SGLT2 Inhibitors: Worry Less, Prescribe More

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Disclosures

Novonordisk: DSMB (semaglutide)

Outline

Background

Cardiovascular Outcomes

Renal Outcomes

Safety

Practice Points

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Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

Approval of New Diabetic Medications

In 2008, FDA published guidance for sponsors of new therapies for diabetes

Reduction in HbA1c is accepted by FDA for approval for new diabetic medications

Sponsors need to prove that the medication does not result in an unacceptable increase in cardiovascular risk

- Focus on ischemic events: cardiovascular mortality, myocardial infarction, stroke (MACE)
- Does not focus on heart failure

The cardiovascular studies can occur post-marketing approval

The unexpected result was that SGLT2 inhibitors had benefit (rather than no harm). The medications also had renal benefit

SGLT2 Inhibitors

The majority of glucose (> 90%) is absorbed in the early proximal tubule by SGLT2, with a small proportion absorbed in the later proximal tubule by SGLT1

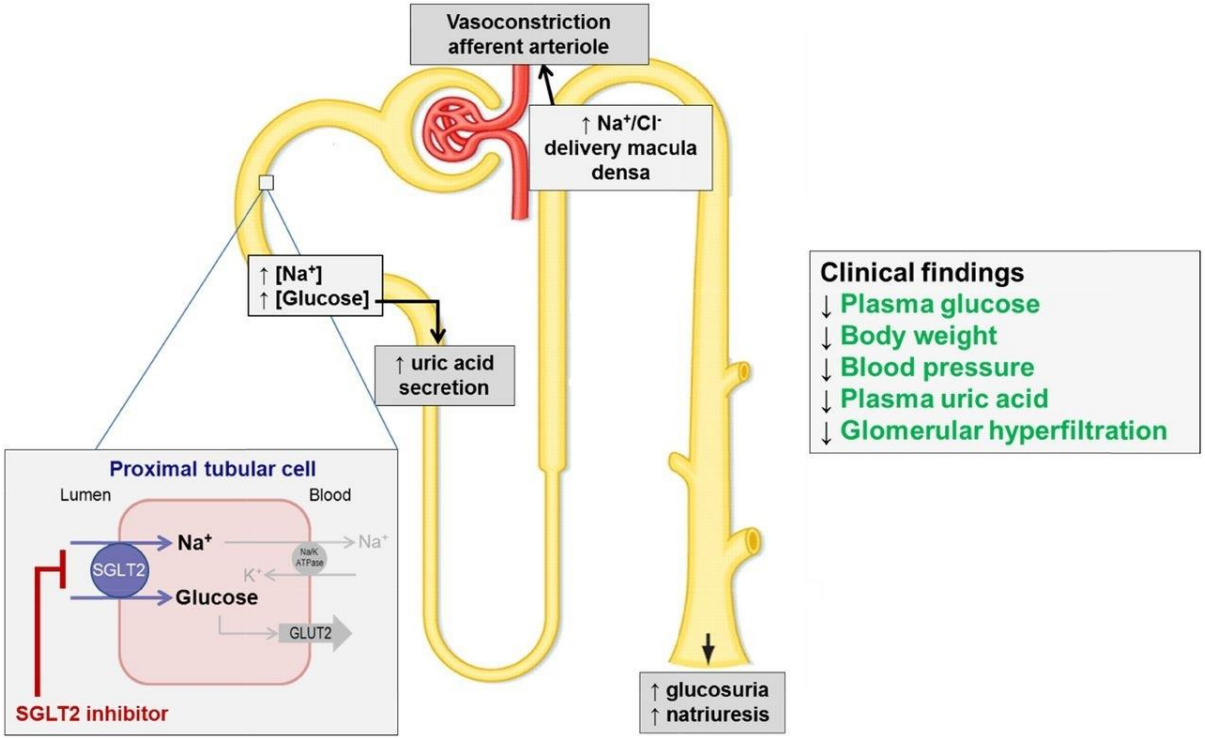
In diabetes with hyperglycemia, SGLT2 is up-regulated

- Increases Tm glucose in patients with diabetes

Blockade leads to glucosuria and natiuresis

- There is decrease in plasma volume with decline in BP

Kidney Effects SGLT2 inhibitors



Van Bommel. CJASN 2017;12;700

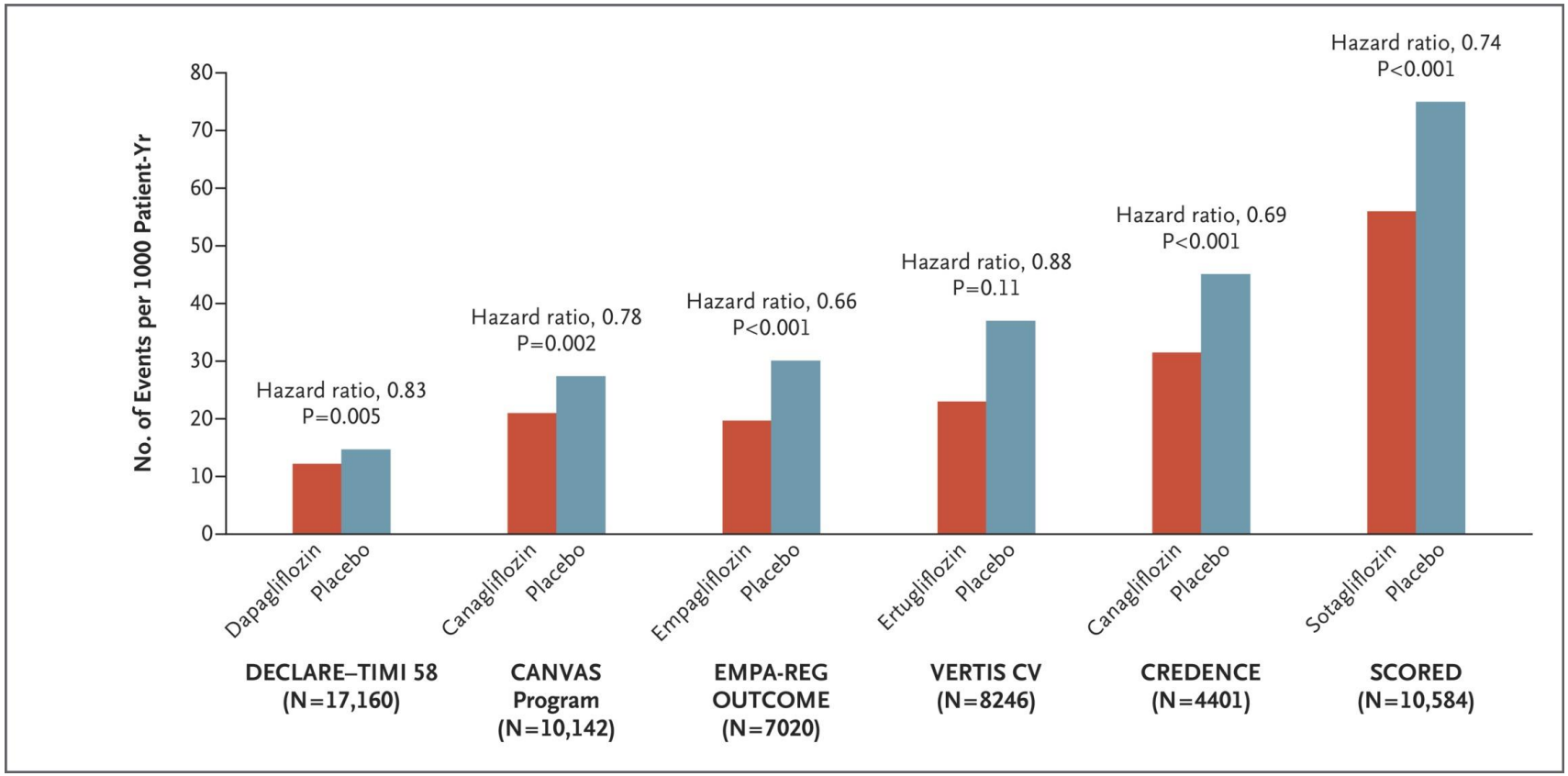
Metabolic effects new diabetic medications

	DPP4	GLP1RA	SGLT2
HbA1c	0.8-1.0%	0.8-1.9% reduction	0.3-0.9% reduction, less effective with lower eGFR
Weight	Minimal effect	2.5-5 kg weight loss	1-3kg loss
Hypoglycemia (monotherapy)	Does not increase risk	Does not increase risk	Does not increase risk
Blood Pressure	Minimal effect	Small reduction	Decreased

Cardiovascular Outcomes in the Initial SGLT2i Studies

	EMPA-REG	CANVAS	DECLARE
Medication	Empagliflozin	Canagliflozin	Dapagliflozin
N	7020	10,142	17,160
% with CVD	99	65	41
% with eGFR < 60	26	21	7
% UACR > 300	11	8	7
MACE	0.86 (0.74, 0.99)	0.86 (0.75, 0.97)	0.93 (0.84, 1.03)
CHF	0.65 (0.50, 0.85)	0.67 (0.52, 0.87)	0.73 (0.61, 0.88)
CV Mortality	0.62 (0.49, 0.77)	0.87 (0.72, 1.06)	0.98 (0.82, 1.17)
All Cause Mortality	0.68 (0.57, 0.82)	0.87 (0.74, 1.01)	0.93 (0.82, 1.04)

Cardiovascular Death or Admission for Heart Failure: SGLT2 Studies



Braunwald E. N Engl J Med2022;386:2024-2034

CHF

The benefit in CHF is broad

- With or without diabetes
  - DAPA-HF, EMPEROR-Reduced and EMPEROR-Preserved
- Low EF
  - DAPA-HF, EMPEROR-Reduced
- Preserved EF
  - EMPEROR-Preserved
- Low GFR
  - EMPEROR-Reduced enrolled individuals as low as eGFR of 20 ml/min/1.73m^2 and showed benefit across eGFR groups

