The role of SGLT-2 inhibitors in management of type 2 diabetes

Fatemeh Rahmani.MD

Research Institute of Endocrine science

Shahid Beheshti University of Medical Science

Agenda

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

- 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

- They have been shown to 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

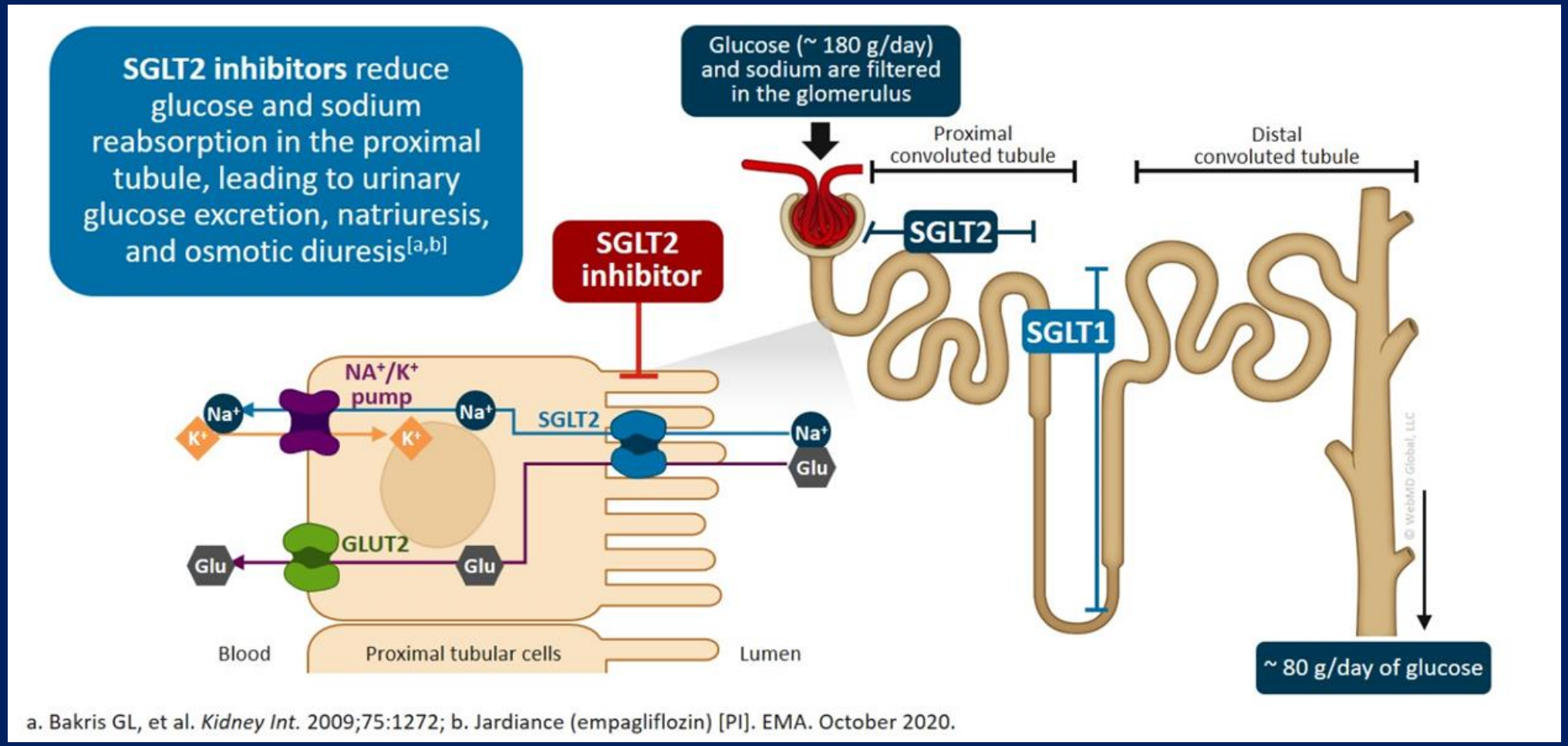
- The kidneys play a role in regulating blood glucose by filtering out glucose in the glomerulus and then reabsorbing it in the proximal tubule

- They can filter and reabsorb approximately 180 g of glucose/day, and < 1% is excreted into the urine

- The transporters responsible for reabsorbing glucose from the tubular lumen into the blood stream are the **SGLT-1** and **SGLT-2**

- **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%**



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

- 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

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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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

- decreasing the basal insulin dose by 20% if the FBS is<106 mg/dL and decreasing it by 10% if FBS is between 106 - 145 mg/dL
- reducing the bolus dose by 20% if the BS is <106 mg/dL before meals, and by 10% if it is between 106 -145 mg/dL
- 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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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

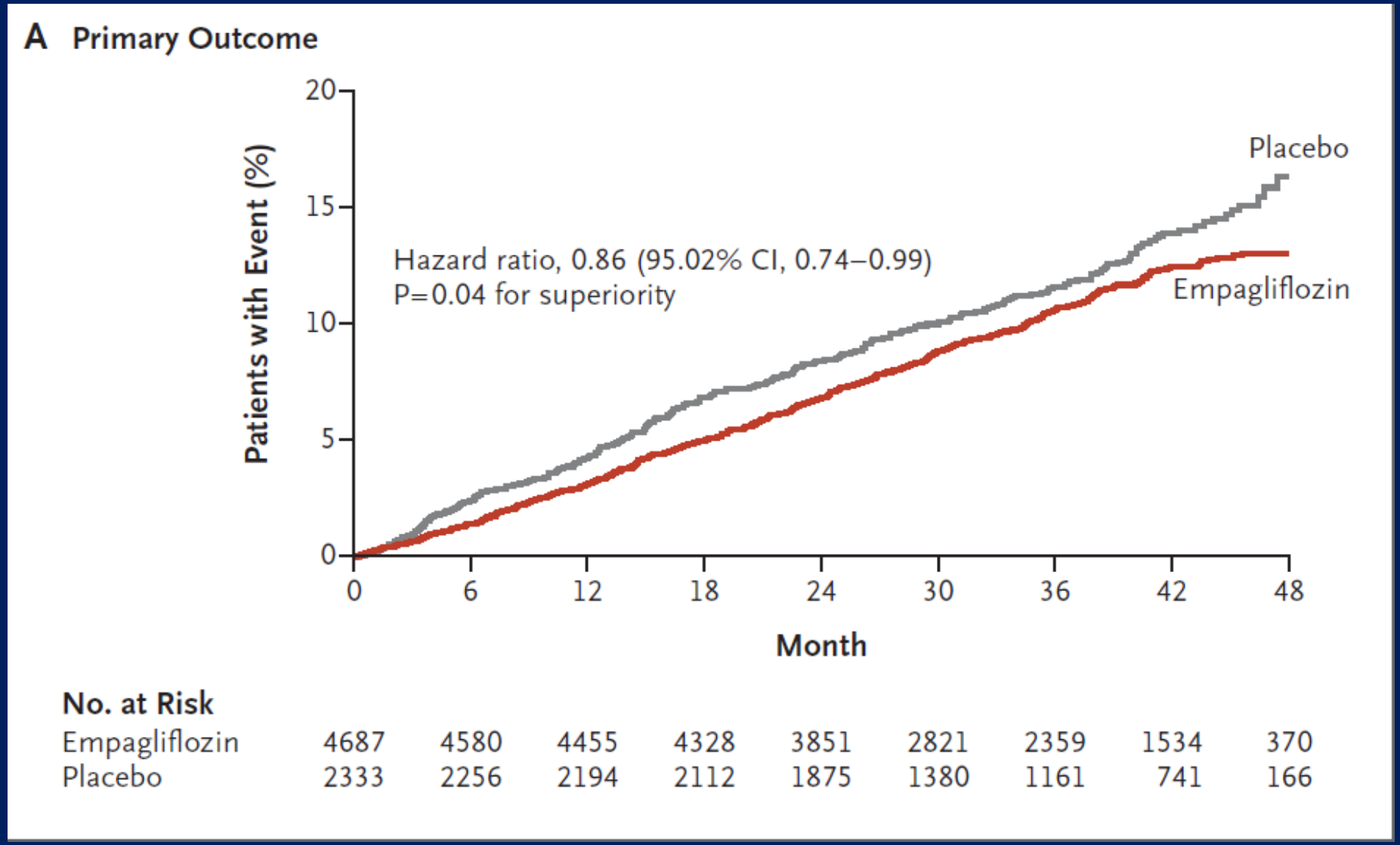
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

