SGLT-2 inhibitors in DM type 2

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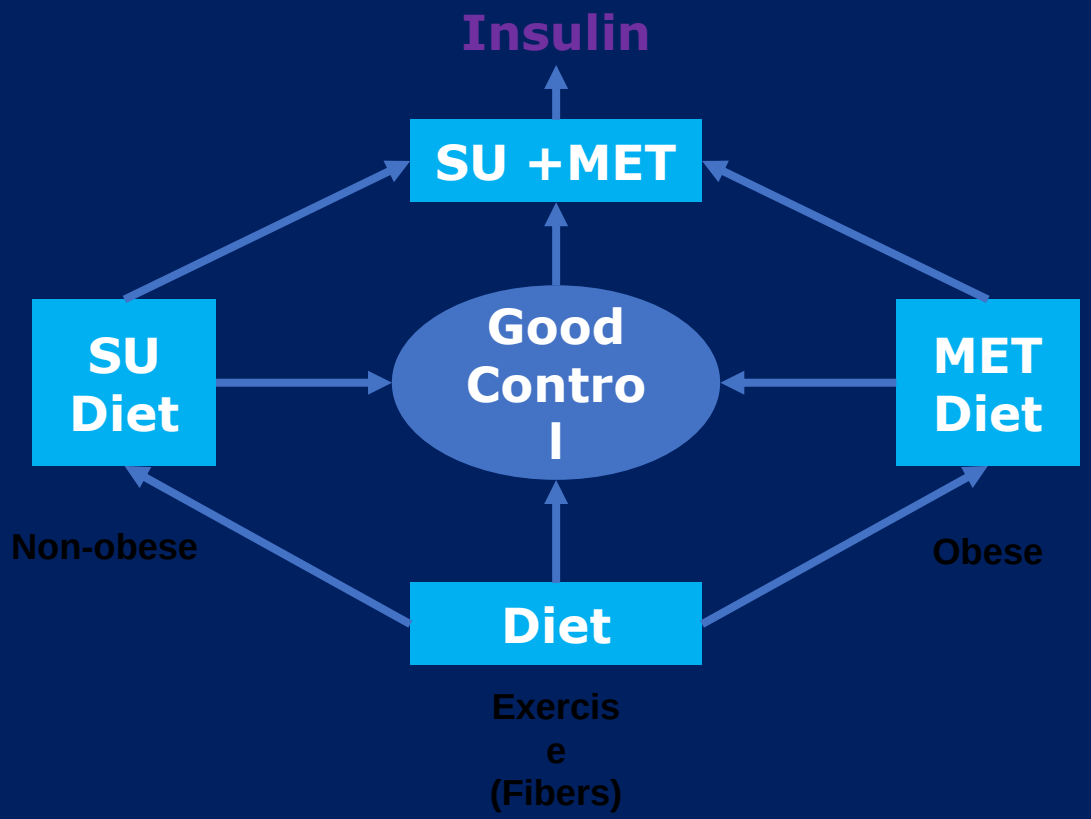
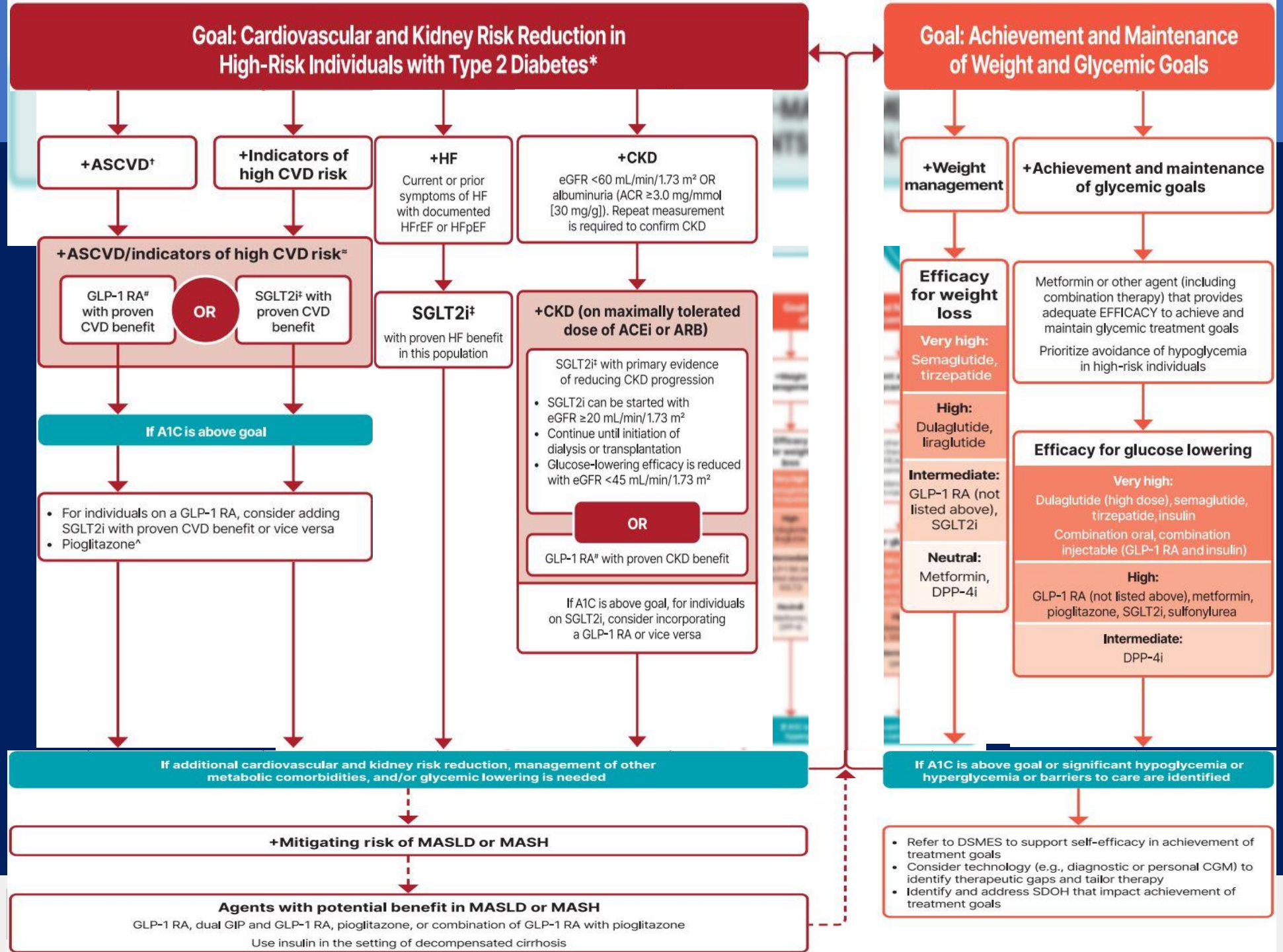
Nov 2025

Agenda

- ***Introduction***
- EFFECT ON GLYCEMIC CONTROL
- EFFECT ON CARDIOVASCULAR OUTCOMES
- EFFECT ON RENAL OUTCOMES
- EFFECT ON Metabolic OUTCOMES
- ADVERSE EFFECTS



Leif S. Hermann. *Diabetes Care* 1990; 13(Suppl. 3):S37-S41. doi: 10.2337/diacare.13.3.37.


Goal: Cardiovascular and Kidney Risk Reduction in High-Risk Individuals with Type 2 Diabetes*
+ASCVD†
+Indicators of high CVD risk
+HF
Current or prior symptoms of HF with documented HFrEF or HFpEF
+CKD
eGFR <60 mL/min/1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). Repeat measurement is required to confirm CKD
+ASCVD/indicators of high CVD risk≈
GLP-1 RA# with proven CVD benefit
OR
SGLT2i‡ with proven CVD benefit
SGLT2i‡
with proven HF benefit in this population
+CKD (on maximally tolerated dose of ACEi or ARB)
SGLT2i‡ with primary evidence of reducing CKD progression
SGLT2i can be started with eGFR ≥20 mL/min/1.73 m²
Continue until initiation of dialysis or transplantation
Glucose-lowering efficacy is reduced with eGFR <45 mL/min/1.73 m²
OR
GLP-1 RA# with proven CKD benefit
If A1C is above goal
For individuals on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
Pioglitazone^
If A1C is above goal, for individuals on SGLT2i, consider incorporating a GLP-1 RA or vice versa
Goal: Achievement and Maintenance of Weight and Glycemic Goals
+Weight management
+Achievement and maintenance of glycemic goals
Efficacy for weight loss
Very high:
Semaglutide, tirzepatide
High:
Dulaglutide, liraglutide
Intermediate:
GLP-1 RA (not listed above), SGLT2i
Neutral:
Metformin, DPP-4i
Metformin or other agent (including combination therapy) that provides adequate EFFICACY to achieve and maintain glycemic treatment goals
Prioritize avoidance of hypoglycemia in high-risk individuals
Efficacy for glucose lowering
Very high:
Dulaglutide (high dose), semaglutide, tirzepatide, insulin
Combination oral, combination injectable (GLP-1 RA and insulin)
High:
GLP-1 RA (not listed above), metformin, pioglitazone, SGLT2i, sulfonylurea
Intermediate:
DPP-4i
If additional cardiovascular and kidney risk reduction, management of other metabolic comorbidities, and/or glycemic lowering is needed
+Mitigating risk of MASLD or MASH
Agents with potential benefit in MASLD or MASH
GLP-1 RA, dual GIP and GLP-1 RA, pioglitazone, or combination of GLP-1 RA with pioglitazone
Use insulin in the setting of decompensated cirrhosis
If A1C is above goal or significant hypoglycemia or hyperglycemia or barriers to care are identified
Refer to DSMES to support self-efficacy in achievement of treatment goals
Consider technology (e.g., diagnostic or personal CGM) to identify therapeutic gaps and tailor therapy
Identify and address SDOH that impact achievement of treatment goals

- Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are an exceptionally versatile class of medication, and their glycemic and nonglycemic benefits could help millions of patients with type 2 DM

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- They improve cardiac and renal outcomes much needed benefits in patients with type 2 DM, who are at a higher risk for developing cardiac and renal dysfunction than those who do not have DM

