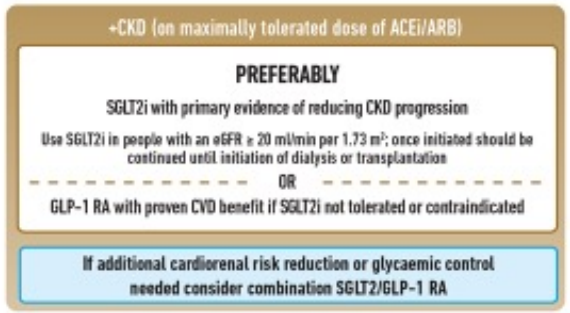
  - Prevent or delay Stage C&D HF

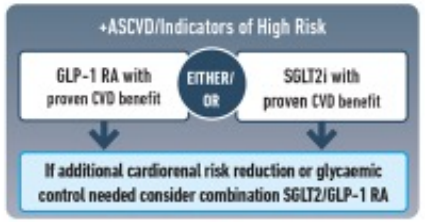


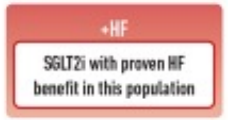
Management of hyperglycemia in type 2 diabetes, 2022.
A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Consensus report (ADA): doi.org/10.2337/dci22-0034 (EASD): doi.org/10.1007/s00125-022-05787-2

FIGURE 4: HOLISTIC PERSON-CENTRED APPROACH TO T2DM MANAGEMENT







1 = American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S144–74.

ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blockers; ASCVD, Atherosclerotic Cardiovascular Disease; BP, Blood Pressure; CKD, Chronic Kidney Disease; CV, Cardiovascular; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes.

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EASD European Association for the Study of Diabetes

Treatment for Glycemia and/or Organ-specific Protection

- The pursuit of glycemic control and the pursuit of organ-specific (e.g., heart and kidney) protection are complementary and not mutually exclusive,
  - SGLT2i & some other agents, have been shown to protect organs (heart, kidney) partly independently of their glucose-lowering effect
- Based on these principles, *regardless* of HbA1c level or the presence of other glucose-lowering agents:
  - all individuals with **diabetes and established or subclinical CVD** should be prescribed an agent with proven cardiovascular benefit from the GLP-1 RA class or SGLT2i class.
  - all individuals with **diabetes and CKD** (eGFR <60 ml/min per 1.73 m2 or UACR >30 mg/g) should receive an agent with proven kidney benefit from the SGLT2i class (or GLP-1 RA class if SGLT2i are contraindicated or not preferred).
  - all individuals with **diabetes with HF** (HF with reduced ejection fraction or HF with preserved ejection fraction) should receive an agent from the SGLT2i class with proven benefit for HF.

SGLT2 inhibitor medications – Benefits & Risks

Benefits

- Glycemic benefits
  - reduced with eGFR <45
- Lower BP
- Weight loss (NAFLD benefit)
- Cardiac protection
  - Heart Failure reduction
  - Reduced MACE/ CVD events
- Renal protection
  - **Slow progression of CKD**
  - Diuresis without risk of AKI
    - Do not increase uric acid
    - Work with diuretics when needed (HF)
    - Potassium moderating

Risks

- Mycotic Genital Infections
- Fournier gangrene
- Euglycemic Diabetic Ketoacidosis (euDKA)
- Urinary Tract Infections (UTI)?
- Amputations ?
- Osteoporosis/fractures?

SGLT2i effectiveness in people with CKD

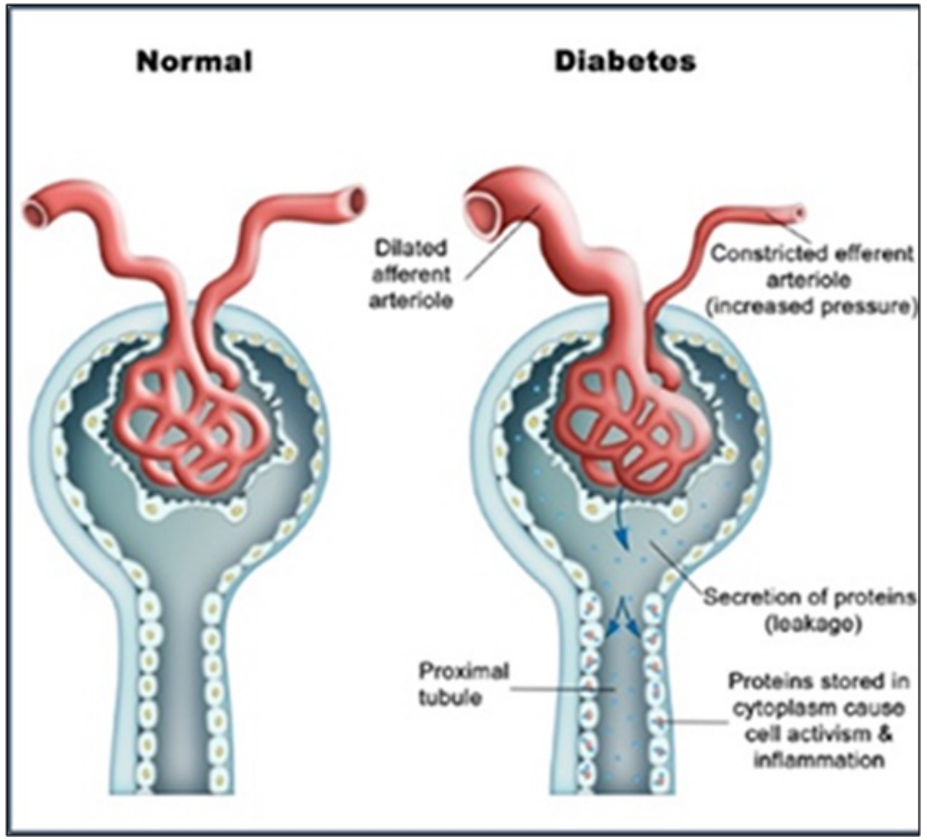
- ***Glycemic efficacy* of SGLT2 inhibitors is dependent on kidney function**.
  - SGLT2 inhibitors have been shown to be very effective in reducing glycated hemoglobin (HbA1c), with an ***average reduction of HbA1c by 0.6 - 1.2*** depending on the baseline level in people with preserved renal function
  - The ***glucose-lowering efficacy*** of SGLT2i in the patients with an **eGFR <45 mL/min/1.73 m2 is *diminished*** because of their *reduced glucose filtration*
    - 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 m2.13

- ***Non-glycemic benefits*** are **not diminished**
  - In patients with T2D and CKD with low eGFR, despite only modest reductions in A1c, SGLT2 inhibitors **reduce the risk of cardiovascular and renal outcomes**, without clear evidence of additional safety concerns.

Hemodynamic Derangements in Diabetic Kidney Disease

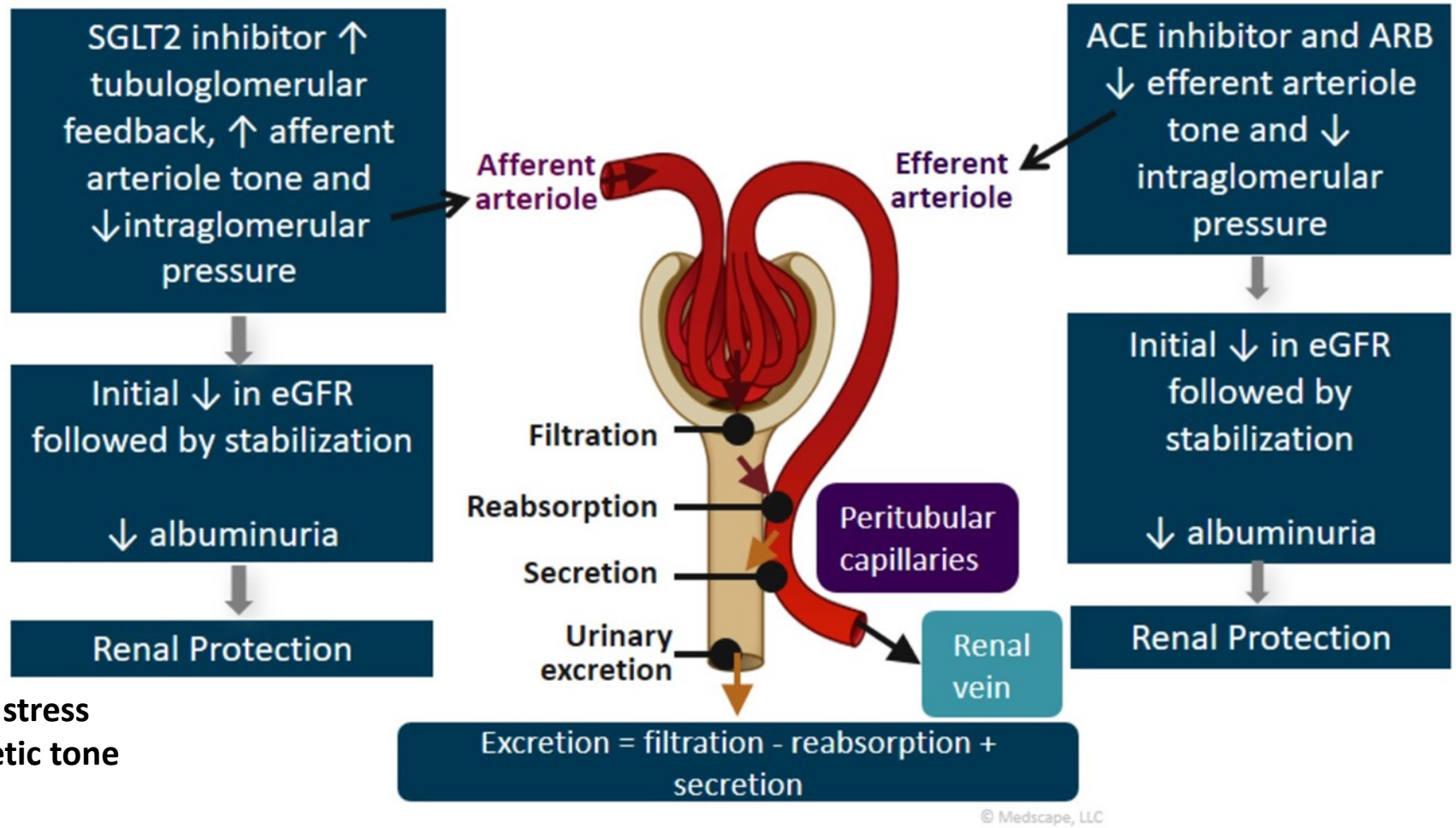
glomerular hypertension and hyperfiltration