SGLT2 and Kidney Outcomes

EMPA-REG

Randomized trial of empagliflozin 10m vs. 25mg vs placebo

Established cardiovascular disease

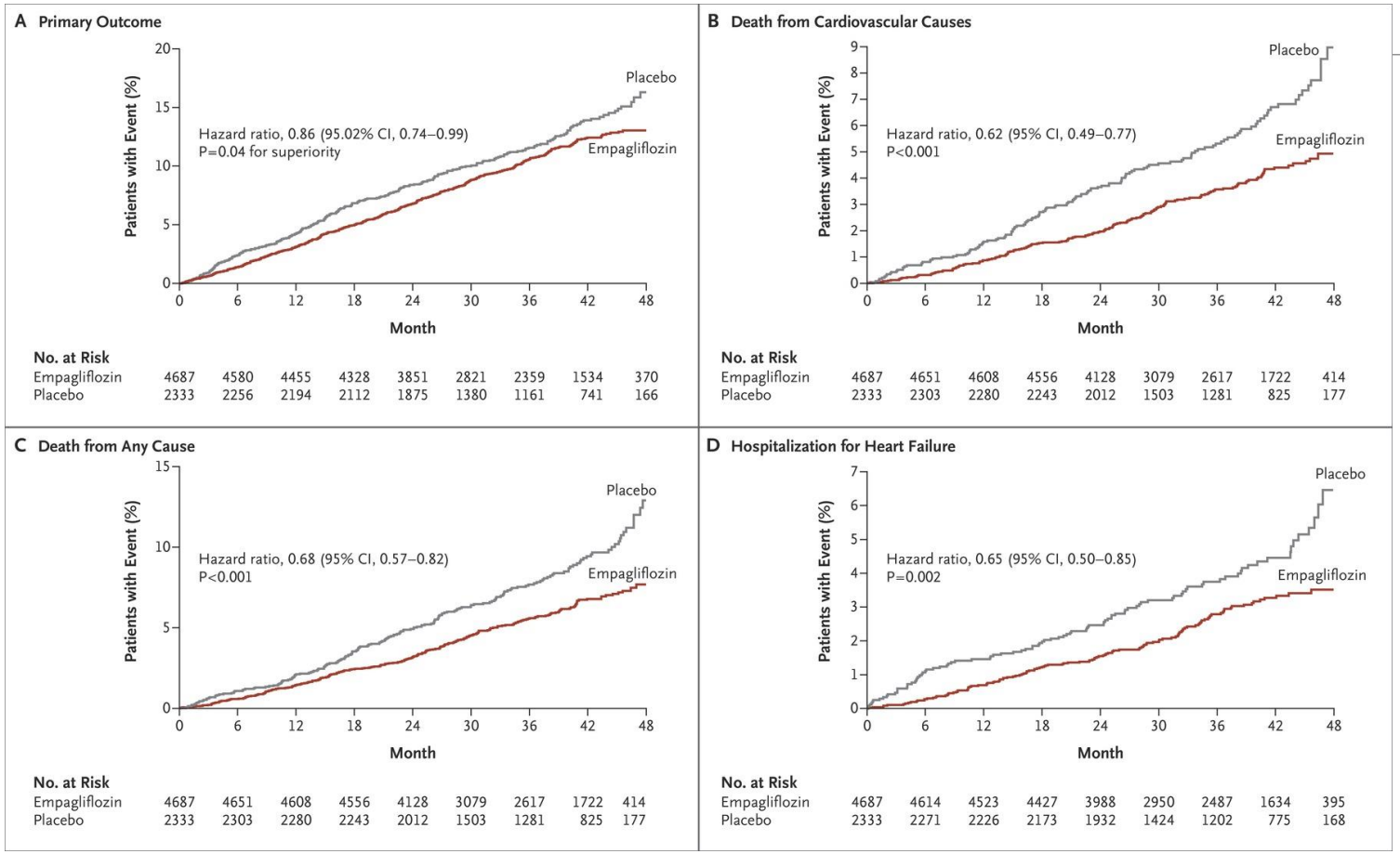
eGFR ≥ 30 ml/min/1.73m2

HbA1c 7-10%

Results were similar for 10mg and 25mg groups

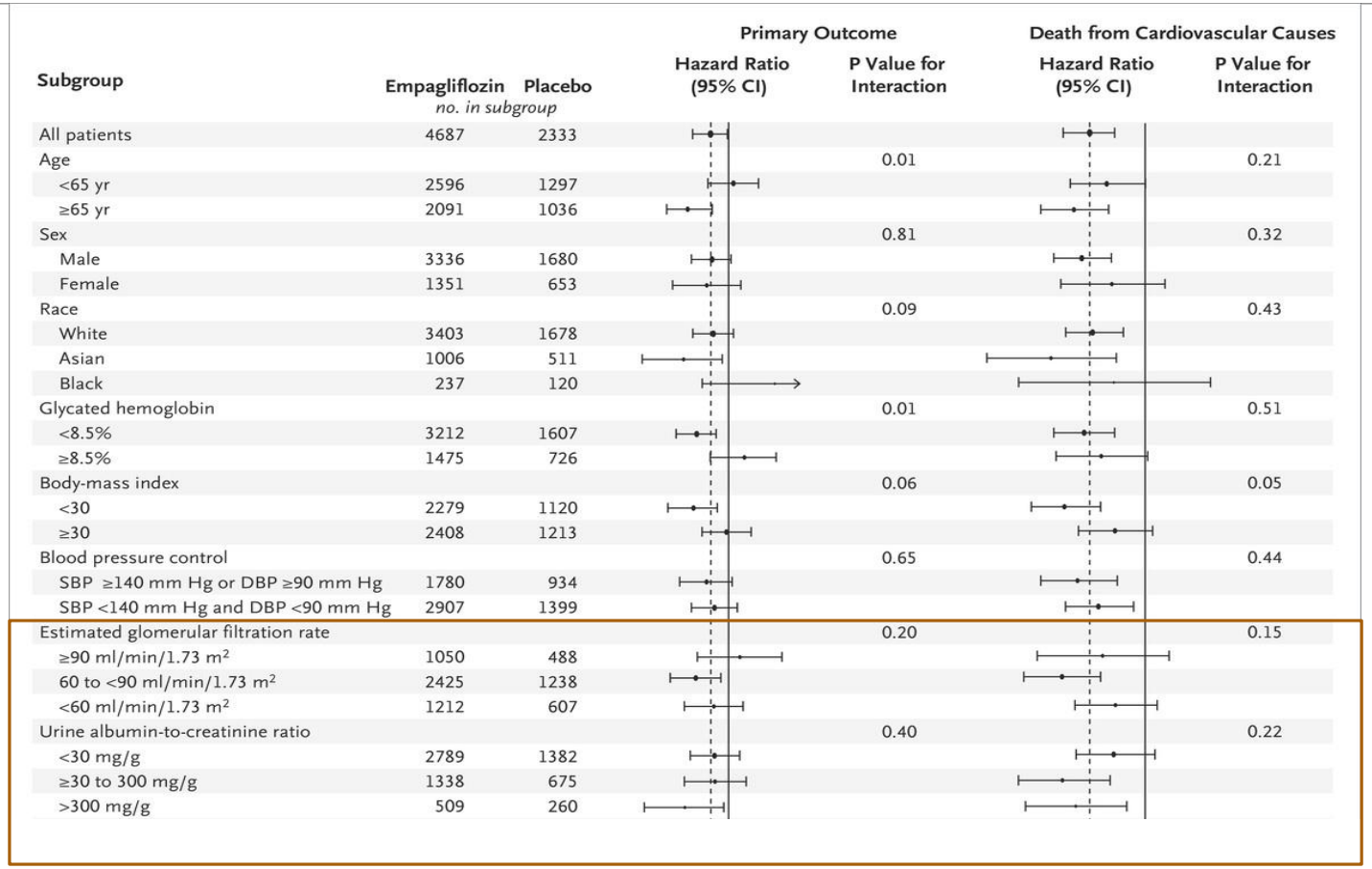
While designed as a cardiovascular study with participants having relatively low renal progression risk, the results suggested renal benefit

EMPA-REG CV Outcomes



Zinman B et al. NEJM 2015;373:2117-28

Subgroup Analysis EMPA-REG

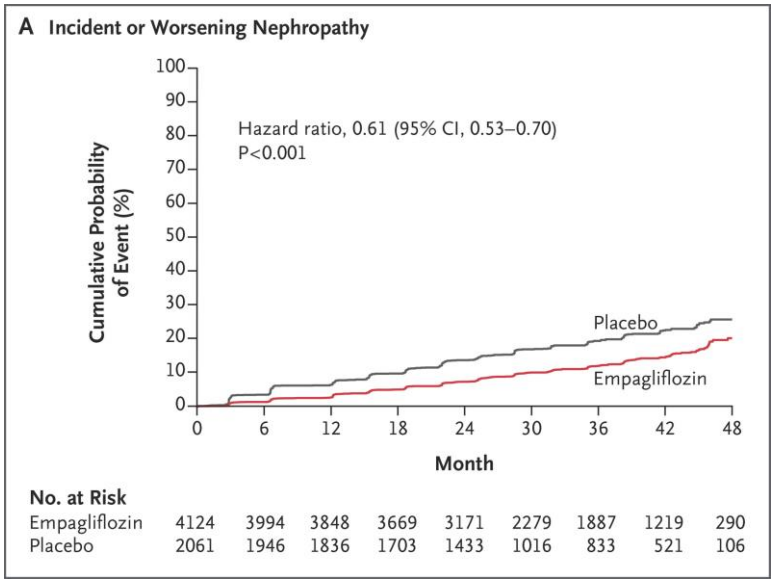


Subgroup	Empagliflozin	Placebo	Primary Outcome: Hazard Ratio (95% CI)	Primary Outcome: P Value for Interaction	Death from Cardiovascular Causes: Hazard Ratio (95% CI)	Death from Cardiovascular Causes: P Value for Interaction
	no. in subgroup					
All patients	4687	2333				
Age				0.01		0.21
<65 yr	2596	1297				
≥65 yr	2091	1036				
Sex				0.81		0.32
Male	3336	1680				
Female	1351	653				
Race				0.09		0.43
White	3403	1678				
Asian	1006	511				
Black	237	120				
Glycated hemoglobin				0.01		0.51
<8.5%	3212	1607				
≥8.5%	1475	726				
Body-mass index				0.06		0.05
<30	2279	1120				
≥30	2408	1213				
Blood pressure control				0.65		0.44
SBP ≥140 mm Hg or DBP ≥90 mm Hg	1780	934				
SBP <140 mm Hg and DBP <90 mm Hg	2907	1399				
Estimated glomerular filtration rate				0.20		0.15
≥90 ml/min/1.73 m^2	1050	488				
60 to <90 ml/min/1.73 m^2	2425	1238				
<60 ml/min/1.73 m^2	1212	607				
Urine albumin-to-creatinine ratio				0.40		0.22
<30 mg/g	2789	1382				
≥30 to 300 mg/g	1338	675				
>300 mg/g	509	260				