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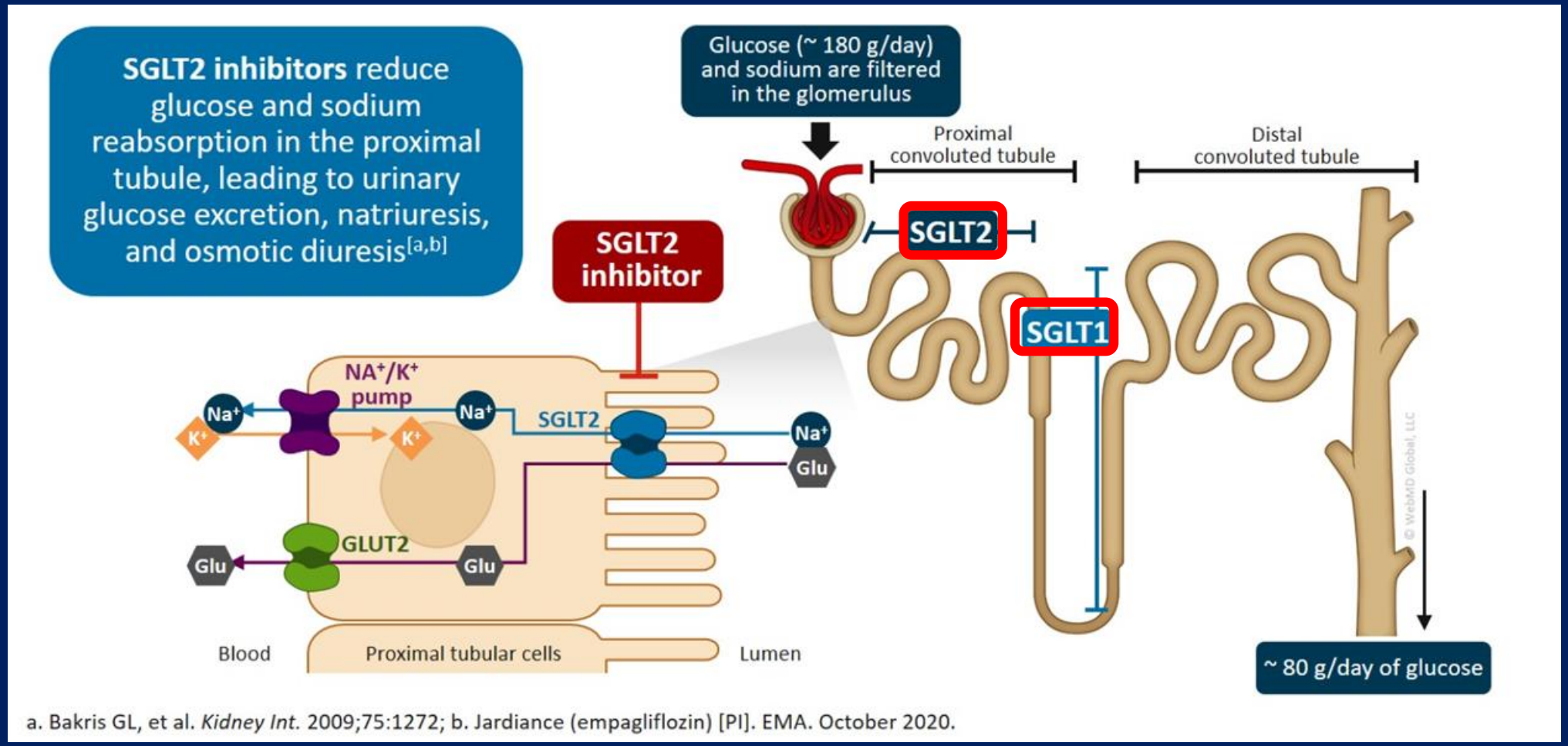
- **SGLT-1** is located in the distal segment of the proximal tubule and reabsorbs approximately **10%** of the glucose

- **SGLT-2** is located in the proximal portion of the proximal tubule and reabsorbs about **90%**

- Drugs that inhibit SGLT-2 promote glycosuria in exchange for lower plasma glucose

- An advantage of these drugs is that their mechanism of action is:

  independent of insulin secretion, beta-cell function, and insulin resistance



a. Bakris GL, et al. *Kidney Int.* 2009;75:1272; b. Jardiance (empagliflozin) [PI]. EMA. October 2020.

SGLT2 inhibitor	FDA approval	Indications	Dose
(canagliflozin)	2013	Type 2 diabetes	100 – 300 mg daily
(dapagliflozin)	2014	Type 2 diabetes	*Type 2 diabetes:* 5 – 10 mg daily *Heart failure:* 10 mg daily
(empagliflozin)	2014	Type 2 diabetes	10 – 25 mg daily
(ertugliflozin)	2017	Type 2 diabetes	5 – 15 mg daily

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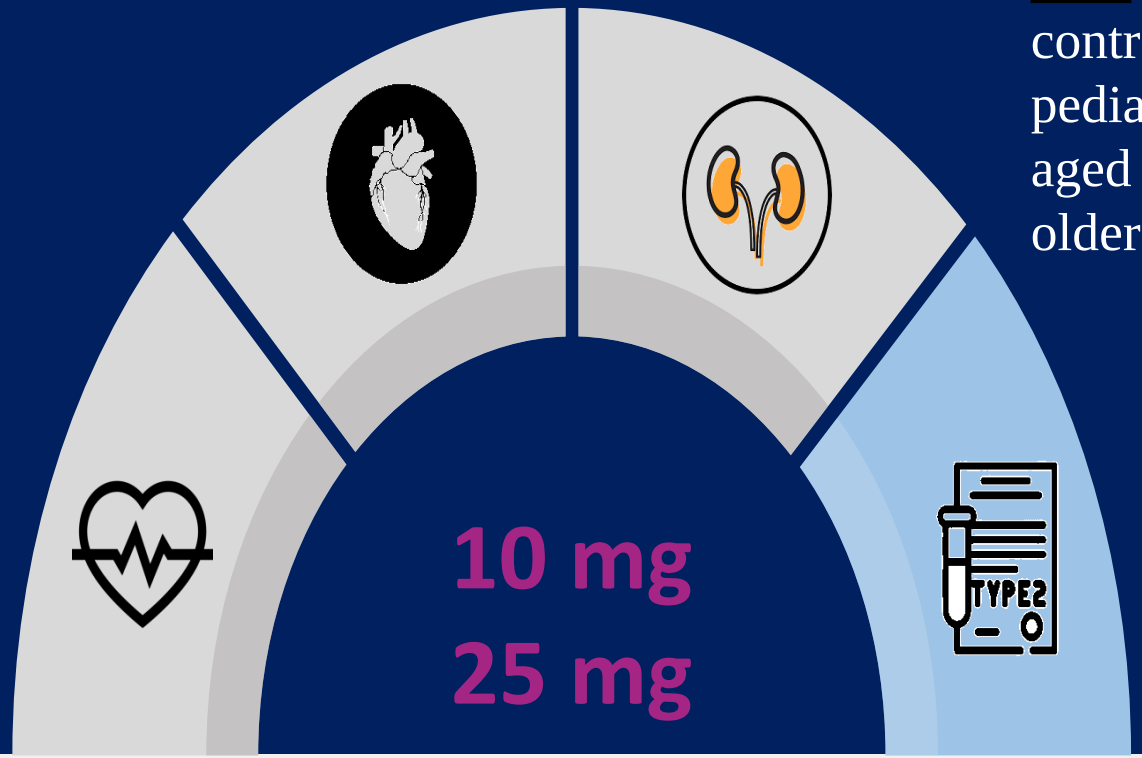
Indications and Recommended Dosage of Empagliflozin[1]

- 10 mg orally once daily in the morning,
- For additional glycemic control, may increase to 25 mg orally once daily in patients tolerating 10 mg once daily



Type 2 DM

To improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 DM

Absolute change in hemoglobin A_{1c} with SGLT-2 inhibitor monotherapy compared with placebo

Empagliflozin[a]		Canagliflozin[b]		Dapagliflozin[c]		Ertugloflozin[d]	
Low dose	High dose	Low dose	High dose	Low dose	High dose	Low dose	High dose
–0.74%	–0.85%	–0.90%	–1.20%	–0.54%	–0.60%	–0.50%	–0.50%

[a] Empagliflozin low dose = 10 mg, high dose = 25 mg.[6]
[b] Canagliflozin low dose = 100 mg, high dose = 300 mg.[5]
[c] Dapagliflozin low dose = 5 mg, high dose = 10 mg.[7]
[d] Ertugloflozin low dose = 5 mg, high dose = 15 mg.[8]

SGLT-2 inhibitors lower glucose independently of insulin, so hypoglycemia is rare

using as monotherapy or in conjunction with noninsulin secretagogue oral agents

Using insulin or insulin secretagogues increase the incidence of hypoglycemia

- Reducing the basal insulin dose by 20% if the FBS is<106 mg/dL and reducing it by 10% if FBS is between 106 - 145 mg/dL

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- For patients using both insulin and an insulin secretagogue, consider reducing the dose of insulin secretagogue or discontinuing it altogether, particularly if BS is <106 mg/dL before starting the SGLT-2 inhibitor

