SGLT2 remmers en GLP-1 agonisten
Van DM naar CKD?

Dr. Gerald Vervoort

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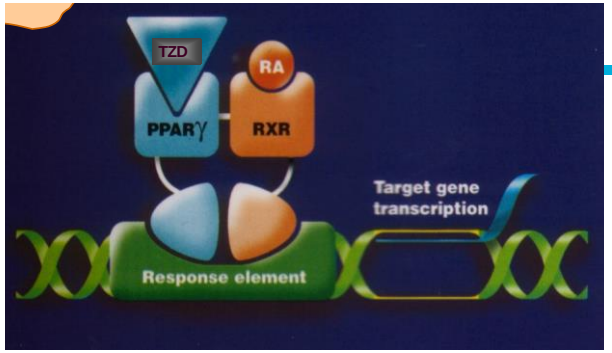


PPAR-gamma agonists (Rosiglitazone) → insulin sensitizer
by binding to PPAR in fat cells and making the cells more responsive to insulin

>1999 in clinical use because of its effectiveness at decreasing blood glucose

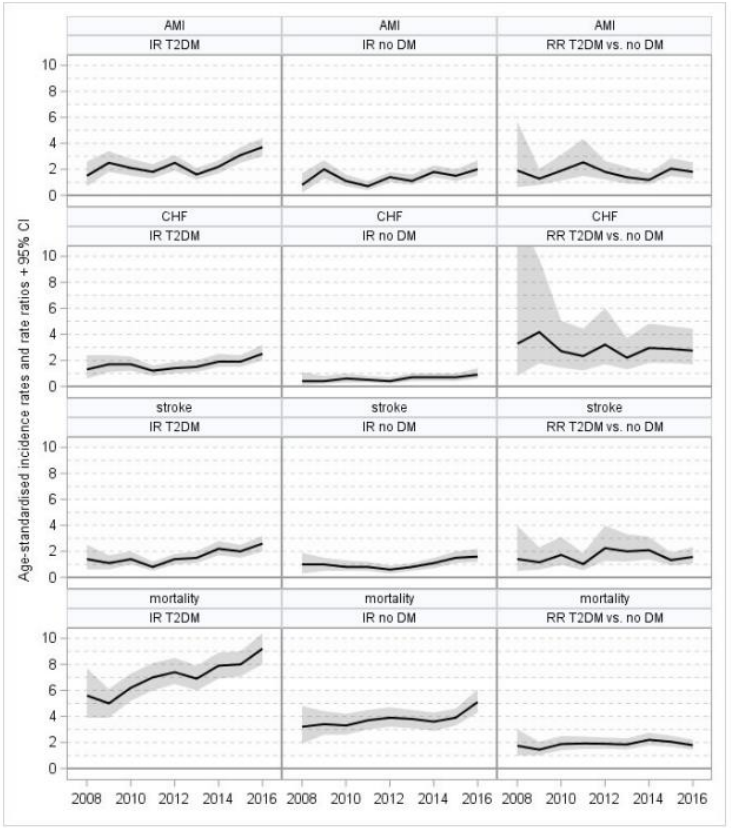
→ EASD 2005: increased risk of heart failure/attacks, death (>13000 lawsuits against GSK)

FDA guideline >2008: To establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk.

Cijfers & Context
Ruim 1,1 miljoen mensen met diabetes

(Type 2) diabetes increases the risk of AMI by 69%, CHF by 185% and stroke by 57%
(data from the Netherlands)

Age-standardised IR and RR of major cardiovascular events and mortality, T2DM vs. no DM



AMI = acute myocardial infarction; CHF = congestive heart failure; CI = confidence interval; DM = diabetes mellitus; IR = incidence rates; RR = rate ratio; T2DM = type 2 diabetes mellitus

Heintjes et al. Trends in diabetes complications and risk factors. Neth J Med: 2019.

Cijfers & Context
Ruim 1,1 miljoen mensen met diabetes

- **Globally, CKD (Chronic Kidney Disease) in diabetes occurs in ±30% in patients with type 1 diabetes and ±40% in type 2 accounting for nearly half of the cases of kidney failure requiring replacement therapy[1].**
- **In the Netherlands the prevalence of CKD stage 1-5 in age group 20-74 years is estimated 3,7% in non-diabetes and 14,1% in diabetes (Lifelines*) and 8,6% vs 21,4% (PREVEND#)[2].**
- **However, patients with (type 2) diabetes and CKD are more likely to die (±90%) than progress to kidney failure (±10%)[3].**
- **The most common causes of death are atherosclerotic cardiovascular disease and heart failure.**

1. National Kidney Foundation. KDOQI clinical guideline for diabetes and CKD: 2012 update. AmJ Kidney Dis: 2012.
2. Brück K. et al. CKD prevalence varies across the European General Population. J Am Soc Nephrol: 2016.
3. Alicic R. et al. Diabetic Kidney Disease: challenges, progress, and possibilities. Clindamycine J Am Soc Nephrol: 2017

** Age range: 20+, general practitioners*
 # Age range 28-75, population register

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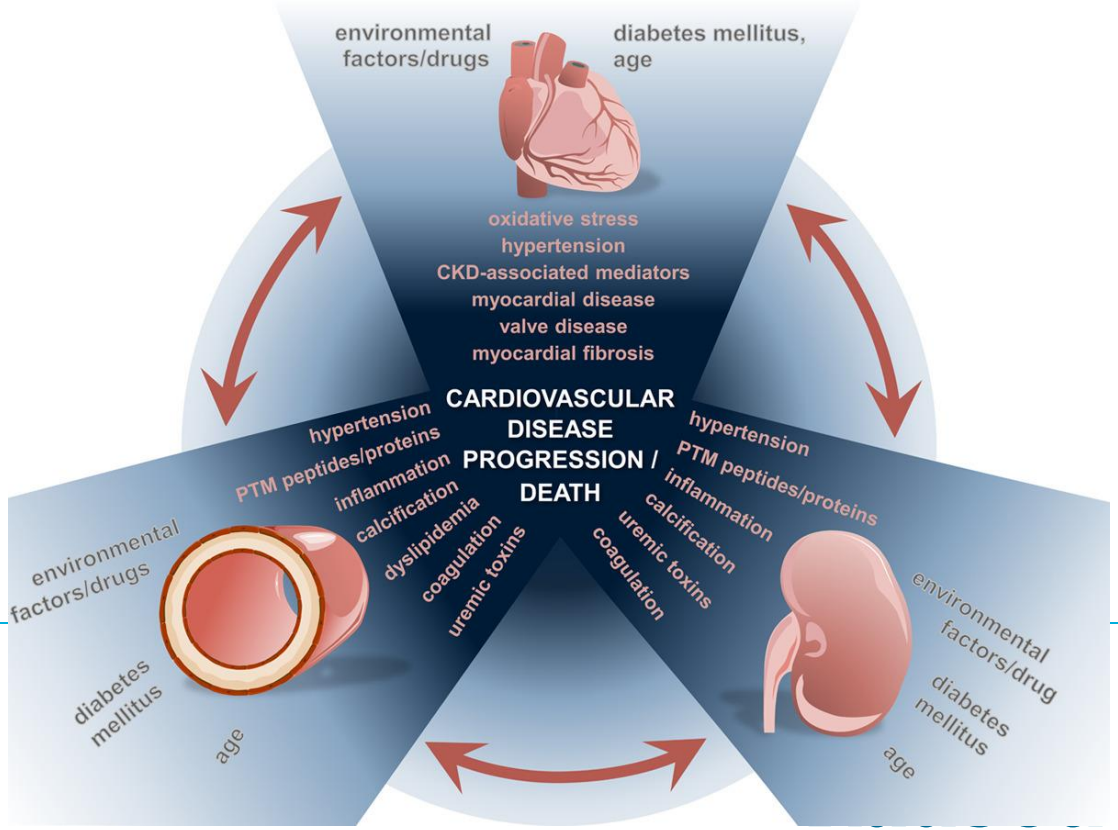
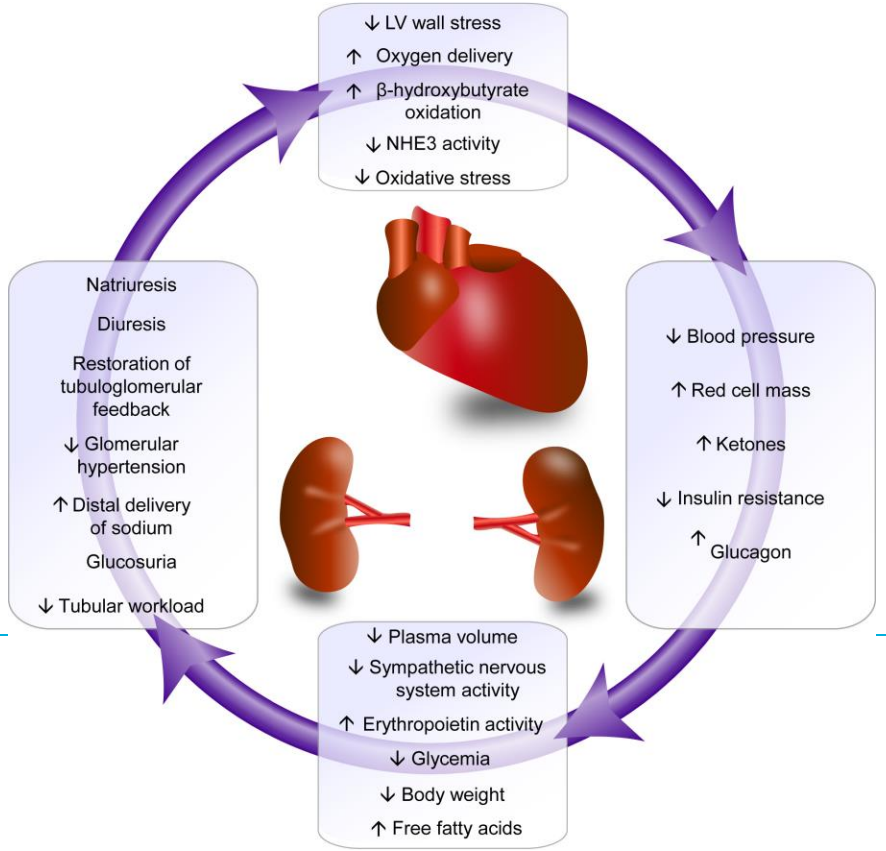
Heart Failure, Diabetes Mellitus, and Chronic Kidney Disease
A Clinical Conundrum



Tuttle K.R. et al. AKKD 2021; 2. Jankowski J. et al. Circulation 2016; 3. Aguilar D. Circulation 2016.

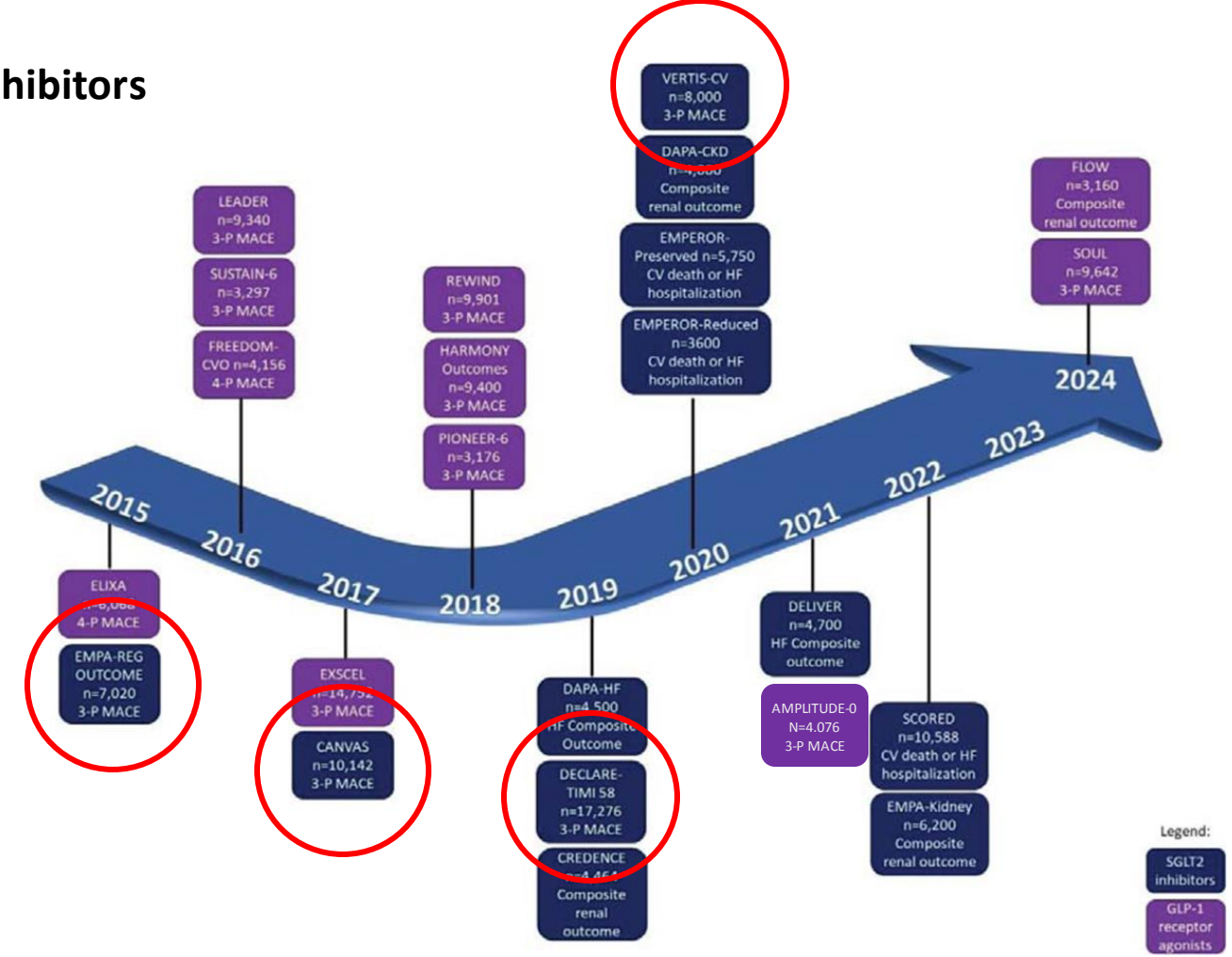
Organ protection

- **Heart Failure, Diabetes Mellitus, and Chronic Kidney Disease**
  A Clinical Conundrum

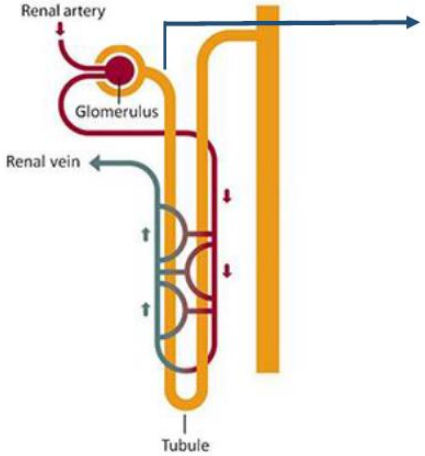


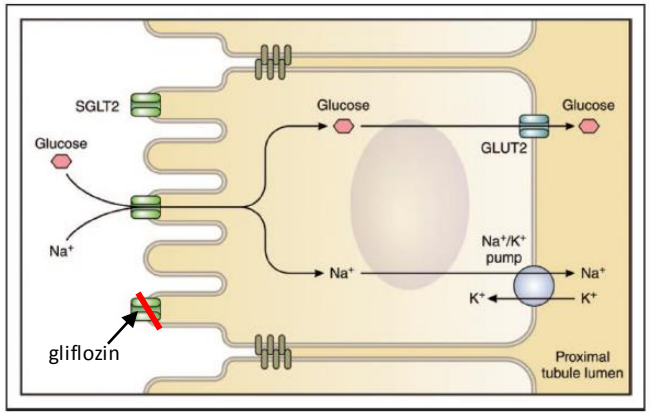
Tuttle K.R. et al. AKKD 2021; 2. Jankowski J. et al. Circulation 2016; 3. Aguilar D. Circulation 2016.

SGLT2 inhibitors



Sodium-glucose cotransporter 2 inhibitors (SGLT2-inh.)