- Auto-regulation of renal blood flow is *impaired* (*faulty tubuloglomerular feedback & RAAS activation*) in CKD in diabetes:
  - abnormal dilation of afferent arteriole &
  - inappropriate constriction of efferent arteriole
  - leads to increased glomerular filtration & perfusion pressure (*glomerular hypertension)*
- This increase in filtration & glomerular hypertension can lead to *glomerular sclerosis* in long term
  - Perpetuated injury: After development of sclerosis blood flow in remaining intact glomeruli increases causing a rise in glomerular pressure and further sclerosis
- Leads to albuminuria & decline in GFR



SGLT2 Inhibition and ACE Inhibition/ARBs Reduce Intraglomerular Pressure

Newer data suggests minimal vasoconstriction of afferent arteriole & increased vasodilatation of efferent arteriole via TGF

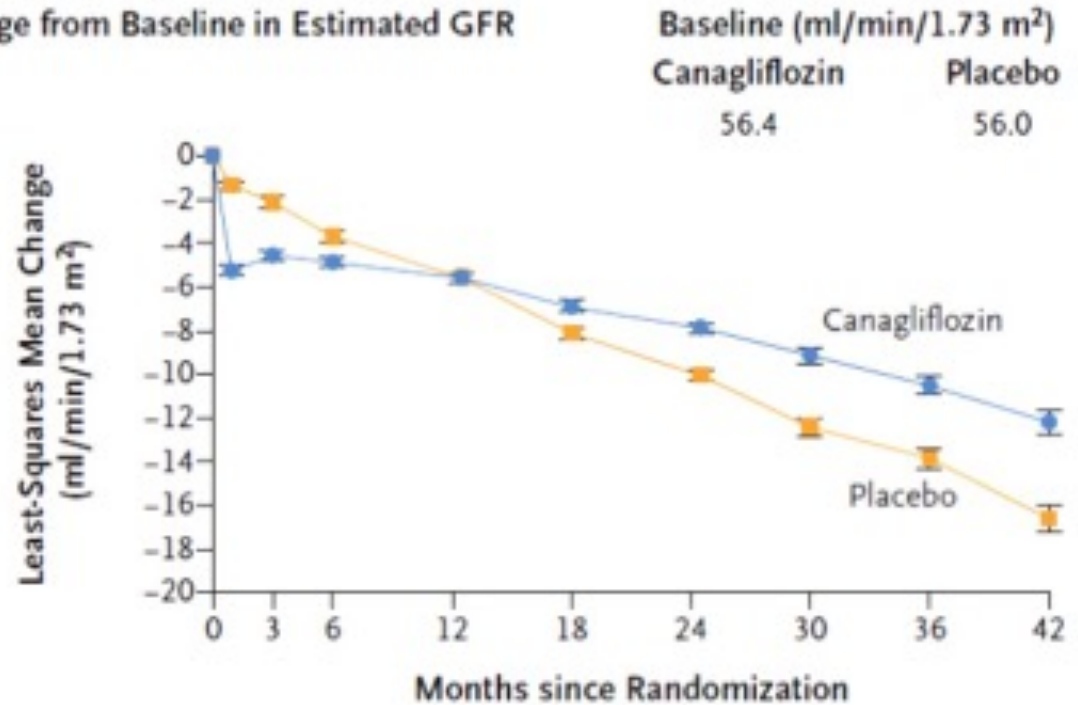


Multiple additional renal protective effects, including:

- **Reduced fibrosis**
- **Reduced oxidative stress**
- **Reduced sympathetic tone**
- **Diuretic sparing**

Cherney DZ, et al. *Circulation*. 2014;129:587-597; Perkovic V, et al. *Curr Med Res Opin*. 2015;31:2219-2231.

Effects of Canagliflozin on eGFR



No. of Patients								
Placebo	2178	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2005	1919	1782	1648	1116	652	241

Acute eGFR slope (3 weeks)
Difference: −3.17 (95% CI: −3.87, −2.47)

Chronic eGFR slope
Difference: 2.74/year (95% CI: 2.37–3.11)

Perkovic V, et al. *N Engl J Med*. 2019;380:2295-2306.

What dose of SGLT2i is needed for renal benefit?

- SGLT2i therapy must be initiated at the ***lowest recommended daily dose*** (10 mg empagliflozin, 100 mg canagliflozin, 10 mg dapagliflozin, or 5 mg ertugliflozin).
  - SGLT2i titration to **a *higher dose is not necessary*** for maximal *cardiorenal benefits*
  - A *higher dose* of SGLT2i can be used to *improve glycemic control*
    - the glucose-lowering effect of SGLT2i declines at lower eGFR
- *It can be continued until the patient initiates dialysis therapy* (currently not recommended to start at eGFR <20)

Real-Life Prescribing of SGLT2 Inhibitors: How to Handle the Other Medications, Including Glucose-Lowering Drugs and Diuretics David Lam and Aisha Shaikh Kidney360 April 2021, 2 (4) 742-746;
https://kidney360.asnjournals.org/content/2/4/742

Additional Benefits – Gout, Edema, Hyperkalemia, AKI

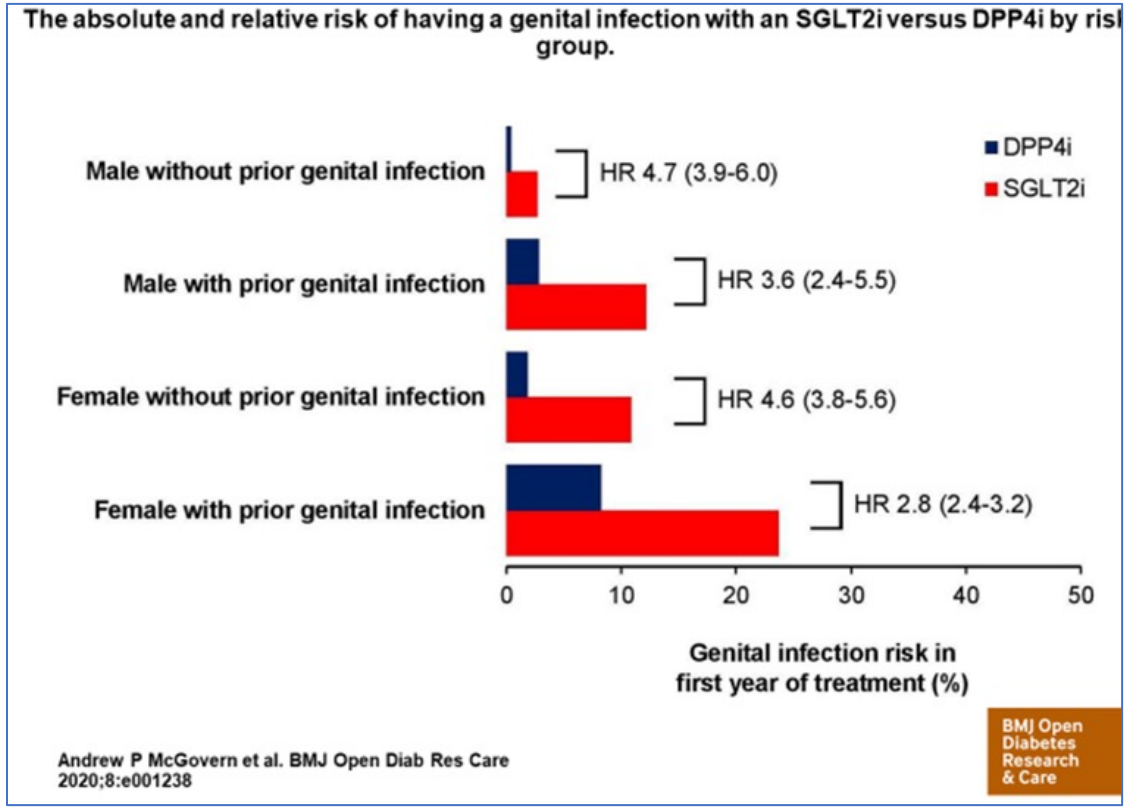
- Reduction in uric acid levels and in incidence of gout
  - In several studies, SGLT2 inhibitor medications consistently **lowered blood urate levels**
  - A 2020 study published in Annals of Internal Medicine found **~ 30% reduced incidence of gout with SGLT2i** therapy compared to *GLP1 RA* therapy in patients with T2D
  - A 2021 Taiwanese study found that use of SGLT2 inhibitors is associated with **~15% lower gout incidence** in patients with T2D compared with *DPP4 inhibitors* (DPP4i meds also reduce gout)