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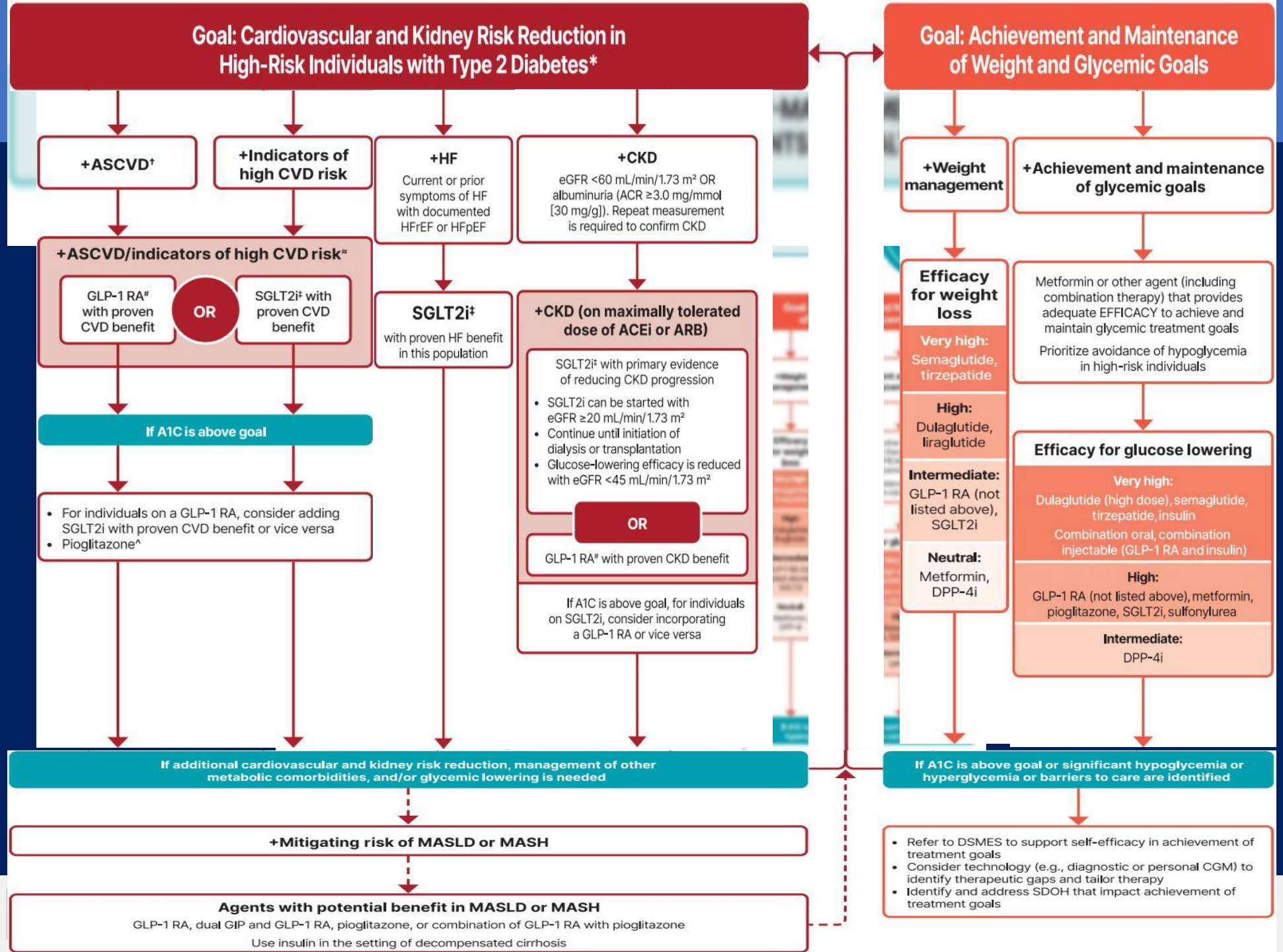
Empagliflozin FDA Label

Highlights of Dosage and Administration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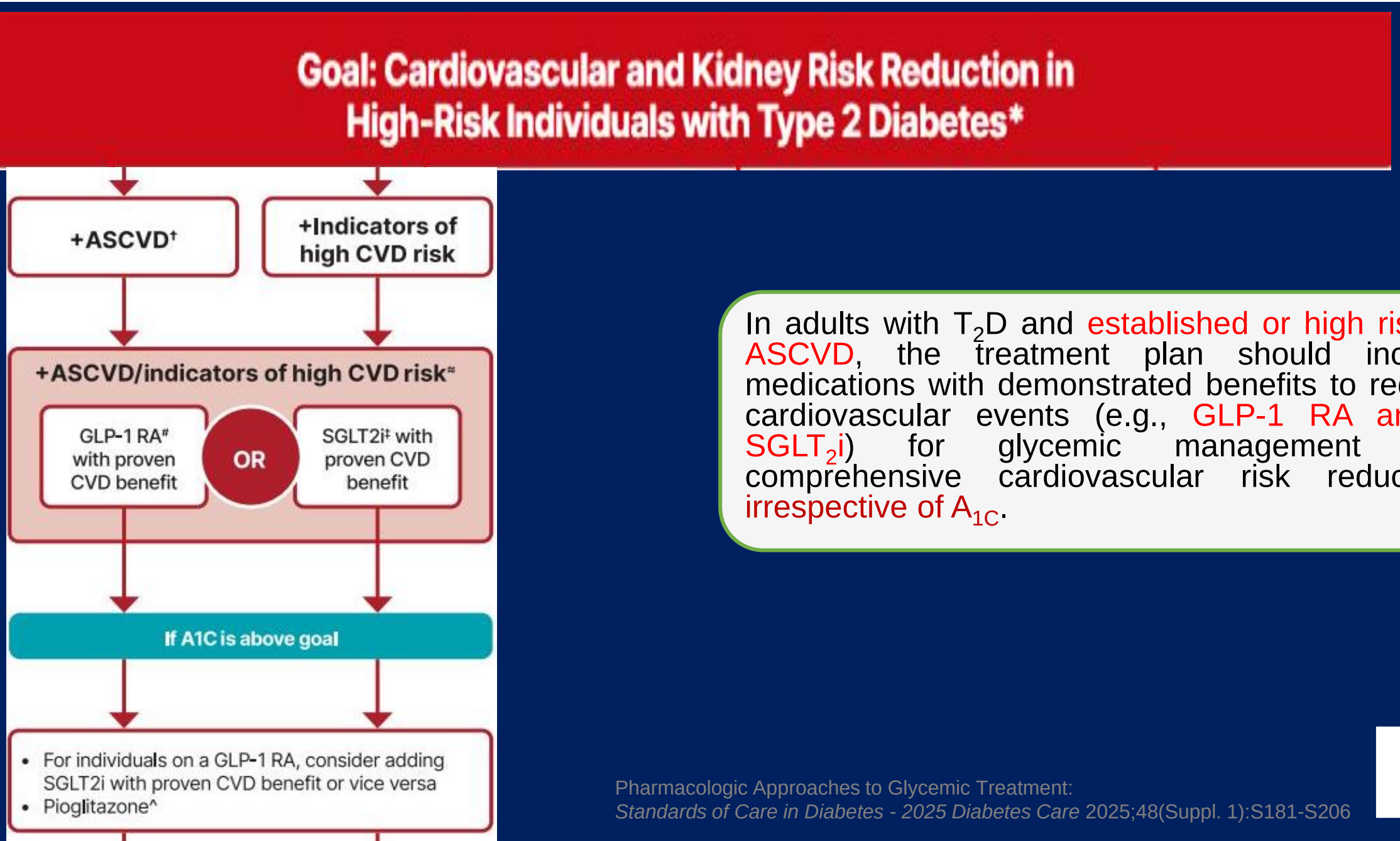
Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes

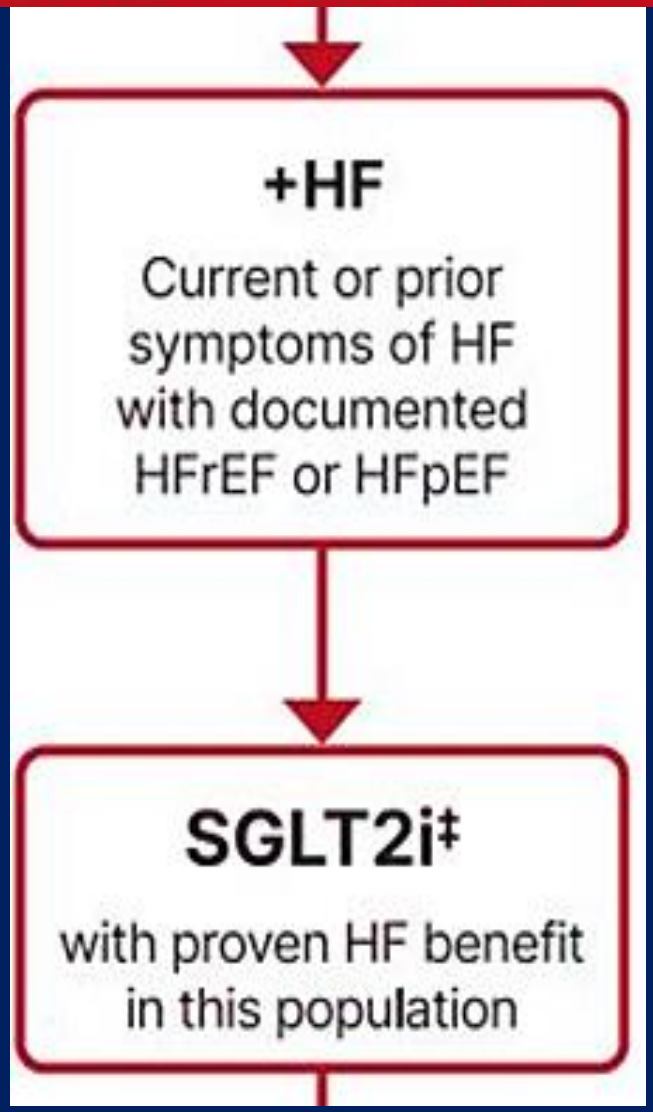


In adults with T_2D and established or high risk of ASCVD, the treatment plan should include medications with demonstrated benefits to reduce cardiovascular events (e.g., GLP-1 RA and/or $SGLT_2i$) for glycemic management and comprehensive cardiovascular risk reduction, irrespective of A_{1C}.

Pharmacologic Approaches to Glycemic Treatment:
Standards of Care in Diabetes - 2025 Diabetes Care 2025;48(Suppl. 1):S181-S206

Goal: Cardiovascular and Kidney Risk Reduction in High-Risk Individuals with Type 2 Diabetes*

In adults with T_2D who have HF, with either reduced or preserved EF, an $SGLT_2i$ is recommended for both glycemic management and prevention of HF hospitalizations, irrespective of A_{1C}.



In adults with T_2D and symptomatic HFpEF and obesity, a GLP-1 RA with demonstrated benefits for both glycemic management and reduction of HF-related symptoms is recommended, irrespective of A_{1C}.