~60 g/day (240kCal)

~25 mmol/day

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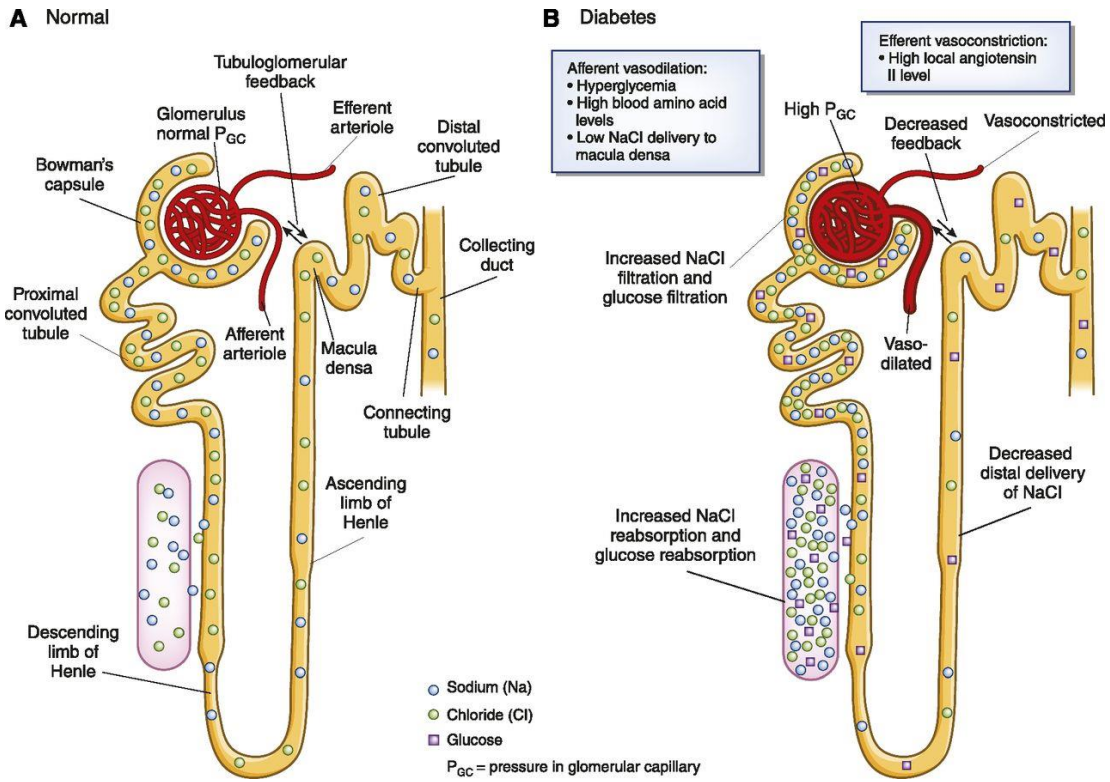
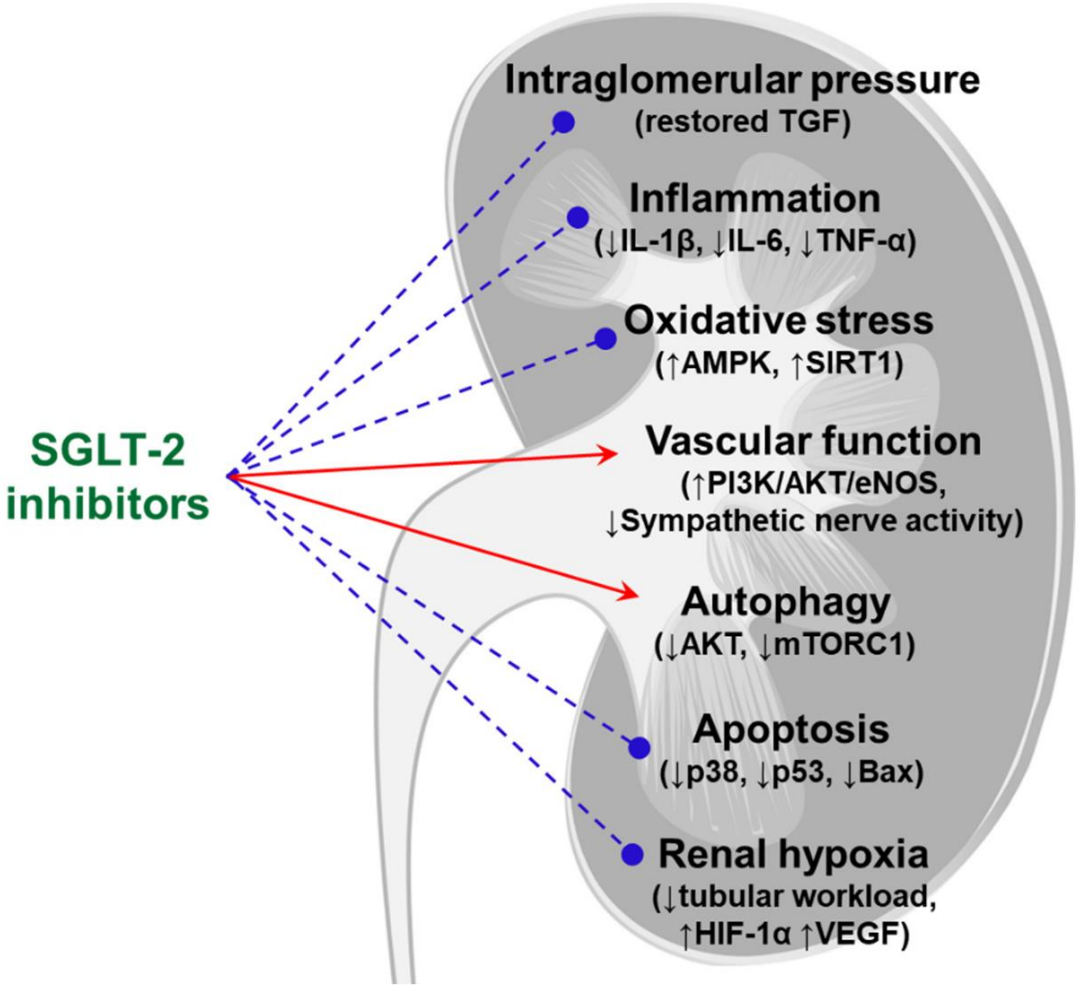
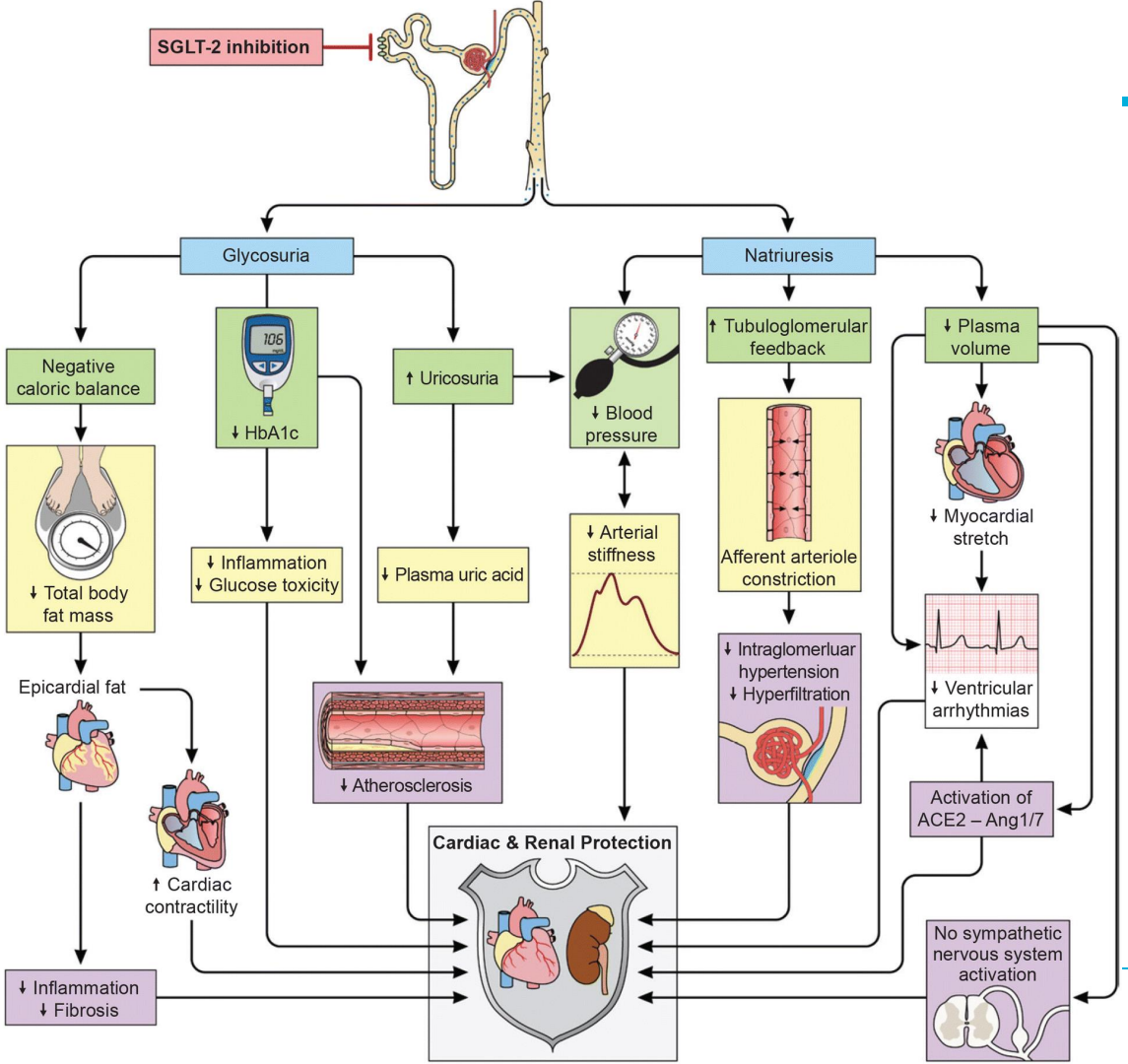
Normal and diabetic nephron with altered renal hemodynamics.

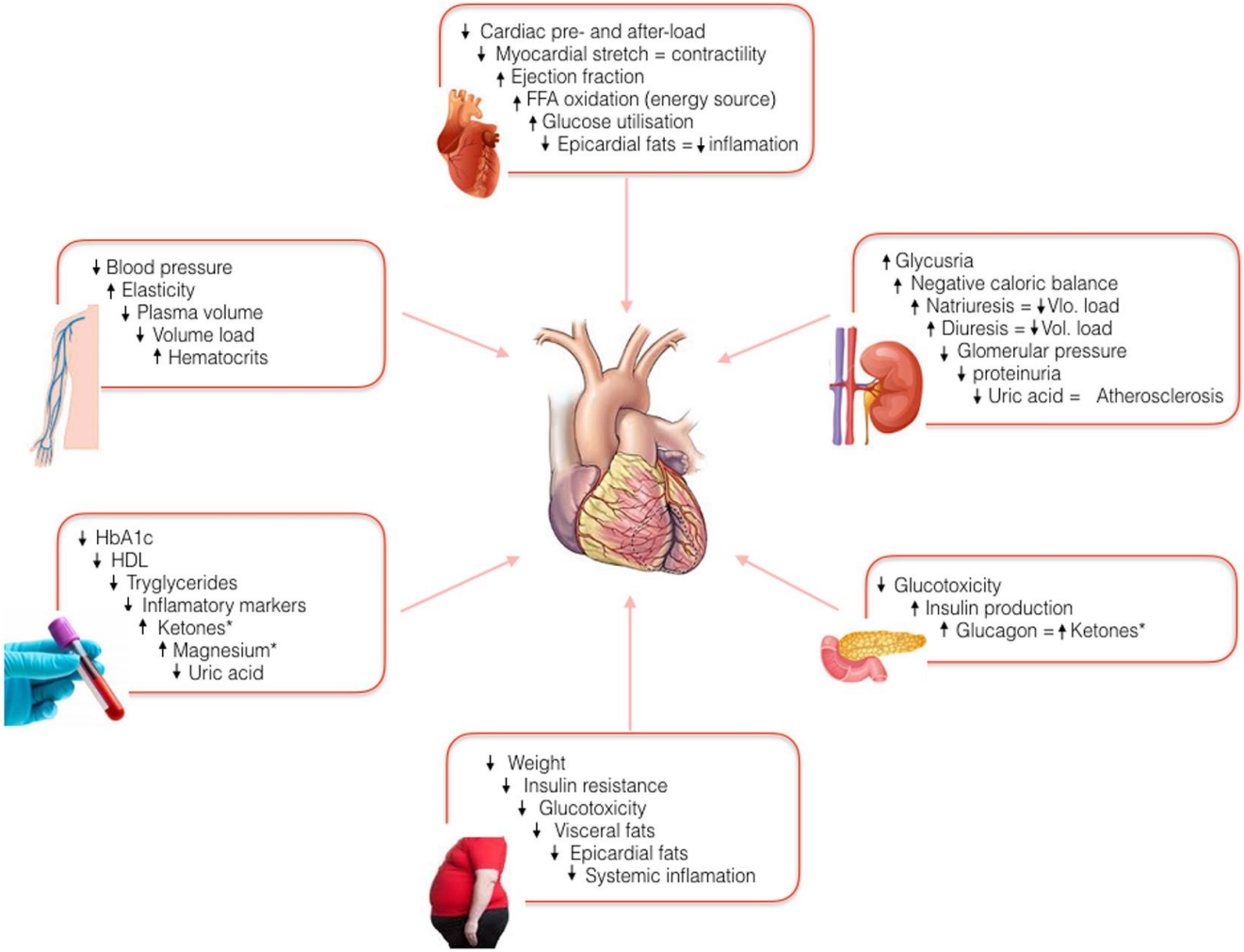


Radica Z. Alicic et al. CJASN doi:10.2215/CJN.11491116


SGLT-2 inhibitors
Intraglomerular pressure
(restored TGF)
Inflammation
(↓IL-1β, ↓IL-6, ↓TNF-α)
Oxidative stress
(↑AMPK, ↑SIRT1)
Vascular function
(↑PI3K/AKT/eNOS,
↓Sympathetic nerve activity)
Autophagy
(↓AKT, ↓mTORC1)
Apoptosis
(↓p38, ↓p53, ↓Bax)
Renal hypoxia
(↓tubular workload,
↑HIF-1α ↑VEGF)


SGLT-2 inhibition
Glycosuria
Natriuresis
Negative caloric balance
↓ HbA1c
↑ Uricosuria
↓ Blood pressure
↑ Tubuloglomerular feedback
↓ Plasma volume
↓ Total body fat mass
↓ Inflammation
↓ Glucose toxicity
↓ Plasma uric acid
↓ Arterial stiffness
Afferent arteriole constriction
↓ Myocardial stretch
Epicardial fat
↓ Atherosclerosis
↓ Intraglomerluar hypertension
↓ Hyperfiltration
↓ Ventricular arrhythmias
↑ Cardiac contractility
Cardiac & Renal Protection
Activation of ACE2 – Ang1/7
↓ Inflammation
↓ Fibrosis
No sympathetic nervous system activation

Current clinical and hypothetical explanations for the cardioprotective effect of SGLT2 inhibitors



* Mild increment is associated with better CV outcome

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Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Major Adverse Cardiovascular Events—Composite of Myocardial Infarction, Stroke, or Cardiovascular Death

A Overall MACEs

	Treatment		Placebo				
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment / Favors placebo	Weight, %
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)		15.72
CANVAS program	NA/5795	26.9	NA/4347	31.5	0.86 (0.75-0.97)		20.12
DECLARE-TIMI 58	756/8582	22.6	803/8578	24.2	0.93 (0.84-1.03)		32.02
CREDENCE	217/2202	38.7	269/2199	48.7	0.80 (0.67-0.95)		10.92
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)		21.23
Fixed-effects model ($Q = 5.22$; $df = 4$; $P = .27$; $I^2 = 23.4\%$)					0.90 (0.85-0.95)		

B MACEs by ASCVD status

	Treatment		Placebo				
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment / Favors placebo	Weight, %
Patients with ASCVD							
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)		19.19
CANVAS program	NA/3756	34.1	NA/2900	41.3	0.82 (0.72-0.95)		21.16
DECLARE-TIMI 58	483/3474	36.8	537/3500	41.0	0.90 (0.79-1.02)		24.90
CREDENCE	155/1113	55.6	178/1107	65.0	0.85 (0.69-1.06)		8.82
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)		25.93
Fixed-effects model ($Q = 4.53$; $df = 4$; $P = .34$; $I^2 = 11.8\%$)					0.89 (0.84-0.95)		
Patients without ASCVD							
CANVAS program	NA/2039	15.8	NA/1447	15.5	0.98 (0.74-1.30)		21.70
DECLARE-TIMI 58	273/5108	13.4	266/5078	13.3	1.01 (0.86-1.20)		62.07
CREDENCE	62/1089	22.0	91/1092	32.7	0.68 (0.49-0.94)		16.23
Fixed-effects model ($Q = 4.59$; $df = 2$; $P = .10$; $I^2 = 56.5\%$)					0.94 (0.83-1.07)		