- ***Safety of Empagliflozin in Patients With Type 2 Diabetes and Chronic Kidney Disease: Pooled Analysis of Placebo-Controlled Clinical Trials*** Katherine R. Tuttle et al Diabetes Care 2022;45(6):1445–1452
  - **Edema** *was less common* in patients receiving empagliflozin versus placebo
  - Studies show **additive or synergistic natriuretic effects** of SGLT1i with loop diuretics when needed
  - *No increase* in **acute renal failure / AKI** or volume depletion
  - *Lower risks* were observed with empagliflozin for **hyperkalemia**
    - Patients with advanced CKD, especially those receiving renin-angiotensin system blockers, are prone to hyperkalemia.
    - This favorable effect of SGLT2 inhibitors on serum potassium in patients with type 2 diabetes and CKD **might permit the broader use of drugs** associated with hyperkalemia, such as mineralocorticoid receptor antagonists

Increased Risk of Genital Mycotic Infections

- SGLT2i treatment is associated with a 3 to 6-fold increased risk of genital mycotic infections
  - Highest risk association
    - Females
    - History of prior infection
      - Especially within past year
    - No higher risk seen with higher A1c
      - Glucosuria threshold ?
    - Lower incidence rates in advanced CKD

"If those at highest risk elect to start an SGLT2i, then practitioners should pay particular attention to counseling regarding genital hygiene and when to start antifungal treatments."



Prevention and management of genital mycotic infections in the setting of sodium-glucose cotransporter 2 inhibitors

Annals of Pharmacotherapy 2020

- The 3- to 4-fold increased incidence of GMIs is considered a class wide effect of SGLT2 inhibitors
  - female sex and a prior history of GMIs are factors associated with the highest risk, whereas
  - circumcised males are at the lowest risk of SGLT2 inhibitor–induced GMI
- Personal hygiene advice/education can reduce the infection risk in patients taking SGLT2 inhibitors
  - i.e., **rinse genital area with water after voiding and before bed**; wear cotton underwear
- When candidiasis occurs, it is often mild and responsive to treatment and often does not require discontinuation of the SGLT2i medication.
  - management strategies may include the use of
    - oral antifungals (i.e., single dose of oral fluconazole)
    - topical antifungal creams (i.e., miconazole or clotrimazole for 1-3 days)
    - over-the-counter topical antifungals in milder cases
- “Strong consideration should be given to avoid SGLT2 inhibitors in female patients with a history of severe, recurrent infections.”

Annals of Internal Medicine |4 JUNE 2019

Fournier Gangrene Associated With Sodium–Glucose Cotransporter-2 Inhibitors: A Review of Spontaneous Postmarketing Cases

Susan J. Bersoff-Matcha, MD; et al

Results: The FDA identified 55 unique cases of FG in patients receiving SGLT2 inhibitors between 1 March 2013 and 31 January 2019 (***55 cases in ~6 years***)

- For comparison, the FDA identified 19 FG cases associated with other anti-glycemic agents between 1984 and 31 January 2019 ***(19 cases in 35 years)***

Fournier Gangrene = A type of necrotizing fasciitis or gangrene affecting the external genitalia or perineum (usually ***bacterial*** etiology)

- Symptoms
  - Fever
  - Pain and swelling in the genitals or anal area
  - Unpleasant odor coming from the affected skin tissue
  - Crackling sound when touching the affected area

Need for Education & Awareness

Causes of Fournier's Gangrene

Fournier's gangrene usually happens because of an **infection near the genitals** including:

- Urinary tract infections/ Bladder infections
- Hysterectomies
- Abscesses
- Piercings

- **Conditions and medications that make it more** likely to get this disease, include:
- Diabetes
- Alcohol abuse
- Trauma to the genital area
- Steroids
- Chemotherapy
- HIV
- Obesity
- Cirrhosis (liver disease)
- Sodium-glucose cotransporter-2 (SGLT2) inhibitor medication use

If patient has multiple risk factors need to be all that more aware of risk

Ketosis vs DKA - Defining

- **Ketosis** results from ***restriction of carbohydrate usage*** with increased reliance on fat oxidation for energy production
  - Fasting (urine ketones usually only 1+, no ketones in blood)
  - Low Carb intake ("ketogenic diet", the Atkins diet, etc.)
  - SGLT-2 inhibitors (Urinary glucose loss (50-100 g/day), lowered insulin levels, raised glucagon level (stimulates ketones))

- **Diabetic Ketoacidosis (DKA)** results when ***absolute insulin deficiency*** occurs in both T1D and T2D,
  - **DKA presents with**
    - ***marked hyperglycemia* (>250 mg/dL, typically 350–800 mg/dL),**
    - ***profuse glycosuria***
    - **elevated *blood ketones* as well urinary ketones**

Euglycemic DKA (euDKA) with SGLT-2 inhibitors

- **<u>euDKA</u>** due to SGLT2i is similar to DKA except—
  - SGLT2i-induced glycosuria *lowers plasma glucose levels,* so you get DKA with **glucose <250 mg%**
  - SGLT2i predisposes to ***increased ketogenesis***
- The risk of bona fide euDKA, vs simple ketosis, in T2D related to the use of SGLT2 inhibitors is generally low
  - keto-acidosis has not been observed in patients without diabetes in the large SGLT2i trials
- Risk may be increased in people with diabetes if
  - ***insulin deficiency*** is more profound—as can happen in
    - T1D patients
      - In the CANVAS study, 6 out of the 12 cases of euDKA had evidence of latent autoimmune diabetes in adults (LADA) or T1D or tested positive for GAD65 antibodies
    - long-standing T2D patients with marked β-cell insufficiency
  - ***carbohydrate availability*** has been drastically ***restricted***
    - during prolonged starvation (carb restriction), keto diet, after surgery, alcohol excess, or during intercurrent illness (and colonoscopy prep)

Annals of Internal Medicine 20 AUGUST 2019

Sodium–Glucose Cotransporter-2 Inhibitors and the Risk for Severe Urinary Tract Infections: A Population-Based Cohort Study

Chintan V. Dave, PharmD, PhD et al

- Objective: To assess whether patients initiating use of SGLT-2 inhibitors were at increased risk for severe UTI events compared with those initiating use of dipeptidyl peptidase-4 (DPP-4) inhibitors or glucagon-like peptide-1 receptor (GLP-1) agonists
  - SGLT-2 inhibitors **were not associated with increased risk for outpatient UTIs**
- Conclusion: In a large cohort of patients seen in routine clinical practice, **risk for severe and non-severe UTI events among those initiating SGLT-2 inhibitor therapy was similar to that among patients initiating treatment with other second-line antidiabetic medications.**

"SGLT2is do not increase the risk of UTIs; however, their use in patients at high risk for UTIs, such as those with an indwelling Foley catheter, recurrent UTIs, or neurogenic bladder, has not been studied." Kidney 360 April 2021

Safety of Empagliflozin in Patients With Type 2 Diabetes and Chronic Kidney Disease: Pooled Analysis of Placebo-Controlled Clinical Trials

Katherine R. Tuttle et al Diabetes Care 2022;45(6):1445–1452

OBJECTIVE: To assess the safety of empagliflozin in patients with ***type 2 diabetes and moderate to severe chronic kidney disease (CKD) (category G3–4)*** enrolled in clinical trials