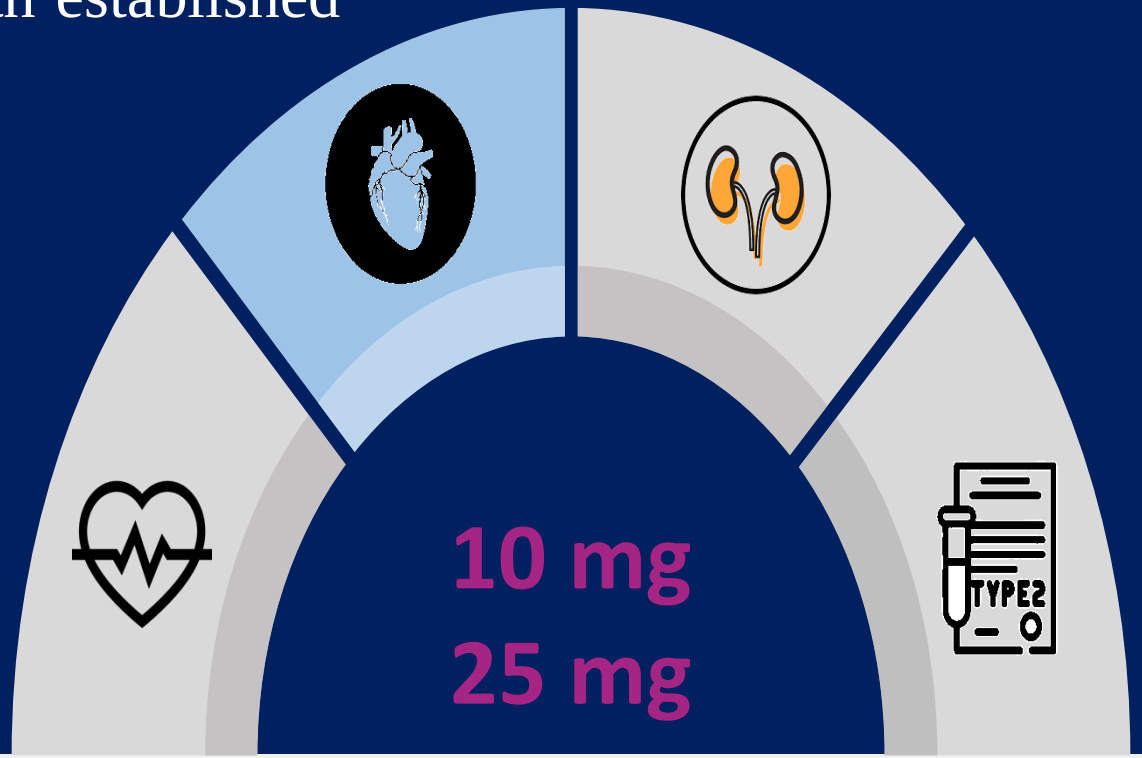
Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes - 2025 Diabetes Care* 2025;48(Suppl. 1):S181-S206

Indications and Recommended Dosage of Empagliflozin[1]

T2 DM and established CVD

To reduce the risk of CV death in patients with T2 DM with established CV disease

10 mg orally once daily



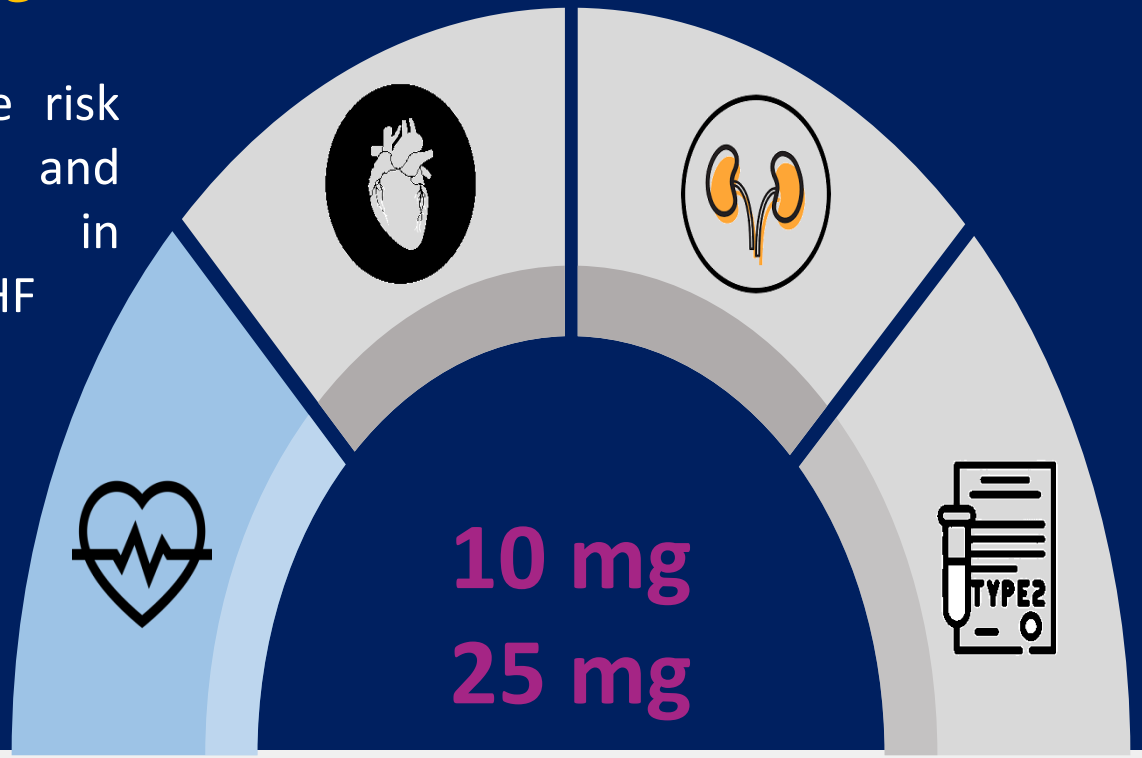
T2DM, Type 2 diabetes mellitus; CVD, Cardiovascular disease

Indications and Recommended Dosage of Empagliflozin[1]

10 mg orally once daily in the morning, taken with or without food

Heart Failure

To reduce the risk of CV death and hospitalization in patients with HF



Effect on cardiovascular outcomes

- One-third of patients with type 2 DM have CVD
- 20% have coronary artery disease
- 15% have heart failure
- Those with type 2 DM who develop heart failure have a 9 to 12 times greater mortality risk than those who do not

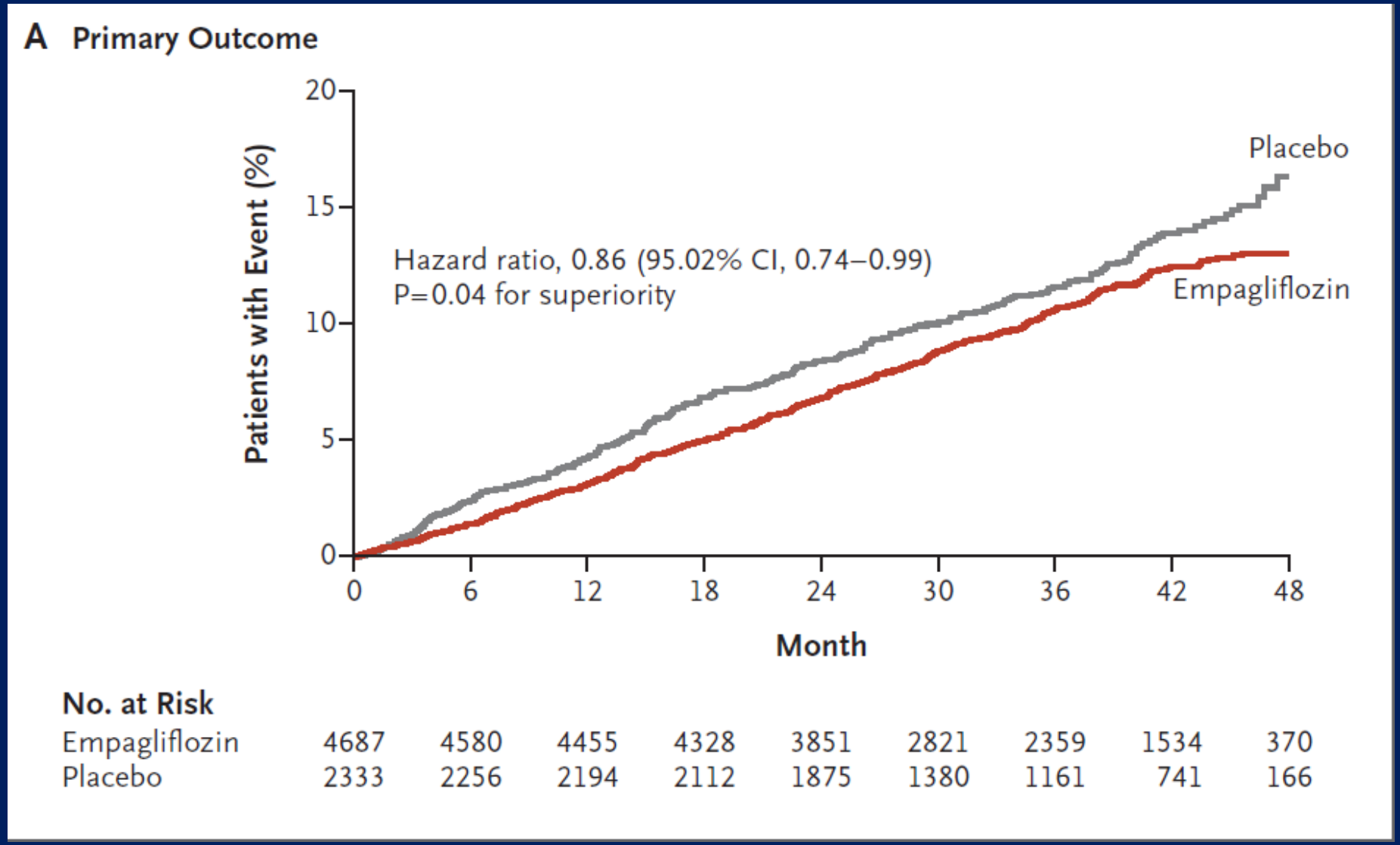
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