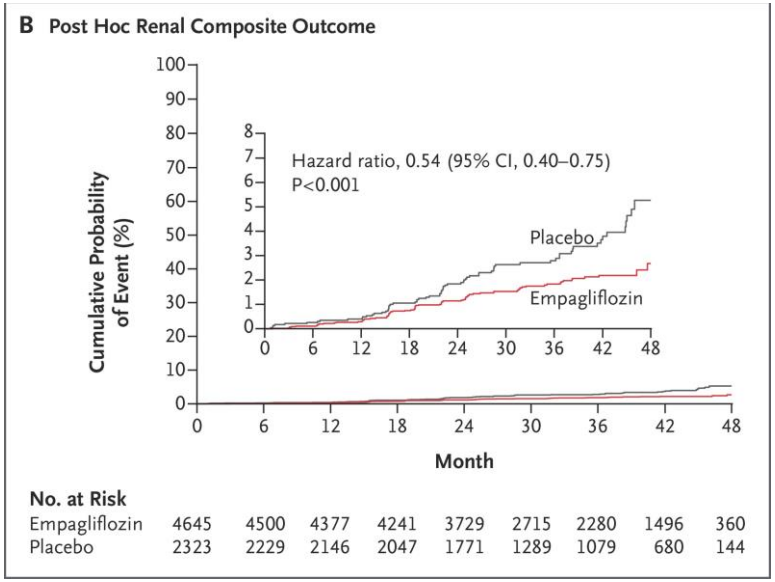
Zinman B et al. NEJM 2015;373:2117-28

Kidney Outcomes in EMPA-REG

Macroalbuminuria, doubling serum Cr RRT, renal death



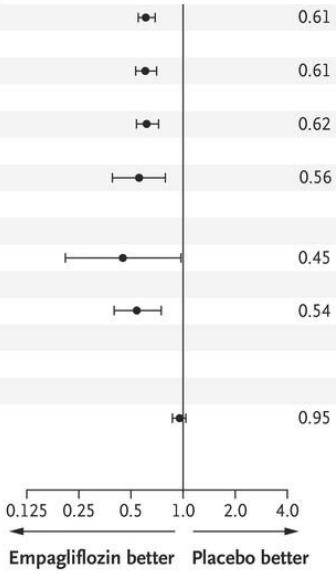
Doubling serum Cr, RRT, renal death



Wanner C et al. NEJM 2016;375:323-334

Renal Outcomes EMPA-REG

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



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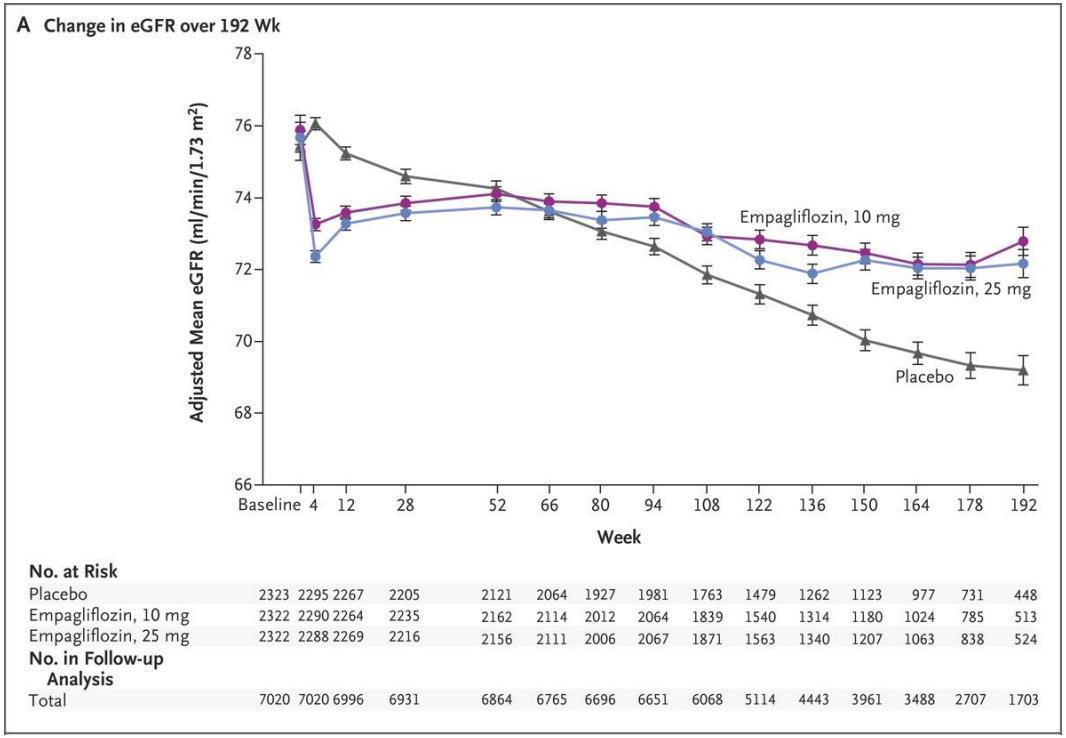
GFR Over Time EMPA-REG: Initial drop then stabilization



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

Wanner C et al. NEJM 2016;375:323-334

Renal Progression in SGLT2i Studies before CREDENCE

sustat	EMPA-REG	CANVAS	DECLARE
Medication	Empagliflozin	Canagliflozin	Dapagliflozin
N	7020	10,142	17,160
Mean eGFR	74	77	85
% with eGFR < 60	26	21	7
% UACR > 300	11	8	7
Decreased progression, RRT or renal death*	0.54 (0.40, 0.75)	0.60 (0.47, 0.77)	0.54 (0.43, 0.67)
ESRD	27 events total HR 0.45 (0.21, 0.97)	Not reported	28 events total HR 0.41 (0.20, 0.82)

*Definition of progression: EMPA-REG: doubling serum creatinine; CANVAS: sustained 40% reduction in eGFR; DECLARE: sustained 40% reduction to less than 60 ml/min/1.73m^2

CREDENCE Study

Age ≥ 30

HbA1c 6.5-12.0

eGFR 30 to < 90 ml/min/1.73m^2

UACR > 300-5000

Stable dose of ACEI or ARB at maximal labeled dose or maximally tolerated

Randomized to canagliflozin 100mg or placebo

Medication continued until initiation of dialysis, kidney transplantation, DKA, pregnancy or receipt of a disallowed therapy (combined ACEI or ARB, mineralocorticoid receptor antagonist, other SGLT2 inhibitor)

Methods: Outcomes

Primary: composite of

- ESRD (dialysis for at least 30 days, kidney transplantation, sustained eGFR <15 ml/min/1.73m^2)
- Doubling of serum creatinine
- Renal or cardiac death

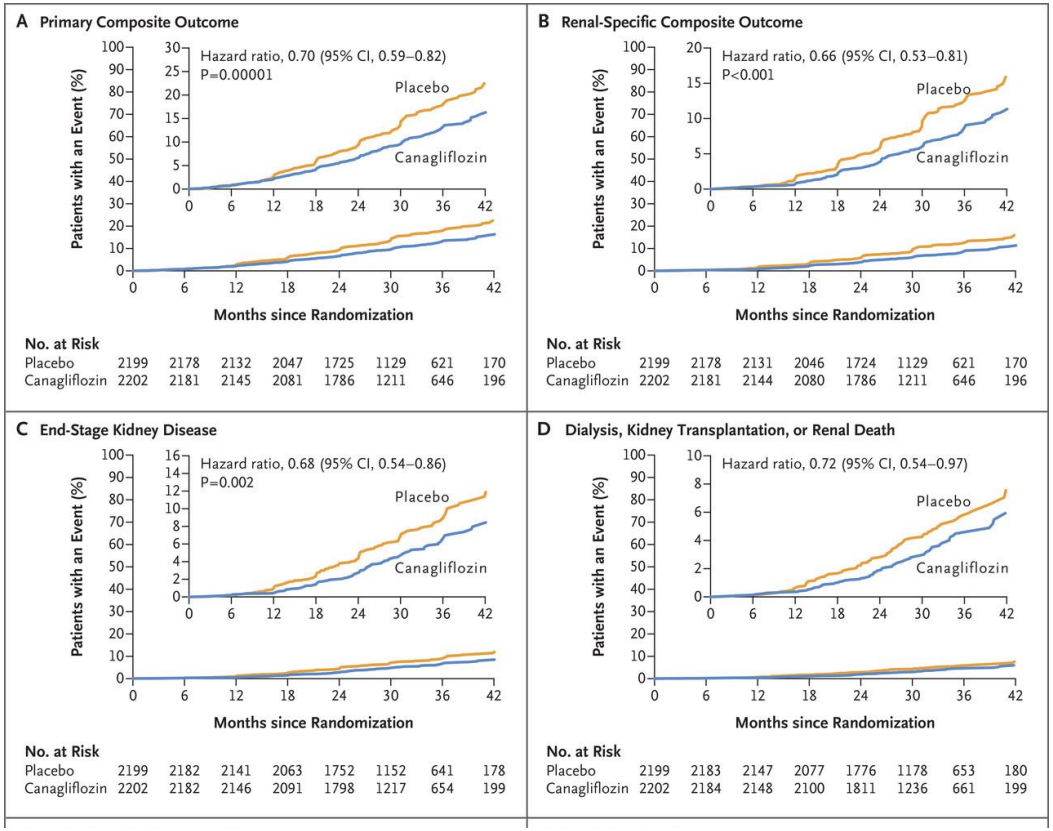
One of the secondary outcomes was composite of ESRD, doubling of serum creatinine or renal death

Participant Characteristics in CREDENCE

	Canagliflozin (n=2202)	Placebo (n=2199)
Age	62.9 ± 9.2	63.2 ± 9.2
Female (%)	34.6	33.3
Race (%) White Black Asian Other	 67.5 5.1 19.3 8.1	 65.7 5.1 20.6 8.7
CHF (%)	14.9	14.7
Duration of Diabetes	15.5 ± 8.7	16.0 ± 8.6
HbA1c	8.3 ± 1.3	8.3 ± 1.3
eGFR	56.3 ± 18.2	56.0 ± 18.3
Median UACR (IQR)	923 (459, 1794)	931 (473, 1868)