- no significant differences between treatment groups for [i.e., *no increase in*]
  - **ARF (AKI)**
  - **volume depletion**
  - **bone fracture**
  - **lower limb amputations**
    - Consider some caution since patients at high risk of lower extremity amputation (LEA) excluded were from some trials following findings in CANVAS (higher incidence of LEA in those on canagliflozin – not seen in trials with dapagliflozin or empagliflozin)
    - Remember increased risk of amputations in patients with CKD

- To build on the promising findings to date, a ***dedicated kidney disease outcome trial*** of empagliflozin versus placebo, enrolling >6,600 patients with and without diabetes, including those with low levels of kidney function with and without albuminuria, is under way (***EMPA-KIDNEY***; NCT03594110)

Summary from the ADA/EASD review

- While early studies brought attention to several safety areas of interest (acute kidney injury, dehydration, orthostatic hypotension, amputation, and fractures), longer-term studies that have prospectively assessed and monitored these events have not seen a significant imbalance in risks.
  - Analyses of SGLT2i outcome trial data also suggest that people with **type 2 diabetes and peripheral arterial disease** derive **greater absolute outcome benefits** from SGLT2i therapy than those without peripheral arterial disease, ***without an increase in risk of major adverse limb events.***
  - In post hoc analyses, SGLT2i use has been associated with *reduced incidence of serious and nonserious kidney-related adverse events* in people with type 2 diabetes and CKD and ***greater full recovery from acute kidney injury***.

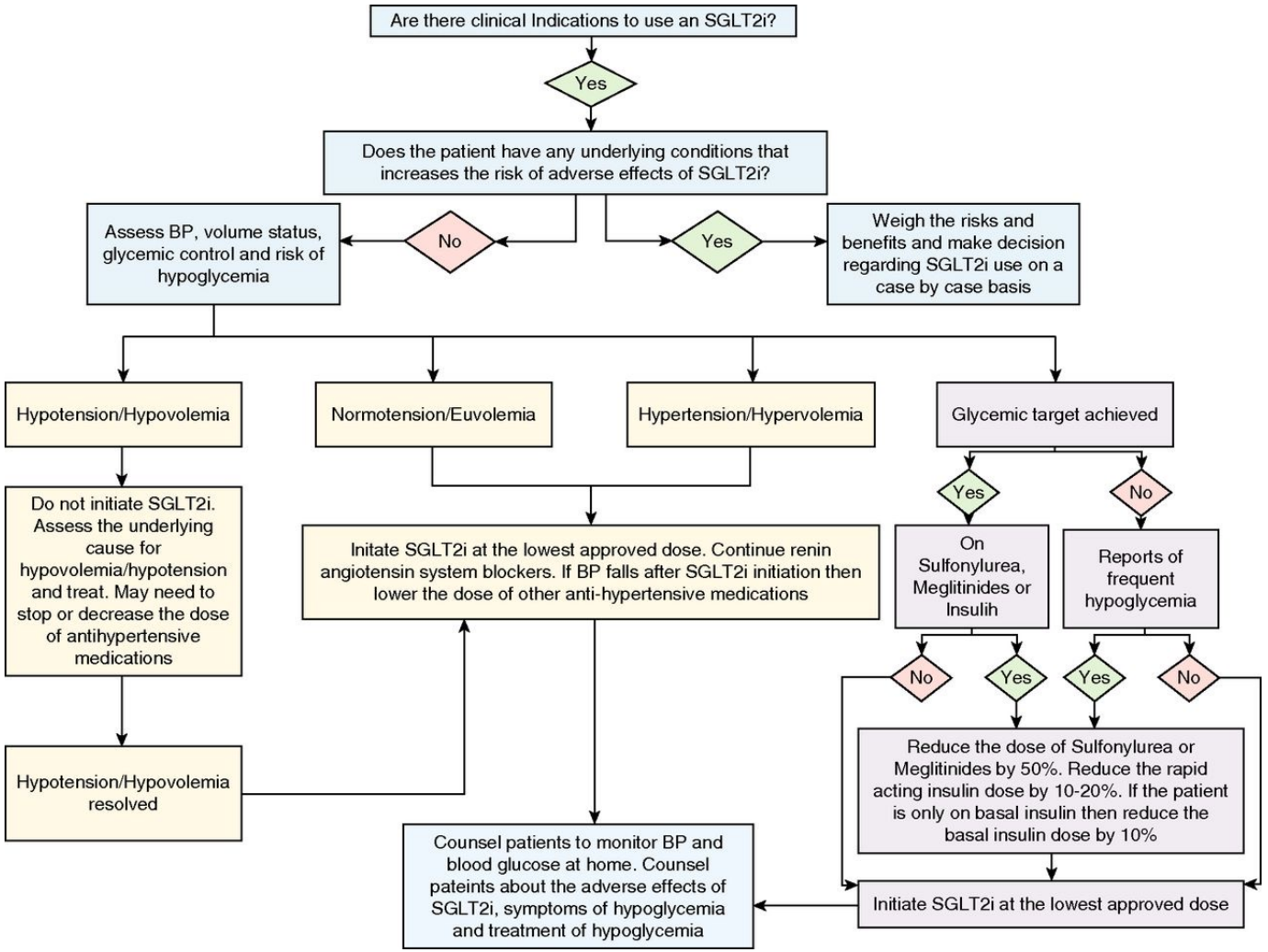
Consider the Patient's BP & Volume Status before Initiating SGLT2i

- Guide from Kidney 360 April 2021
  - If the patient is **hypotensive/hypovolemic**, then SGLT2is must not be initiated
    - In patients who are hypotensive, the antihypertensive medications, including diuretics, may need to be stopped or reduced to restore normotension.
  - If the patient is **hypervolemic/hypertensive**, then SGLT2i therapy can be initiated without adjusting the dose of other antihypertensive medications.
  - If the patient is **euvolemic/normotensive** then the *antihypertensive agents*, including *diuretics*, *may need to be reduced or stopped* if the BP decreases.

  - In the SGLT2i CV and kidney outcome trials, patients were required to be on the ***maximally tolerated dose of renin-angiotensin system (RAS) blockers*** **-** A similar strategy to continue RAS blockers must be adopted in clinical practice.

  - ***Monotherapy with SGLT2i*** is reasonable in patients who *are unable to tolerate RAS blockers.*

Algorithm to assess BP, volume status and glycemic control at the time of sodium-glucose cotransporter-2 inhibitor (SGLT2i) initiation.



David Lam, and Aisha Shaikh Kidney360 2021;2:742-746

Handout for the Patients when initiating SGLT-2 Inhibitor Therapy

- Increase in Urine Output
  - You may notice an increase in your urine output after starting this medication
  - Monitor your weight at home
- Blood Pressure
  - Monitor your blood pressure at home as this medicine may lower blood pressure
  - Inform your doctor if your blood pressure is too low, or if you experience lightheadedness or dizziness
- Blood Glucose
  - Monitor your blood glucose level at home as this medicine may lower blood glucose
  - Inform your doctor if your blood glucose is low
- Redness or itching in the genital area, or foul smelling vaginal or penile discharge
  - Keep the genital area clean
  - If you notice redness or itching in the genital area, or foul-smelling vaginal or penile discharge, then inform your doctor. You may need a cream or oral medication to treat an underlying infection
- Follow the 'Sick Day Rule'
  - On days that you are unable to eat because you are feeling sick due to fever, infection, poor appetite, nausea, vomiting or diarrhea then hold this medicine.
  - You can resume the medicine once you are able to eat and drink.
  - If you continue to feel sick, then call your doctor as you may need to have blood tests to rule out Diabetic ketoacidosis
  - Stop the medication 3 to 4 days before a scheduled surgery that requires you to be NPO (meaning you are instructed to not eat or drink anything for several hours before your surgery) (including colonoscopy)
  - Avoid very low Carbohydrate diet and Keto diet as it may increase the risk of Diabetic Ketoacidosis
- Wound on your feet or legs
  - If you notice a wound, ulcer or skin breakdown on your feet or legs, then hold this medicine and inform your doctor
- Burning or pain during urination
  - If you experience pain or burning on urination, then inform your doctor as you may need further evaluation

Summary – SGLT2i Medications

- SGLT2i medications provide both glycemic and non-glycemic (organ-specific protection) benefits for people with diabetes
  - Cardio (ASCVD & HF) and Renal risk reduction
- Additional studies have shown that many of the side effects/risks that we were initially concerned about with SGLT2i are not substantiated
  - No increased risk & reduced risk of Acute Kidney Injury
  - No documented increased risk of fracture & reduced risk of kidney stones
  - No increased risk of UTI in patients without high-risk conditions
  - Increasing reassurance regarding risk of amputations
- Risks do include
  - Increased genital mycotic infections – not a contra-indication
  - Euglycemic DKA
  - Fournier Gangrene
- Additional non-glycemic benefits include
  - Reduced uric acid & reduced episodes of gout
  - Moderation of potassium (especially hyperkalemia)
  - Improved edema

PC clinicians need to be comfortable utilizing SGLT2i to improve outcomes & quality of life for their patients with diabetes

Post-Question – which statement is accurate

- SGLT2i medications
  - Increase the risk of gout
  - Increase the risk of acute kidney injury (AKI)
  - Have evidence of “non-glycemic” benefit for CKD, ASCVD and Heart Failure (HF)
  - Should only be used as a third-line treatment option in diabetes management


Questions?
Comments?
Suggestions?