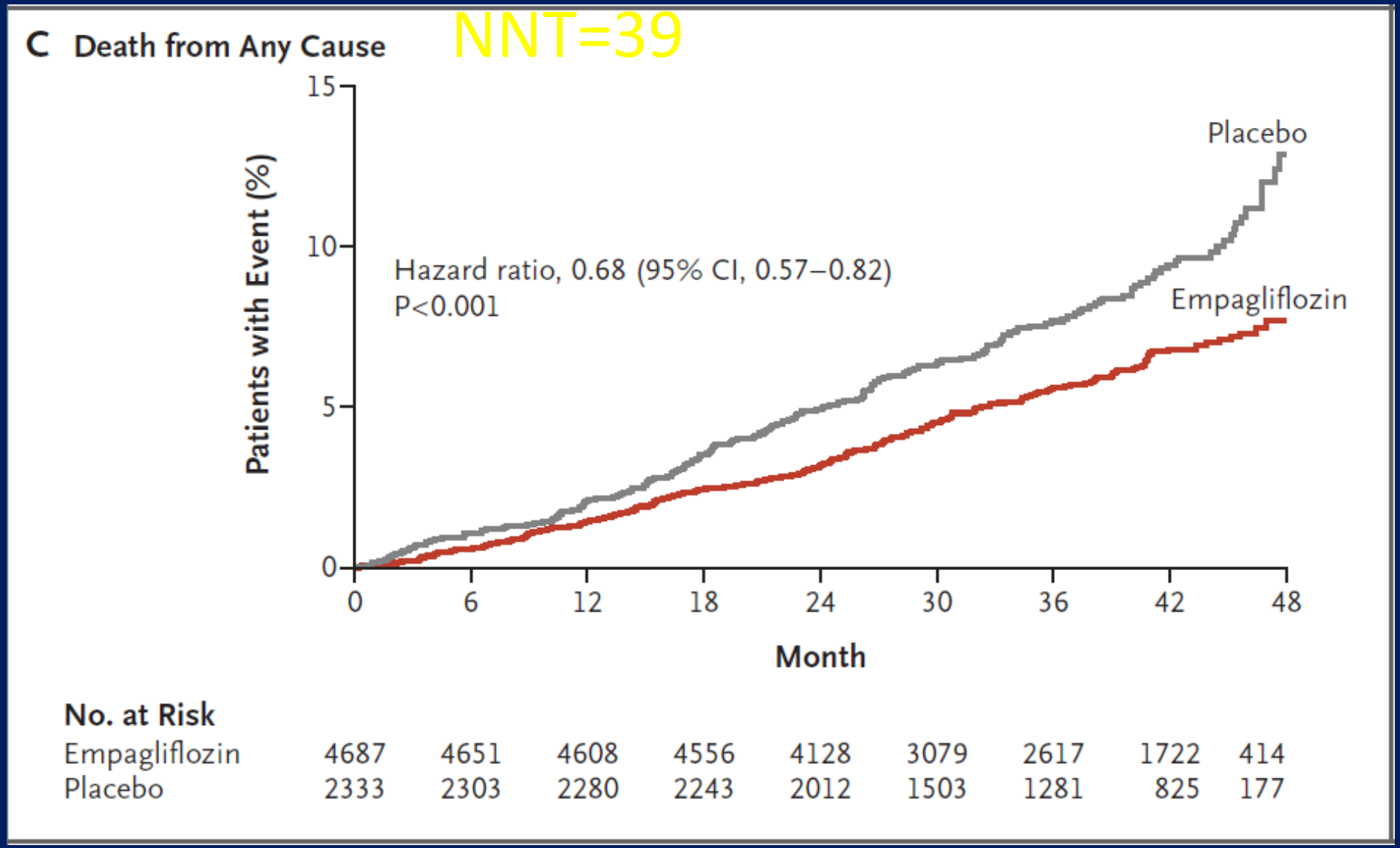
- Randomized, double-blind, placebo-controlled trial
- Intervention : Empagliflozin (at a dose of 10 or 25 mg) versus placebo
- Sample size: 7020
- Median F/U: 3.1 years
- Outcome : A composite of death from CV causes, nonfatal MI (excluding silent MI), or nonfatal stroke.