V Perkovic et al. NEJM 2019;380:2295-306

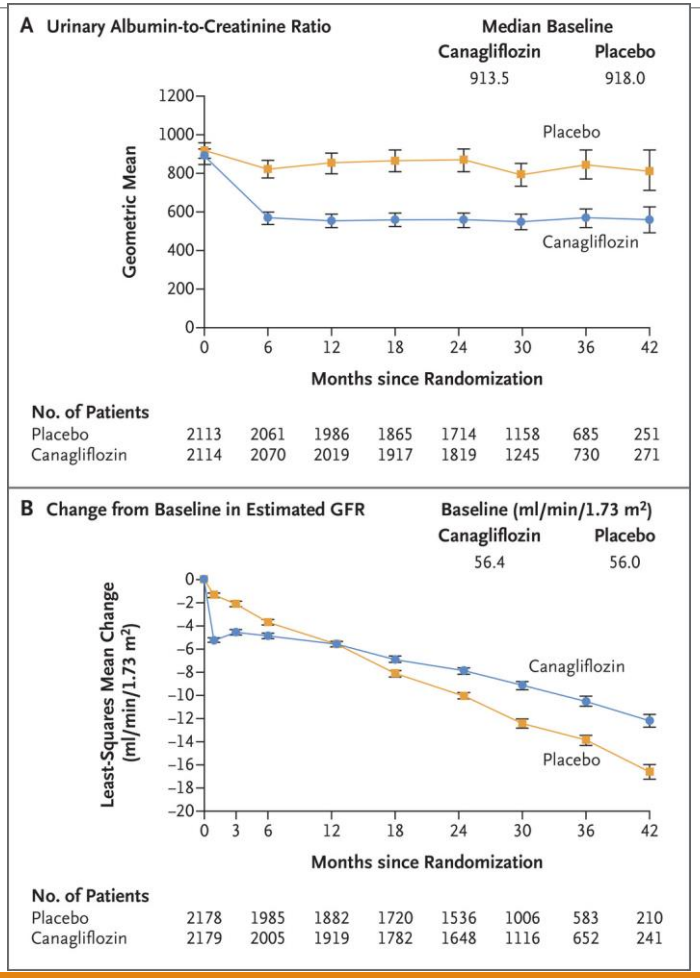
Primary and Renal Outcomes in Credence



Note that difference In HbA1c between The two groups only averaged 0.25% during the study

V Perkovic et al. NEJM 2019;380:2295-306

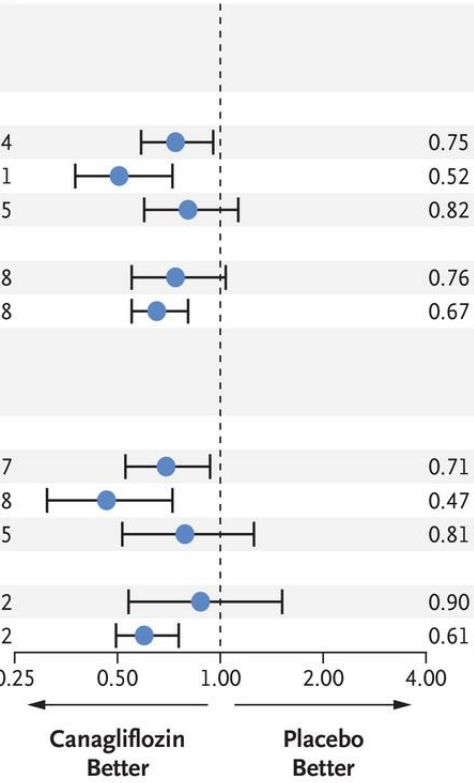
Effects of Canigliflozin on UACR and eGFR in CREDENCE



V Perkovic et al. NEJM 2019;380:2295-306

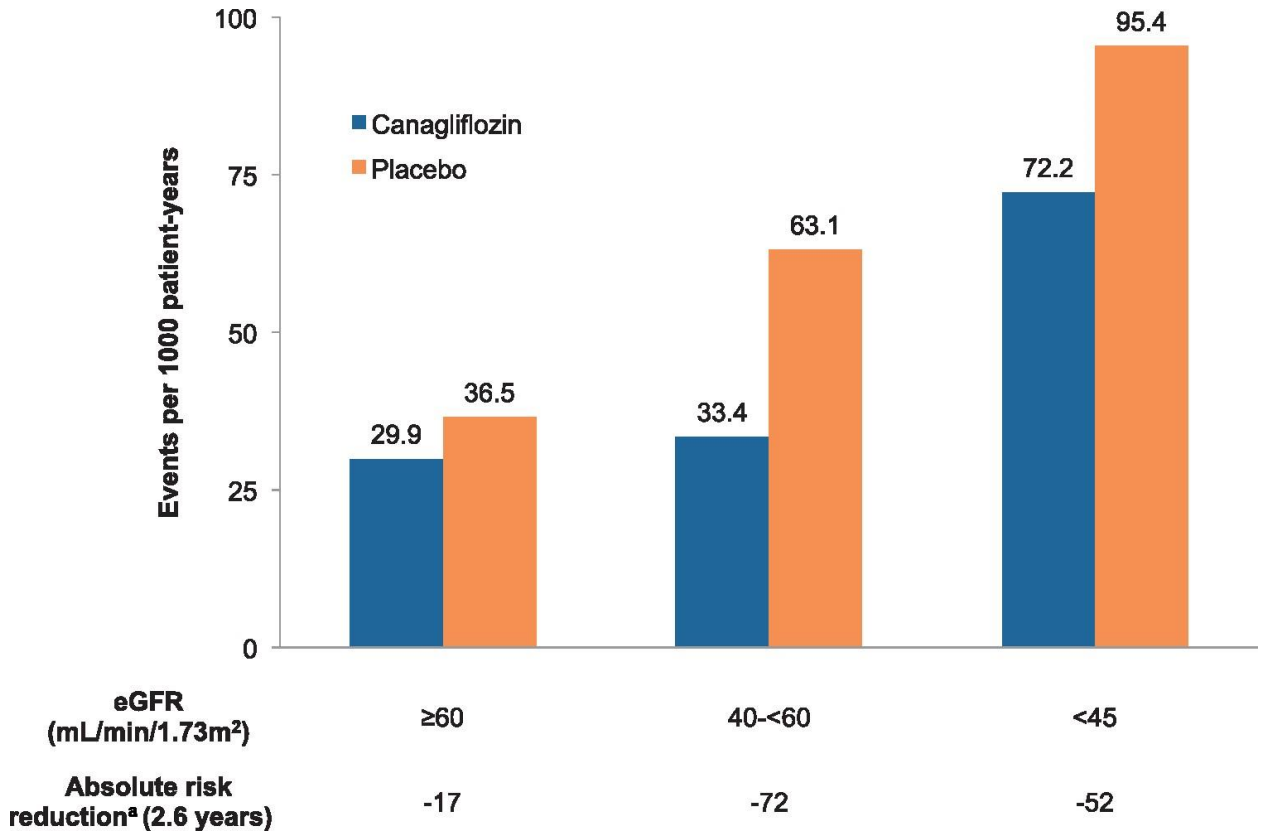
Results by baseline kidney function in CREDENCE

Subgroup	Canagliflozin (no. of patients/total no.)	Placebo (no. of patients/total no.)	Canagliflozin (events/1000 patient-yr)	Placebo (events/1000 patient-yr)	Hazard Ratio (95% CI)	P Value for Interaction
Primary composite outcome of ESKD, doubling of serum creatinine, or renal or CV death						
Screening estimated GFR						0.11
30 to <45 ml/min/1.73 m^2	119/657	153/656	72.2	95.4	0.75 (0.59–0.95)	
45 to <60 ml/min/1.73 m^2	56/640	102/639	33.4	63.1	0.52 (0.38–0.72)	
60 to <90 ml/min/1.73 m^2	70/905	85/904	29.9	36.5	0.82 (0.60–1.12)	
Baseline UACR						0.49
≤1000	69/1185	88/1163	22.0	28.8	0.76 (0.55–1.04)	
>1000	176/1017	252/1036	69.6	100.8	0.67 (0.55–0.81)	
Renal-specific composite outcome of ESKD, doubling of serum creatinine, or renal death						
Screening estimated GFR						0.18
30 to <45 ml/min/1.73 m^2	85/657	115/656	51.6	71.7	0.71 (0.53–0.94)	
45 to <60 ml/min/1.73 m^2	33/640	66/639	19.7	40.8	0.47 (0.31–0.72)	
60 to <90 ml/min/1.73 m^2	35/905	43/904	14.9	18.5	0.81 (0.52–1.26)	
Baseline UACR						0.16
≤1000	29/1185	31/1163	9.2	10.2	0.90 (0.54–1.50)	
>1000	124/1017	193/1036	49.1	77.2	0.61 (0.49–0.76)	



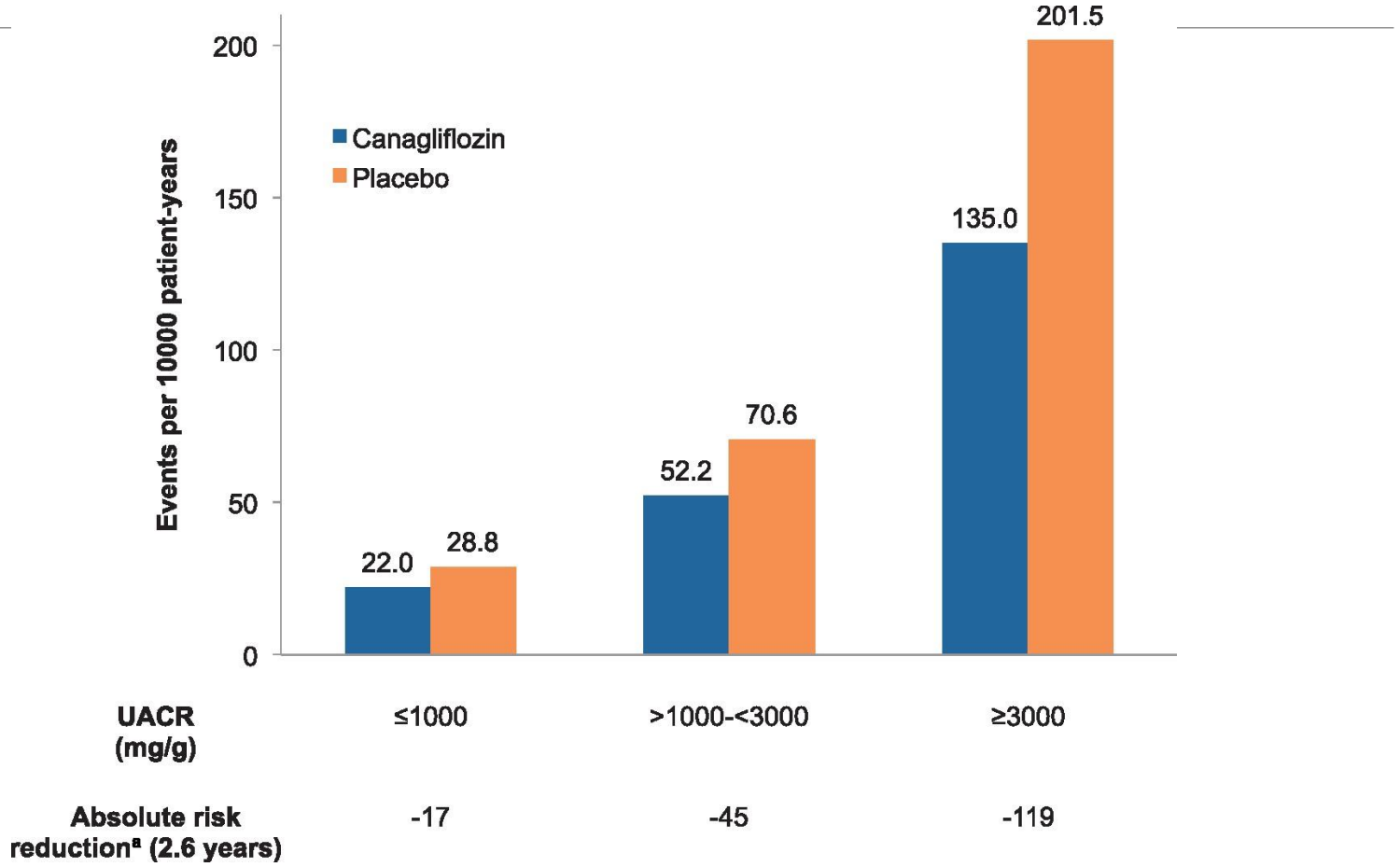
V Perkovic et al. NEJM 2019;380:2295-306