Extra Slides

SGLT2 Inhibitors

	Efficacy[1]	Hypoglycaemia	Weight change[2]	CV effects		Renal effects		Oral/SQ	Cost
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*		
SGLT2 Inhibitors	Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	• See labels for renal dose considerations of individual agents • Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR	Oral	High

- *Glucose-lowering mechanism of action:* Reduce renal tubular glucose reabsorption
- *Clinical Efficacy Profile:* Intermediate to high glucose-lowering efficacy, lower at lower eGFR; low inherent risk of hypoglycaemia; intermediate weight loss
- *Cardiorenal Effects:* Demonstrated protective effects in studied trial populations:
  - Reduction in major adverse cardiovascular events
  - Reduction in overall CV death (with heterogeneity across the class)
  - Reduction in risk of hospitalisation for heart failure
  - Reduction in risk of kidney outcomes
- Increased confidence surrounding safety issues of interest

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

Diabetes Care 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2.

American Diabetes Association.

EASD European Association for the Study of Diabetes

CHOICE OF GLUCOSE-LOWERING MEDICATION

Providers should continually update their knowledge on the efficacy and side effects of diabetes pharmacotherapy (see Table 1).

Identify relevant comorbidities (e.g. obesity, CVD, HF, CKD, NAFLD).

Assess the profile of the person with diabetes (e.g. younger age, frailty, limited life expectancy, cognitive impairment, social determinants of health).

Consider risk factors for medication adverse events (e.g. hypoglycaemia, volume depletion, genital infections, history of pancreatitis).

Prioritise the use of organ-protective medications (GLP-1 RA, SGLT2i, TZD) in those with cardiorenal disease or NASH or at high risk.

American Diabetes Association®

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

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EASD European Association for the Study of Diabetes

FIGURE 4: HOLISTIC PERSON-CENTRED APPROACH TO T2DM MANAGEMENT

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥ 20 ml/min per 1.73 m^2; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If additional cardiorenal risk reduction or glycaemic control needed consider combination SGLT2/GLP-1 RA

+ASCVD/Indicators of High Risk

GLP-1 RA with proven CVD benefit — EITHER/OR — SGLT2i with proven CVD benefit

If additional cardiorenal risk reduction or glycaemic control needed consider combination SGLT2/GLP-1 RA

+HF

SGLT2i with proven HF benefit in this population

1 = American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S144–74.

ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blockers; ASCVD, Atherosclerotic Cardiovascular Disease; BP, Blood Pressure; CKD, Chronic Kidney Disease; CV, Cardiovascular; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes.

American Diabetes Association®

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

Diabetes Care 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2.

EASD European Association for the Study of Diabetes

Choosing glucose-lowering medication in people with heart failure

In people with heart failure SGLT2i should be used because they improve heart failure and kidney outcomes.

American Diabetes Association.

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

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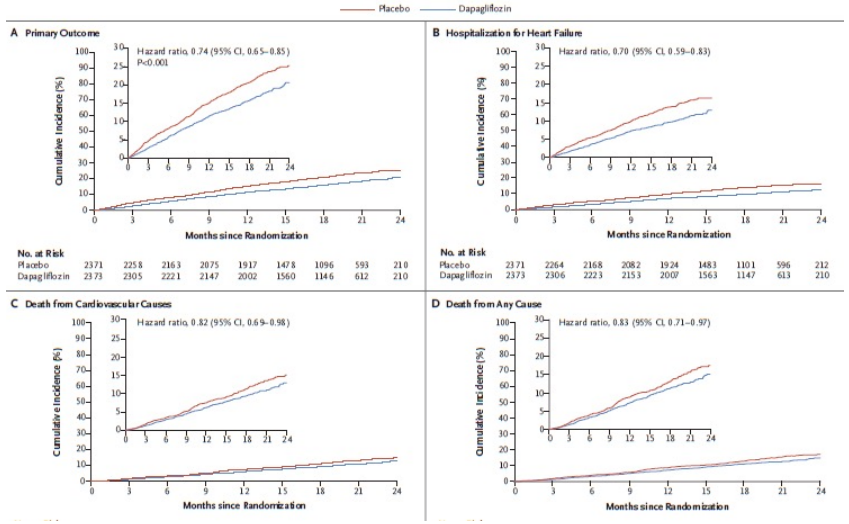
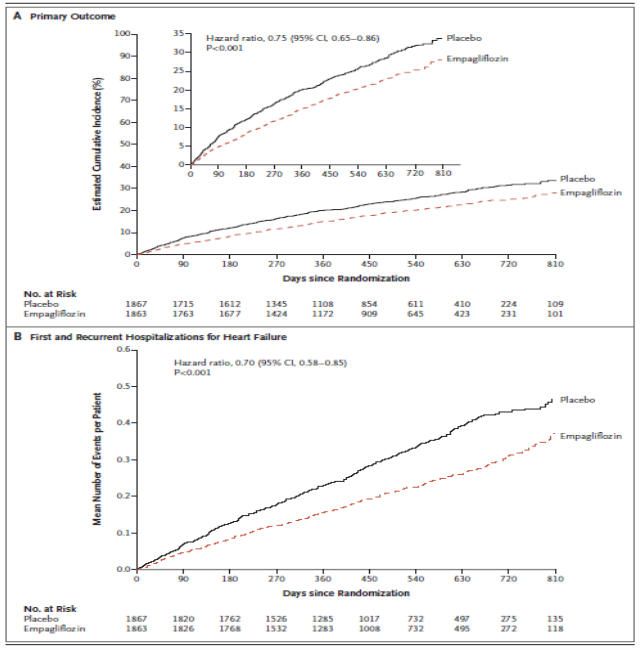
Effect of SGLT2i in people with heart failure

DAPA-HF



N Engl J Med 2019;381:1995-2008

EMPEROR-REDUCED



N Engl J Med 2020;383:1413-1424

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EMPEROR-PRESERVED

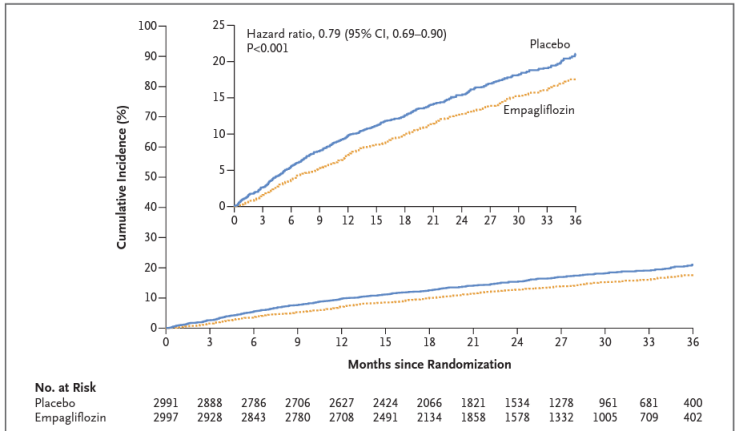

Figure 1. Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.
The estimated cumulative incidence of the primary outcome in the two groups is shown. The inset shows the same data on an expanded y axis.

N Engl J Med 2021;385:1451-1461

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Consensus recommendations

- In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1RA or an SGLT2i with proven benefit should be independent of background use of metformin.

- In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1RA or an SGLT2i with proven benefit should be independent of baseline HbA_{1c}.