3,7 → 3,3%/yr

McGuire et al., JAMA Cardiology 2020

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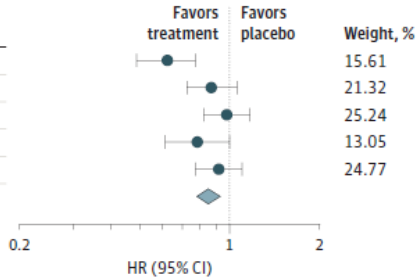
Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Cardiovascular Death

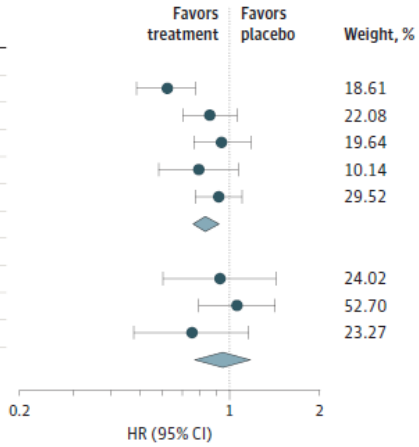
A Overall CV death

	Treatment		Placebo		Hazard ratio (95% CI)	Weight, %
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years		
EMPA-REG OUTCOME	172/4687	12.4	137/2333	20.2	0.62 (0.49-0.77)	15.61
CANVAS program	NA/5795	11.6	NA/4347	12.8	0.87 (0.72-1.06)	21.32
DECLARE-TIMI 58	245/8582	7.0	249/8578	7.1	0.98 (0.82-1.17)	25.24
CREDENCE	110/2202	19.0	140/2199	24.4	0.78 (0.61-1.00)	13.05
VERTIS CV	341/5499	17.6	184/2747	19.0	0.92 (0.77-1.10)	24.77
Fixed-effects model (Q = 11.22; *df* = 4; *P* = .02; I^2 = 64.3%)					0.85 (0.78-0.93)	



B CV death by ASCVD status

	Treatment		Placebo		Hazard ratio (95% CI)	Weight, %
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years		
Patients with ASCVD						
EMPA-REG OUTCOME	172/4687	12.4	137/2333	20.2	0.62 (0.49-0.77)	18.61
CANVAS program	NA/3756	14.8	NA/2900	16.8	0.86 (0.70-1.06)	22.08
DECLARE-TIMI 58	153/3474	10.9	163/3500	11.6	0.94 (0.76-1.18)	19.64
CREDENCE	75/1113	25.7	93/1107	32.4	0.79 (0.58-1.07)	10.14
VERTIS CV	341/5499	17.6	184/2747	19.0	0.92 (0.77-1.10)	29.52
Fixed-effects model (Q = 9.10; *df* = 4; *P* = .06; I^2 = 56.1%)					0.83 (0.76-0.92)	
Patients without ASCVD						
CANVAS program	NA/2039	6.5	NA/1447	6.2	0.93 (0.60-1.43)	24.02
DECLARE-TIMI 58	92/5108	4.4	86/5078	4.1	1.06 (0.79-1.42)	52.70
CREDENCE	35/1089	12.2	47/1092	16.4	0.75 (0.48-1.16)	23.27
Fixed-effects model (Q = 1.65; *df* = 2; *P* = .44; I^2 = 0.0%)					0.95 (0.77-1.17)	



1,67 → 1,35 %/yr

McGuire et al., JAMA Cardiology 2020

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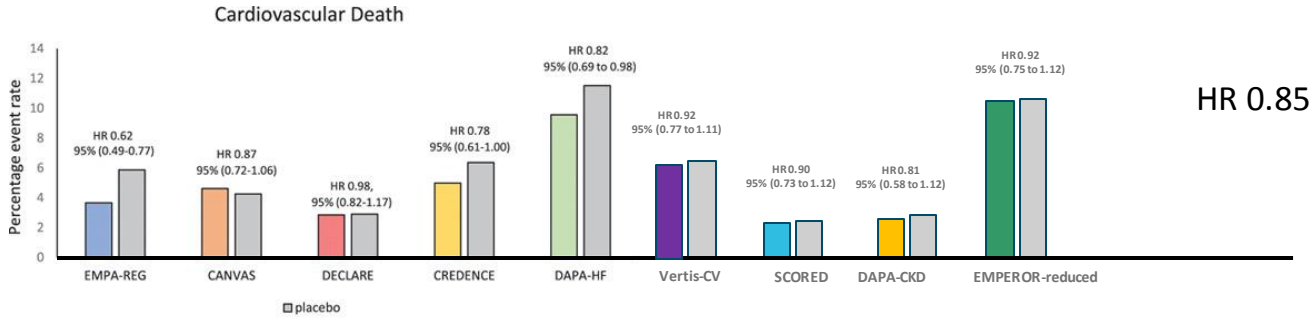
Hazard ratios (HRs) for key cardiovascular outcomes in cardiovascular and renal outcome trials with the SGLT2 inhibitors



HR 0.85

In addition to Rangaswami et al., Circulation 2020

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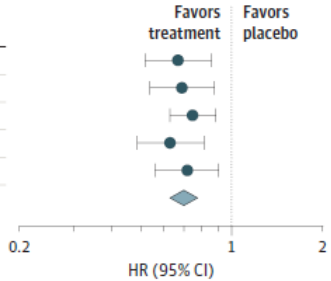
Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Hospitalization for Heart Failure

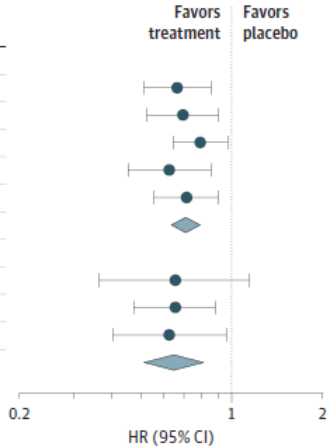
A Overall HHF

	Treatment		Placebo			Favors treatment	Favors placebo	Weight, %
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)			
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)			16.09
CANVAS program	NA/5795	5.5	NA/4347	8.7	0.67 (0.52-0.87)			17.10
DECLARE-TIMI 58	212/8582	6.2	286/8578	8.5	0.73 (0.61-0.88)			33.72
CREDENCE	89/2202	15.7	141/2199	25.3	0.61 (0.47-0.80)			16.01
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)			17.08
Fixed-effects model ($Q = 1.39$; $df = 4$; $P = .85$; $I^2 = 0.0\%$)					0.68 (0.61-0.76)			



B HHF by ASCVD status

	Treatment		Placebo			Favors treatment	Favors placebo	Weight, %
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)			
Patients with ASCVD								
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)			19.62
CANVAS program	NA/3756	7.3	NA/2900	11.3	0.68 (0.51-0.90)			17.13
DECLARE-TIMI 58	151/3474	11.1	192/3500	14.1	0.78 (0.63-0.97)			29.66
CREDENCE	59/1113	20.6	92/1107	33.2	0.61 (0.44-0.85)			12.74
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)			20.84
Fixed-effects model ($Q = 1.97$; $df = 4$; $P = .74$; $I^2 = 0.0\%$)					0.70 (0.62-0.78)			
Patients without ASCVD								
CANVAS program	NA/2039	2.6	NA/1447	4.2	0.64 (0.35-1.15)			16.38
DECLARE-TIMI 58	61/5108	3.0	94/5078	4.6	0.64 (0.46-0.88)			55.07
CREDENCE	30/1089	10.6	49/1092	17.5	0.61 (0.39-0.96)			28.56
Fixed-effects model ($Q = 0.03$; $df = 2$; $P = .99$; $I^2 = 0.0\%$)					0.63 (0.50-0.80)			



6,75 → 4,4%/yr

McGuire et al., JAMA Cardiology 2020

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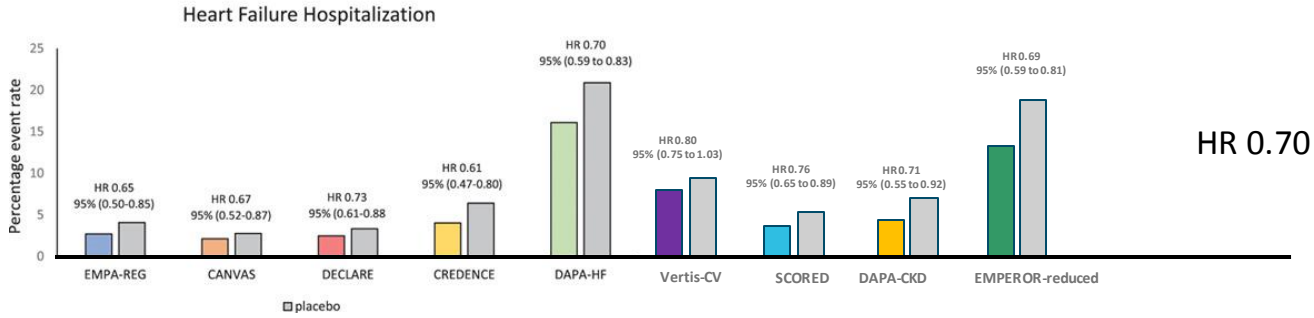
Hazard ratios (HRs) for key cardiovascular outcomes in cardiovascular and renal outcome trials with the SGLT2 inhibitors



HR 0.70

In addition to Rangaswami et al., Circulation 2020

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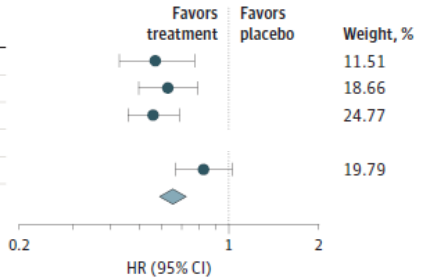
Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Kidney-Related Outcomes

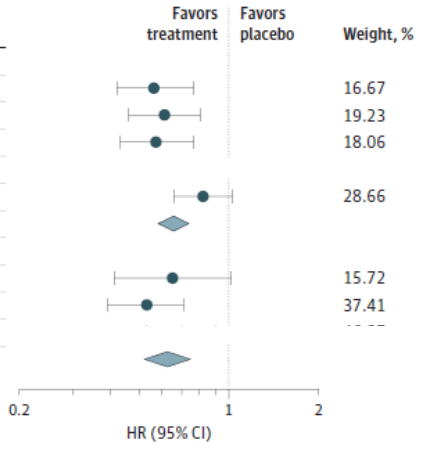
A Overall kidney outcomes

	Treatment		Placebo		Hazard ratio (95% CI)	Weight, %
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years		
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)	11.51
CANVAS program	NA/5795	5.5	NA/4347	9.0	0.60 (0.47-0.77)	18.66
DECLARE-TIMI 58	127/8582	3.7	238/8578	7.0	0.53 (0.43-0.66)	24.77
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)	19.79
Fixed-effects model ($Q = 7.96$; $df = 4$; $P = .09$; $I^2 = 49.7\%$)					0.62 (0.56-0.70)	



B Kidney outcomes by ASCVD status

	Treatment		Placebo		Hazard ratio (95% CI)	Weight, %
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years		
Patients with ASCVD						
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)	16.67
CANVAS program	NA/3756	6.4	NA/2900	10.5	0.59 (0.44-0.79)	19.23
DECLARE-TIMI 58	65/3474	4.7	118/3500	8.6	0.55 (0.41-0.75)	18.06
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)	28.66
Fixed-effects model ($Q = 6.09$; $df = 4$; $P = .19$; $I^2 = 34.4\%$)					0.64 (0.56-0.72)	
Patients without ASCVD						
CANVAS program	NA/2039	4.1	NA/1447	6.6	0.63 (0.39-1.02)	15.72
DECLARE-TIMI 58	62/5108	3.0	120/5078	5.9	0.51 (0.37-0.69)	37.41
Fixed-effects model ($Q = 1.86$; $df = 2$; $P = .40$; $I^2 = 0.0\%$)					0.60 (0.50-0.73)	



Remarks:

1. studies were designed as non-inferiority cardiovascular safety trials
2. Different renal outcomes

McGuire et al., JAMA Cardiology 2020

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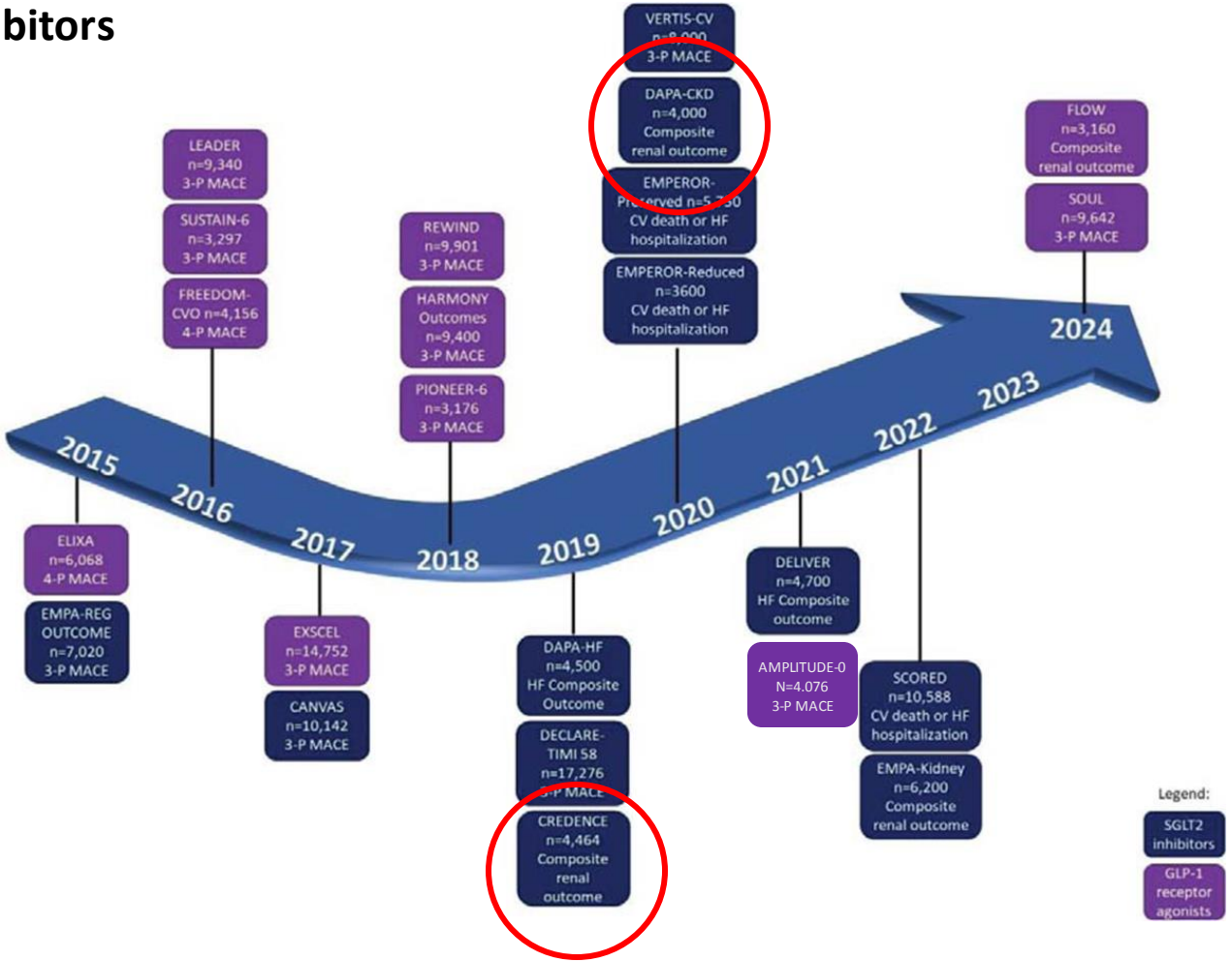
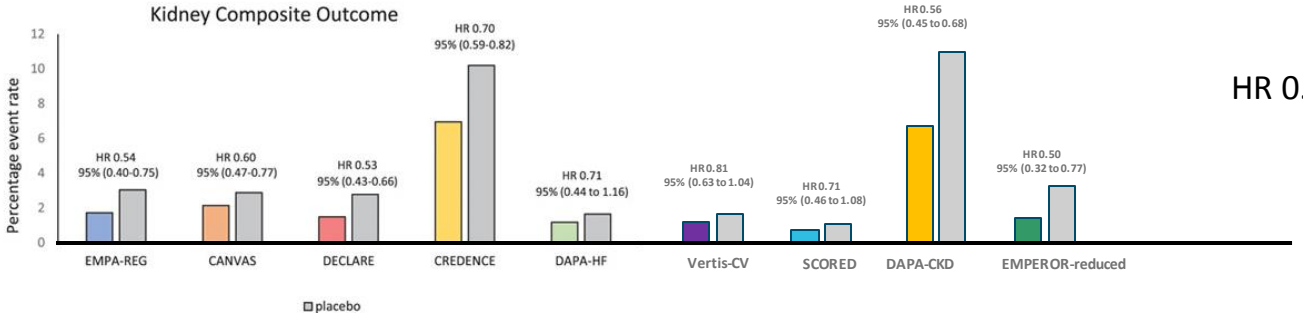
SGLT2 inhibitors