Estimated number of primary events (doubling of serum creatinine, ESKD or cardiovascular or kidney-related death in CREDENCE



Perkovic Nephrol Dial Transplant, Volume 35, Issue Supplement_1, January 2020, Pages i48–i55

Estimated number of primary events (doubling of serum creatinine, ESKD or cardiovascular or kidney-related death in CREDENCE



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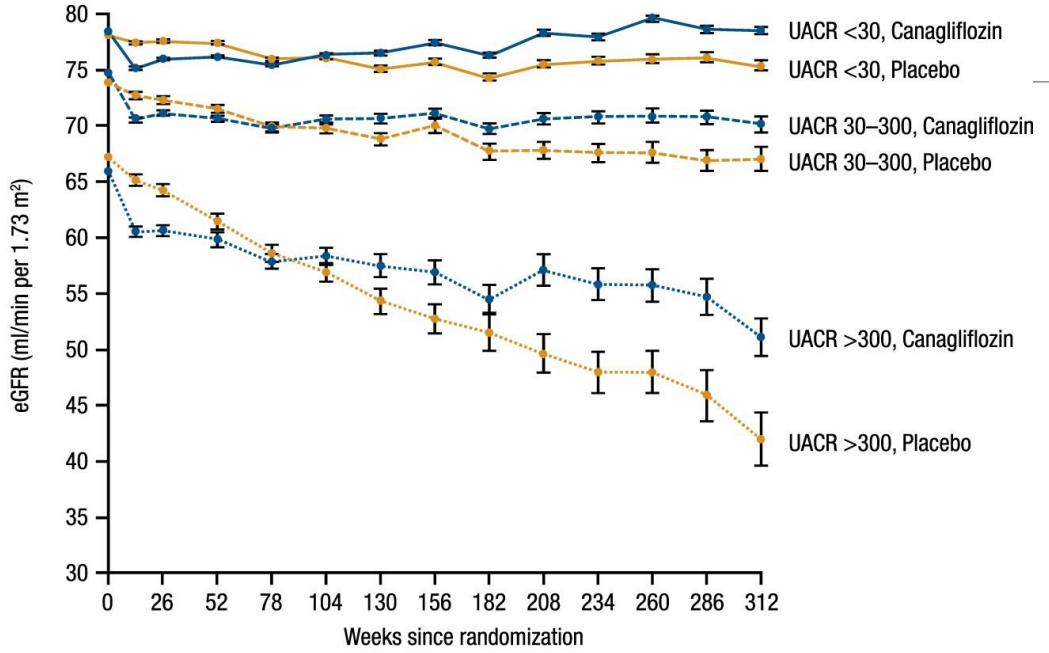
Effect of canagliflozin on eGFR over time by baseline UACR in the Canagliflozin Cardiovascular Assessment Program (CANVAS)



Participants, n													
UACR <30	Canagliflozin	3960	3739	3613	3390	3206	2126	1622	1433	1498	1327	1408	1264	1231
	Placebo	2947	2788	2677	2473	2263	1239	742	636	646	564	587	523	504
UACR 30–300	Canagliflozin	1300	1232	1181	1098	1030	645	499	435	454	387	407	358	349
	Placebo	933	876	837	759	680	352	225	193	200	178	183	170	159
UACR >300	Canagliflozin	398	373	368	331	287	157	97	82	77	72	68	64	63
	Placebo	344	325	306	263	227	110	58	49	48	40	34	30	26

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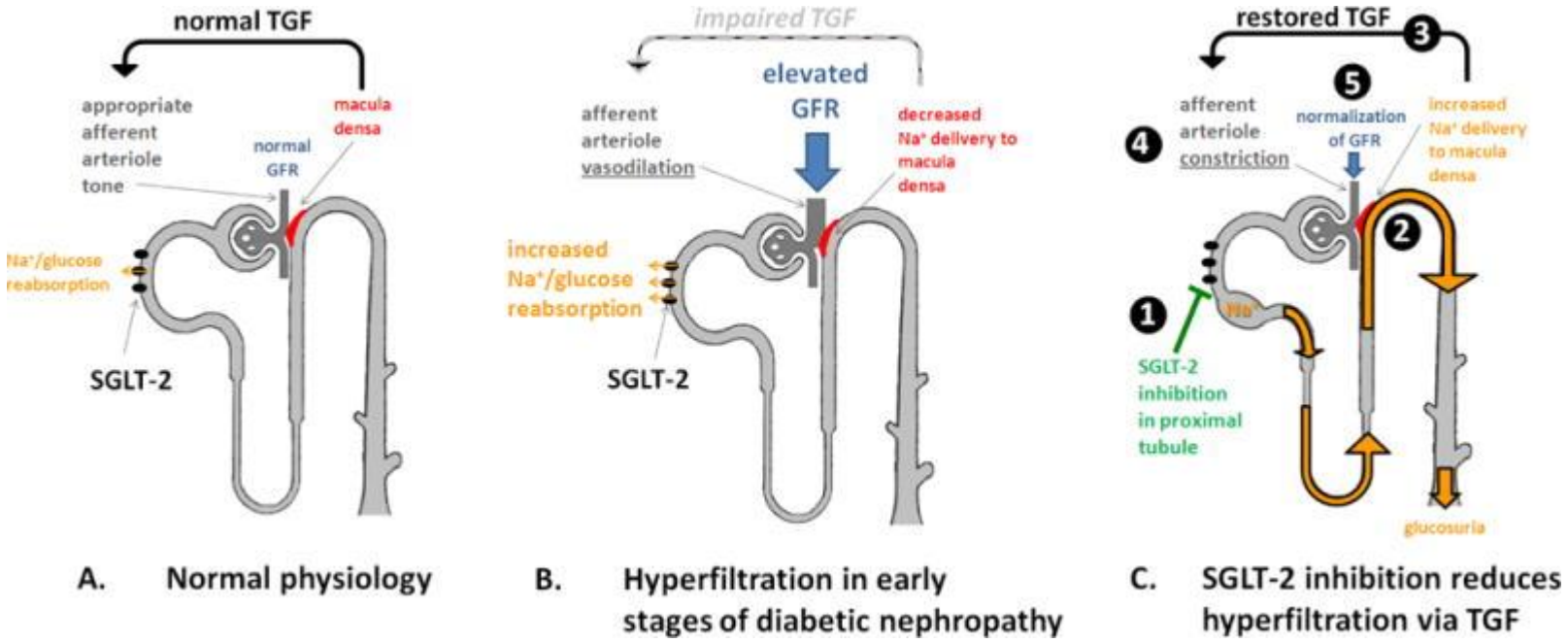
TGF Hypothesis of Benefit



Lytvyn Y et al. Curr Opin Nephrol Hypertens. 2016 May; 25(3): 232–239.