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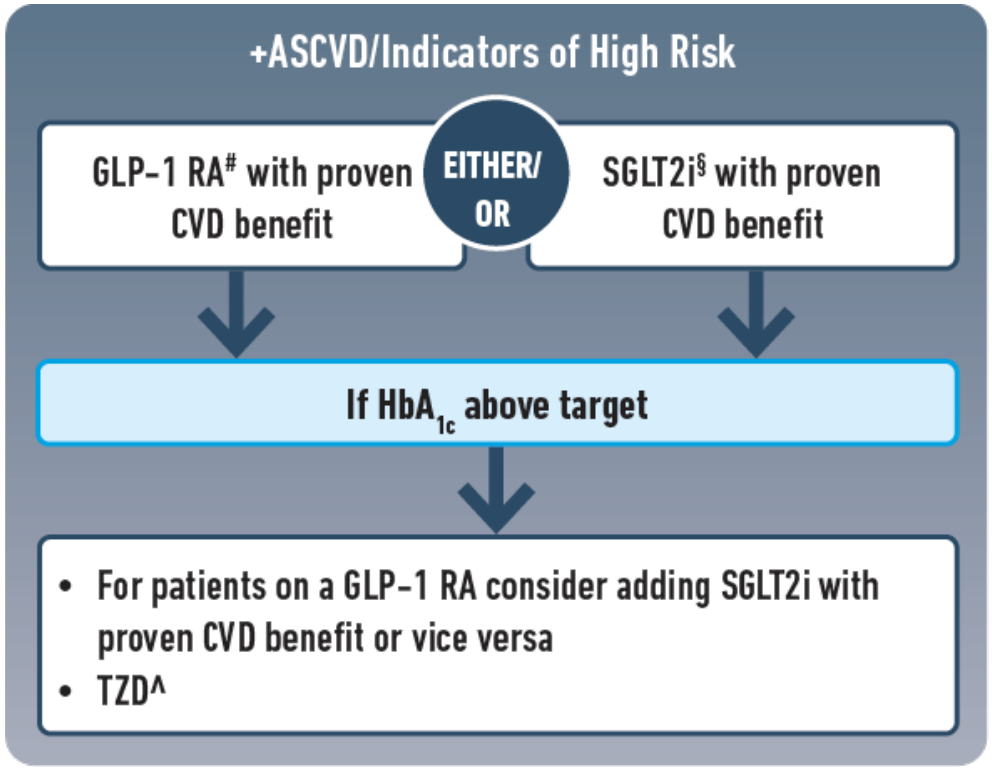
Choosing glucose-lowering medication in people with CVD



ASCVD = atherosclerotic cardiovascular disease

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Consensus recommendations

- In people with established CVD, a GLP-1RA with proven benefit should be used to reduce MACE or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes.

MACE = major adverse cardiovascular events

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Consensus recommendations

- In people with established CVD, a GLP-1RA with proven benefit should be used to reduce MACE or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes.
- In people without established CVD but with multiple cardiovascular risk factors (such as age ≥55, obesity, hypertension, smoking, dyslipidaemia, or albuminuria), a GLP-1RA with proven benefit could be used to reduce MACE or an SGLT2i with proven benefit could be used to reduce MACE and heart failure and improve kidney outcomes.

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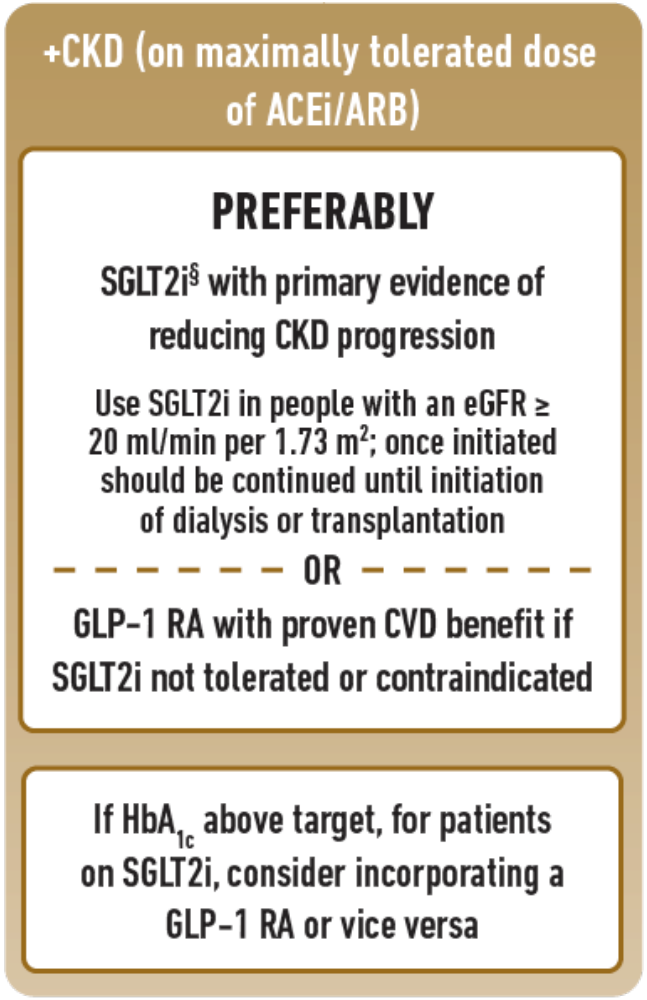
Choosing glucose-lowering medication in people with chronic kidney disease



Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

Diabetes Care 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2.

Consensus recommendations

- In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1RA or an SGLT2i with proven benefit should be independent of background use of metformin.

- In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1RA or an SGLT2i with proven benefit should be independent of baseline HbA_{1c}.

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Conclusions and recommendations

- In people with CKD, SGLT-2 inhibitors and GLP-1RA reduce risk of MACE independent of eGFR.
- In people with CKD, SGLT2i also reduce risks of HF and kidney outcomes (including end-stage kidney disease).
- In people with CKD and eGFR≥ 20 ml/min per 1.73 m^2, an SGLT2i with proven benefit should be initiated to reduce risks of MACE, HF and kidney outcomes.
- If such treatment is not tolerated or is contraindicated, a GLP-1RA with proven CV outcomes benefit could be considered

American Diabetes Association.