HR 0.63

Kidney outcomes:

- Decline in kidney function (doubling Screat, 40 or 50% decline GFR)
- ESRD
- Renal and cardiovascular death

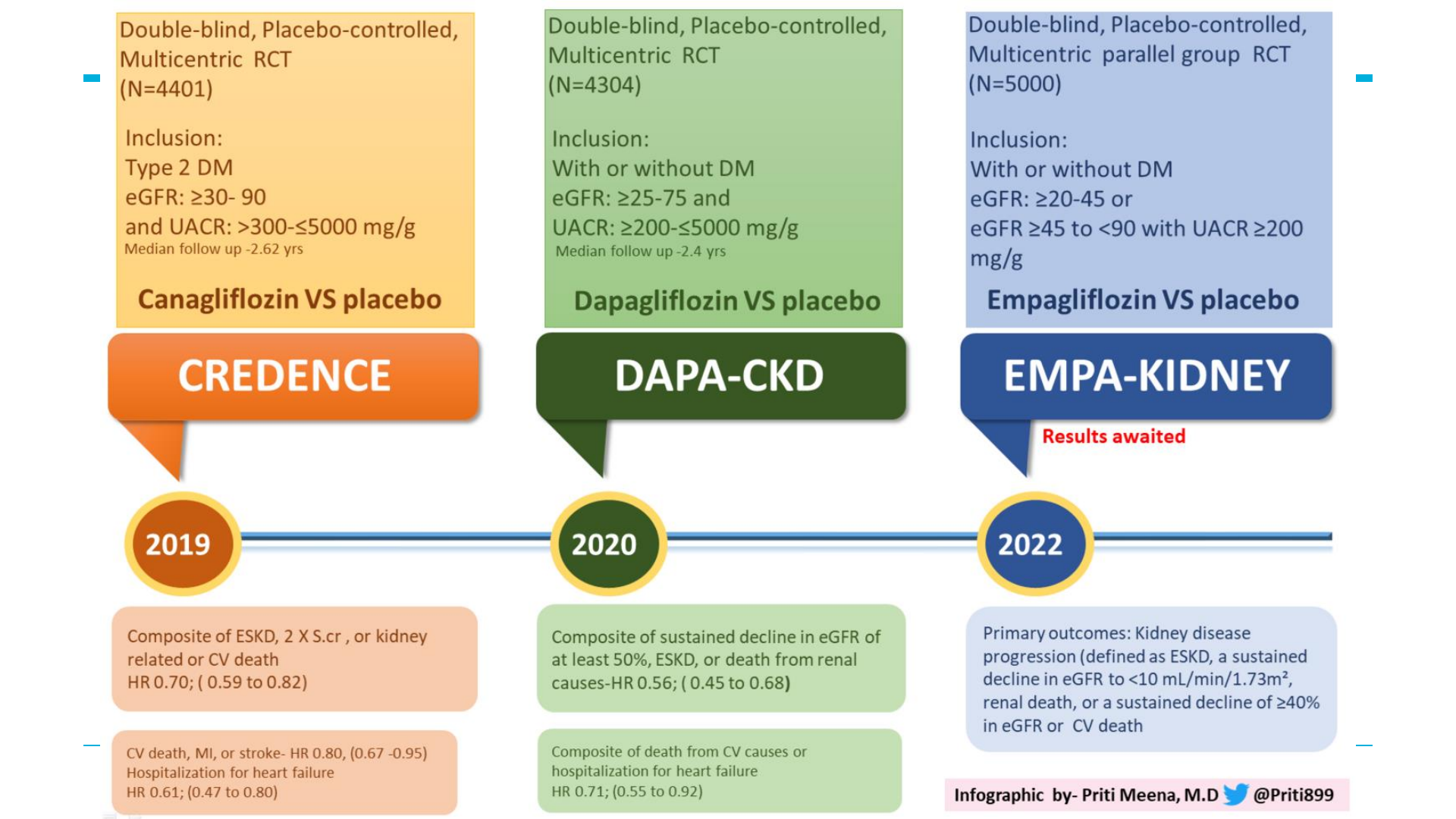
In addition to Rangaswami et al., Circulation 2020

B

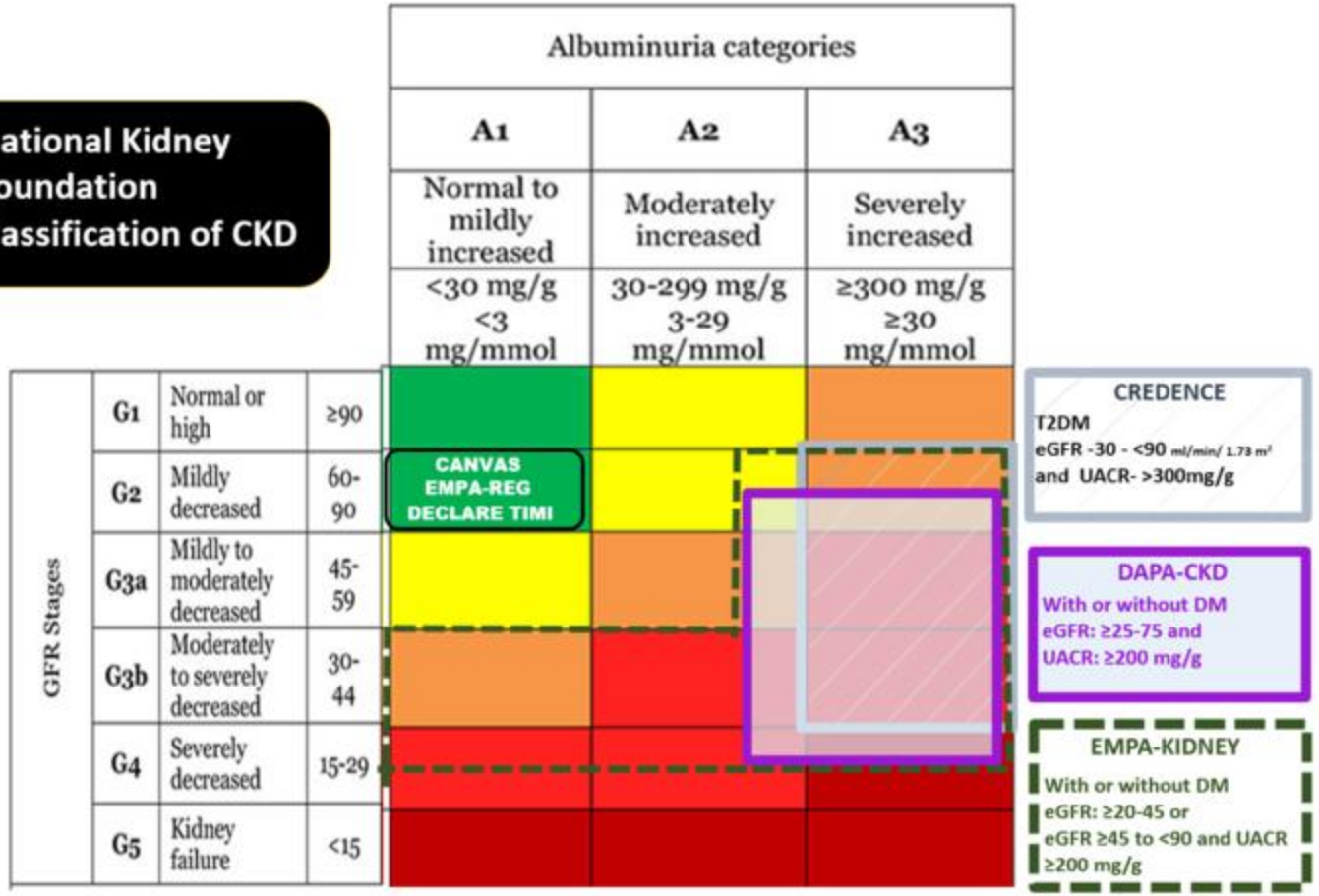
Incident or worsening nephropathy			Albuminuria Category		
			Normal to mildly increased	Moderately increased	Severely increased
			< 30	30-300	> 300
eGFR category (ml/min/1.73m²)	Normal or high	≥ 90	0.67	0.58	0.52
	Mildly decreased	60-89	0.67	0.58	0.52
	Mild to moderately decreased	45-59	0.58	0.52	0.68
	Moderately to severely decreased	30-44	0.69	0.68	0.68
	Severely decreased	15-29	0.68	0.68	0.68
	Kidney failure	≤ 15	0.68	0.68	0.68

0.61

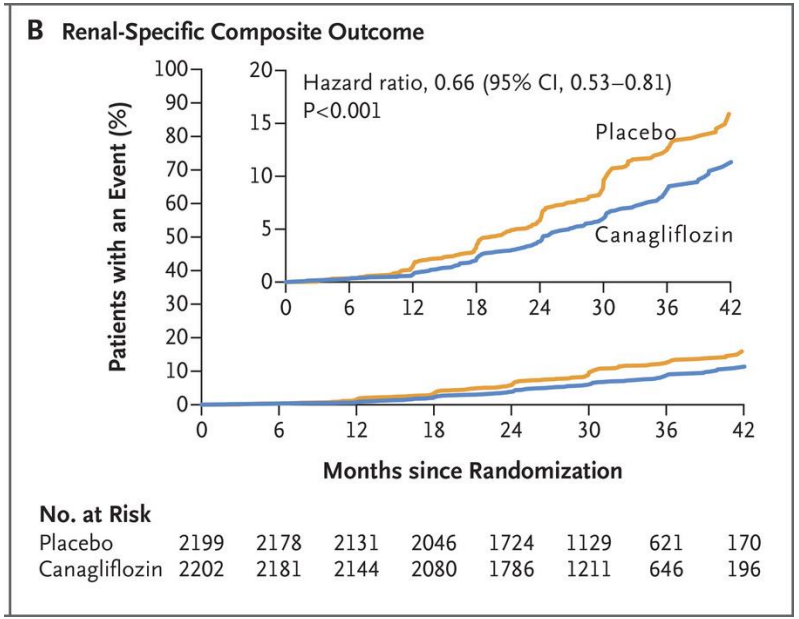
0.61

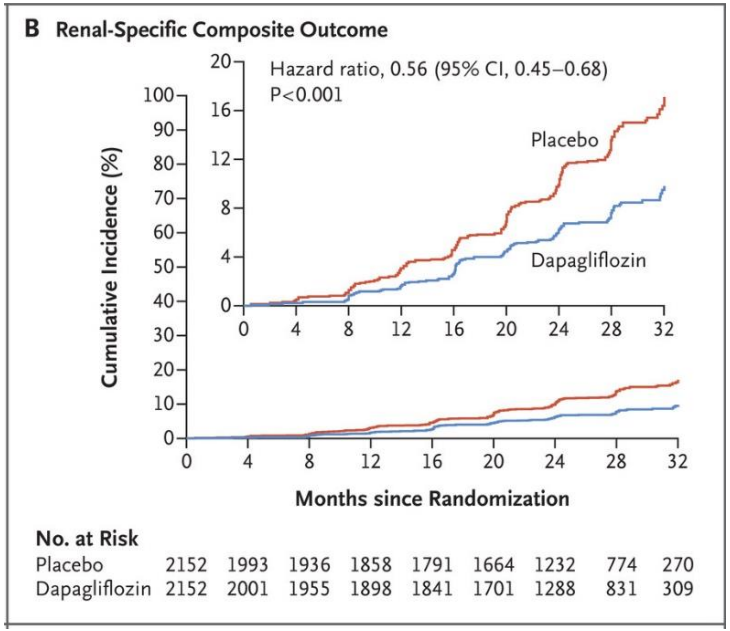

Double-blind, Placebo-controlled, Multicentric RCT
(N=4401)
Inclusion:
Type 2 DM
eGFR: ≥30- 90
and UACR: >300-≤5000 mg/g
Median follow up -2.62 yrs
Canagliflozin VS placebo
Double-blind, Placebo-controlled, Multicentric RCT
(N=4304)
Inclusion:
With or without DM
eGFR: ≥25-75 and
UACR: ≥200-≤5000 mg/g
Median follow up -2.4 yrs
Dapagliflozin VS placebo
Double-blind, Placebo-controlled, Multicentric parallel group RCT
(N=5000)
Inclusion:
With or without DM
eGFR: ≥20-45 or
eGFR ≥45 to <90 with UACR ≥200 mg/g
Empagliflozin VS placebo
CREDENCE
DAPA-CKD
EMPA-KIDNEY
Results awaited
2019
2020
2022
Composite of ESKD, 2 X S.cr , or kidney related or CV death
HR 0.70; (0.59 to 0.82)
CV death, MI, or stroke- HR 0.80, (0.67 -0.95)
Hospitalization for heart failure
HR 0.61; (0.47 to 0.80)
Composite of sustained decline in eGFR of at least 50%, ESKD, or death from renal causes-HR 0.56; (0.45 to 0.68)
Composite of death from CV causes or hospitalization for heart failure
HR 0.71; (0.55 to 0.92)
Primary outcomes: Kidney disease progression (defined as ESKD, a sustained decline in eGFR to <10 mL/min/1.73m², renal death, or a sustained decline of ≥40% in eGFR or CV death
Infographic by- Priti Meena, M.D @Priti899

National Kidney Foundation classification of CKD



Renal specific outcomes in CREDENCE and DAPA-CKD





Renal composite outcome:
a decline of at least 50% in the estimated GFR/doubling of serum creatinine, the onset of end-stage kidney disease (defined as maintenance dialysis for ≥28 days, kidney transplantation, or an estimated GFR of <15 ml per minute per 1.73 m^2 confirmed by a second measurement after ≥28 days), or death from renal causes

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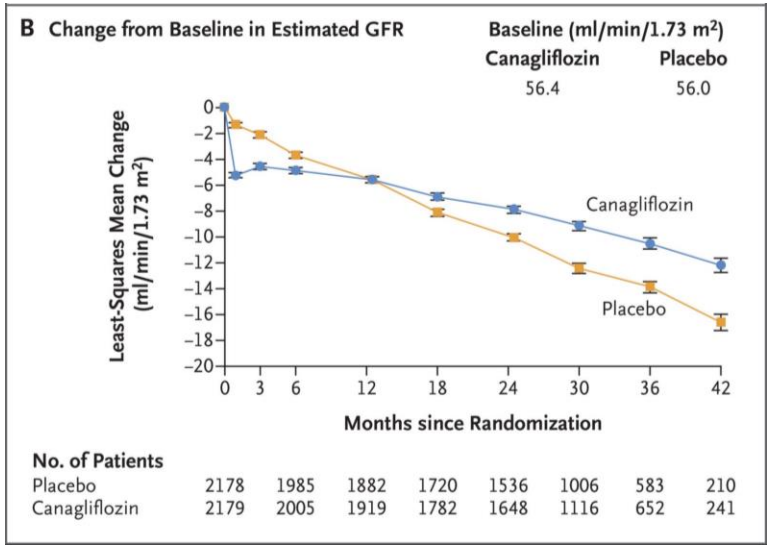
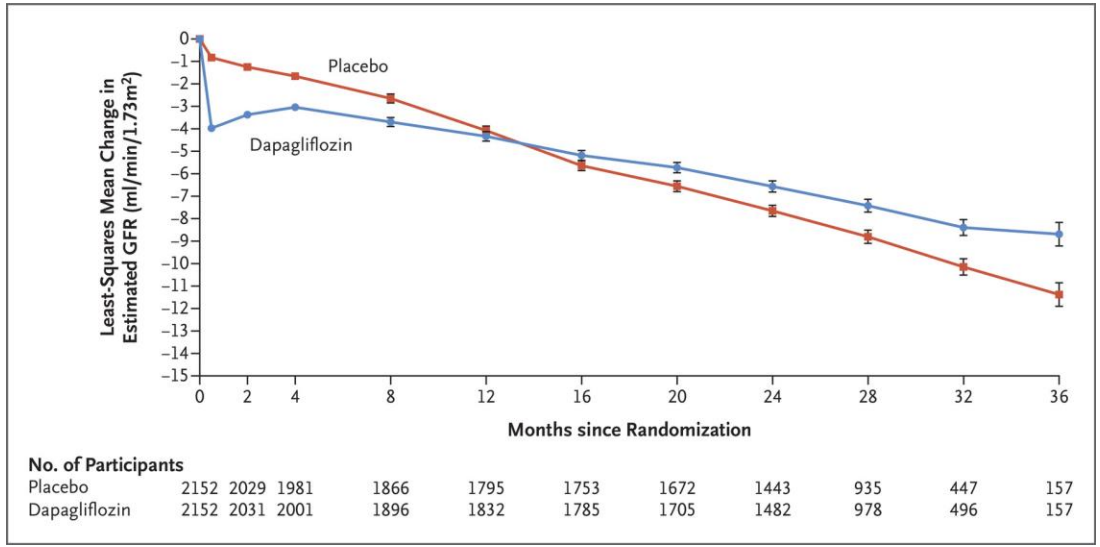
Effects on e-GFR in CREDENCE and DAPA-CKD