2015 Nov 26;373(22):2117-28

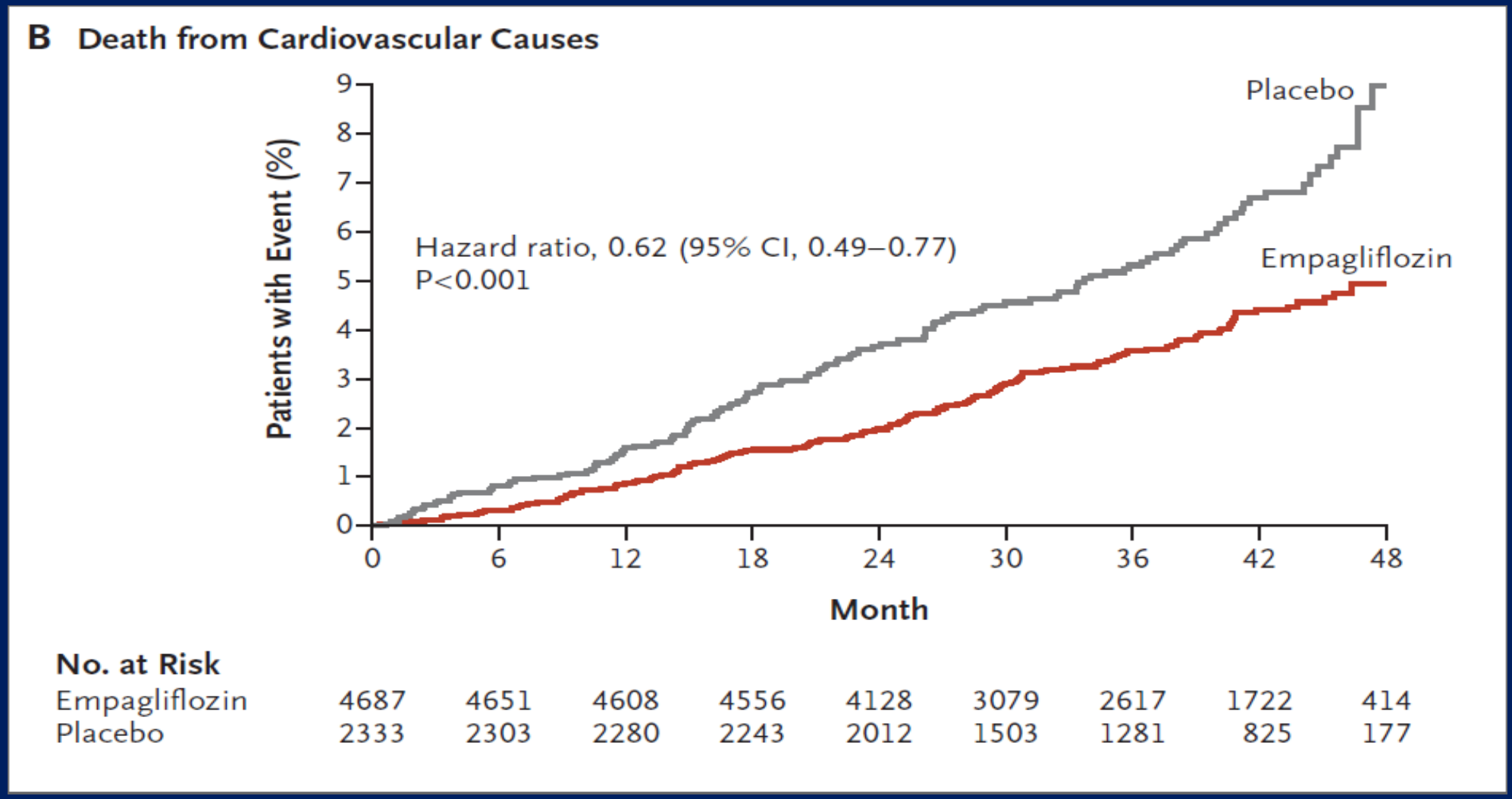
Primary outcome



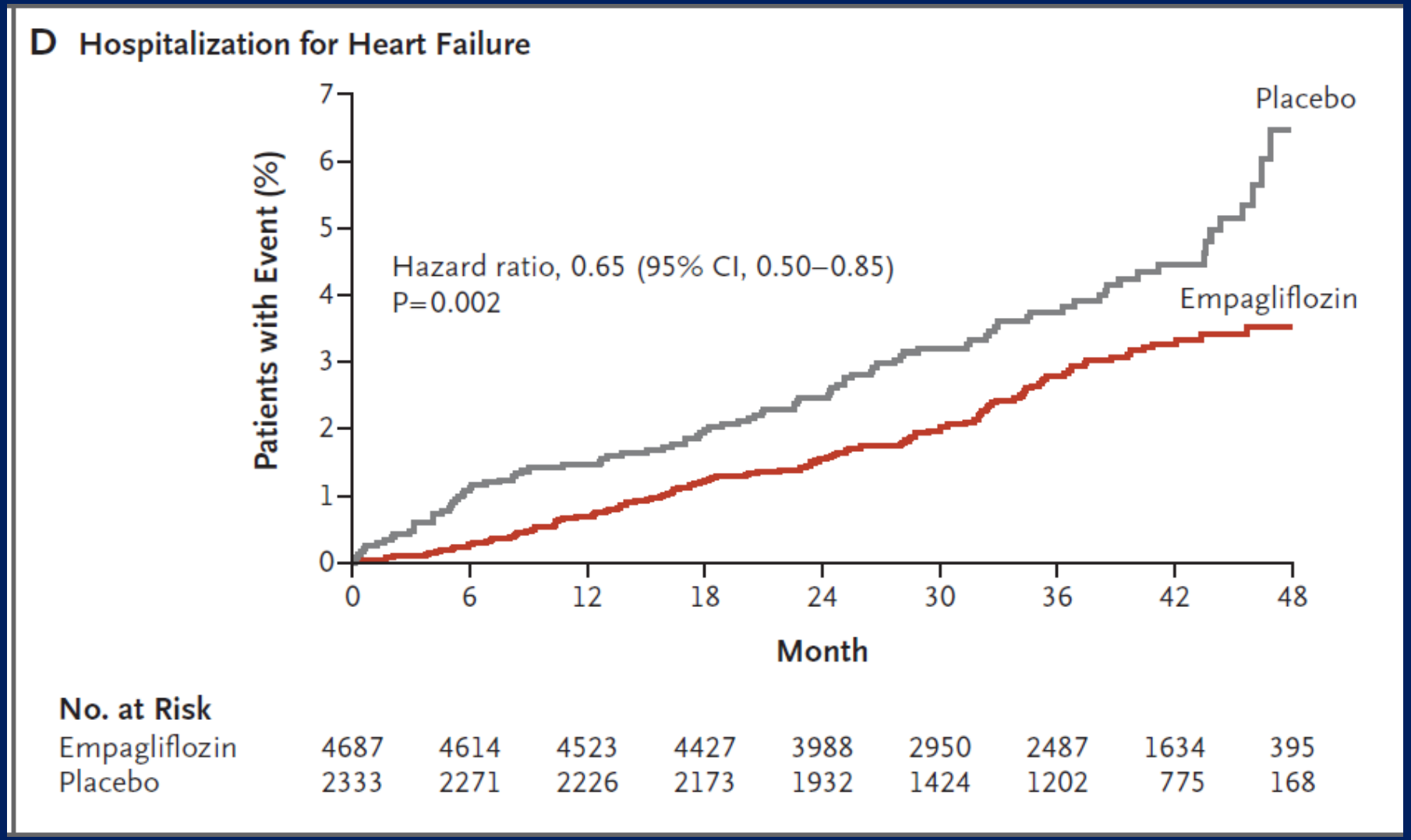
All cause mortality



Cardiovascular Death



Hospitalization for HF



Cardiovascular outcomes in 4 major trials of SGLT-2 inhibitors

	EMPA-REG OUTCOME[21]	CANVAS[22]	DECLARE-TIMI 58[23]	VERTIS-CV[24]
Population	Type 2 diabetes + cardiovascular disease	Type 2 diabetes + cardiovascular disease or multiple risk factors for it	Type 2 diabetes + cardiovascular disease or multiple risk factors for it	Type 2 diabetes + cardiovascular disease
Number of patients	7,020	10,142	17,160	8,246
History of cardiovascular disease	99%	65.6%	40.6%	100%
History of heart failure	10.1%	14.4%	10.2%	23.7%
Outcomes with SGLT-2 inhibitor				
MACE (relative risk reduction)	14%	14%	Not significant	Not significant
MACE (number needed to treat)	63	217	Not available	Not available
Cardiovascular death (relative risk reduction)	38%	Not significant	Not significant	Not significant
Hospitalization for heart failure (relative risk reduction)	35%	33%	27%	30%
Hospitalization for heart failure (number needed to treat)	71	312	125	91

CANVAS = Canagliflozin Cardiovascular Assessment Study; DECLARE-TIMI 58 = Dapagliflozin Effect on Cardiovascular Events; EMPA-REG OUTCOME = Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; MACE = major atherosclerotic cardiovascular events; VERTIS CV = Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes

- SGLT-2 inhibitors' effect on MACE appears to be confined to patients with established ASCVD

- Their effect on reducing hospitalizations for HF appears to be independent of established ASCVD, risk factors, or history of HF

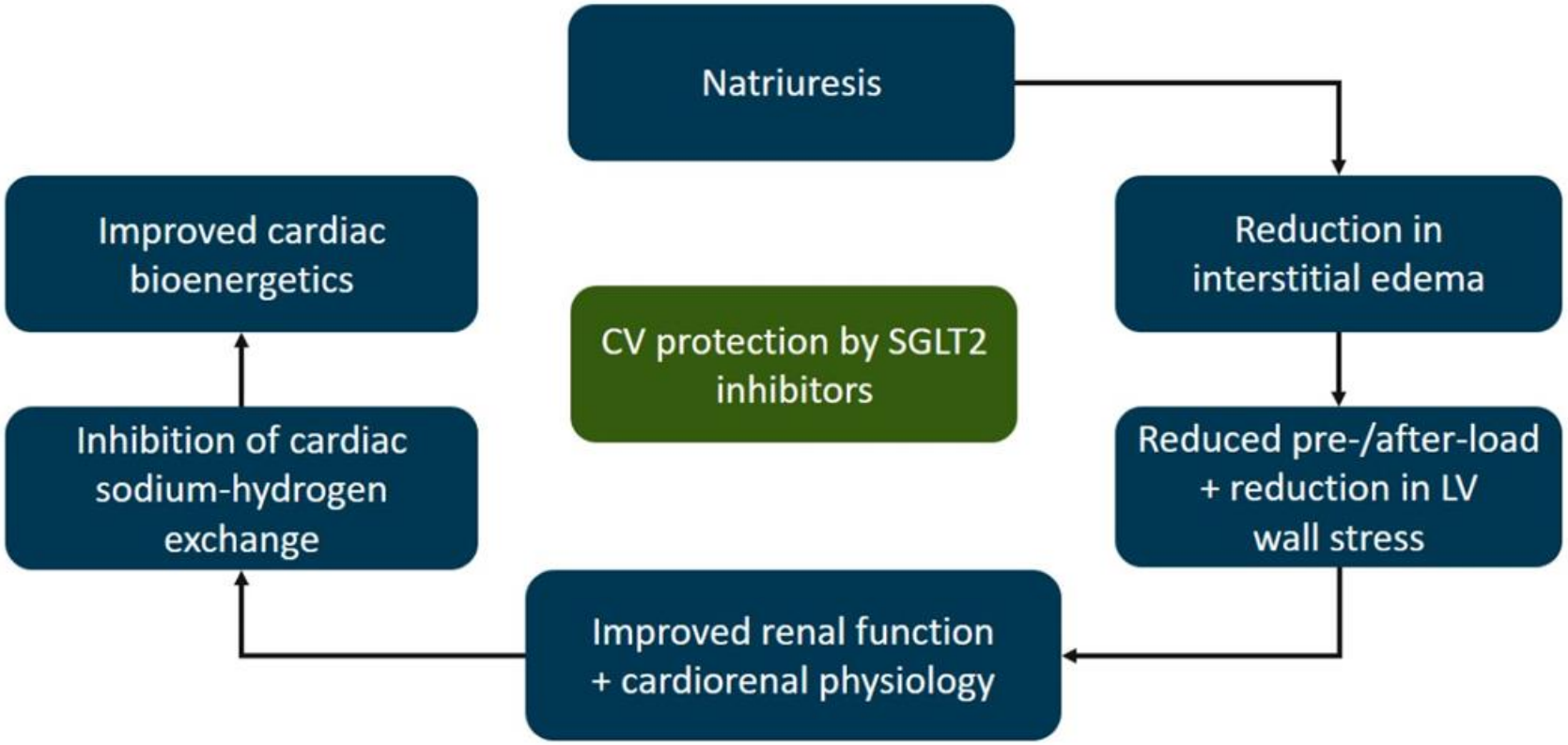
POSSIBLE MECHANISMS OF CARDIOVASCULAR BENEFIT

- ***Osmotic diuresis:*** By increasing glycosuria and natriuresis, increase urine output , so decrease plasma volume and ventricular preload

- ***Inhibition of the sodium-hydrogen exchanger*** **:** Cytosolic sodium concentration and sodium-hydrogen exchanger activity are both increased in the myocytes in DM and HF, and sodium-hydrogen exchanger inhibition has been shown to reduce hypertrophy in HF

- ***Inhibition of fibrosis:*** empagliflozin suppressed gene expression of key profibrotic markers such as type I collagen and connective tissue growth factor. This inhibition may lead to protection from cardiac fibrosis independent of glycemic status

CV Protection by SGLT2 Inhibitors



Farkouh ME, et al. *J Am Coll Cardiol.* 2018;71:2507-2510.

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Empagliflozin FDA Label

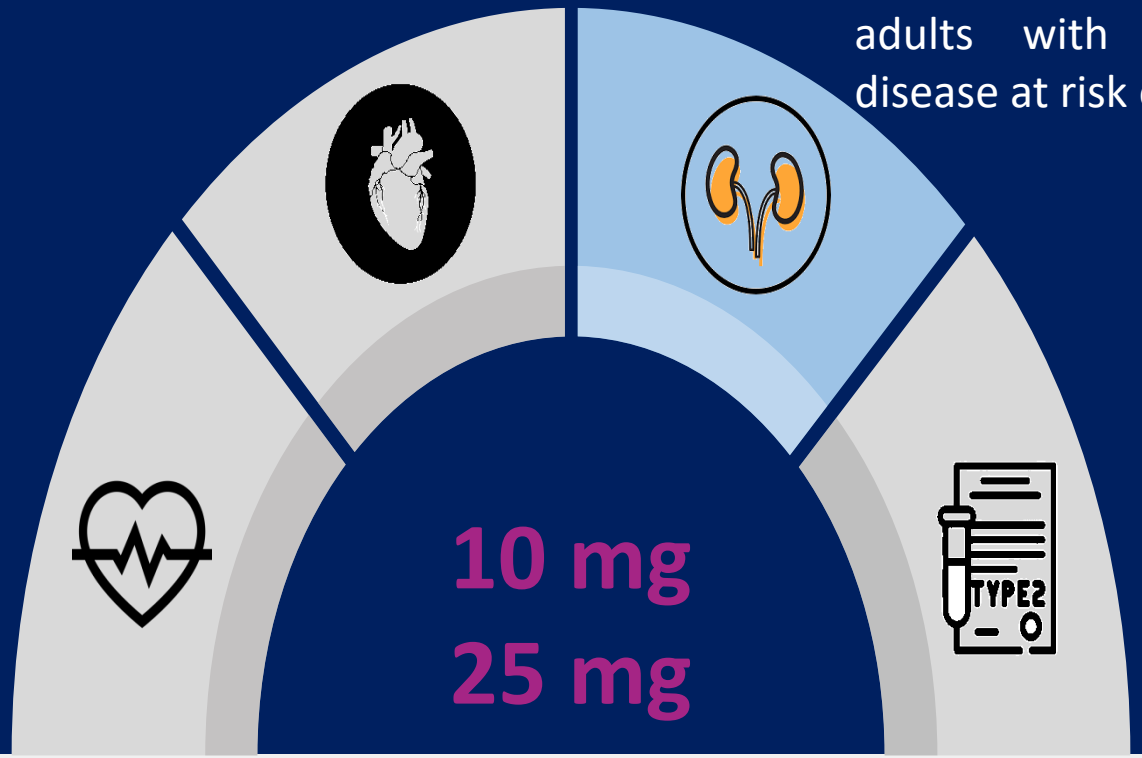
Highlights of Dosage and Administration

Indications and Recommended Dosage of Empagliflozin[1]

Chronic Kidney Disease

To reduce the risk of **sustained decline in eGFR**, end-stage kidney disease, **cardiovascular death**, and **hospitalization** in adults with chronic kidney disease at risk of progression