Dapa-CKD

eGFR 25-75

UACR 200-5000

On maximally tolerated ACEI or ARB

Either diabetic or nondiabetic, though 2/3 with diabetes

Primary endpoint

- Halving eGFR
- ESRD
- Renal or cardiovascular death

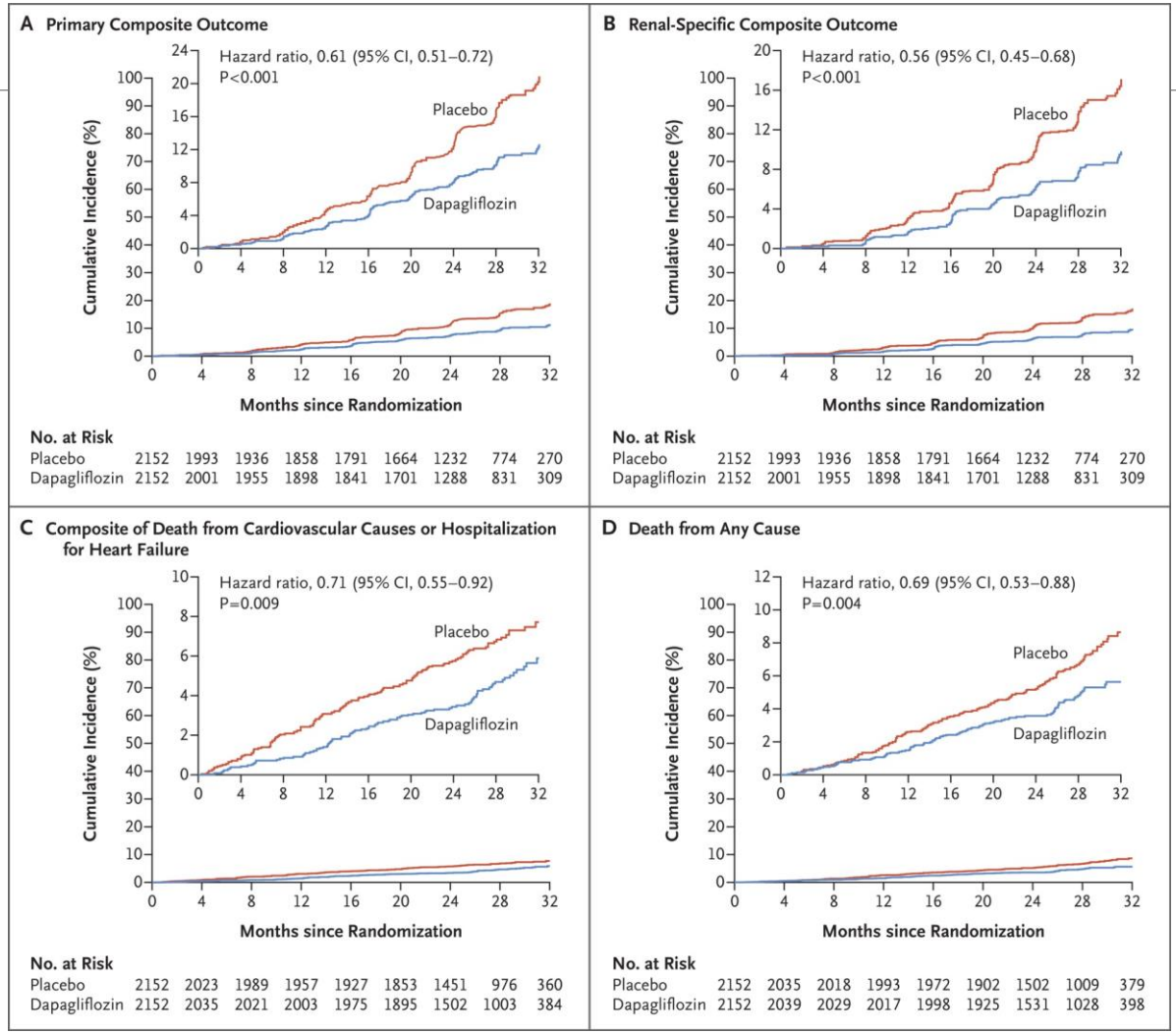
Study stopped early for efficacy

Participant Characteristics in DAPA CKD

	Dapagliflozin (n=2152)	Placebo (n=2152)
Age	61.8 ± 12.1	61.9 ± 12.1
Female (%)	32.9 (%)	33.3 (%)
Race (%) White Black Asian Other	 52.2 4.8 34.8 8.1	 54.2 4.0 33.4 8.4
ACEI or ARB (%)	98.4	97.9
Diabetes (%)	67.6	67.4
eGFR % below 30 ml/min/1.73m^2	43.2 ± 12.3 13.6%	43.0 ± 12.4 15.4%
Median UACR (IQR)	965 (472, 1903)	934 (482, 1868)

Heerspink et al NEJM 2020;381:1436-46

DAPA CKD Results



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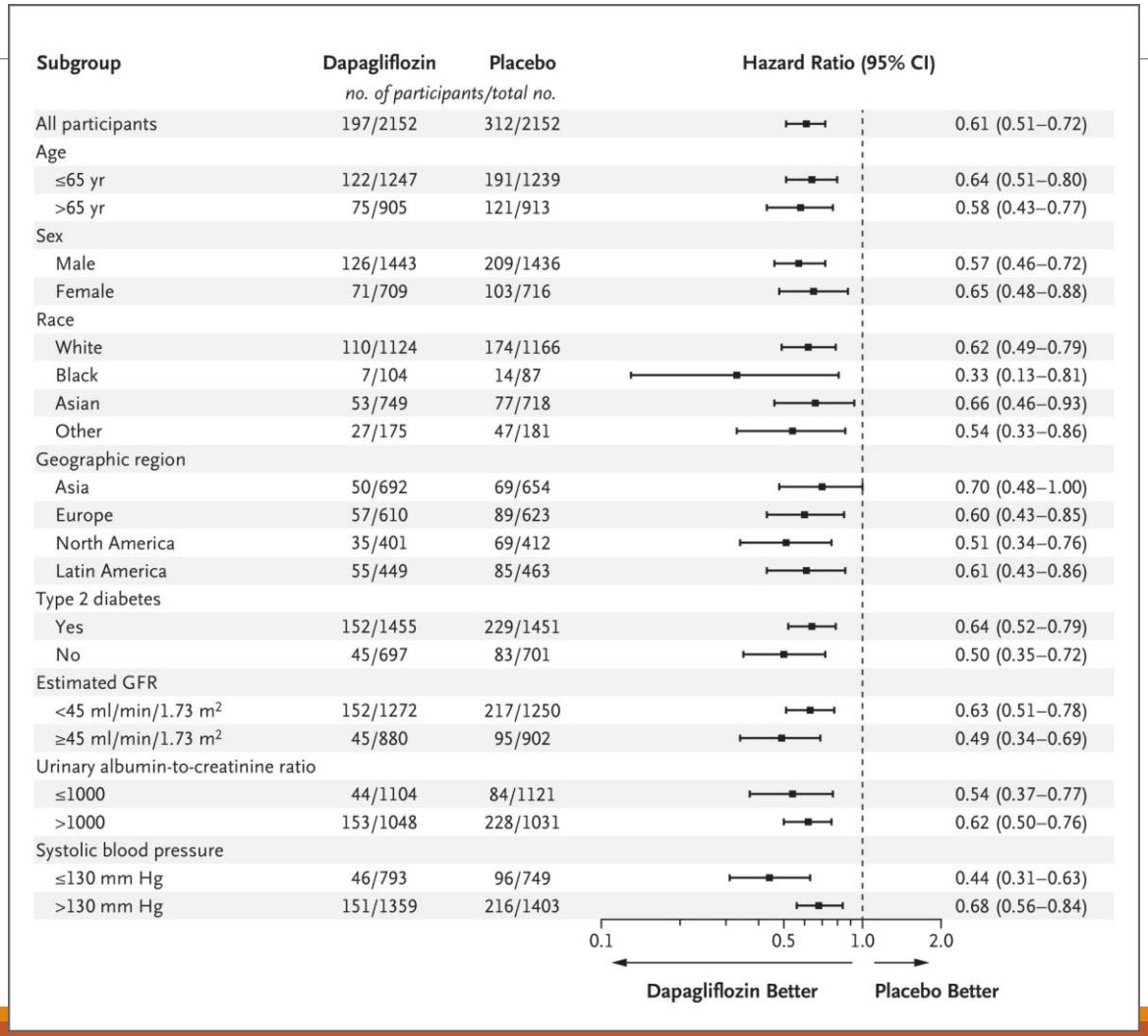
Subgroups DAPA CKD



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)

Heerspink et al NEJM 2020;381:1436-46

EMPA-KIDNEY

eGFR 20 to <45 regardless of albuminuria or eGFR 45 to < 90 with UACR at least 200 mg/g

Either diabetic or nondiabetic

Primary endpoint

- eGFR < 10 ml/min/1.73m^2
- 40% decline in eGFR
- ESRD
- Renal death

Study stopped early for efficacy

Participant Characteristics in EMPA-KIDNEY

	Empagliflozin (n=3304)	Placebo (n=3305)
Age	63.9 ± 13.9	63.8 ± 13.9
Female (%)	332 (%)	33.1 (%)
Race (%) White Black Asian Other	 58.7 3.9 36.1 1.3	 58.1 4.1 36.3 1.6
ACEI or ARB (%)	85.7	84.6
Diabetes (%)	46.2	45.8
eGFR % below 30 ml/min/1.73m^2	37.4 ± 14.5 34.2%	37.3 ± 14.4 34.8%
Median UACR (IQR)	331 (46, 1061)	327 (54, 1074)

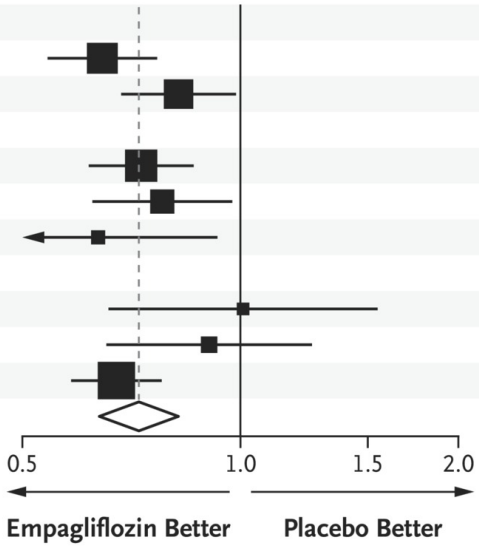
Outcomes in EMPA-KIDNEY

	Empagliflozin (3304) n, %	Placebo (3305) n, %	HR (95% CI)
Primary Outcome (Progression of kidney disease or CV death)	432 (13.1)	558 (16.9)	0.72 (0.63,0.82)
Hospitalization for CHF or CV death	131 (4.0)	152 (4.6)	0.84 (0.67, 1.07)
All cause death	148 (4.5)	167 (5.1)	0.87 (0.70, 1.08)
CV death	59 (1.8)	699 (2.1)	0.84(0.60, 1.19)
ESRD or CV death	163 (4.9)	217 6.6)	0.73 (0.59, 0.89)
Progression of Kidney Disease*	384 (11.6)	504 (15.2)	0.71 (0.62, 0.81)

Defined as ESRD, decrease eGFR to 10 ml/min/1.73m2, 40% decline in eGFR, or renal death

Subgroups EMPA Kidney

Subgroup	Empagliflozin (*no. of patients with event/total no.*)	Placebo (*no. of patients with event/total no.*)	Hazard Ratio for Progression of Kidney Disease or Death from Cardiovascular Causes (95% CI)
Diabetes mellitus			
Present	218/1525	306/1515	0.64 (0.54–0.77)
Absent	214/1779	252/1790	0.82 (0.68–0.99)
Estimated GFR			
<30 ml/min/1.73 m^2	247/1131	317/1151	0.73 (0.62–0.86)
≥30 to <45 ml/min/1.73 m^2	140/1467	175/1461	0.78 (0.62–0.97)
≥45 ml/min/1.73 m^2	45/706	66/693	0.64 (0.44–0.93)
Urinary albumin-to-creatinine ratio			
<30	42/665	42/663	1.01 (0.66–1.55)
≥30 to ≤300	67/927	78/937	0.91 (0.65–1.26)
>300	323/1712	438/1705	0.67 (0.58–0.78)
All patients	432/3304	558/3305	0.72 (0.64–0.82)



The EMPA-KIDNEY Collaborative Group. N Engl J Med2023;388:117-127

Side Effects

Initial Prescribing Information

The first FDA approved SGLT2 inhibitor was canagliflozin in 2017

- Approved for treatment of diabetes
- Initiation was not recommended if eGFR < 45 and contraindicated if eGFR < 30 ml/min/1.73m^2

Table 1: Adverse Reactions From Pool of Four 26−Week Placebo-Controlled Studies Reported in ≥ 2% of INVOKANA-Treated Patients*

Adverse Reaction	Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Urinary tract infections‡	3.8%	5.9%	4.4%
Increased urination§	0.7%	5.1%	4.6%
Thirst#	0.1%	2.8%	2.4%
Constipation	0.9%	1.8%	2.4%
Nausea	1.6%	2.1%	2.3%
	N=312	**N=425**	**N=430**
Female genital mycotic infections†	2.8%	10.6%	11.6%
Vulvovaginal pruritus	0.0%	1.6%	3.2%
	N=334	**N=408**	**N=404**
Male genital mycotic infections¶	0.7%	4.2%	3.8%