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 (Median)
- Outcome : A composite of death from CV causes, nonfatal MI (excluding silent MI), or nonfatal stroke.
-

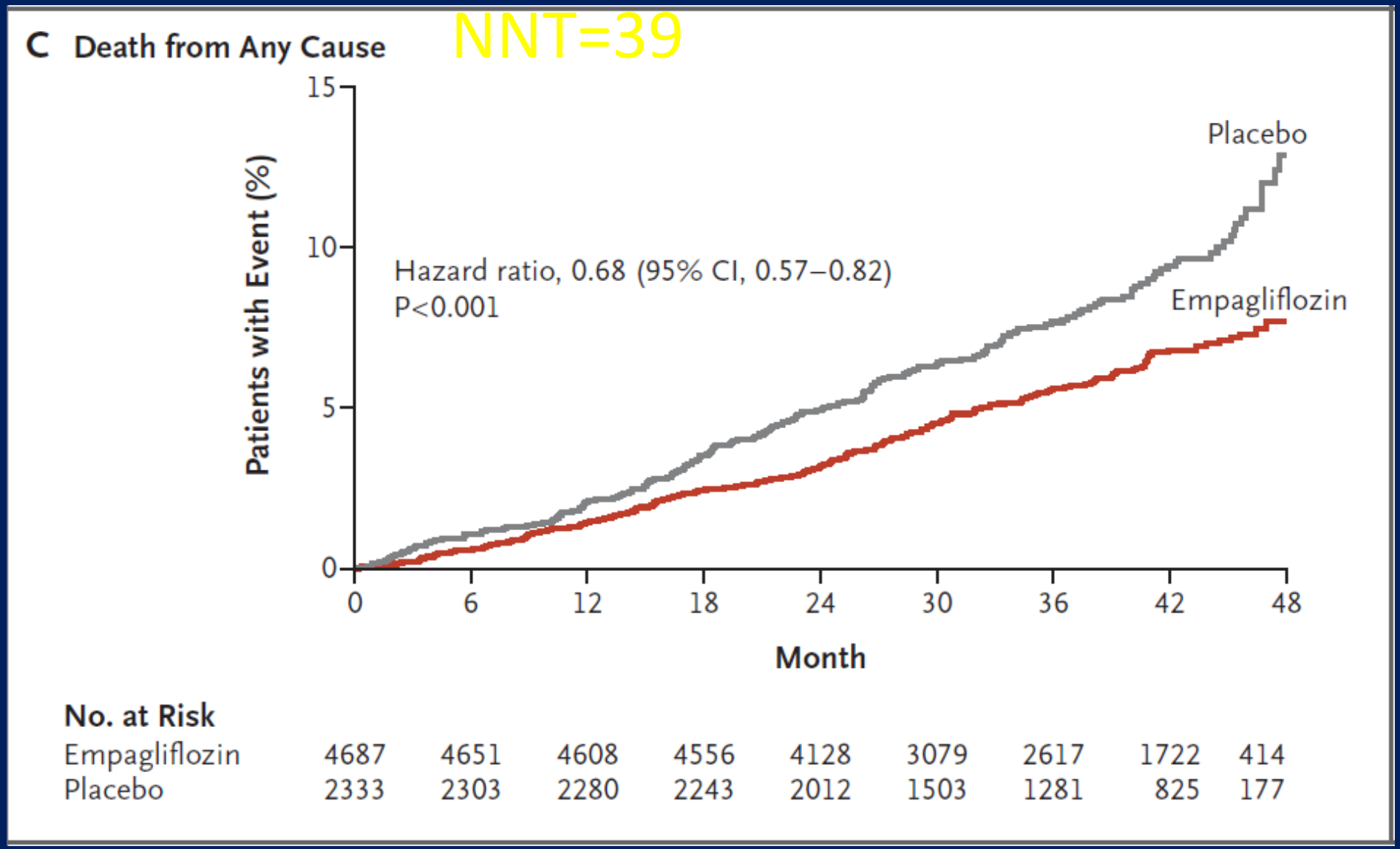
2015 Nov 26;373(22):2117-28

Primary outcome

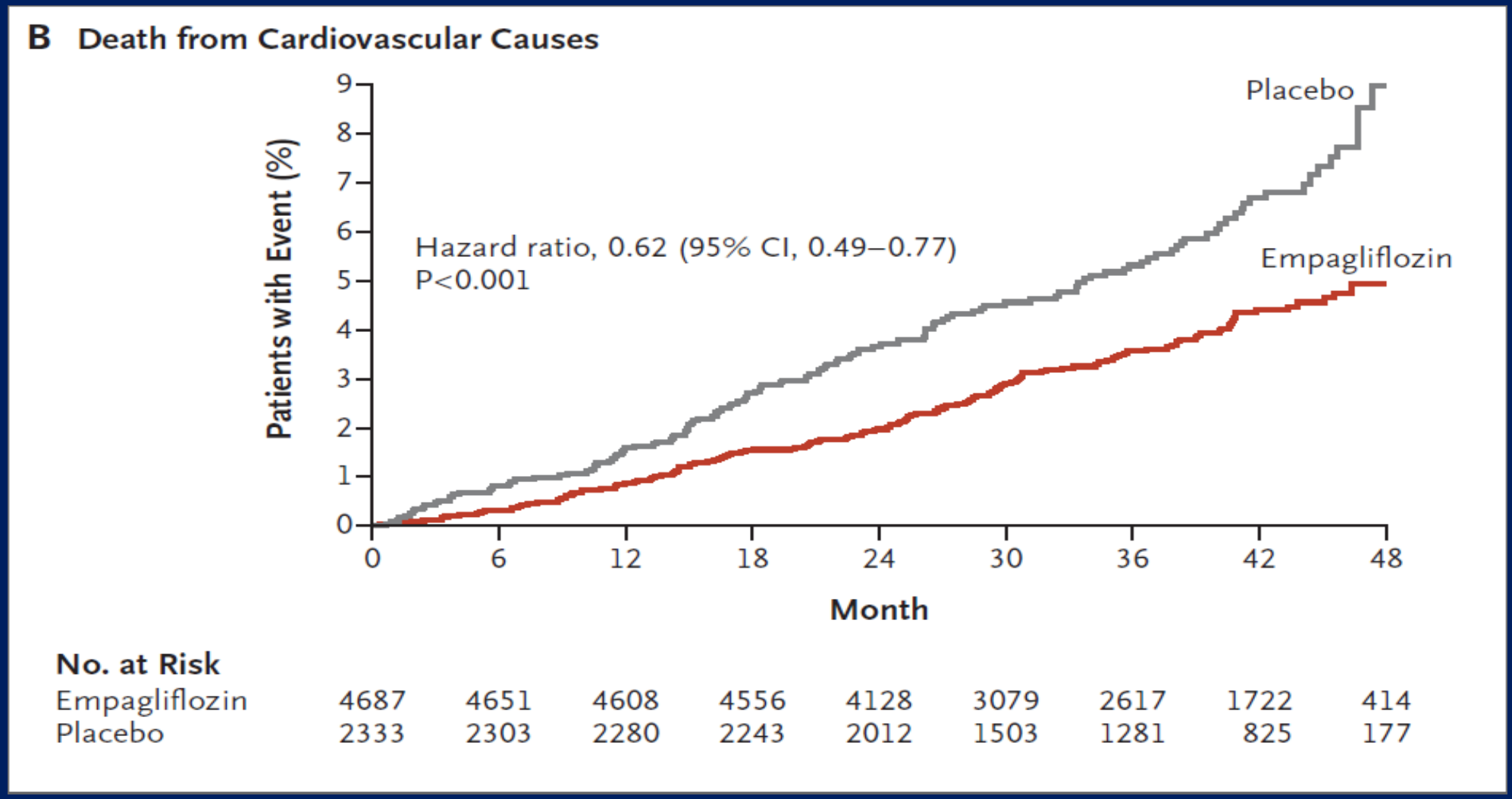