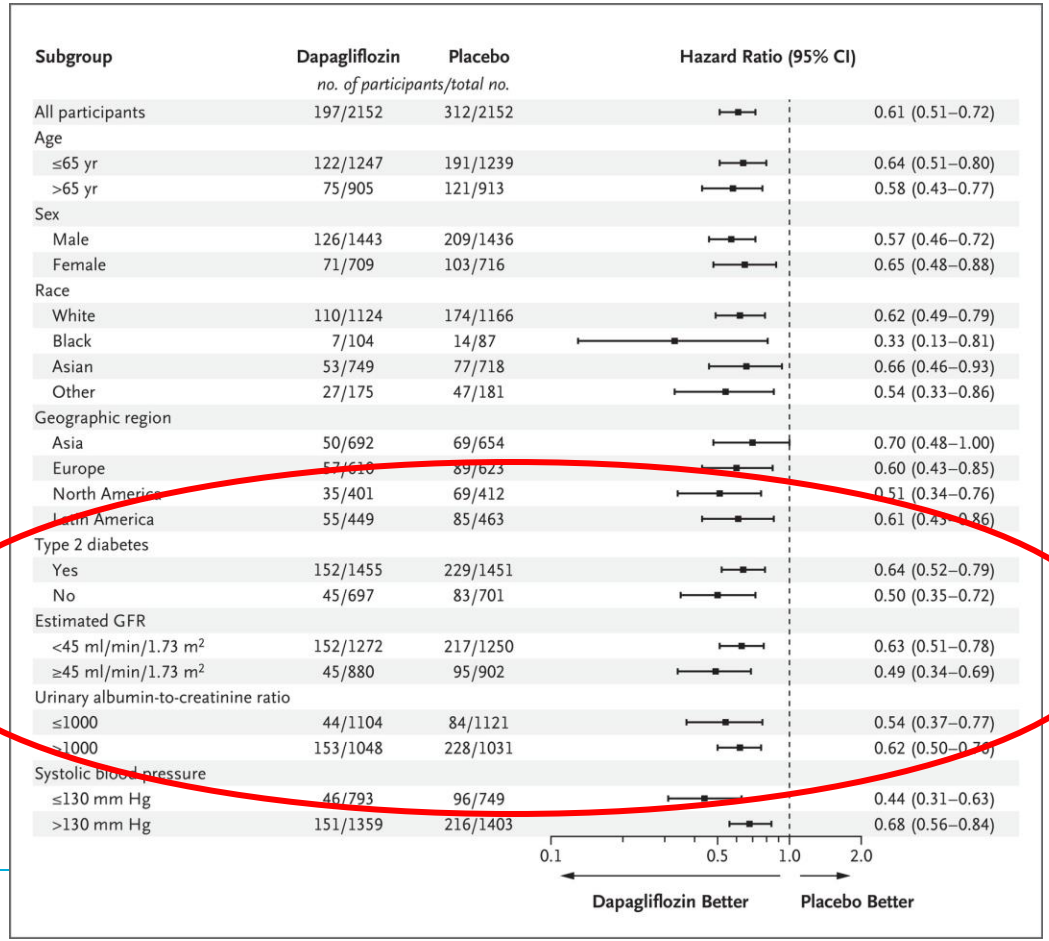


Decline in GFR: –1.85±0.13 vs. –4.59±0.14 ml/min/1.73 m^2 per year

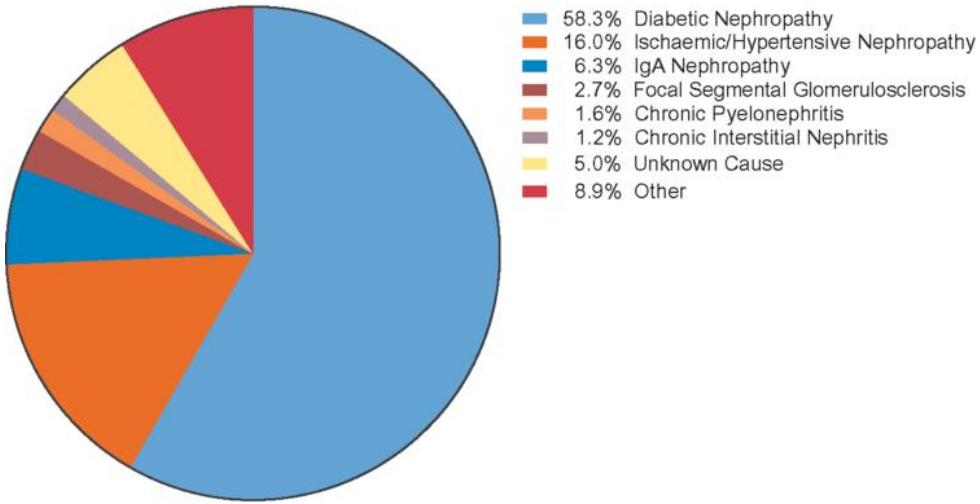
Decline in GFR: –1.67±0.11 vs. –3.59±0.11 ml/min/1.73 m^2 per year

Dapagliflozin in Patients with Chronic Kidney Disease (with and without diabetes)

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)

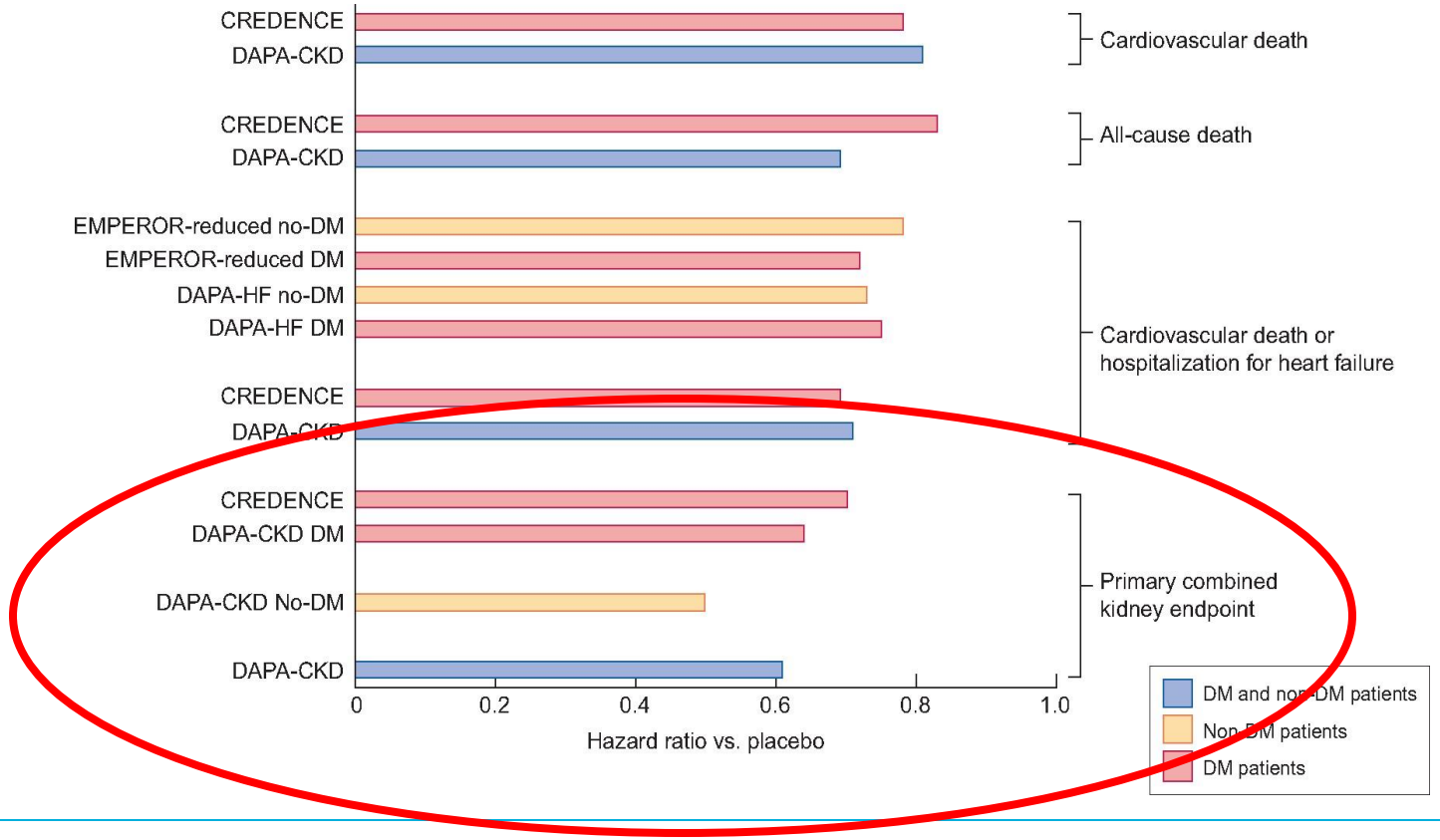


Heerspink et al., NEJM 2020



from DAPA-CKD, NEJM 2020

Key outcomes of RCTs assessing SGLT2 inhibitors in patients with HF or CKD.



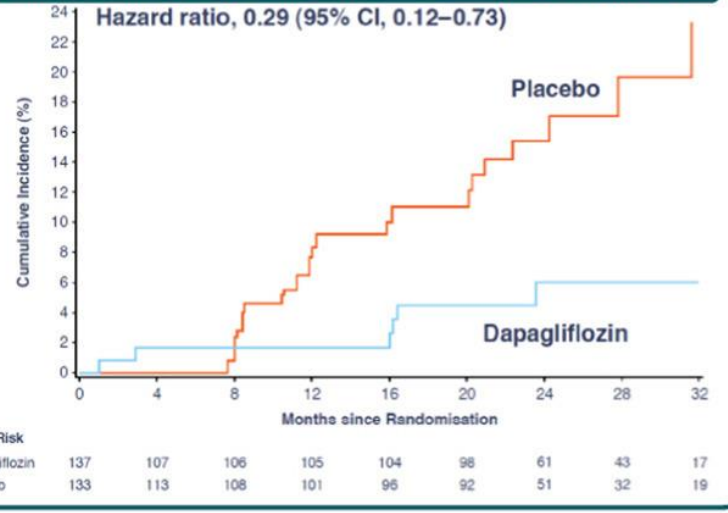
A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy.

DAPA-CKD population:

- eGFR 25-75 mL/min/1.73m^2
- UACR 200-5000 mg/g
- Receiving a stable, maximally tolerable ACEi/ARB dose
- With and without type 2 diabetes

⇨ **270 participants with IgA nephropathy** ⇨ **254 participants with biopsy-confirmed IgA nephropathy**

Composite primary endpoint in patients with IgA nephropathy (n=270)



	Hazard Ratio (95%CI)	P Value
Composite primary endpoint (≥50% eGFR decline/ESKD/CV or kidney death)		
Patients with IgA nephropathy	0.29 (0.12, 0.73)	0.005
Patients with biopsy-confirmed IgA nephropathy	0.28 (0.11, 0.72)	0.005
Composite of kidney endpoint (≥50% eGFR decline/ESKD/kidney death)		
Patients with IgA nephropathy	0.24 (0.09, 0.65)	0.002
Patients with biopsy-confirmed IgA nephropathy	0.23 (0.09, 0.63)	0.002

IgA, immunoglobulin A; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; ESKD, end-stage kidney disease

CONCLUSION:

In patients with IgA nephropathy, when added to ACEi/ARB therapy, dapagliflozin significantly and substantially reduced the risk of CKD progression

kidney INTERNATIONAL ISN

Wheeler et al, 2021

A pre-specified subgroup analysis specifically investigated safety and efficacy in study patients with FSGS.

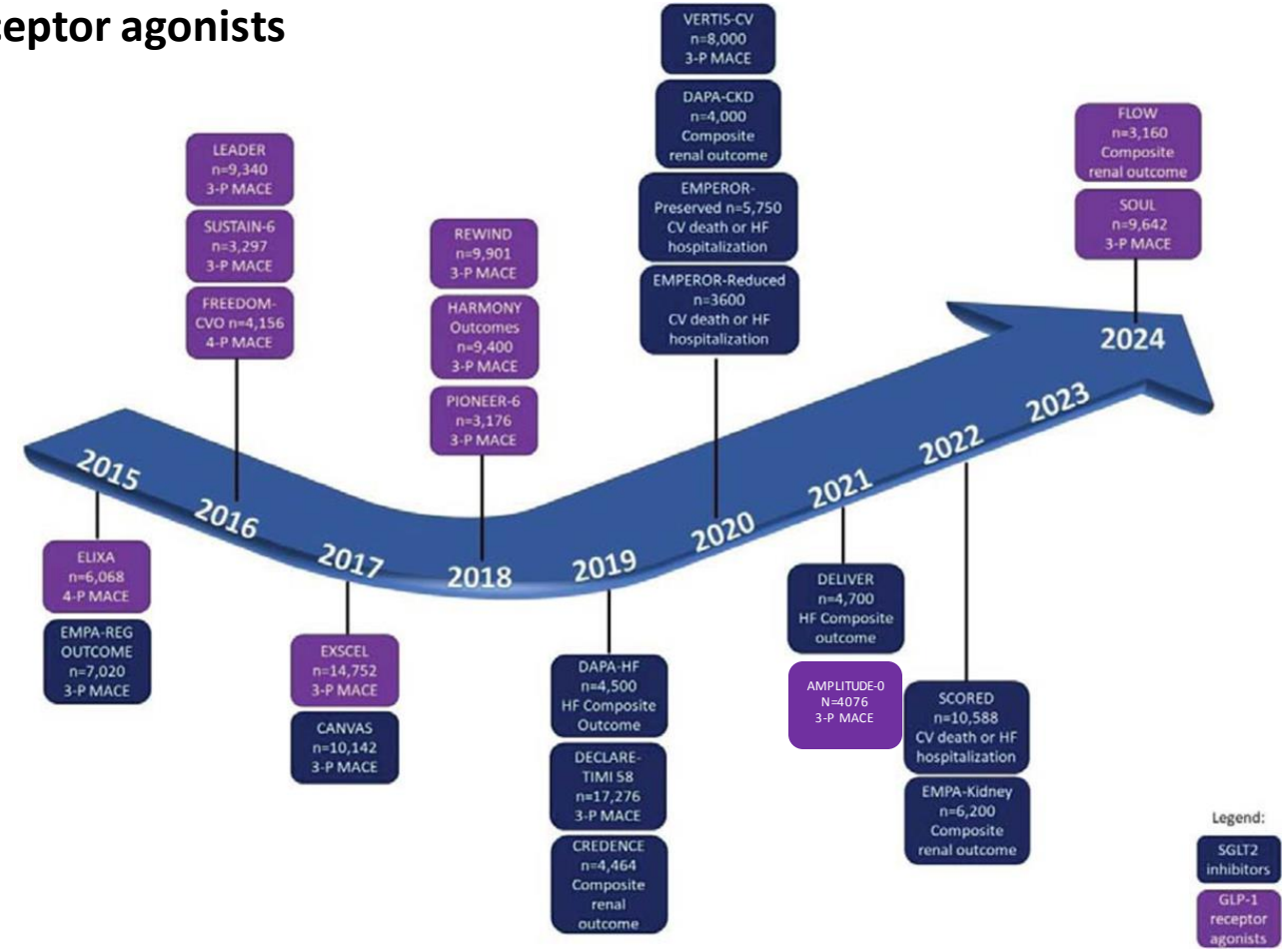
- 115 participants with FSGS randomized to dapagliflozin (n=53) or placebo (n=62) on top of standard treatment.
- The combined primary endpoint included a ~50% decrease in eGFR, reaching dialysis requirement, or cardiovascular death. In the present analysis, the course of kidney function (eGFR) was specifically investigated during the median 2.4-year follow-up.
- The FSGS patients were 53.7±13.9 years old, eGFR of 41.6±11.6 ml/min/1.73 m^2 and a median urinary protein excretion of 1553 (758-2257) mg/g.
- **Four out of 53 patients on dapagliflozin (7.5%) and nine out of 62 patients on placebo (14.5%) reached the primary endpoint (HR 0.54).**
- In the first two weeks after the start of the study, the familiar phenomenon of initial eGFR decline occurred (eGFR dip of -4.5 ml/min/1.73m2 in the dapagliflozin group compared to -0.8 ml/min/1.73m2 in the placebo group). Over the remainder of the study, the annual eGFR loss was -1.9 versus -4.2 ml/min/1.73 m^2.