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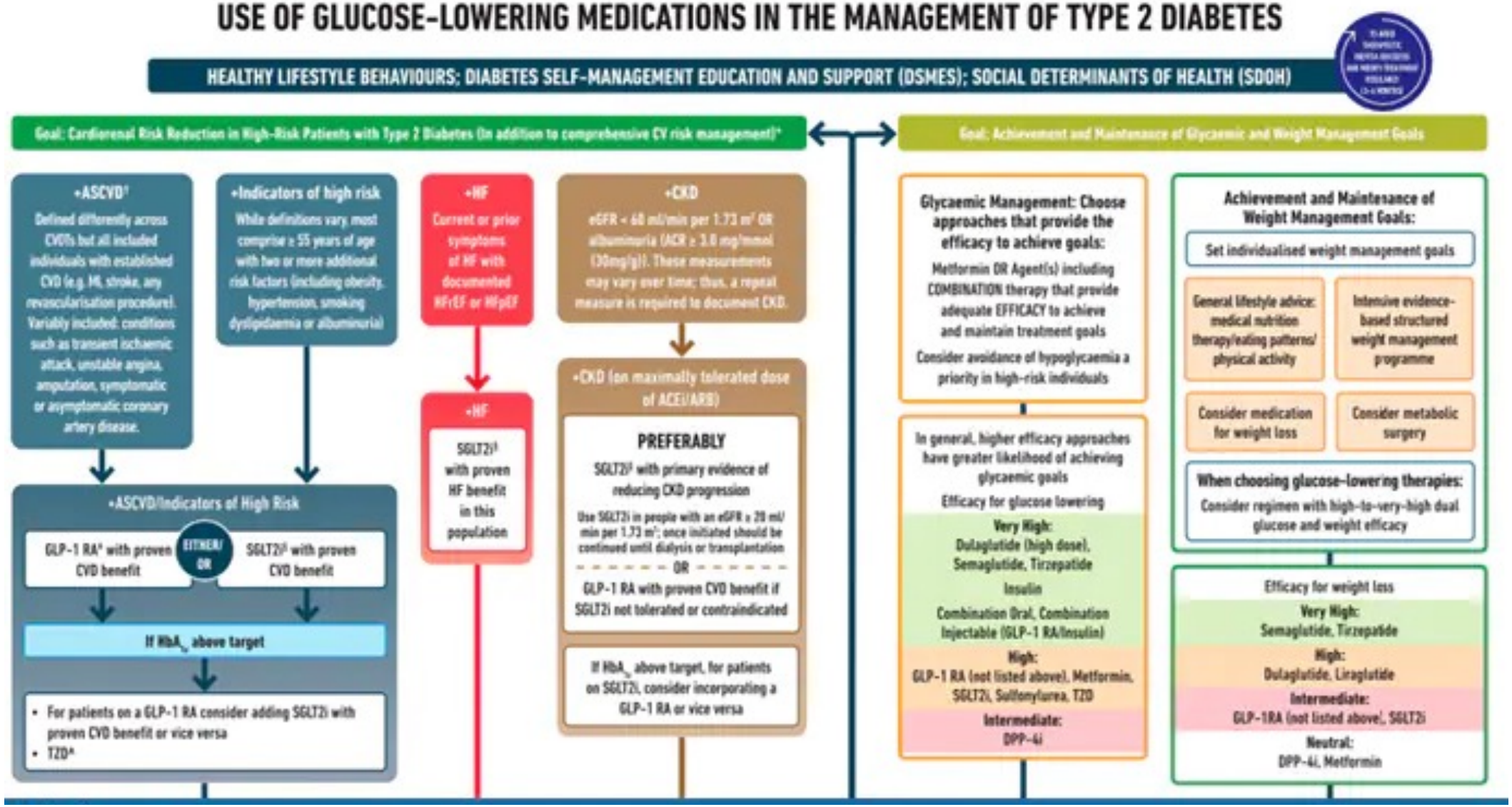
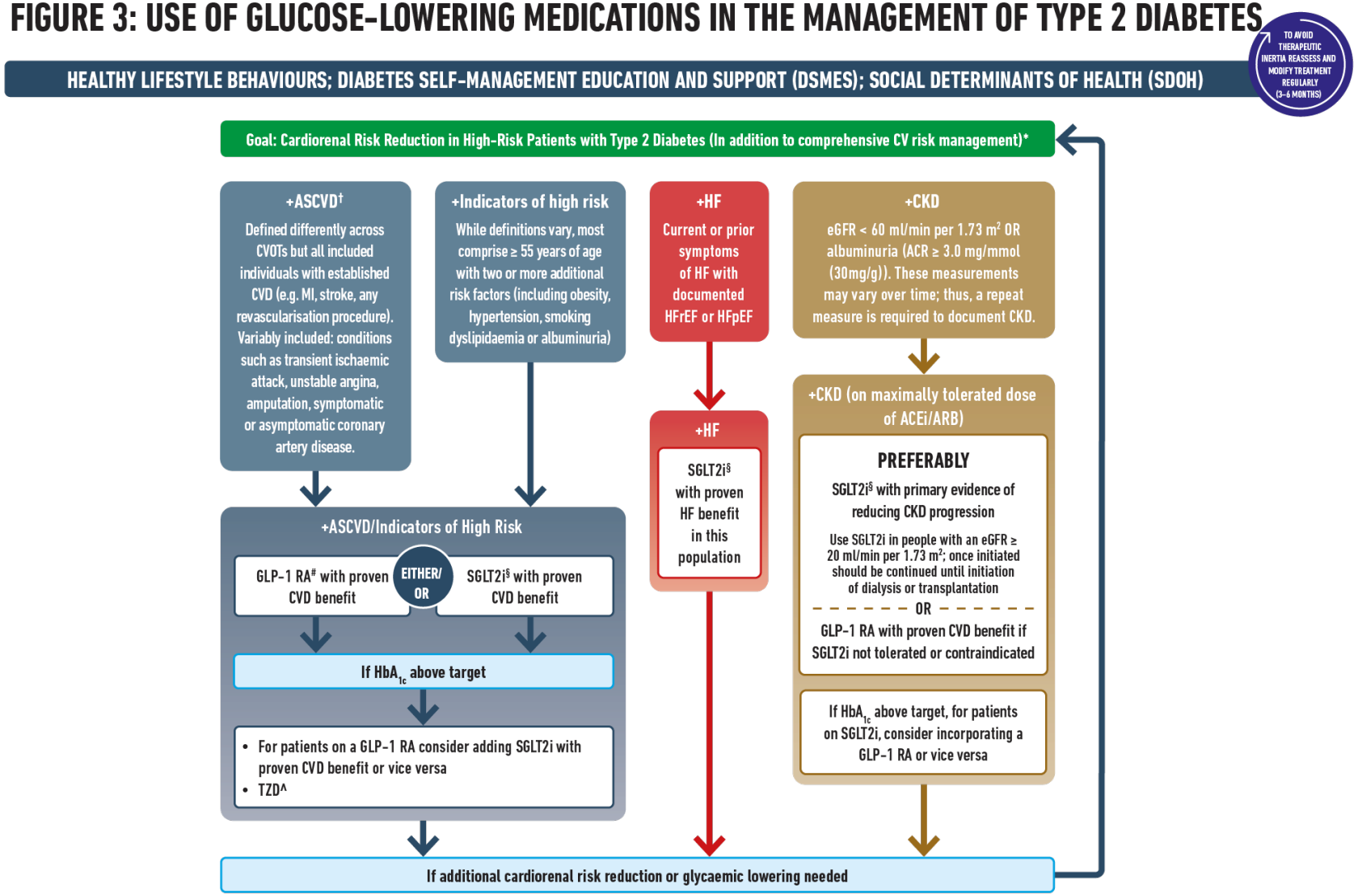


ADA and EASD – updated standards for management of hyperglycemia 2022

FIGURE 3: USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



ACEi, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Outcomes Trial; DPP-4i, Dipeptidyl Peptidase-4 Inhibitor; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with reduced Ejection Fraction; HHF, Hospitalisation for Heart Failure; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; SDOH, Social Determinants of Health; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes; TZD, Thiazolidinedione.

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin;† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.

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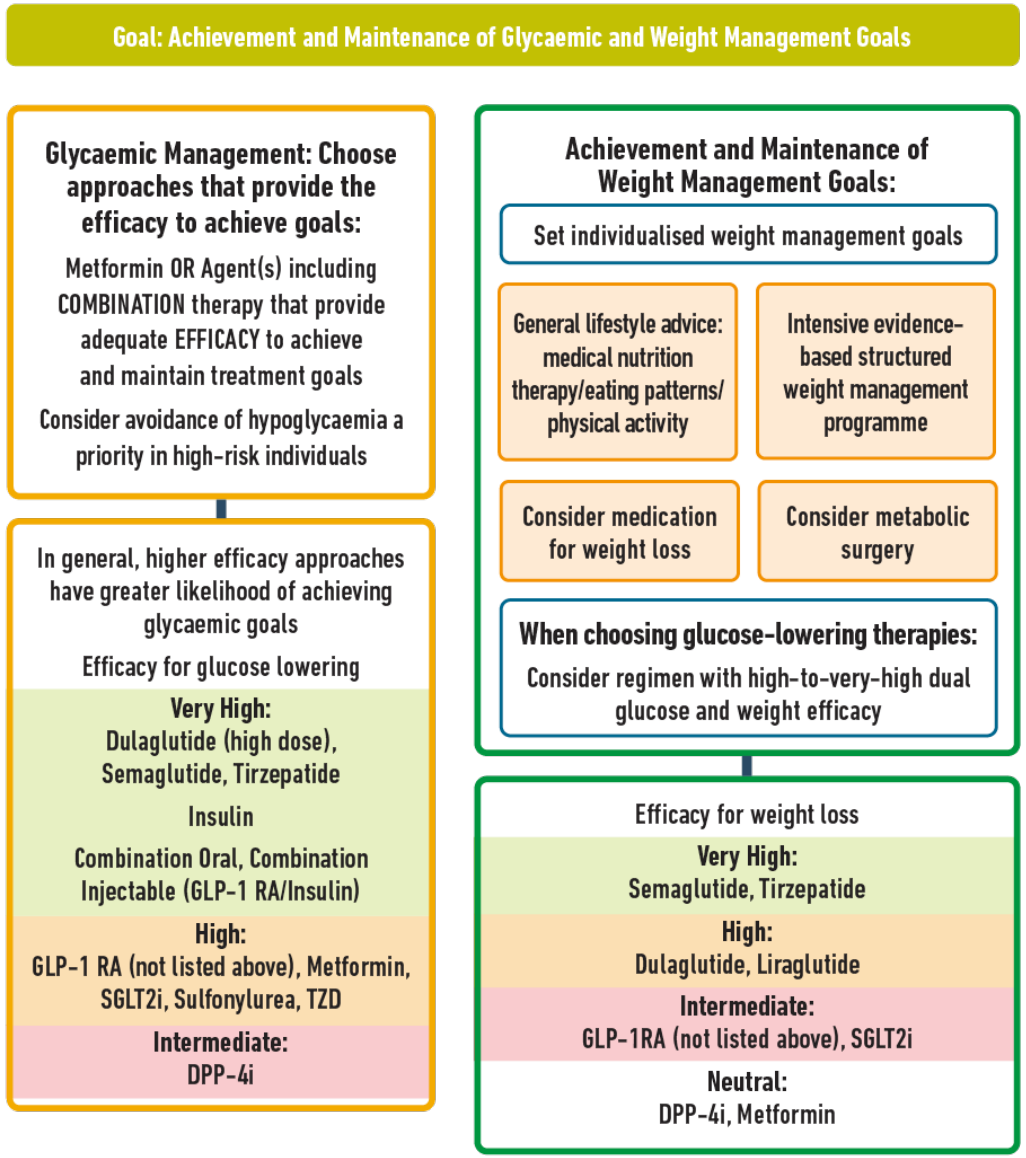