All cause mortality

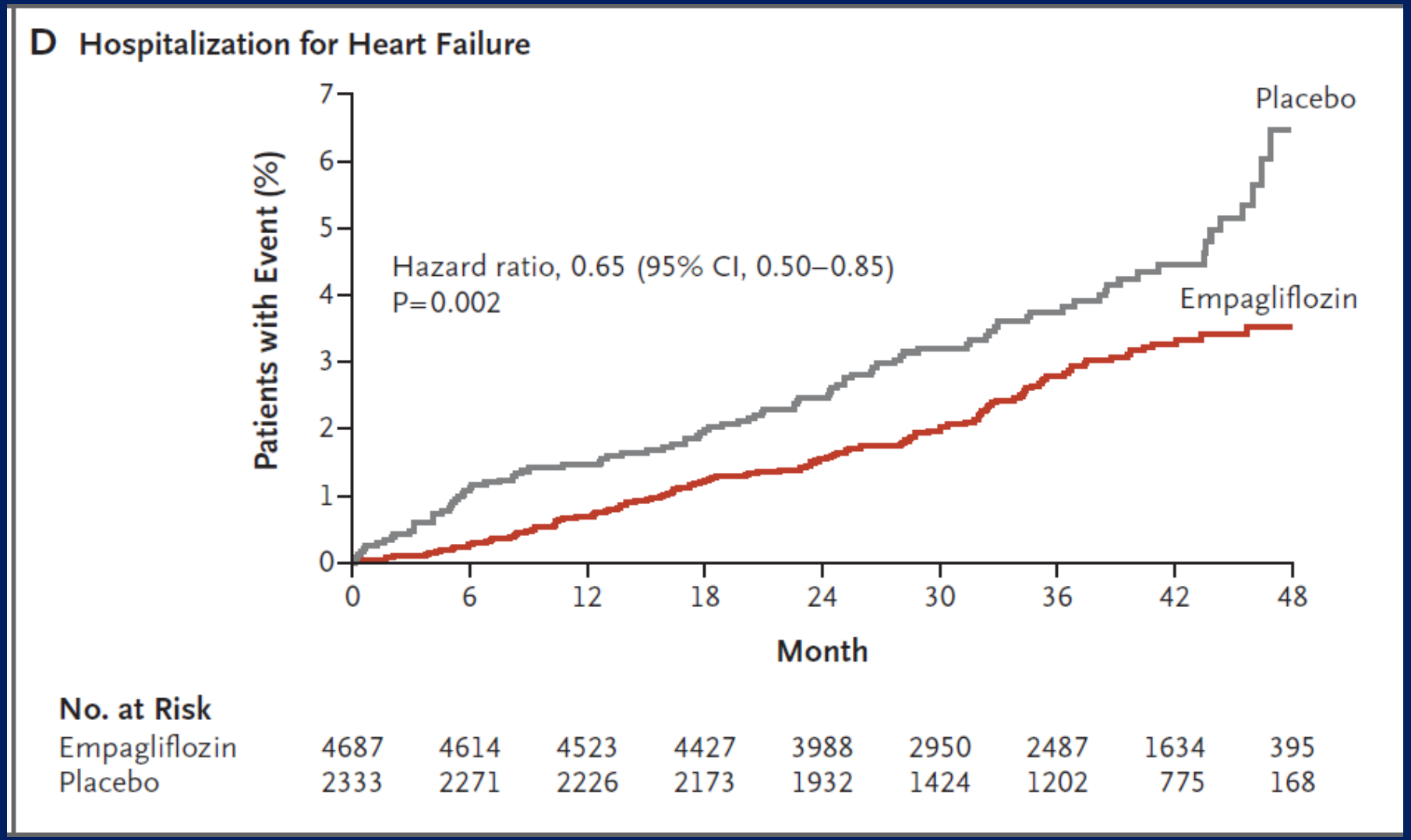
NNT=39



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

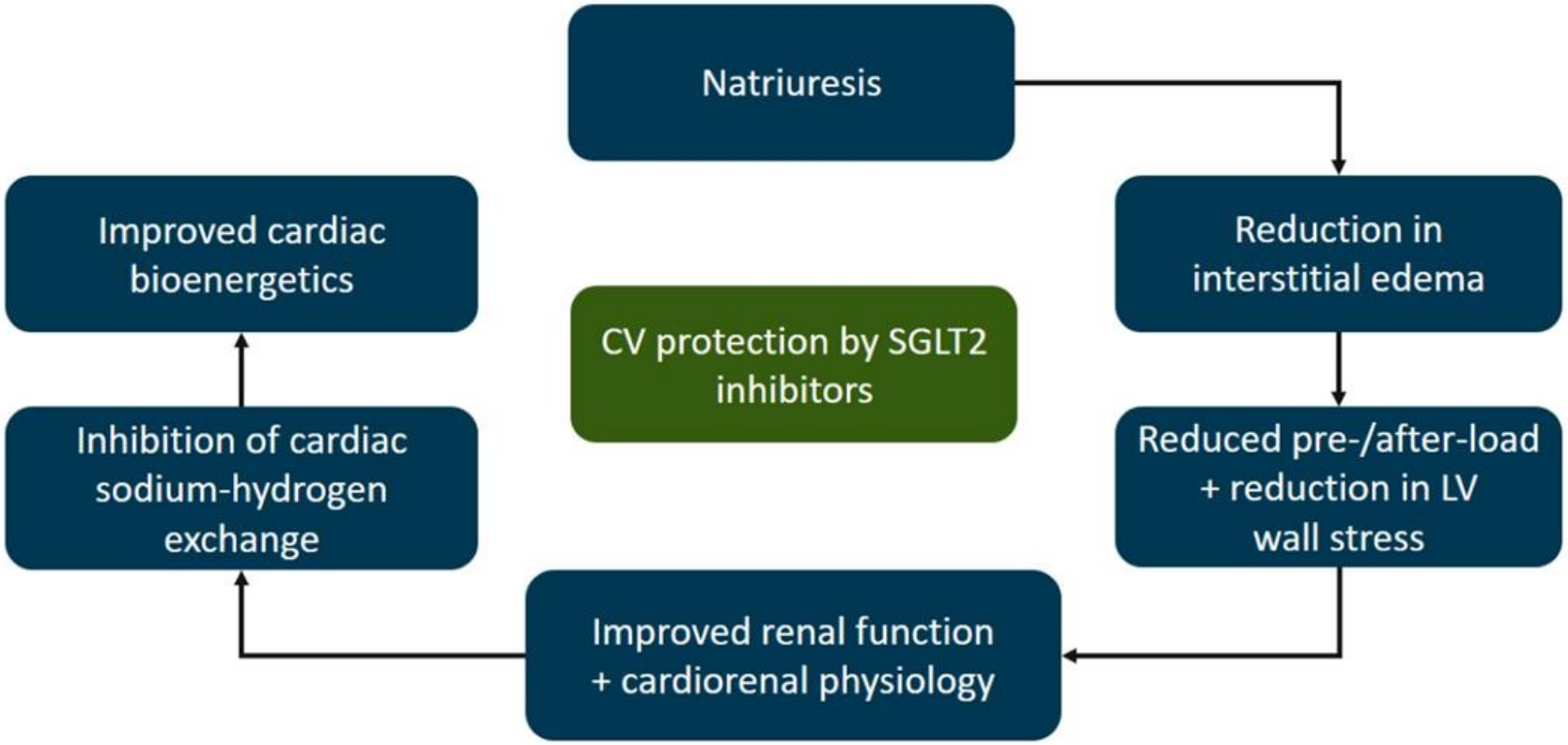
POSSIBLE MECHANISMS OF CARDIOVASCULAR BENEFIT

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



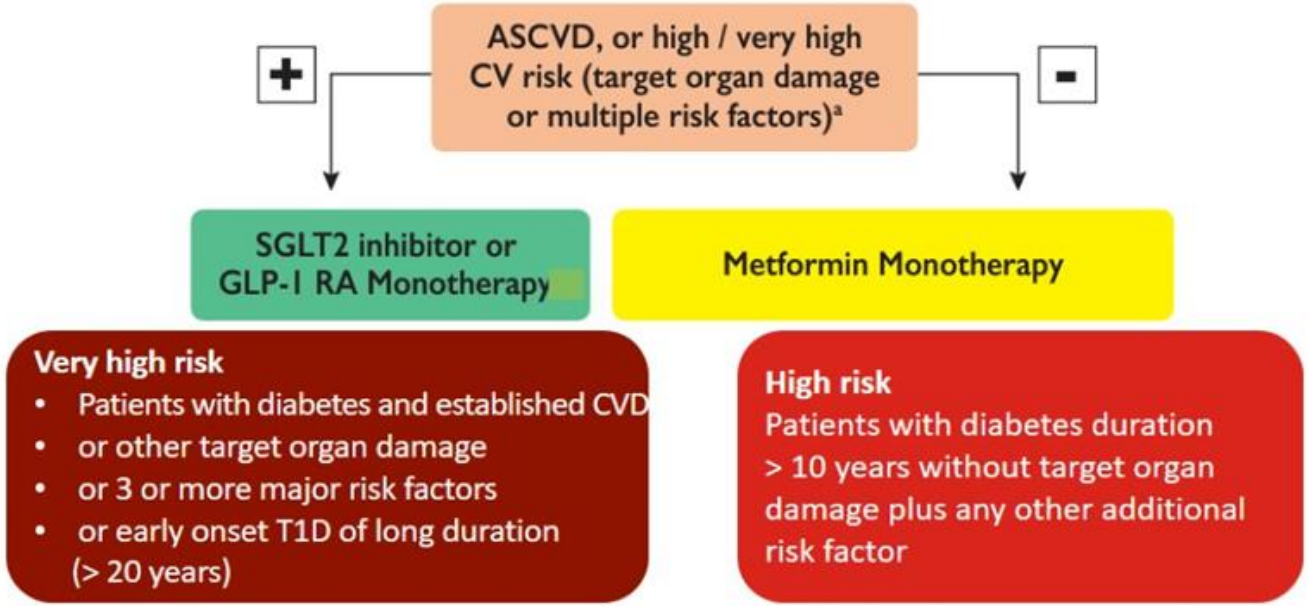
Farkouh ME, et al. *J Am Coll Cardiol.* 2018;71:2507-2510.

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

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- 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 and Progression of Kidney Disease in Type 2 Diabetes