*

Warnings and Precautions: Canagliflozin Initial FDA Label

Lower Limb Amputation

Hypotension

Ketoacidosis

AKI and Impairment in Renal Function

Hyperkalemia

Urosepsis and Pyelonephritis

Hypoglycemia and Concomitant Use with Insulin and Insulin Secretagogues

Genital Mycotic Infections

Hypersensitivity reactions

Bone fracture

Increase in LDL

Amputation

Initial CANVAS studies suggested a 2 fold increase in amputation

- 95 amputations canagliflozin vs. 22 (1.5%) Placebo
- Most amputations were toe or foot

There was a black box warning regarding leg and foot amputation. This box was removed in 2020

- FDA felt that there was an increased risk, but less than previous trials suggested
- Balanced by benefit on cardiovascular and renal outcomes
- Risk may be less with other SGLT2 inhibitors

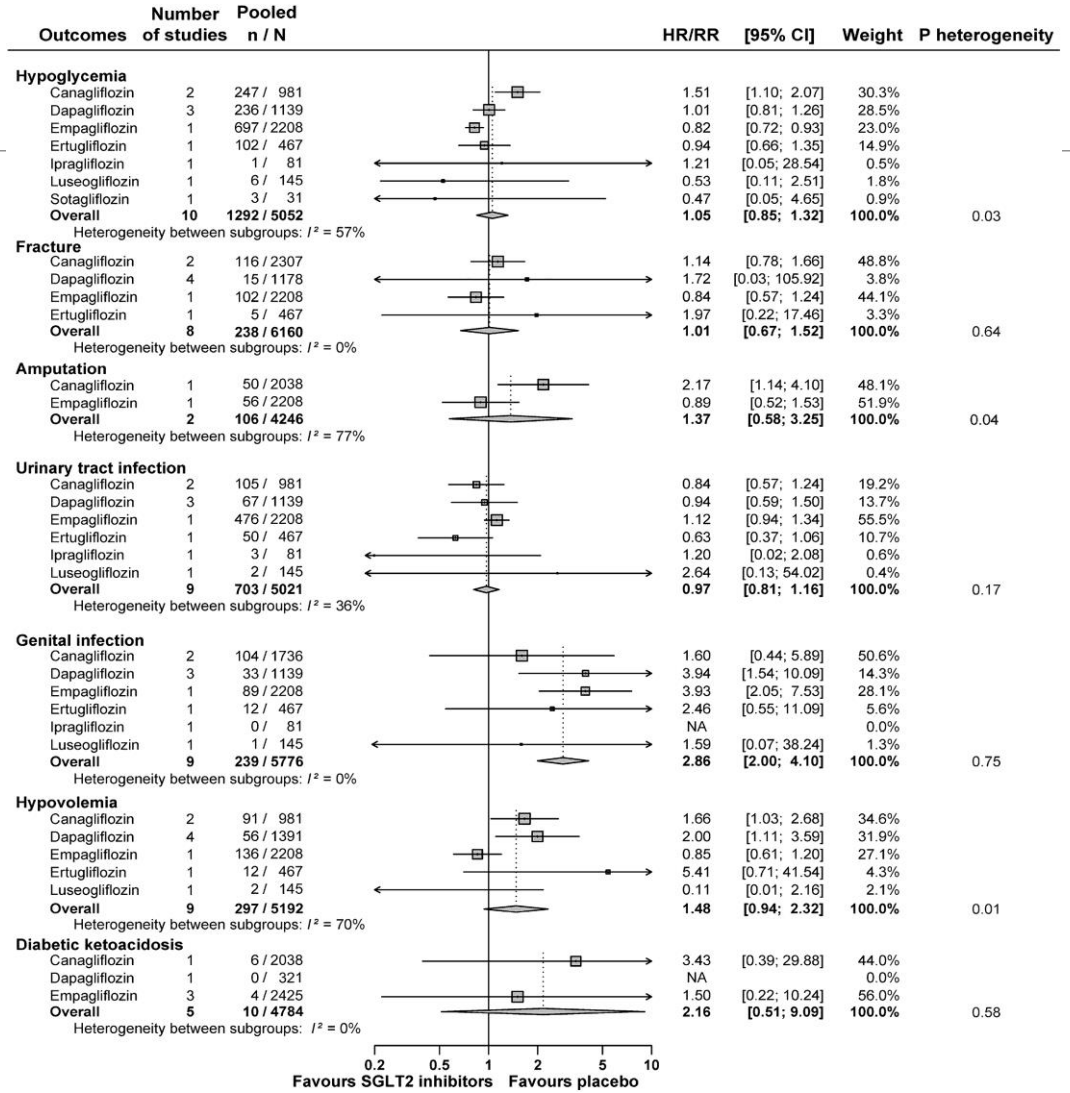
Pooled analyses suggest side effect incidence lower

With more clinical trials, pooled analyses of safety outcomes suggests that other risks are lower than previously thought

Most consistent increased risks are

- Volume depletion
- Genital infections
- Ketoacidosis

Safety Outcomes SGLT2 inhibitors: Meta-analysis



Ketoacidosis

Increased occurrence of ketoacidosis with SGLT2 inhibitors

- Wasn't very common in trials (<1%)
- Post-marketing risk appears to be higher
  - Estimated rate 1.4 per 1,000 person years, which was 3 fold higher than DPP-4 inhibitors (Douros et al Ann Intern Med 2020;173:417)
- Risk higher in Type 1 diabetes. Not approved for use by FDA, though dapagliflozin is approved for Type 1 diabetes in Europe
- Risk higher with
  - Reduction in insulin dose
  - Sudden restriction of carbohydrate availability (fasting, decreased intake in illness)
  - Surgical stress, trauma, intercurrent illness
  - Heavy alcohol use

Safety Outcomes in EMPA-KIDNEY

	Empagliflozin (3304) n, %	Placebo (3305) n, %	HR (95% CI)
Serious UTI	52 (1.6)	54 (0.84)	0.94 (0.64,1.37)
Serious Genital Infection	1 (< 0.1)	1 (< 0.1)	
Serious Hyperkalemia	92 (2.8)	109 (3.3)	0.83 (0.63, 1.09)
Serious AKI (admission)	107 (3.2)	135 (4.1)	0.78 (0.60, 1.00)
Serious Dehydration	30 (0.9)	24 (0.7)	1.25 (0.73, 2.14)
Ketoacidosis	6 (0.2)	1 (<0.1)	
Lower-limb amputation	28 (0.8)	19 (0.6)	1.43 (0.80,2.57)
Bone Fracture	133 (4.0)	123 (3.7)	1.08 (0.84,1.38)
Symptomatic Dehydration	83 (2.5)	76 (2.3)	1.10 (0.81, 1.15)

In Practice

Indications for SGLT2 inhibitors

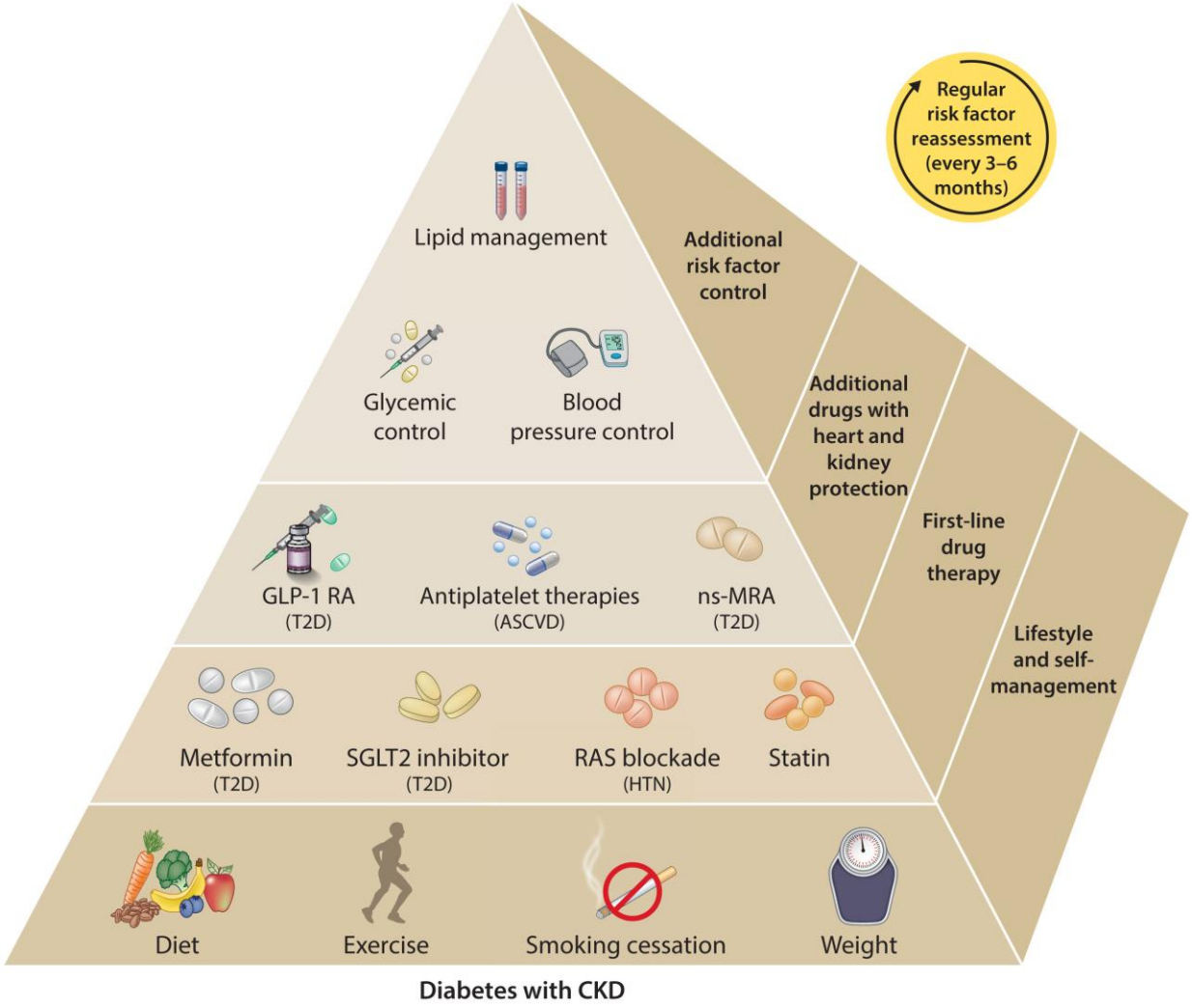
Table 1. Current indications for SGLT2 inhibitors