10 mg orally once daily

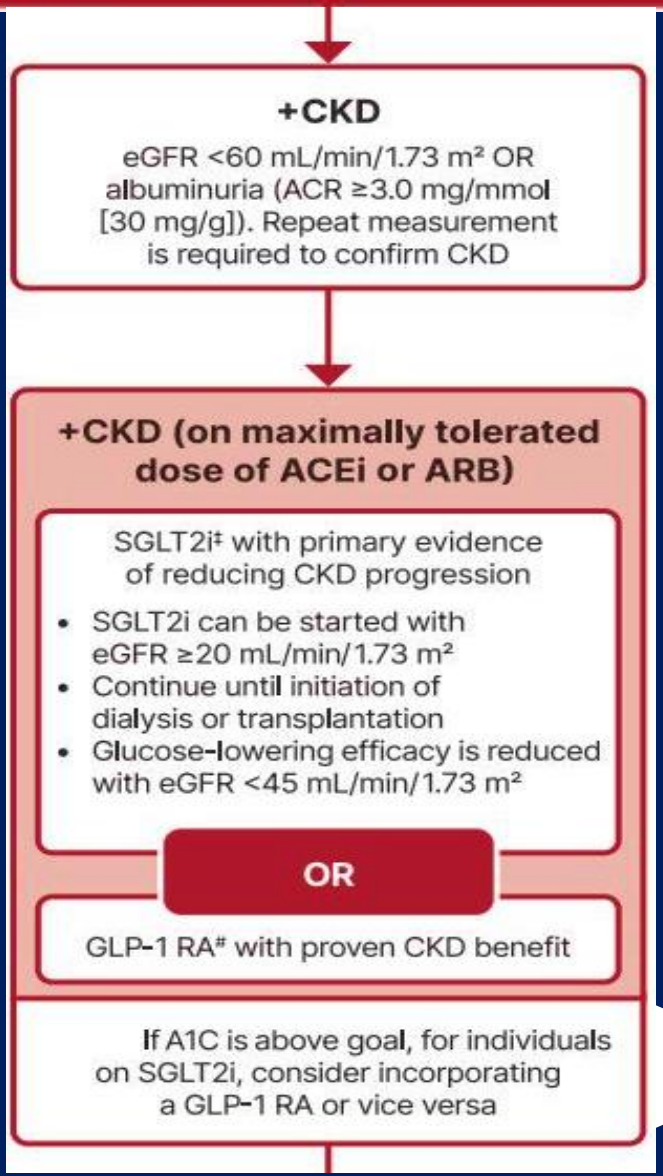


eGFR, estimated glomerular filtration rate.

Goal: Cardiovascular and Kidney Risk Reduction in High-Risk Individuals with Type 2 Diabetes*

In adults with T_2D who have CKD (eGFR 20–60 mL/min/1.73 m^2 and/or albuminuria), an $SGLT_2i$ or GLP-1 RA with demonstrated benefit in this population should be used for both glycemic management and for slowing progression of CKD and reduction in cardiovascular events.

In adults with T_2D and eGFR <30 mL/min/1.73 m^2, a GLP-1 RA is preferred for glycemic management due to lower risk of hypoglycemia and for cardiovascular event reduction. **B**



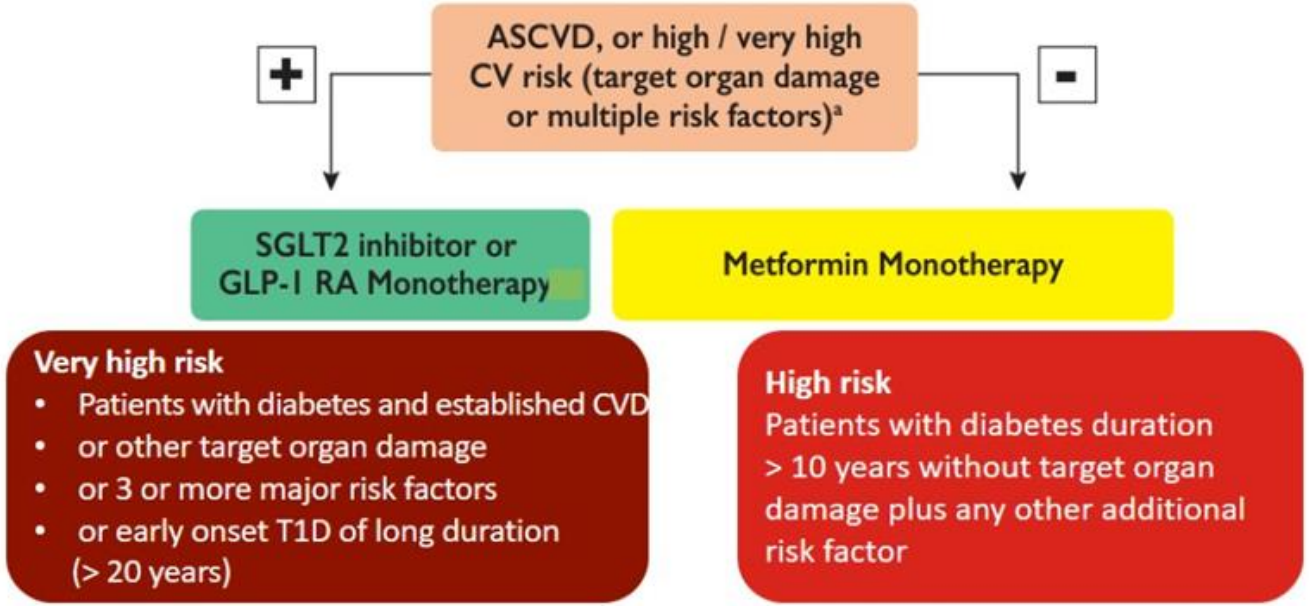
Pharmacologic Approaches to Glycemic Treatment:
Standards of Care in Diabetes - 2025 Diabetes Care 2025;48(Suppl. 1):S181-S206

First-Line Therapy in T2D in the ESC Guidelines

ESC Guidelines now suggest for glucose-lowering treatment:

- Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce CV events

A Type 2 DM - Drug naïve patients



Cosentino F, et al. *Eur Heart J* 2020;41:255

- SGLT-2 inhibitors inhibit uptake of glucose and sodium in the proximal tubule, leading to an increase in delivery of sodium to the distal tubule and juxtaglomerular apparatus

- Causing the vasoconstriction of afferent arteriole

- This afferent arteriolar constriction manifests as a transient reduction in eGFR of approximately 3 to 4 mL/min/1.73 m2 in the first few weeks of SGLT-2 therapy and a reductionin albuminuria.

Empagliflozin

Dosage and Administration[1]

- Assess renal function before initiating and as clinically indicated. Assess volume status and correct volume depletion before initiating.

- Recommended dosage is 10 mg orally once daily in the morning, taken with or without food.

- For additional glycemic control, dosage may be increased to 25 mg orally once daily in patients tolerating Empagliflozin.

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

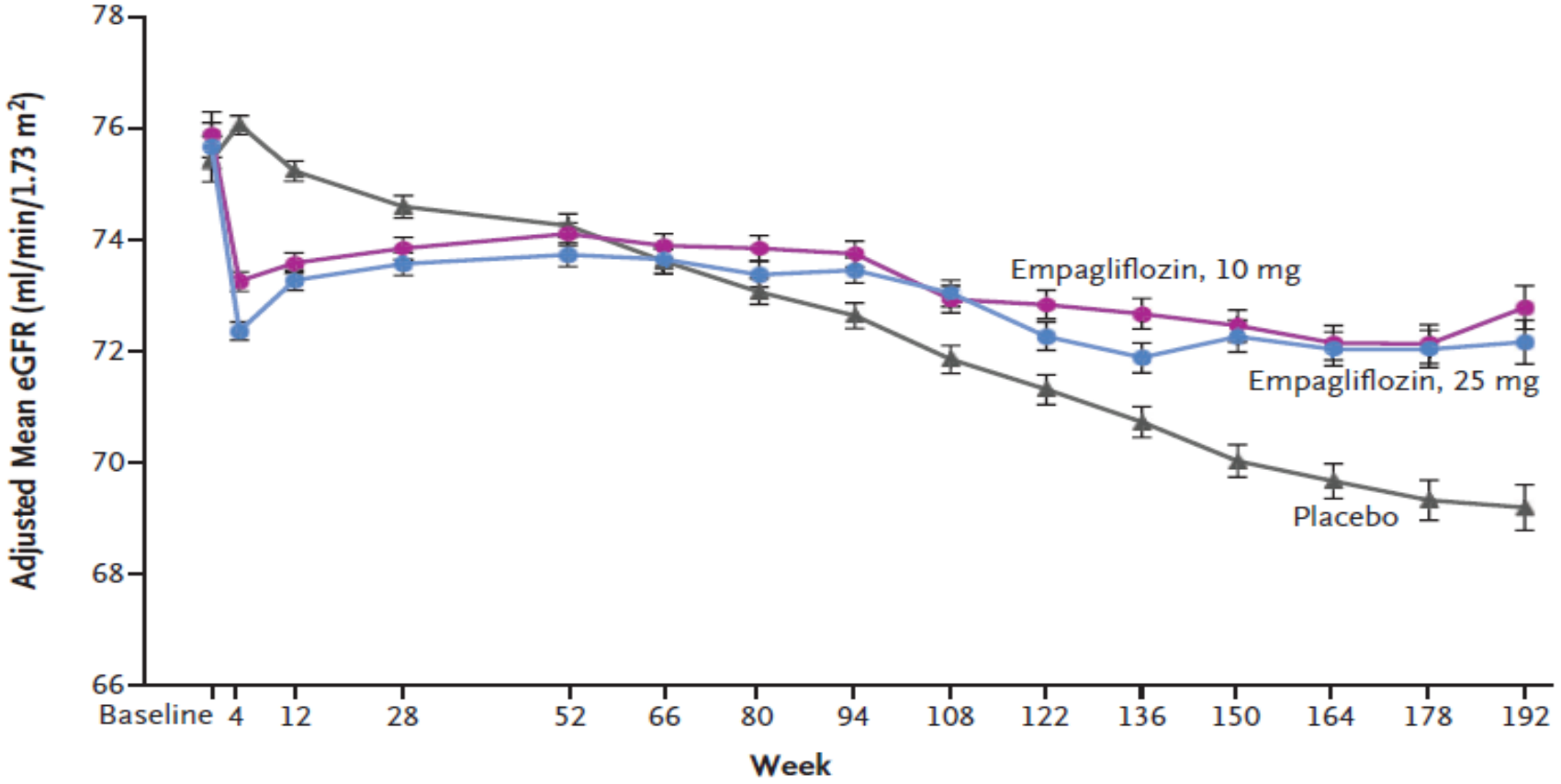
Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*

- Aim :To determine the long-term renal effects of empagliflozin, an analysis that was a prespecified component of the secondary microvascular outcome of that trial

- Prespecified renal outcomes : Incident or worsening nephropathy, defined as progression to macroalbuminuria (urinary albuminto- creatinine ratio >300 mg of albumin per gram of creatinine); a doubling of the serum creatinine level, accompanied by an eGFR of ≤45 ml/ min/ 1.73 m2; the initiation of renal-replacement therapy; or death from renal disease