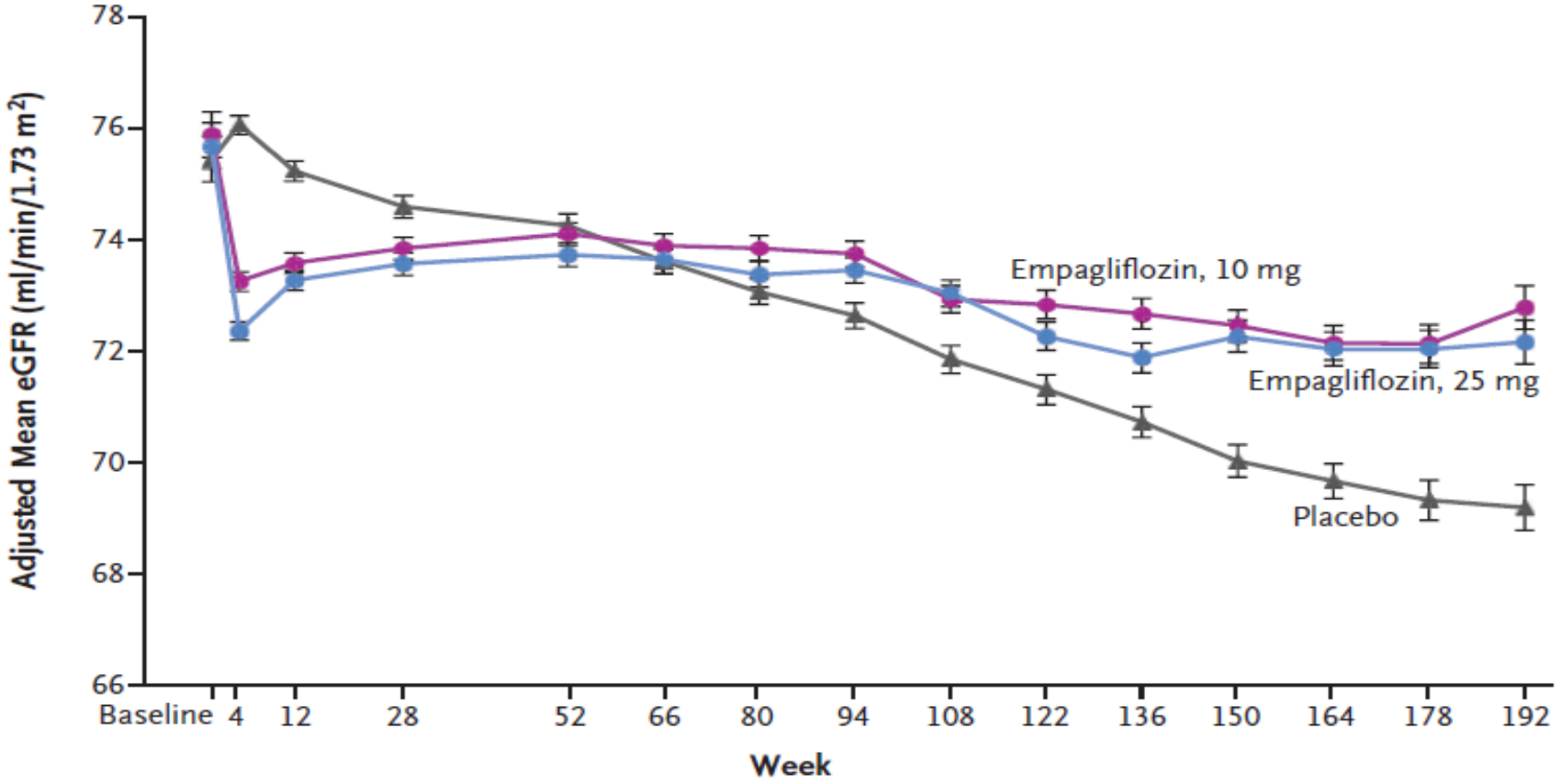
Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*