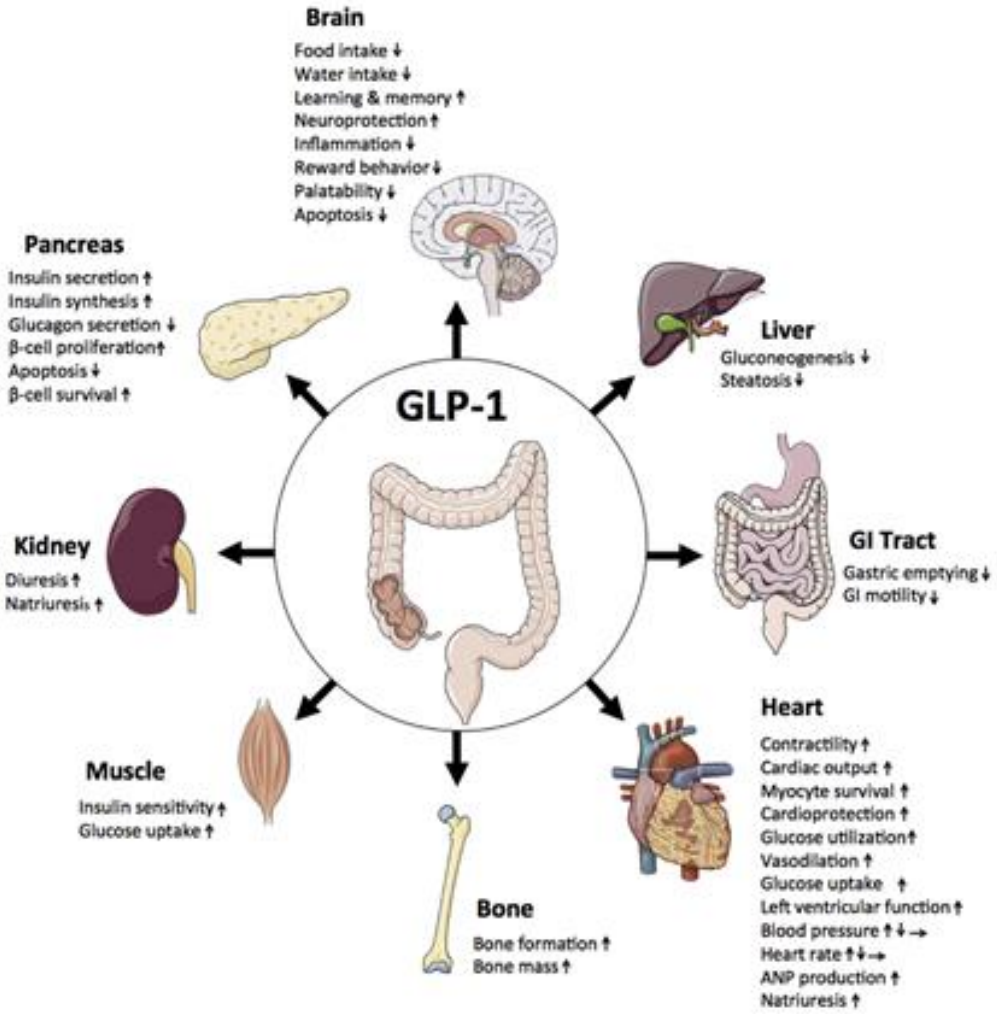
SGLT2 INHIBITORS ADDITIONALLY IMPROVE KIDNEY AND CV OUTCOMES IN NON-DIABETIC PATIENTS WITH CKD

A further RCT of SGLT2 inhibitors in diabetics and non-diabetics with CKD is ongoing, testing empagliflozin.

The Study of Heart and Kidney Protection With Empagliflozin (**EMPA-KIDNEY**) will be a larger trial that will also enroll patients with Type 1 diabetes (T1DM) in addition to T2DM and non-diabetics and will have a lower eGFR entry criteria (20–90 mL/min/1.73 m^2) than other CKD trials and will not require pathological albuminuria to enroll patients with low eGFR (20–<45 mL/min/1.73 m^2), potentially expanding the population that benefits from SGLT2 inhibition if it meets the primary endpoint

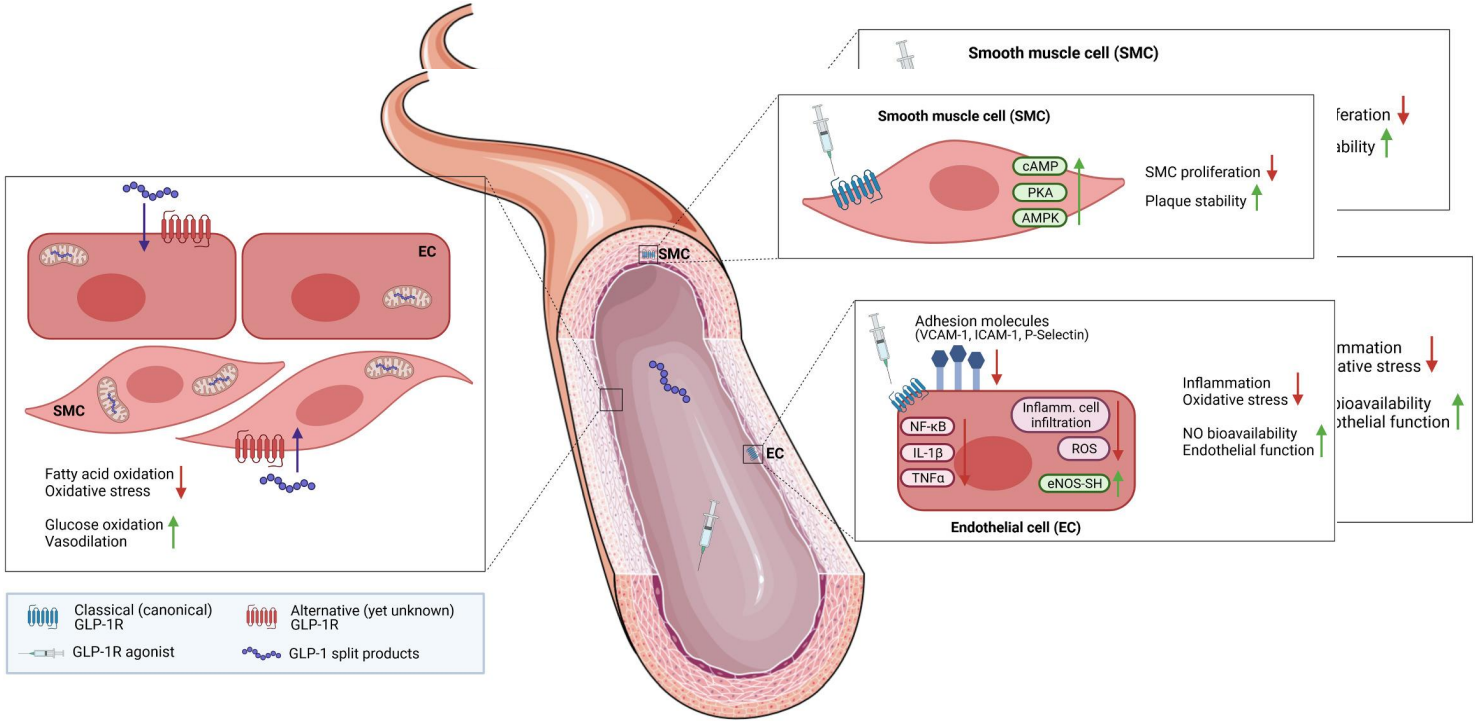
GLP-1 receptor agonists

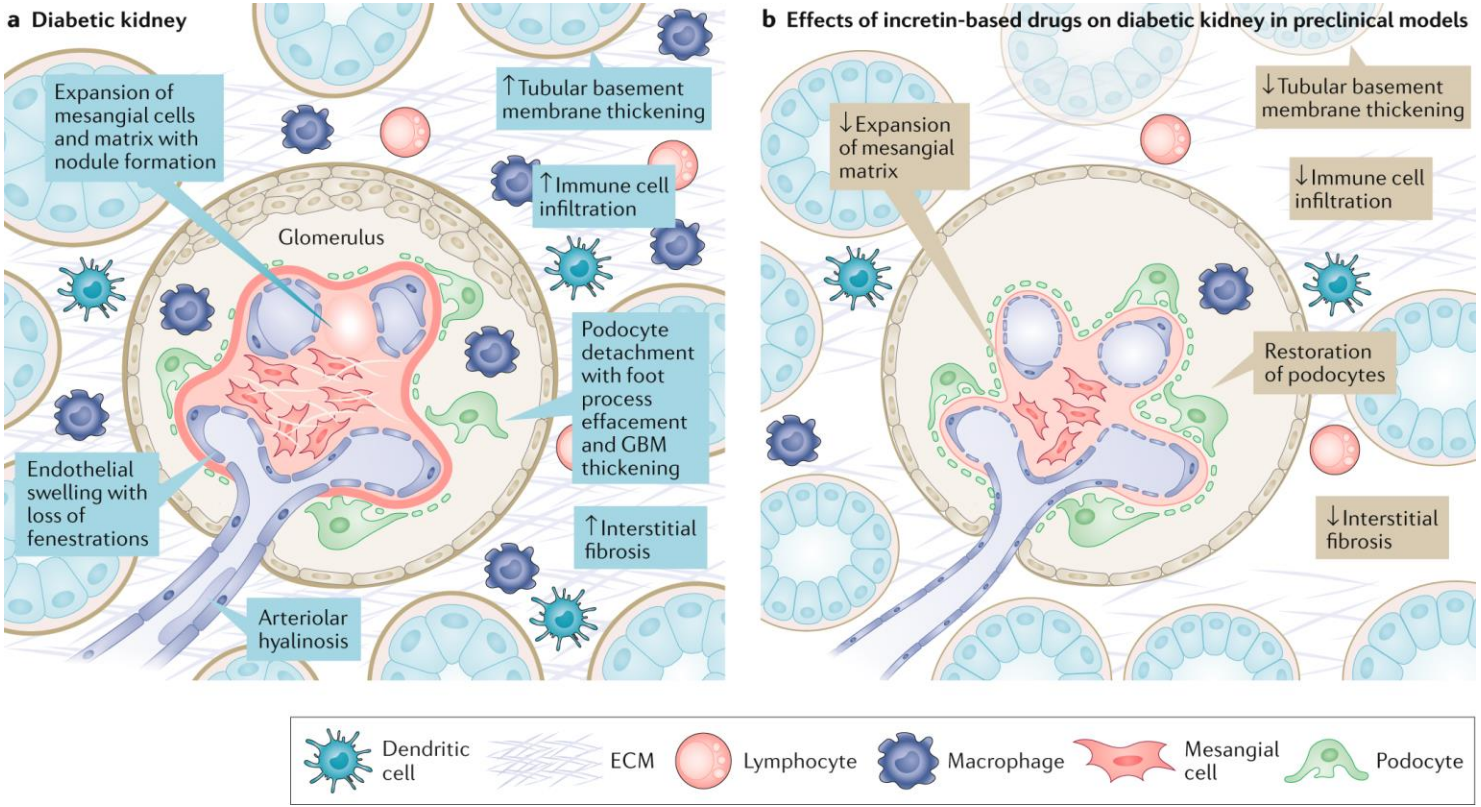




GLP-1 exerts its main effect by **stimulating glucose-dependent insulin release from the pancreatic islets**. It has also been shown to slow gastric emptying, inhibit inappropriate post-meal glucagon release, and reduce food intake .

Glucagon-like peptide-1 (GLP-1) receptor agonists and their cardiovascular benefits—The role of the GLP-1 receptor





Alicic R.Z. et al., Nature Reviews Nephrology, 2021

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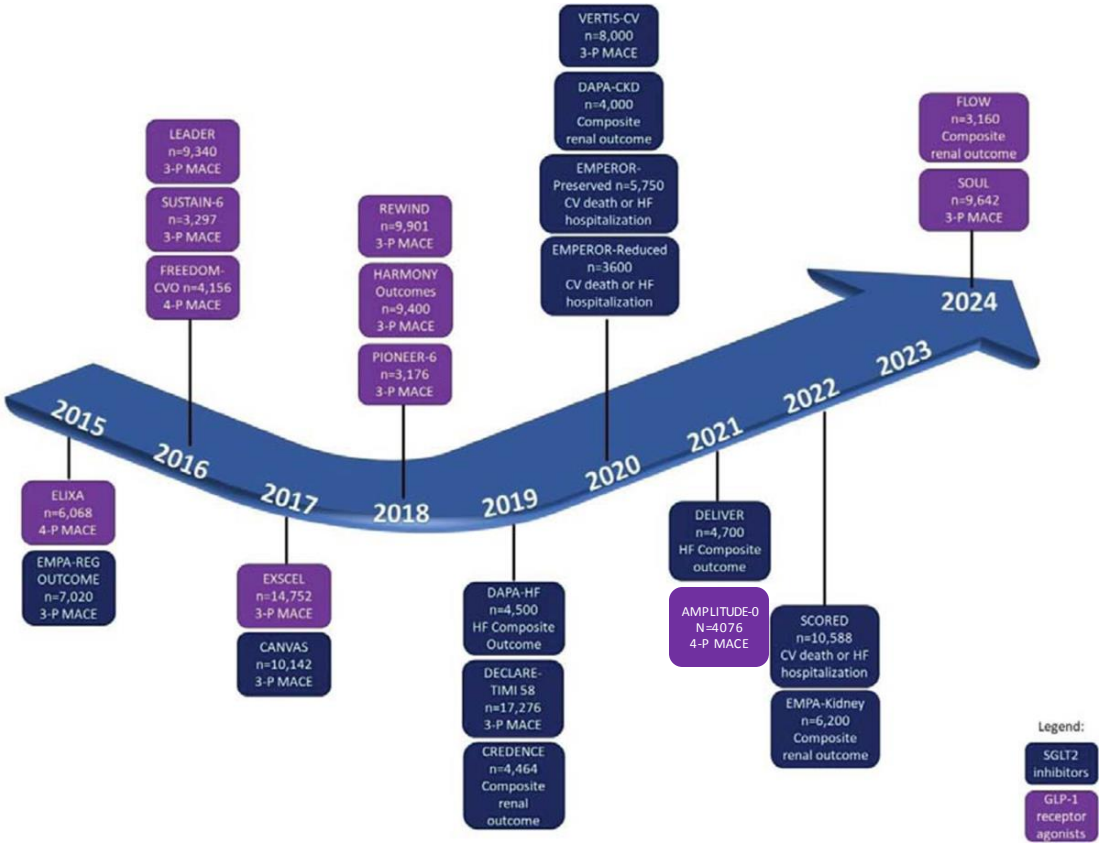
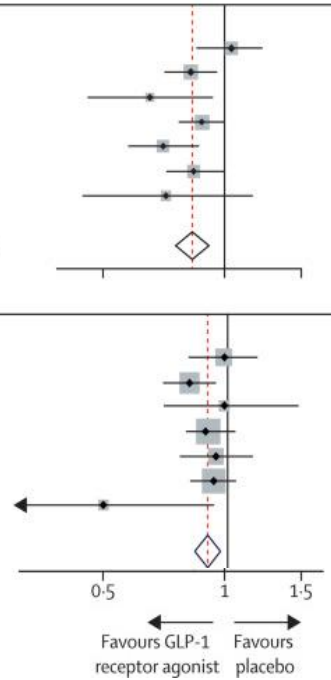

2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
ELIXA n=6,068 4-P MACE
EMPA-REG OUTCOME n=7,020 3-P MACE
LEADER n=9,340 3-P MACE
SUSTAIN-6 n=3,297 3-P MACE
FREEDOM-CVO n=4,156 4-P MACE
EXSCEL n=14,752 3-P MACE
CANVAS n=10,142 3-P MACE
REWIND n=9,901 3-P MACE
HARMONY Outcomes n=9,400 3-P MACE
PIONEER-6 n=3,176 3-P MACE
VERTIS-CV n=8,000 3-P MACE
DAPA-CKD n=4,000 Composite renal outcome
EMPEROR-Preserved n=5,750 CV death or HF hospitalization
EMPEROR-Reduced n=3600 CV death or HF hospitalization
DAPA-HF n=4,500 HF Composite Outcome
DECLARE-TIMI 58 n=17,276 3-P MACE
CREDENCE n=4,464 Composite renal outcome
DELIVER n=4,700 HF Composite outcome
AMPLITUDE-O N=4076 4-P MACE
SCORED n=10,588 CV death or HF hospitalization
EMPA-Kidney n=6,200 Composite renal outcome
FLOW n=3,160 Composite renal outcome
SOUL n=9,642 3-P MACE
Legend:
SGLT2 inhibitors
GLP-1 receptor agonists