Indication	Criteria	Kidney function
Congestive heart failure	• NYHA classes II–IV • Elevated NT-proBNP • All ejection fractions	• eGFR >20 ml/min per 1.73 m^2
Glycemic control or metabolic risk	• Type 2 diabetes mellitus • First-line for glycemic control (along with metformin)	• eGFR ≥60 ml/min per 1.73 m^2 • Anticipated HbA1c ↓: 0.6%–0.9% • Anticipated weight ↓: 2–3 kg
		• eGFR 45–59 ml/min per 1.73 m^2 • Anticipated HbA1c ↓: 0.3%–0.5% • Anticipated weight ↓: 1–2 kg
		• eGFR < 45 ml/min per 1.73 m^2 • Anticipated HbA1c ↓: minimal • Anticipated weight ↓: 1–2 kg
Reduction in ASCVD	• Type 2 diabetes mellitus • Established ASCVD or high risk for ASCVD[a]	• eGFR ≥ 30 ml/min per 1.73 m^2
* Diabetic kidney disease	• Type 2 diabetes mellitus	• eGFR ≥25 ml/min per 1.73 m^2 • UACR 200–5000 mg/g[b]
* Nondiabetic kidney disease	• Etiology of kidney disease: ischemic ne phropathy, IgA nephropathy, FSGS, chronic pyelonephritis, chronic interstitial nephritis • No immunosuppression in prior 6 mo	• eGFR ≥ 25 ml/min per 1.73 m^2 • UACR 200–5000 mg/g[b]

*Note that this is before EMPA Kidney was reported with inclusion eGFR ≥ 20 ml/min/1.73m^2

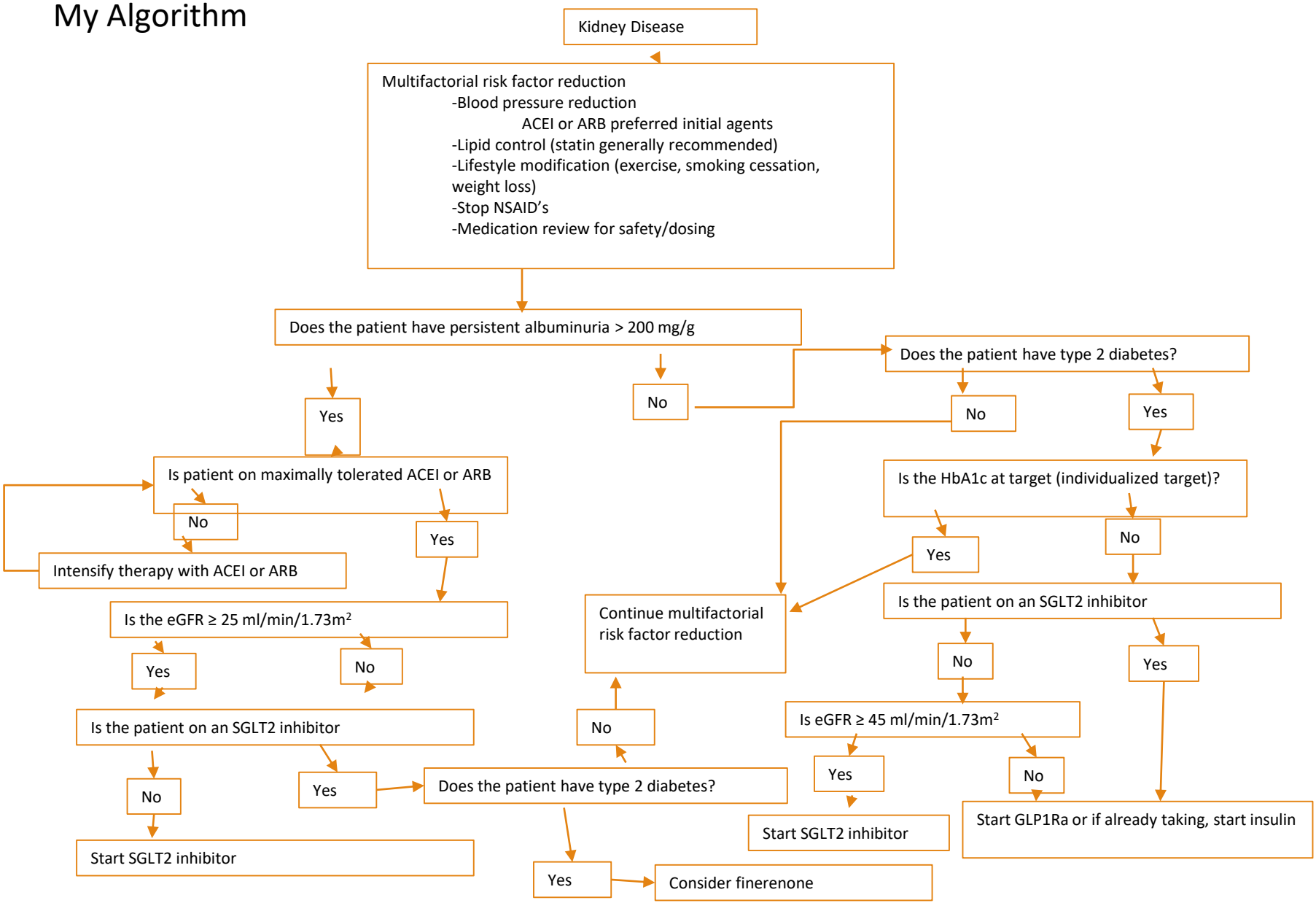
Yau KI reports. 2022;7:1463-76

KDIGO Diabetes with CKD Care



Kidney International 2022 102S1-S127DOI: (10.1016/j.kint.2022.06.008)

My Algorithm



KDIGO Practice points SGLT2

It is reasonable to withhold SGLT2i in times of prolonged fasting, surgery or critical medical illness to decrease risk of ketosis

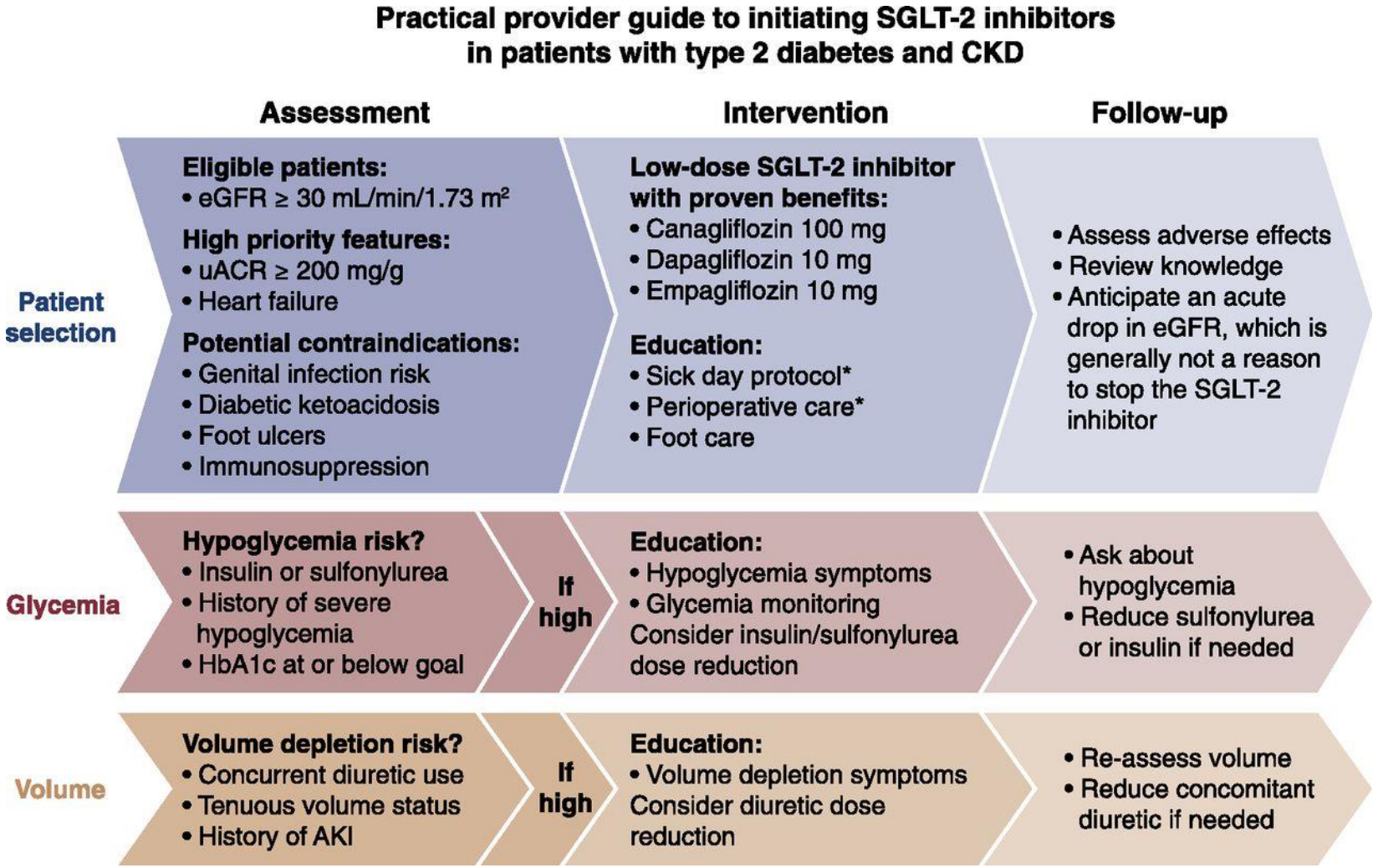
If a patient is at risk for hypovolemia,

- decreasing thiazide or loop diuretics before commencement of SGLT2i treatment
- Advise on symptoms of hypovolemia and hypotension
- F/U on volume status

A reversible decrease in the eGFR with initiation may occur and is generally not an indication to discontinue treatment

Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 ml/min per 1.73 m^2, unless it is not tolerated or kidney replacement therapy is initiated

Practical approach to initiating sodium-glucose transport protein 2 (SGLT2) inhibitors in patients with type 2 diabetes and CKD. *Sick day protocol (for illness or excessive exercise or alcohol intake): temporarily withhold sodium-glucose transport protein ...



Sophia Zoungas, and Ian H. de Boer CJASN 2021;16:631-633

Summary 1

While initially approved as a diabetic medication, SGLT2 inhibitors decrease cardiovascular outcomes (especially CHF) and progression of kidney disease

As a nephrologist, I do not consider these diabetes medications, I consider them medications to slow progression to dialysis

They should be standard of care in patients with CKD and proteinuria

- They can be started if eGFR ≥ 20 ml/min/1.73m^2
- They should be continued until dialysis

Summary 2

When starting, evaluate volume status as the medications are mild diuretics

- If euvolemic, consider decreasing diuretic

When starting, evaluate glucose control and hypoglycemia risk

- By themselves, do not cause hypoglycemia but can when combined with sulfonylurea or insulin
- If risk for hypoglycemia and on other agents, decrease those agent

Hold with acute illness or if going to be NPO

Increased risks of DKA, mycotic infections

- Small but present risk of amputation. May avoid in those with foot lesions