- 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

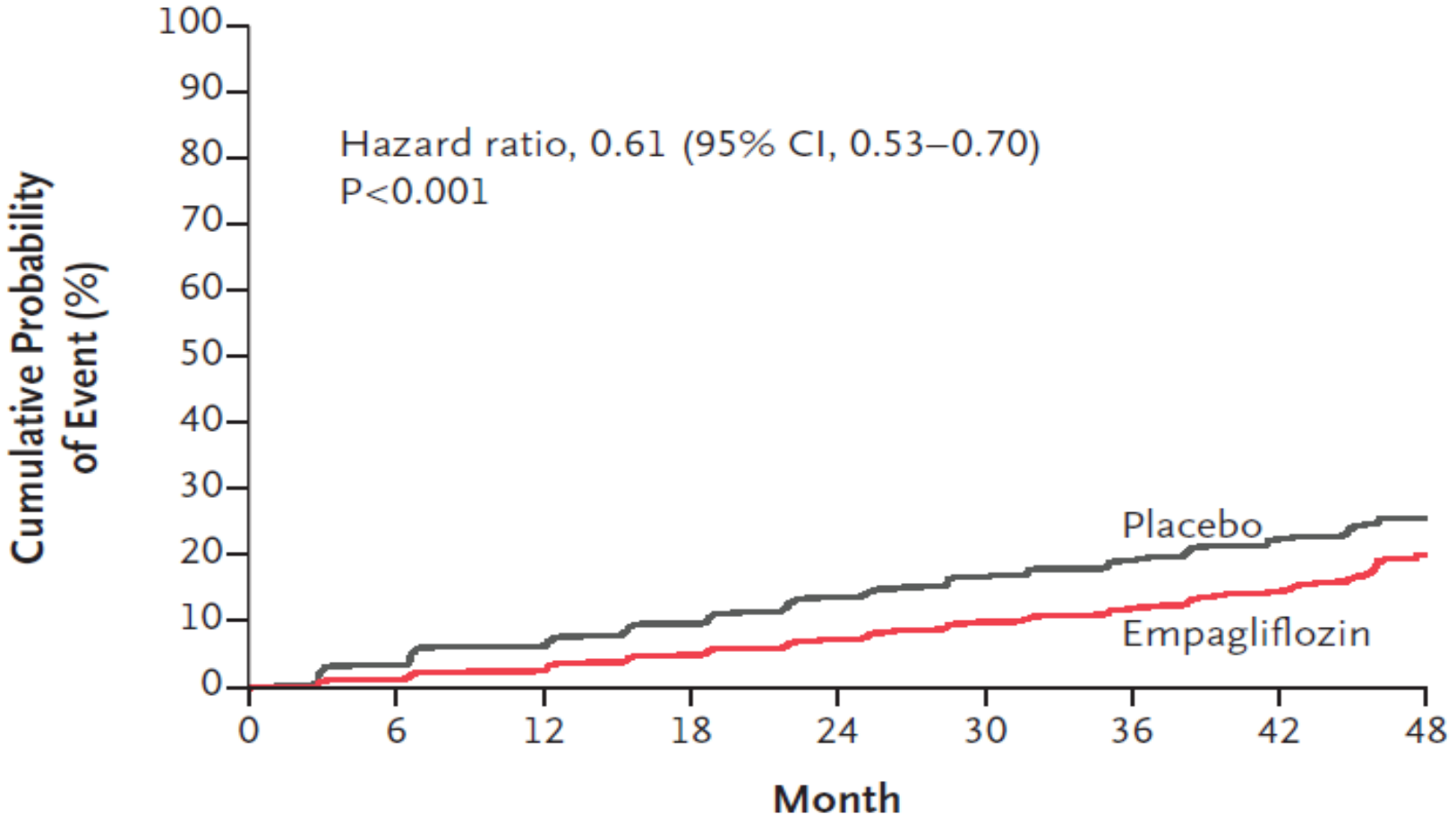
N Engl J Med 2016;375:323-34

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

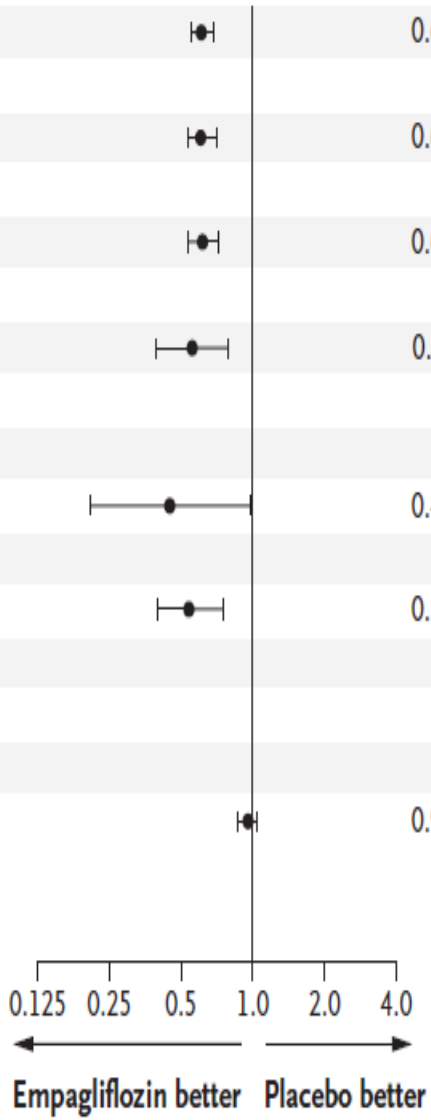
A Incident or Worsening Nephropathy



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



ORIGINAL ARTICLE

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

Aim : To assess the effects of the SGLT2 inhibitor canagliflozin on renal outcomes in patients with type 2 DM and albuminuric chronic kidney disease

N Engl J Med 2019; 380:2295-2306

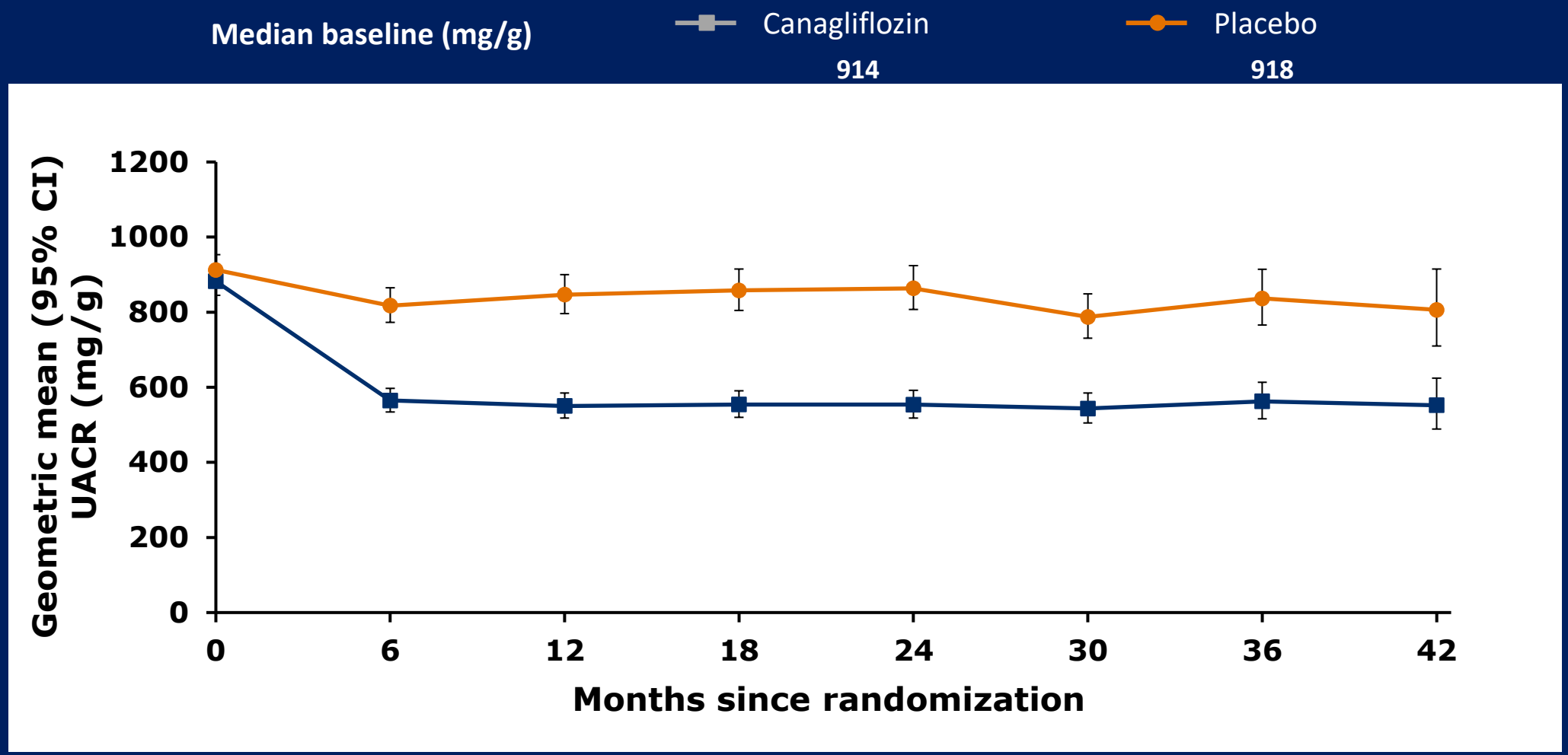
Study Design

Key inclusion criteria
- ≥30 years of age
- T2DM and HbA1c 6.5% to 12.0%
- eGFR 30 to 90 mL/min/1.73 m^2
- UACR 300 to 5000 mg/g
- Stable max tolerated labelled dose of ACEi or ARB for ≥4 weeks

Key exclusion criteria
- Other kidney diseases, dialysis, or kidney transplant
- Dual ACEi and ARB; direct renin inhibitor; MRA
- Serum K^+ >5.5 mmol/L
- CV events within 12 weeks of screening
- NYHA class IV heart failure
- Diabetic ketoacidosis or T1DM

Participants continued treatment if eGFR was <30 mL/min/1.73 m^2 until chronic dialysis was initiated or kidney transplant occurred.