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Three-component MACE					
ELIXA	400/3034 (13%)	392/3034 (13%)	1·02 (0·89–1·17)		0·78
LEADER	608/4668 (13%)	694/4672 (15%)	0·87 (0·78–0·97)		0·015
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	0·74 (0·58–0·95)		0·016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0·91 (0·83–1·00)		0·061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)	0·78 (0·68–0·90)		<0·001
REWIND	594/4949 (12%)	663/4952 (13%)	0·88 (0·79–0·99)		0·026
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0·79 (0·57–1·11)		0·17
Overall (I^2=40·9%, p=0·118)	**2948/27977 (11%)**	**3304/28027 (12%)**	**0·88 (0·82–0·94)**	**75 (50–151)**	**<0·001**
Cardiovascular death					
ELIXA	156/3034 (5%)	158/3034 (5%)	0·98 (0·78–1·22)		0·85
LEADER	219/4668 (5%)	278/4672 (6%)	0·78 (0·66–0·93)		0·007
SUSTAIN-6	44/1648 (3%)	46/1649 (3%)	0·98 (0·65–1·48)		0·92
EXSCEL	340/7356 (5%)	383/7396 (5%)	0·88 (0·76–1·02)		0·096
Harmony Outcomes	122/4731 (3%)	130/4732 (3%)	0·93 (0·73–1·19)		0·58
REWIND	317/4949 (6%)	346/4952 (7%)	0·91 (0·78–1·06)		0·18
PIONEER 6	15/1591 (1%)	30/1592 (2%)	0·49 (0·27–0·92)		0·021
Overall (I^2=0·0%, p=0·557)	**1213/27977 (4%)**	**1371/28027 (5%)**	**0·88 (0·81–0·96)**	**175 (110–524)**	**0·003**

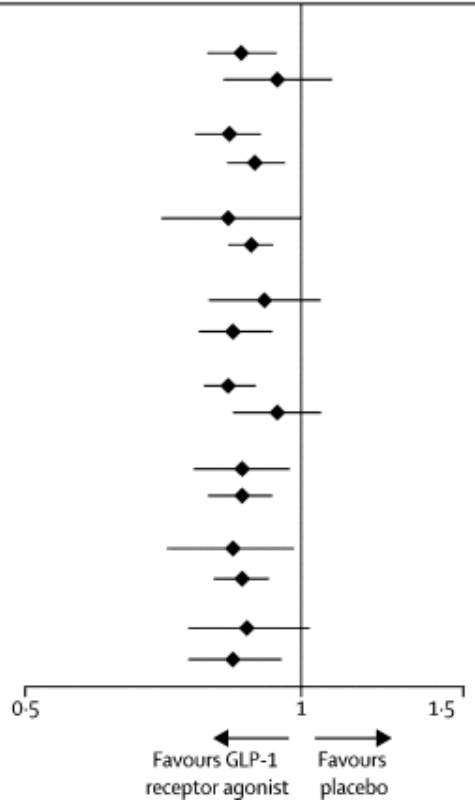


3P MACE

S.L. Kristensen et al., Lancet Diabetes Endocrinol. 2019

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	$p_{interaction}$
Established cardiovascular disease				0·24
Yes	2431/21253 (11%)	2755/21202 (13%)	0·86 (0·80–0·93)	
No	480/6428 (7%)	518/6555 (8%)	0·94 (0·83–1·07)	
Baseline HbA_{1c}*				0·22
High	1645/14507 (11%)	1865/14298 (13%)	0·85 (0·78–0·91)	
Low	1300/13407 (10%)	1442/13661 (11%)	0·91 (0·84–0·98)	
Median duration of follow–up				0·53
<3 years	907/11004 (8%)	1042/11007 (9%)	0·84 (0·71–1·00)	
≥3 years	2041/16973 (12%)	2262/17020 (13%)	0·89 (0·84–0·94)	
Drug dosing				0·34
Daily	1069/9293 (12%)	1162/9298 (12%)	0·92 (0·80–1·05)	
Weekly	1879/18684 (10%)	2142/18729 (11%)	0·85 (0·78–0·93)	
Human GLP–1 homology				0·06
Yes	1709/17587 (10%)	2007/17597 (11%)	0·84 (0·79–0·90)	
No	1239/10390 (12%)	1297/10430 (12%)	0·95 (0·85–1·06)	
BMI, kg/m²				1·00
<30†	1254/11752 (11%)	1403/11904 (12%)	0·87 (0·78–0·98)	
≥30†	1679/16116 (10%)	1892/16011 (12%)	0·87 (0·81–0·92)	
Age, Years				0·79
<65‡	1249/14195 (9%)	1346/13948 (10%)	0·85 (0·72–0·99)	
≥65‡	1705/13782 (12%)	1965/14079 (14%)	0·87 (0·81–0·93)	
Baseline eGFR, mL/min per m²				0·72
<60	771/5341 (14%)	865/5432 (16%)	0·88 (0·76–1·03)	
≥60	1576/17653 (9%)	1773/17598 (10%)	0·85 (0·76–0·96)	



S.L. Kristensen et al., Lancet Diabetes Endocrinol. 2019

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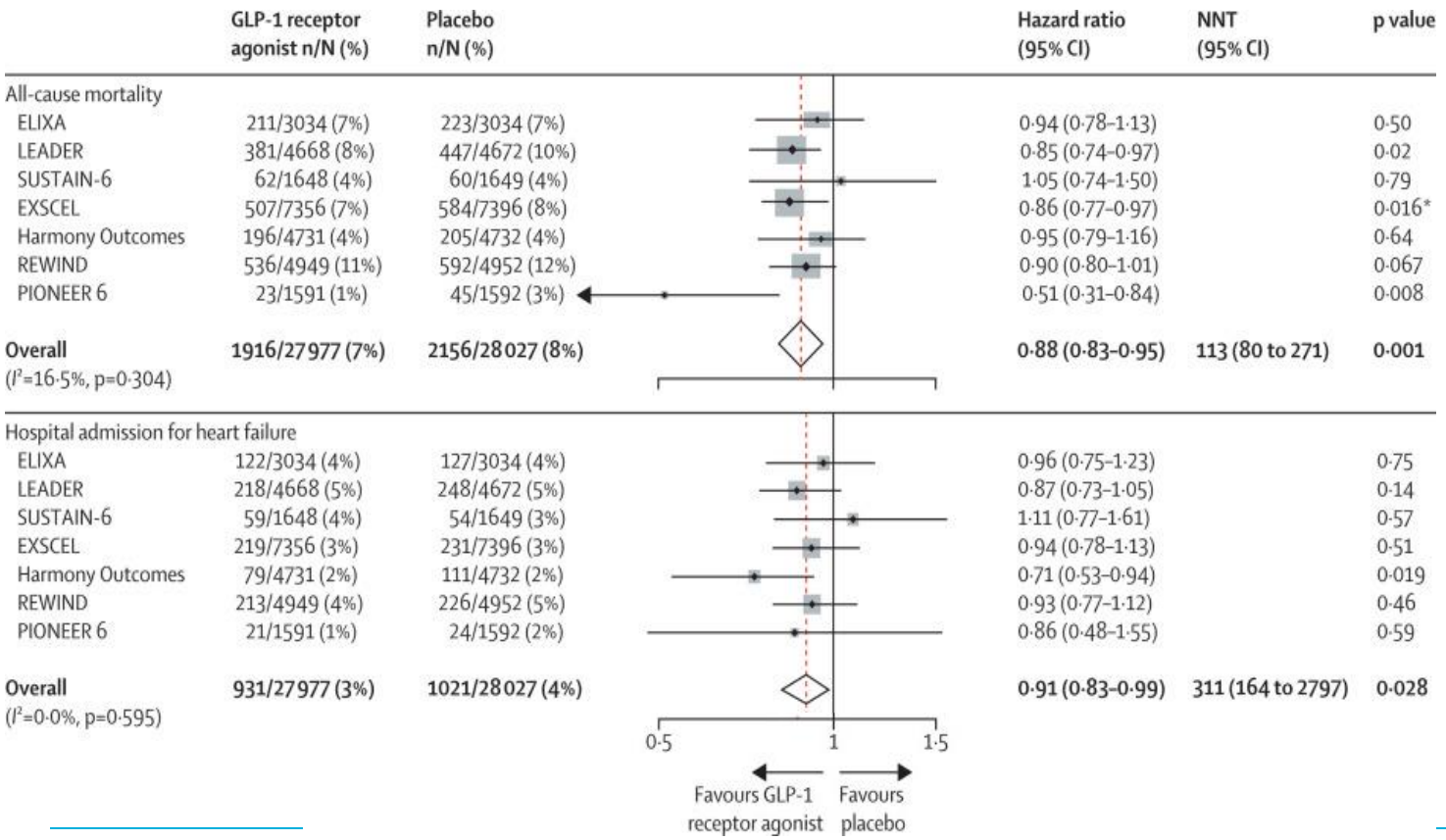
Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials



All-cause mortality

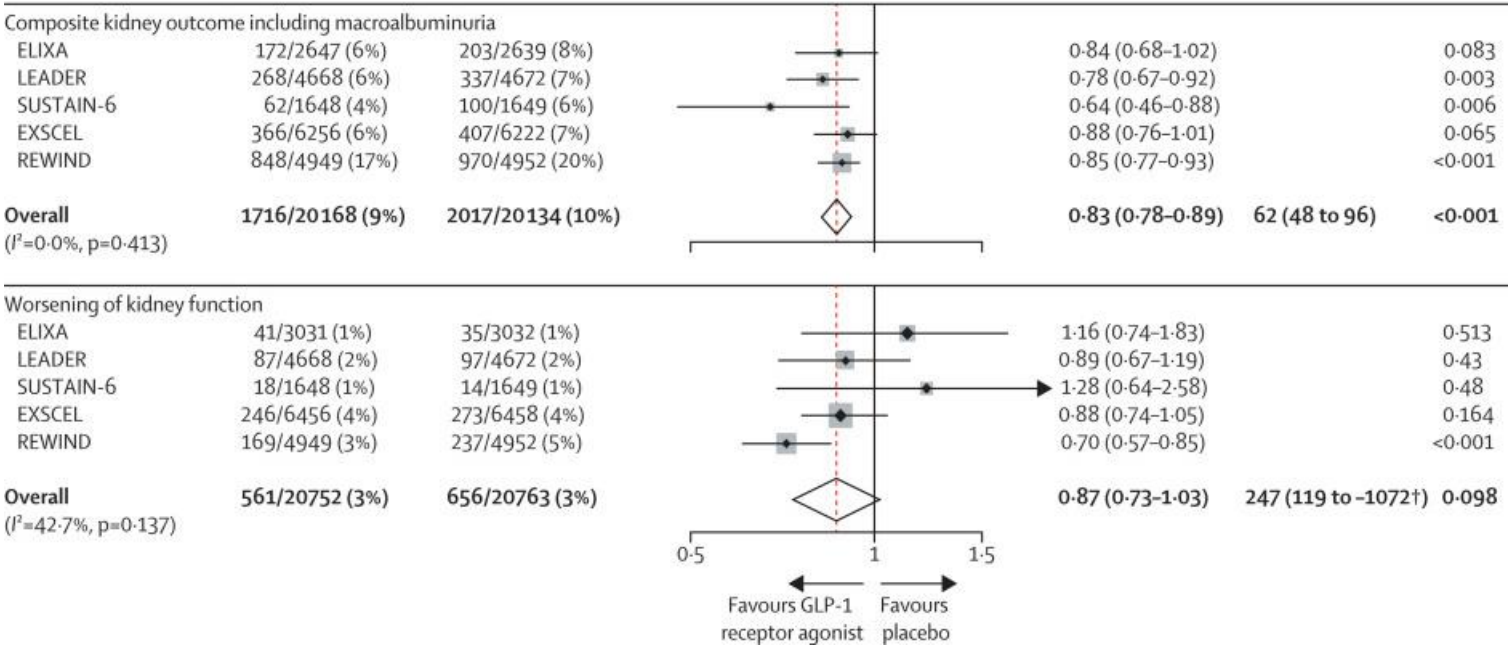
Heart failure

S.L. Kristensen et al., Lancet Diabetes Endocrinol. 2019

Radboudumc

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Kidney outcomes



S.L. Kristensen et al., Lancet Diabetes Endocrinol. 2019

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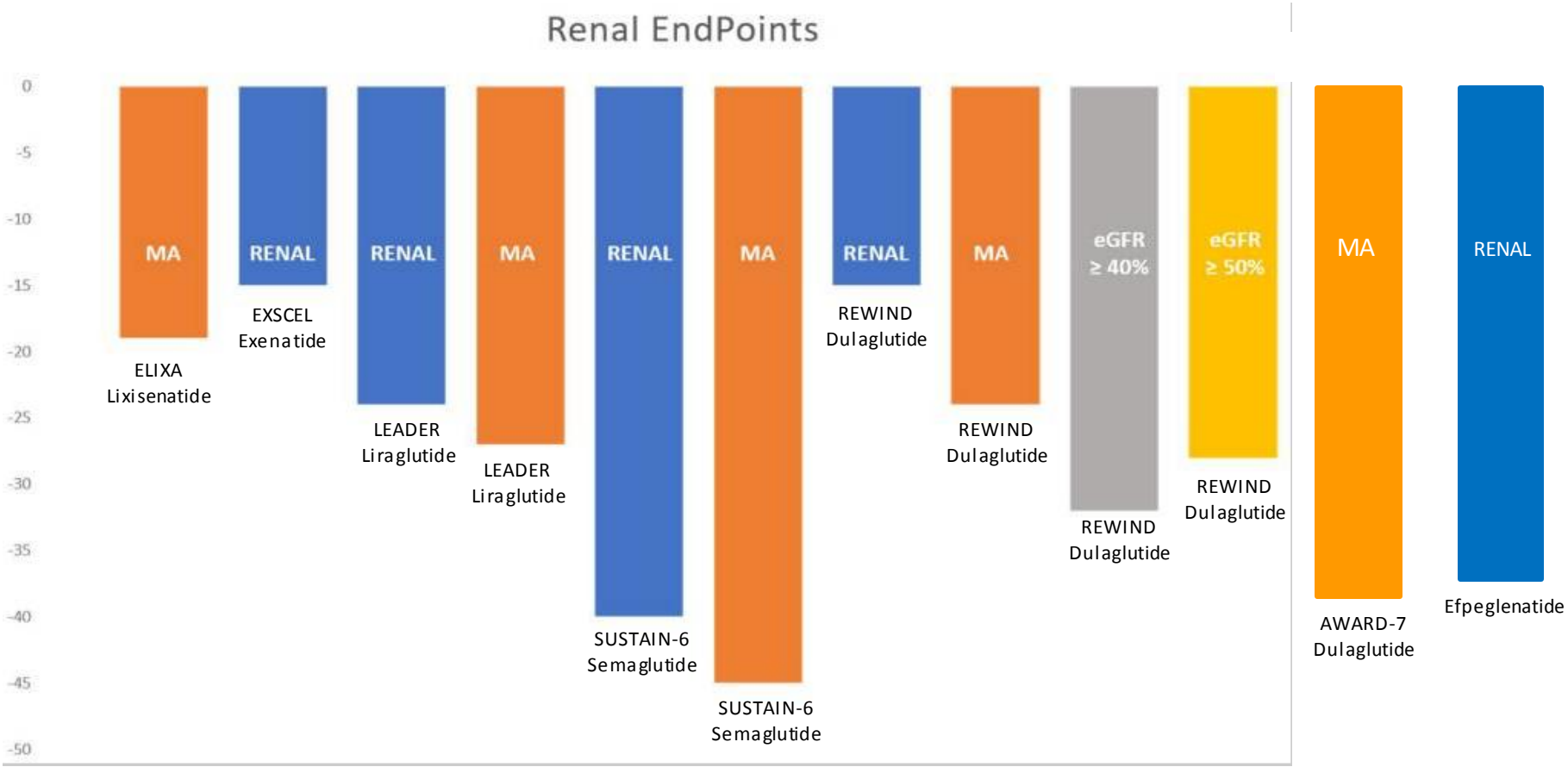
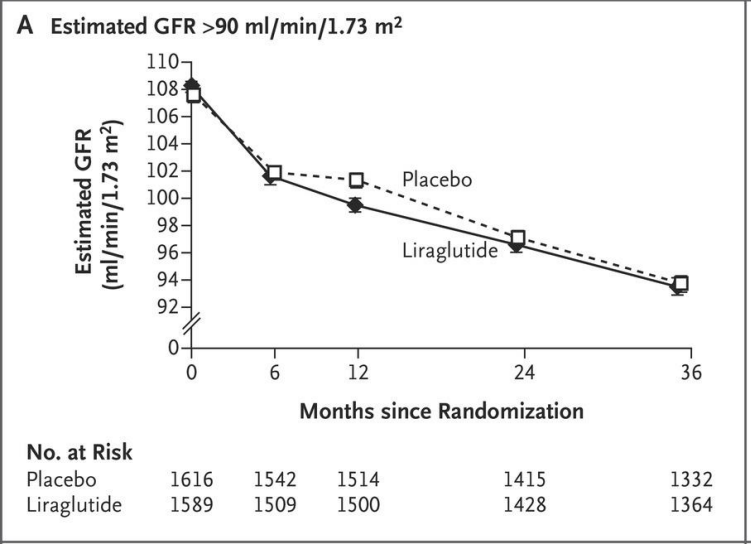
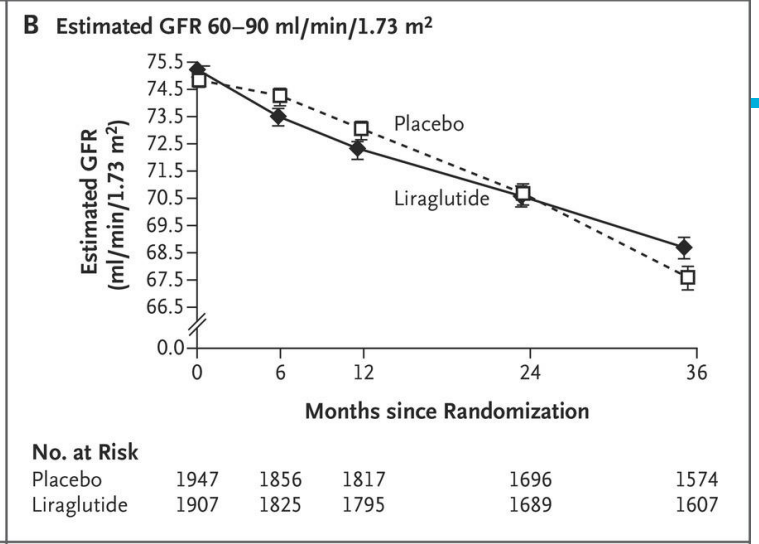
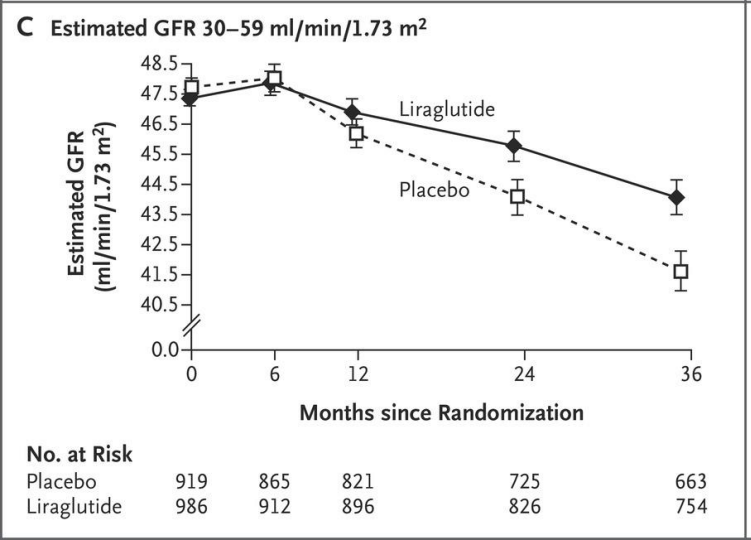
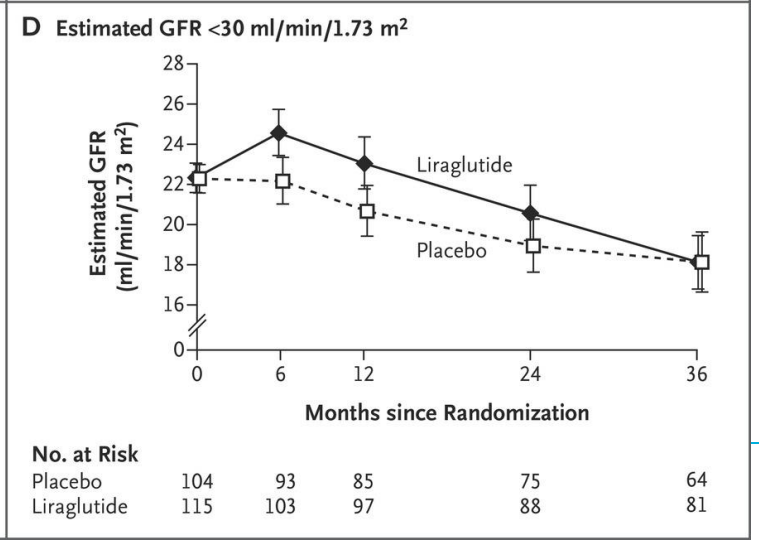