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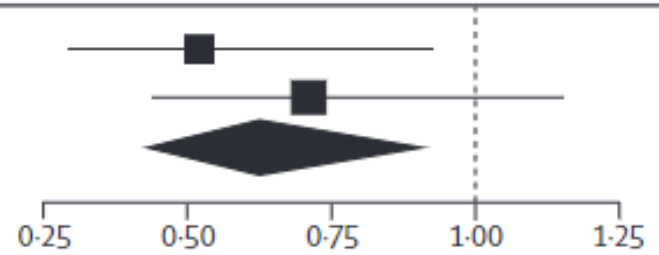
Effect of SGLT2i in people with heart failure

Meta-analysis of HFrEF trials: First Kidney Outcome Composite

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	18/1863 (1·0%)	33/1867 (1·8%)	0·52 (0·29–0·92)
DAPA-HF	28/2373 (1·2%)	39/2371 (1·6%)	0·71 (0·44–1·16)
Total			**0·62 (0·43–0·90)**
Test for overall treatment effect p=0·013 Test for heterogeneity of effect p=0·42			



Kidney composite was defined as time to first occurrence of any of the components of 50% or higher sustained decline in eGFR, end-stage renal disease, or renal death. End-stage renal disease was defined as either sustained eGFR lower than 15 mL/min per 1·73 m^2, chronic dialysis treatment, or receiving a renal transplant.

American Diabetes Association.

Lancet 2020;396:819-29

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- In Depth Article (also available as 2-hour Webinar) Expert Insights for Primary Care Physicians in Managing Chronic Kidney Disease in T2DM (medscape.org)
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Reference on safety of Empa in CKD

- Safety of Empagliflozin in Patients With Type 2 Diabetes and Chronic Kidney Disease: Pooled Analysis of Placebo-Controlled Clinical Trials
- Katherine R. Tuttle; Adeera Levin; Masaomi Nangaku; Takashi Kadowaki; Rajiv Agarwal; Sibylle J. Hauske; Amelie Elsäßer; Ivana Ritter; Dominik Steubl; Christoph Wanner; David C. Wheeler
- Diabetes Care 2022;45(6):1445–1452
- https://doi.org/10.2337/dc21-2034

CARDIOVASCULAR AND METABOLIC RISK| APRIL 26 2022

Safety of Empagliflozin in Patients With Type 2 Diabetes and Chronic Kidney Disease: Pooled Analysis of Placebo-Controlled Clinical Trials

Katherine R. Tuttle Diabetes Care

dc212034 https://doi.org/10.2337/dc21-2034

- Tuttle et al assess the safety profile of empagliflozin in type 2 diabetic patients with chronic kidney disease (CKD) G3A, G3B and G4 in a pooled analysis across 19 randomized, placebo-controlled trials. The rates of serious adverse events (SAEs) were similar across all stages of CKD compared to placebo, though when stratified by stage, rates were higher in CKD G4; however, their low numbers and wide confidence intervals make these data difficult to interpret. Importantly, rates of drug discontinuation due to SAE, in addition to clinically relevant events such as bone fracture and lower limb amputation, were similar amongst both groups regardless of the stage of CKD. Although hypoglycemia becomes more common as estimated glomerular filtration rate (eGFR) declines and insulin clearance decreases, treated patients did not have significantly higher rates of hypoglycemia. Interestingly, rates of edema and hyperkalemia—common occurrences in the CKD population—were reduced in the intervention arm, although volume depletion and acute renal failure were not increased. Unfortunately, due to low incidence rates, this study was unable to assess the rates of euglycemic diabetic ketoacidosis, which a serious, though rare side effect of sodium–glucose cotransporter 2 inhibitors.

- Empagliflozin is safe in patients with type 2 diabetes with reduced renal function up to CKD G4. Given the safety profile and benefit in edema and hyperkalemia, prescribers should feel comfortable prescribing even for patients with reduced eGFR. The safety of empagliflozin in other non-diabetic forms of kidney disease still needs to be addressed

Safety in patients with CKD

- Neuen BL, Young T, Heerspink HJL, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2019;7:845–854
- a meta-analysis of SGLT2 inhibitor studies, which included cardiovascular outcome trials and the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial that was conducted in patients with type 2 diabetes and CKD, demonstrated a 25% reduction in the risk of acute kidney injury

Lower risk of hyperkalemia, edema & gout with SGLT2i

- Safety of Empagliflozin in Patients With Type 2 Diabetes and Chronic Kidney Disease: Pooled Analysis of Placebo-Controlled Clinical Trials Katherine R. Tuttle, et al **Diabetes Care** dc212034 https://doi.org/10.2337/dc21-2034

- https://pubmed.ncbi.nlm.nih.gov/31931526/ Ann Intern Med. 2020 Feb 4;172(3):186-194. doi: 10.7326/M19-2610. Epub 2020 Jan 14. Assessing the Risk for Gout With Sodium-Glucose Cotransporter-2 Inhibitors in Patients With Type 2 Diabetes: A Population-Based Cohort Study Michael Fralick, Sarah K Chen, Elisabetta Patorno, Seoyoung C Kim PMID: 31931526 PMCID: PMC7217750 DOI: 10.7326/M19-2610

Reference showing slight increase in amputations

- Risk of amputations associated with SGLT2 inhibitors compared to DPP-4 inhibitors: A propensity-matched cohort study - PubMed (nih.gov)

Initial Decline in eGFR After Dapagliflozin Initiation and Its Associated Outcomes in Patients With HFrEF Journal Scan / Research・May 12, 2022, Circulation

- TAKE-HOME MESSAGE
- In this post hoc analysis of the DAPA-HF trial including more than 4000 participants with HFrEF, the mean changes in estimated glomerular filtration rate (eGFR) between days 0 and 14 were –1.1 mL/min/1.73m2 and –4.2 mL/min/1.73m2 with placebo and dapagliflozin, respectively. Overall, 38.2% of patients — with older age, lower baseline eGFR, higher LVEF, and type 2 diabetes — experienced a >10% early decline in eGFR with dapagliflozin compared with placebo (OR, 2.36). In the dapagliflozin group, a >10% initial decline in eGFR was associated with a 27% reduced risk of the primary outcome compared with those with a ≤10% decline (HR, 0.73).
- These findings highlight that an early decline in eGFR following dapagliflozin initiation is common, small, and associated with better clinical outcomes in patients with HFrEF.

- Overview written by Steven G. Coca DO, MS
- The hyperfiltration theory of progressive kidney damage is one of the most seminal hypothesis in nephrology.1 This theory is one of the major mechanisms purported to be operative in renoprotection mediated by antagonists of the renin-angiotensin-aldosterone system, in which a decrease angiotensin-mediated vasoconstriction of the efferent arteriole results in reductions in intraglomerular pressures, and while first abruptly lowering GFR in some, results in long-term improvement in kidney outcomes.2 The sodium-glucose cotransporter-2 (SGLT2) inhibitors have also been shown to improve intraglomerular pressures, partially mediated through tubuloglomerular feedback and vasoconstriction of the afferent arterioles.3
- In the post-hoc analysis of the DAPA-HF trial, average eGFR dips, and association of dichotomized dips (>10% decline in eGFR) in the placebo and dapagliflozin arms with the clinical outcomes were examined.4 As shown repeatedly in the literature, in patients with HFrEF, acute declines in eGFR, whether due to RAAS antagonists, aggressive decongestion, and now due to SGLT2i, the “treatment-induced declines” in eGFR are well-tolerated, and often are associated with better outcomes.5
- What is remarkable in this analysis of the DAPA-HF trial is that those that had > 10% decrease in eGFR (38% of dapa-treated), >20% decrease (13% of dapa-treated), and > 25% decrease (7% in dapa-treated), changes that in clinical practice may cause clinicians to react with panic and potentially discontinue the SGLT2i due to “hypercreatinemia-phobia”, was associated with 18-39% reduction in risk in the primary outcome. While mechanisms to explain why this profound protection would occur with lowering of GFR (e.g., improvements in metabolic demand, oxygenation of kidney tissue, mitochondrial function), it serves as yet another example to practice a “zen-like” approach to medicine and allow permissive hypercreatinemia prevail in treatment of this high-risk patients to allow for improved clinical outcomes.6

- https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.048057
- lick here for more information.

- ×
- HomeCirculationVol. 142, No. 11Sodium-Glucose Cotransporter-2 Inhibitors and Loop Diuretics for Heart Failure
- Sodium-Glucose Cotransporter-2 Inhibitors and Loop Diuretics for Heart Failure
- Priming the Natriuretic and Metabolic Reserve of the Kidney
- Justin L. Grodin and W.H. Wilson Tang
- Originally published14 Sep 2020https://doi.org/10.1161/CIRCULATIONAHA.120.048057Circulation. 2020;142:1055–1058