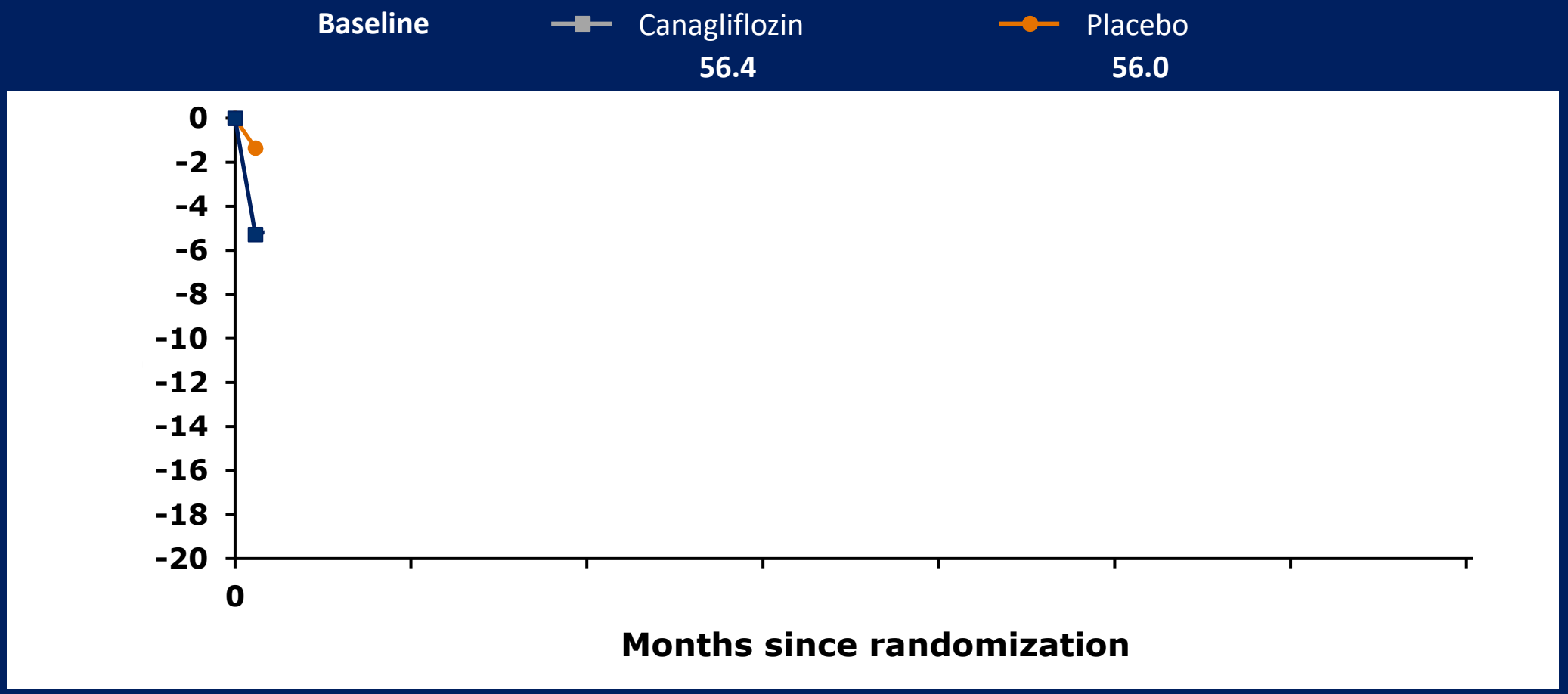
Effects on Albuminuria (UACR)



No. of participants								
Placebo	2113	2061	1986	1865	1714	1158	685	251
Canagliflozin	2114	2070	2019	1917	1819	1245	730	271

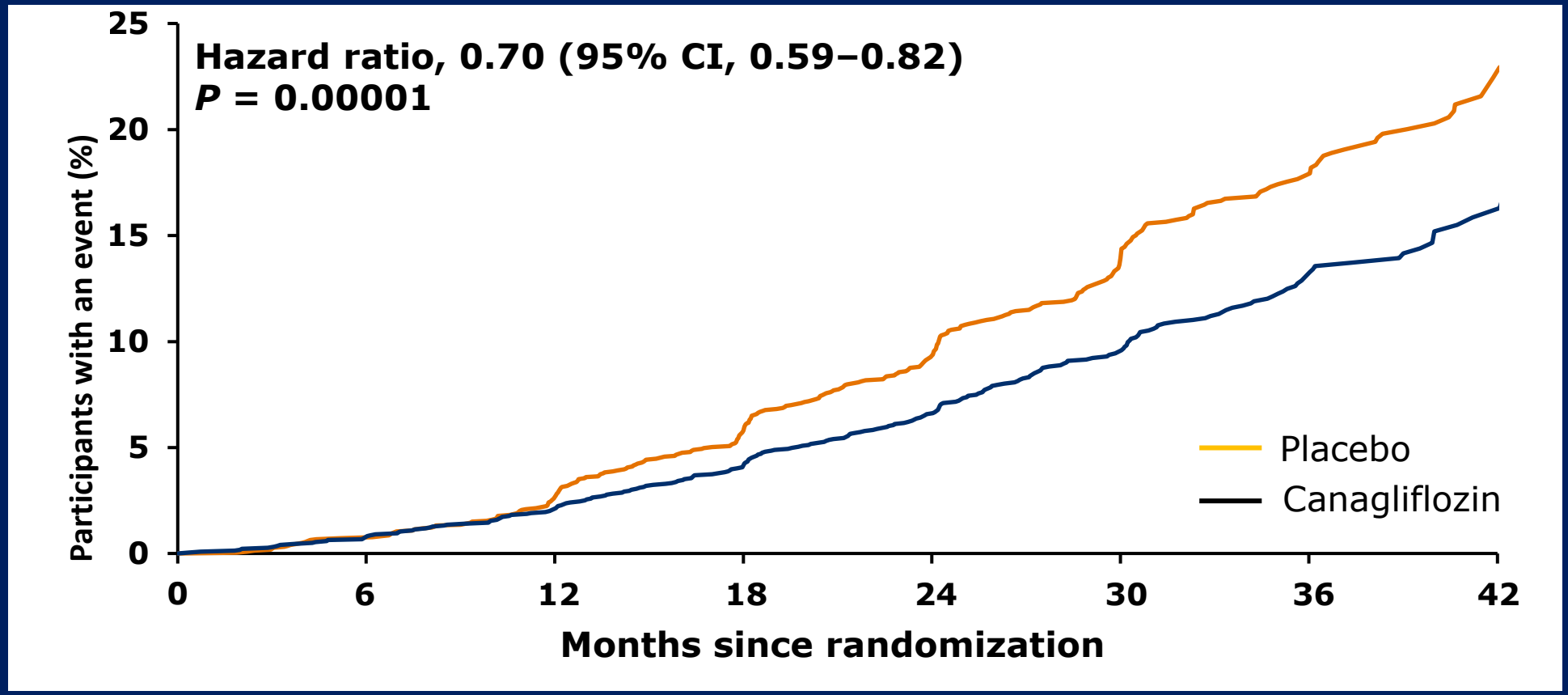
ITT analysis

Effects on eGFR



No. of Participants										
Placebo	2178	2084	1985	1882	1720	1536	1006	583	210	
Canagliflozin	2179	2074	2005	1919	1782	1648	1116	652	241	On treatment

Primary Outcome:
ESKD, Doubling of Serum Creatinine, or Renal or CV Death



No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D.,
Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D.,
Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D.,
Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D.,
Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D.,
for the DAPA-CKD Trial Committees and Investigators*

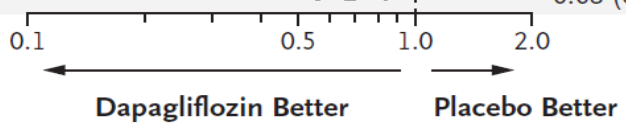
- 4304 participants with an estimated GFR of 25 to 75 ml/min/per 1.73 m2 and a urinary albumin/cr ratio (with albumin measured in milligrams and creatinine) of 200 to 5000 were randomized to receive dapagliflozin (10 mg once daily) or placebo.