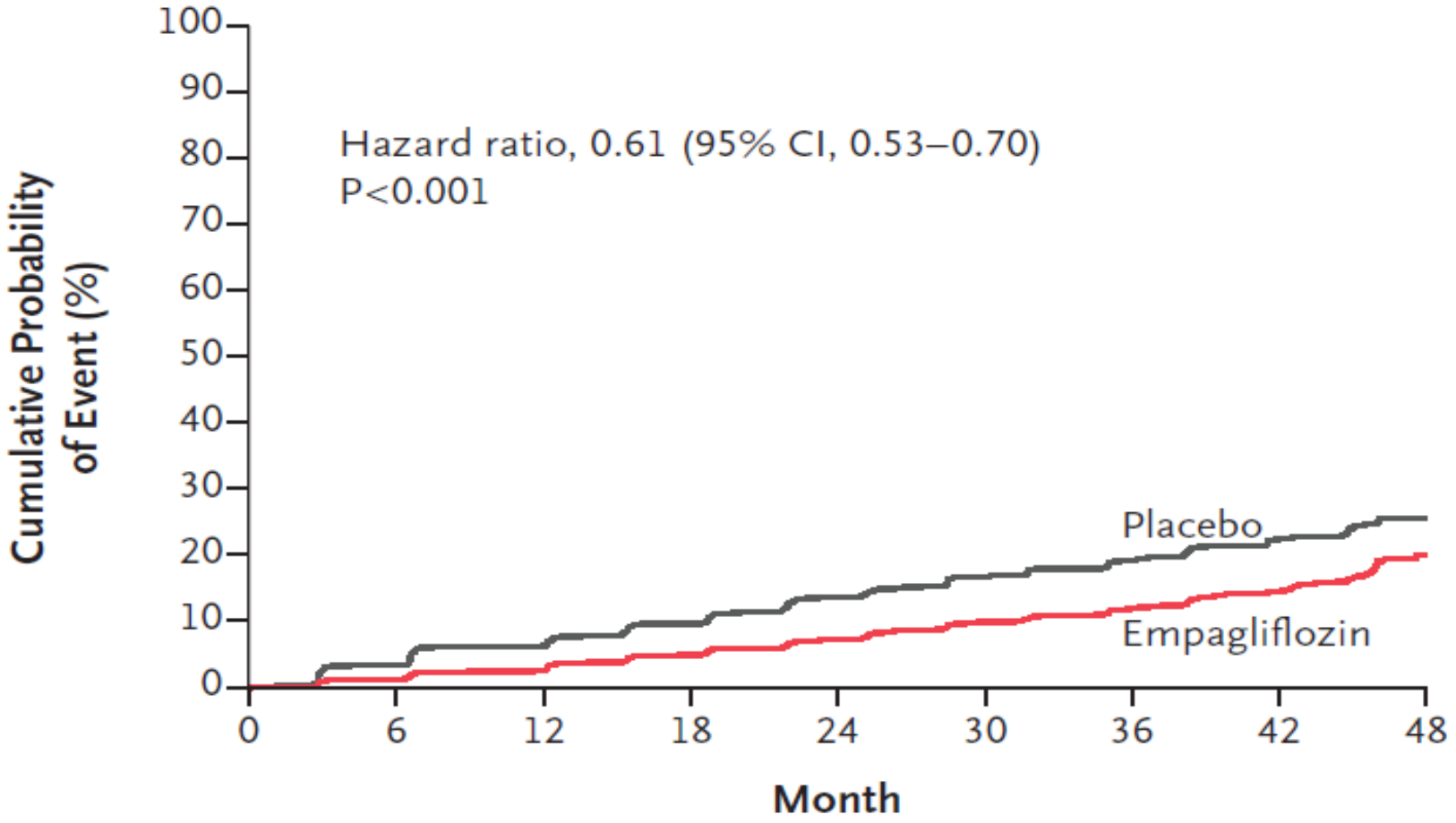
N Engl J Med 2016;375:323-34

A Change in eGFR over 192 Wk



No. at Risk															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin, 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin, 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in Follow-up Analysis															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703

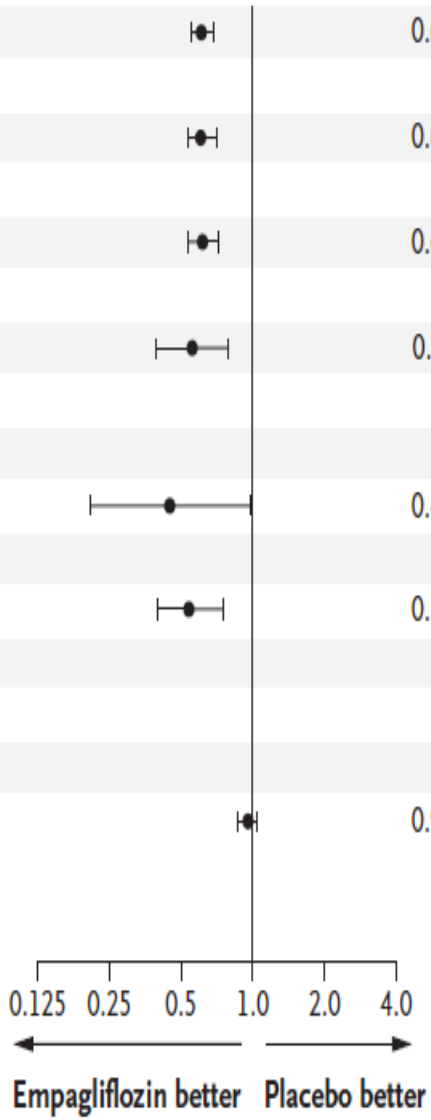
A Incident or Worsening Nephropathy



No. at Risk

Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

Renal Outcome Measure	Empagliflozin no. with event/ no. analyzed (%)	Empagliflozin rate/1000 patient-yr	Placebo no. with event/ no. analyzed (%)	Placebo rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25



Agenda

- Introduction
- EFFECT ON GLYCEMIC CONTROL
- EFFECT ON CARDIOVASCULAR OUTCOMES
- EFFECT ON RENAL OUTCOMES
- ***EFFECT ON Metabolic OUTCOMES***
- ADVERSE EFFECTS

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- Taking these drugs as monotherapy for 24 -26 weeks:

  weight loss was approximately 2.3 - 3.5 kg

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- SGLT-2 inhibitors have not been approved for use solely as weight-loss medications

STUDIES IN NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

- Empagliflozin, dapagliflozin, and canagliflozin have been shown to decrease ALT and improve steatosis and fibrosis along with reducing HbA1c and body weight

- Further randomized controlled trials are needed to evaluate the benefit of SGLT-2 inhibitors in NAFLD in patients with and without diabetes

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Euglycemic Diabetic ketoacidosis

- Ketoacidosis (pH < 7.3 or serum bicarbonate < 18mmol/L)
- Mild degree of hyperglycemia (11-14 mmol/L or 180-250 mg/dL)
- Occurs infrequently; so, the benefits of SGLT-2 inhibitors clearly outweigh the risk

How to Avoid Diabetic Ketoacidosis

- In 2020, the FDA approved a label change for all SGLT-2 inhibitors, recommending temporary discontinuation of the drug before scheduled surgery.

- Empagliflozin, canagliflozin, and dapagliflozin should be discontinued 3 days before scheduled surgery and ertugliflozin should be discontinued 4 days before.

- The drug can be reinitiated after surgery when oral intake has returned to baseline

Genital and urinary infections.

- As a class, SGLT-2 inhibitors increase the risk of genital infections.

- Urinary tract infections were generally not significantly increased as a class, but an increase in female urinary tract infections was seen with empagliflozin

Fournier gangrene

- In a postmarketing analysis based on the FDA adverse event reporting system SGLT-2 inhibitors were associated with an increased risk of Fournier gangrene:

- 55 cases of fournier gangrene were identified from 2013 -2019; 21 cases were attributed to canagliflozin, 16 to dapagliflozin, and 18 to empagliflozin

- Due to the severe and fatal nature of this infection, it is crucial to have a high index of suspicion for it in order to detect these cases in the early stages.

Fractures, amputations with canagliflozin

- In the CANVAS trial : the hazard ratio for the risk of fractures with canagliflozin was 1.26 (95% CI 1.04–1.52),and the hazard ratio for the risk of amputations was 1.97 (95% CI 1.41–2.75)

- In the CREDENCE trial: the hazard ratios for these 2events were not significant

- The increased risk for fractures and amputations has not been seen in RCT of empagliflozin , dapagliflozin, and ertugliflozin

Risks and benefits of SGLT-2 inhibitors

	Benefits					Risks	
	Hemoglobin A_{1c}	Weight and blood pressure	Heart failure hospitalizations	Cardiovascular events	Progression of renal disease	Fracture, amputation	Genital infection
Empagliflozin	Decrease	Decrease	Decrease	Decrease	Decrease	No change	Increase
Canagliflozin	Decrease	Decrease	Decrease	No change	Decrease	No change[a]	Increase
Dapagliflozin	Decrease	Decrease	Decrease	No change	Decrease	No change	Increase
Ertugliflozin	Decrease	Decrease	Decrease	No change	No change	No change	Increase

[a]Changed from "increases risk" to "no change" after the removal of the black box warning by the US Food and Drug Administration.

Empagliflozin

- Not recommended for use to improve glycemic control in patients with type 1 DM
  It may increase the risk of diabetic ketoacidosis in these patients.

- Not recommended for use to improve glycemic control in patients with type 2 DM with an eGFR less than 20 mL/min/1.73 m2.

- Not recommended for the treatment of CKD in patients with polycystic kidney disease or patients requiring or with a recent history of intravenous immunosuppressive therapy or greater than 45 mg of prednisone or equivalent for kidney disease. Empagliflozin is not expected to be effective in these populations.

Conclusion

- SGLT-2 inhibitors improve glycemic control, reduce hospitalizations for HF , and slow the progression of renal disease
- Consider an SGLT-2 inhibitor as first in patients with type 2 DM with CVD or renal disease, or both, regardless of glycemic control
- Consider an SGLT-2 inhibitor in overweight or obese patients with type 2 DM
- Be aware of the possibility of genital infections and diabetic ketoacidosis with SGLT-2 inhibitor use

Thank You For Your Kind Attention