- The primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes

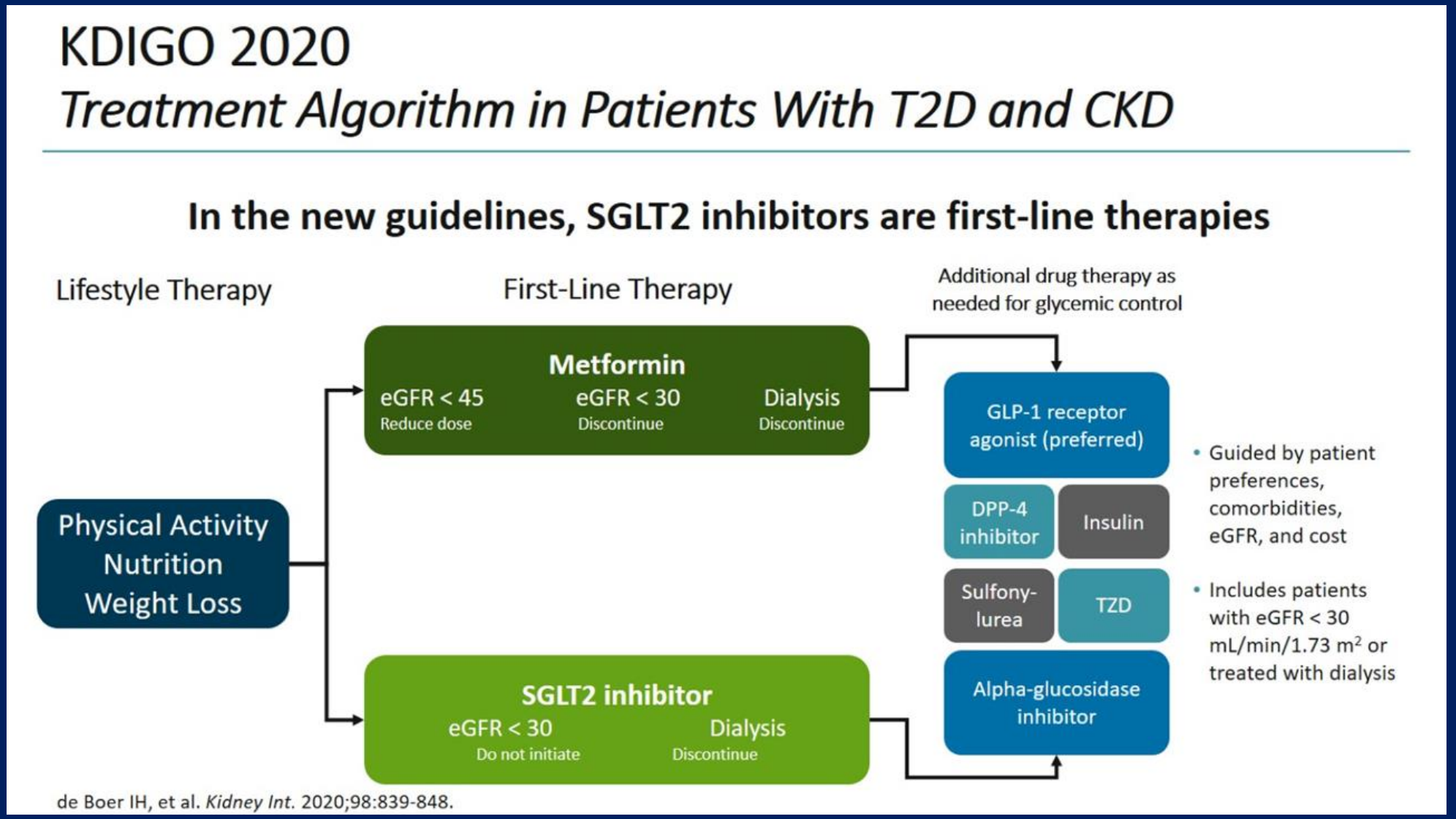
- Median follow up : 2.4 years

N Engl J Med 2020;383:1436-46

Subgroup	Dapagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of participants/total no.		
All participants	197/2152	312/2152	0.61 (0.51–0.72)
Age			
≤65 yr	122/1247	191/1239	0.64 (0.51–0.80)
>65 yr	75/905	121/913	0.58 (0.43–0.77)
Sex			
Male	126/1443	209/1436	0.57 (0.46–0.72)
Female	71/709	103/716	0.65 (0.48–0.88)
Race			
White	110/1124	174/1166	0.62 (0.49–0.79)
Black	7/104	14/87	0.33 (0.13–0.81)
Asian	53/749	77/718	0.66 (0.46–0.93)
Other	27/175	47/181	0.54 (0.33–0.86)
Geographic region			
Asia	50/692	69/654	0.70 (0.48–1.00)
Europe	57/610	89/623	0.60 (0.43–0.85)
North America	35/401	69/412	0.51 (0.34–0.76)
Latin America	55/449	85/463	0.61 (0.43–0.86)
Type 2 diabetes			
Yes	152/1455	229/1451	0.64 (0.52–0.79)
No	45/697	83/701	0.50 (0.35–0.72)
Estimated GFR			
<45 ml/min/1.73 m^2	152/1272	217/1250	0.63 (0.51–0.78)
≥45 ml/min/1.73 m^2	45/880	95/902	0.49 (0.34–0.69)
Urinary albumin-to-creatinine ratio			
≤1000	44/1104	84/1121	0.54 (0.37–0.77)
>1000	153/1048	228/1031	0.62 (0.50–0.76)
Systolic blood pressure			
≤130 mm Hg	46/793	96/749	0.44 (0.31–0.63)
>130 mm Hg	151/1359	216/1403	0.68 (0.56–0.84)



Kidney disease improving global outcome



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- SGLT-2 inhibitors have been shown to promote weight loss and lower BP

- Taking these drugs as monotherapy for 24 -26 weeks:
  weight loss was approximately 2.3 - 3.5 kg
  Systolic BP decreased by 1.4 to 3.7 mmHg
  diastolic BP decreased by 0.6 to 2.0 mmHg

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

- A meta-analysis of 4 large, RCT showed that patients who received combination therapy lost significantly more weight loss than those who received SGLT-2 inhibitor monotherapy (difference = –1.61 kg,*P* = .01)

- they had significantly reduced BP(difference = –3.32 mmHg, *P* < .001)

- HbA1c reduction was also greater in the combination therapy group compared with monotherapy (difference = –0.74%, *P* < .001).

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.

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 or second-line therapy(after metformin) 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 attention