HARMONY/PIONEER-6:
no kidney endpoints
analyzed





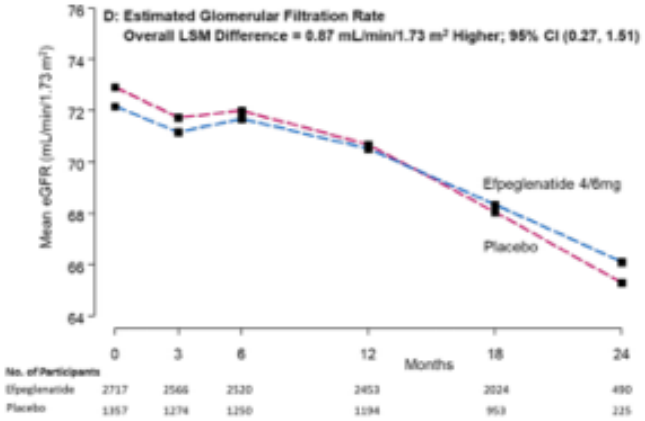




Liraglutide and Renal Outcomes in Type 2 Diabetes

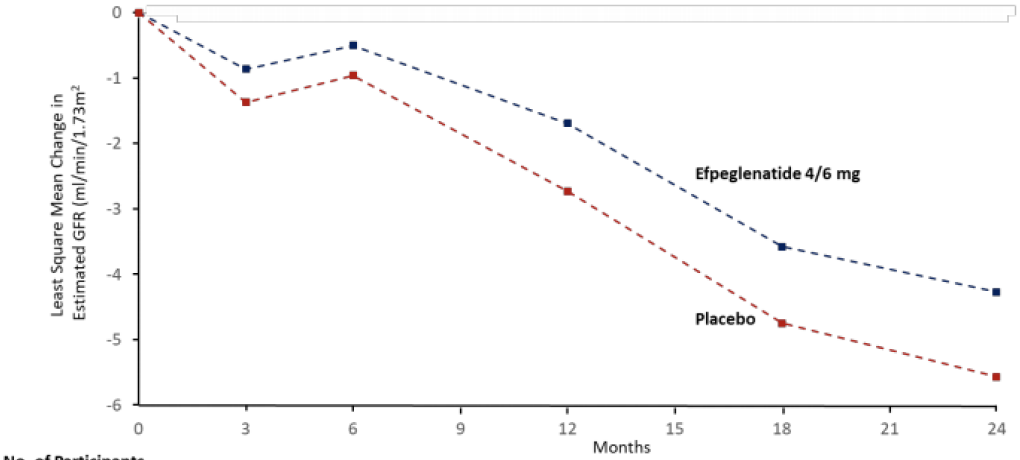
NEJM 2017

Radboudumc



AMPLITUDE-O TRIAL
NEJM september 2021

Figure S5: Effects of Efpeglenatide 4 or 6 mg Weekly on Change in eGFR



No. of Participants						
Efpeglenatide	2717	2566	2520	2453	2024	490
Placebo	1357	1274	1250	1194	953	225

Shown are the effects on the least square mean change in estimated glomerular filtration rate (eGFR).

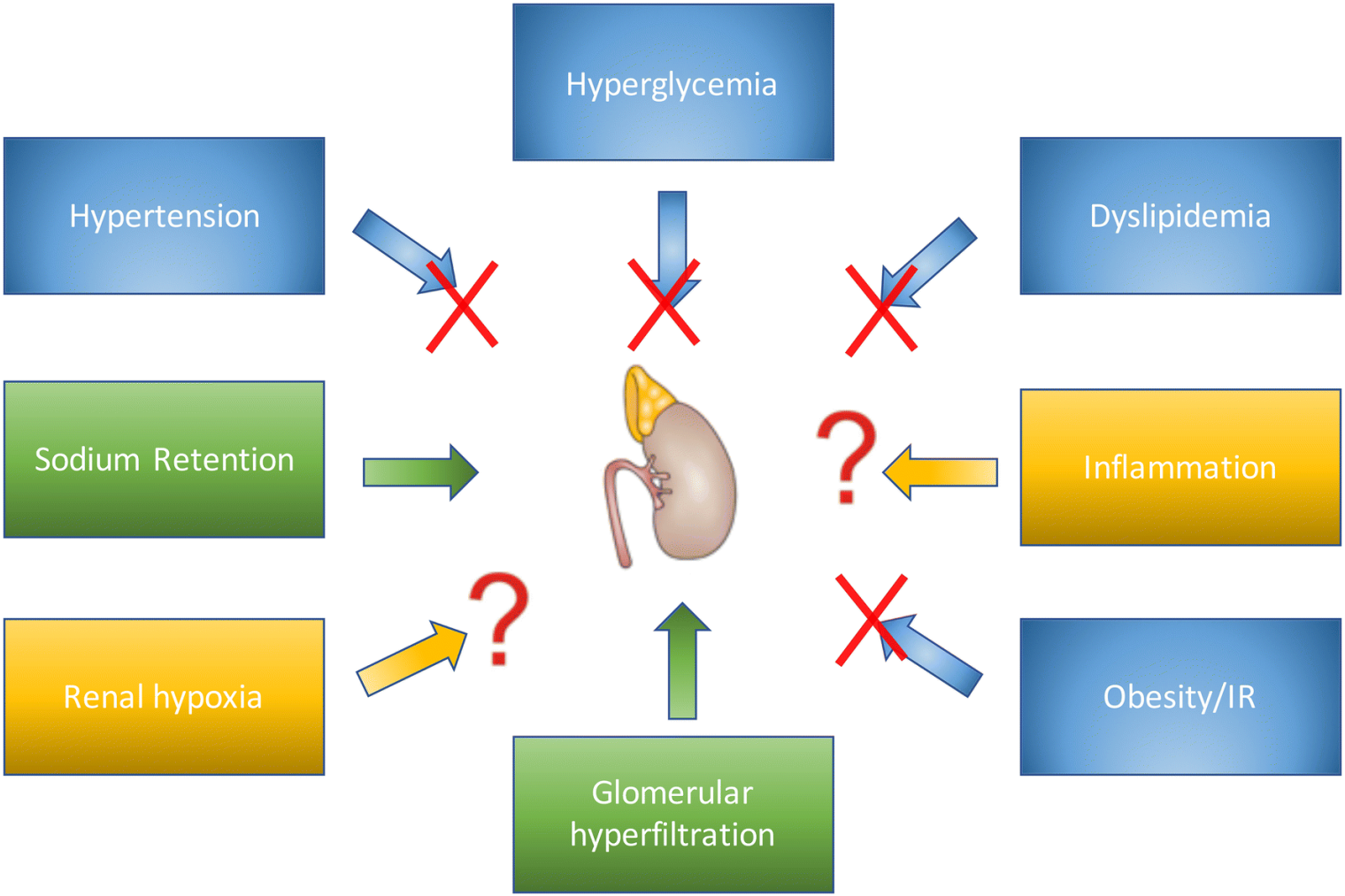
- GLP-1 receptor agonists have an important role in the management of hyperglycemia in type 2 diabetes given their potent glucose-lowering actions.

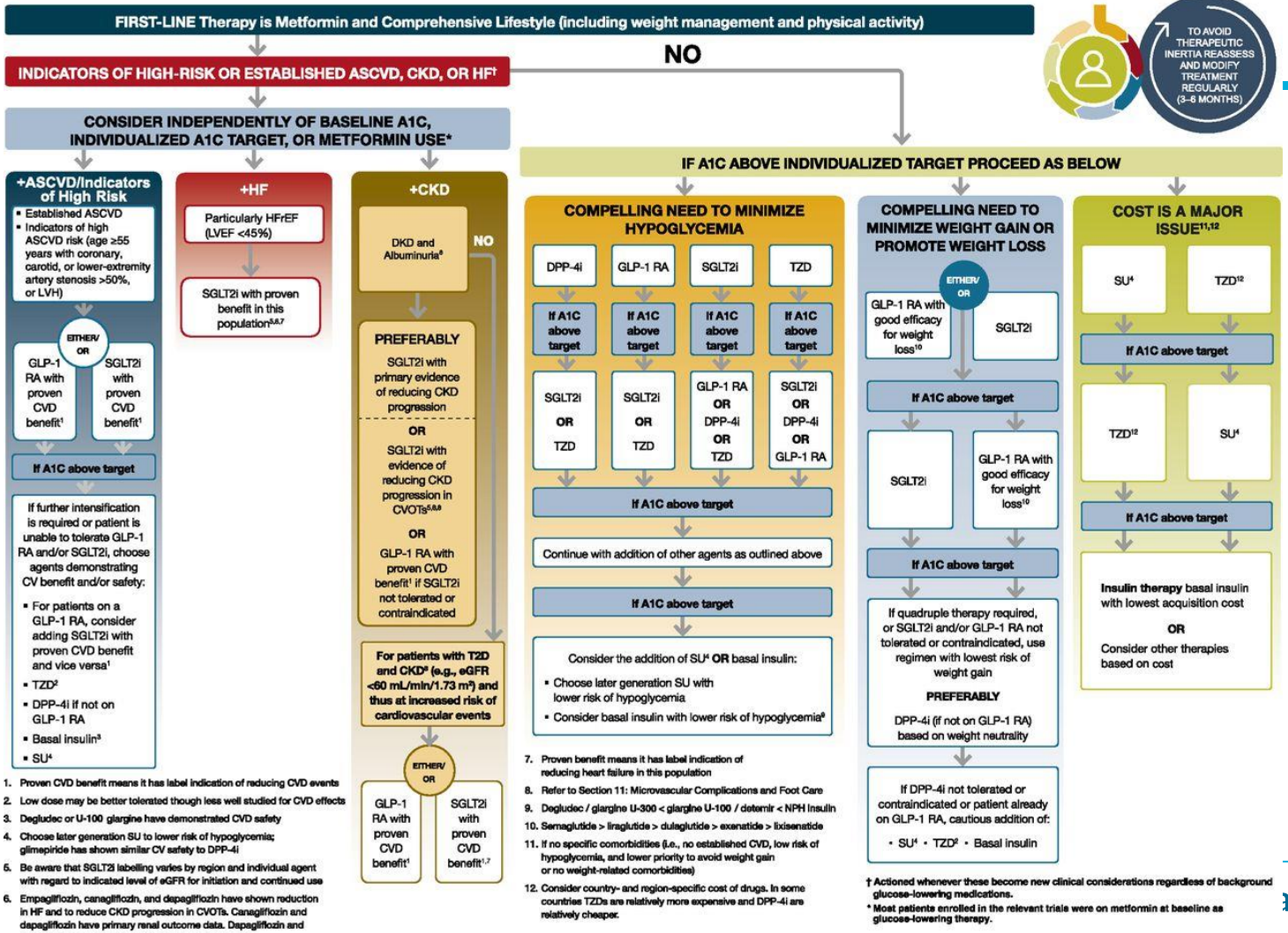
- They improve blood pressure, body weight and dyslipidemia and reduce CVD in a high-risk T2D population.

- The GLP-1 receptor agonists are safe to use in people with DKD, however, **whether they are truly nephroprotective remains to be seen**. Trials have shown that GLP-1 receptor agonists lower albuminuria, however it is uncertain whether this will translate into improvements in hard renal outcomes. Similarly, the small changes in eGFR trajectories (i.e. subtle reductions in eGFR decline versus placebo or titrated insulin) do not necessarily indicate renoprotection. As the GLP-1 receptor agonists induce an initial upsurge in eGFR with similar trajectories over time, this pattern may not indicate a reduction of glomerular pressure.

- The answers to these outstanding gaps in knowledge are currently addressed in the **FLOW trial** (Semaglutide on the Progression of Renal Impairment in Subjects With Type 2 Diabetes and Chronic Kidney Disease; NCT03819153). In this trial, the effects of once weekly subcutaneous semaglutide in patients with macro-albuminuria and impaired eGFR are examined over 5 years of follow-up. The primary endpoint is a composite of persistent eGFR decline of > 50%, reaching ESKD, death from kidney disease or death from CVD.

Modified after Mosterd et al; J Nephrol 2019


Hyperglycemia
Hypertension
Dyslipidemia
Sodium Retention
Inflammation
Renal hypoxia
Obesity/IR
Glomerular hyperfiltration



Glucose-lowering medication in type 2 diabetes: 2021 ADA Professional Practice Committee (PPC) adaptation of Davies et al.

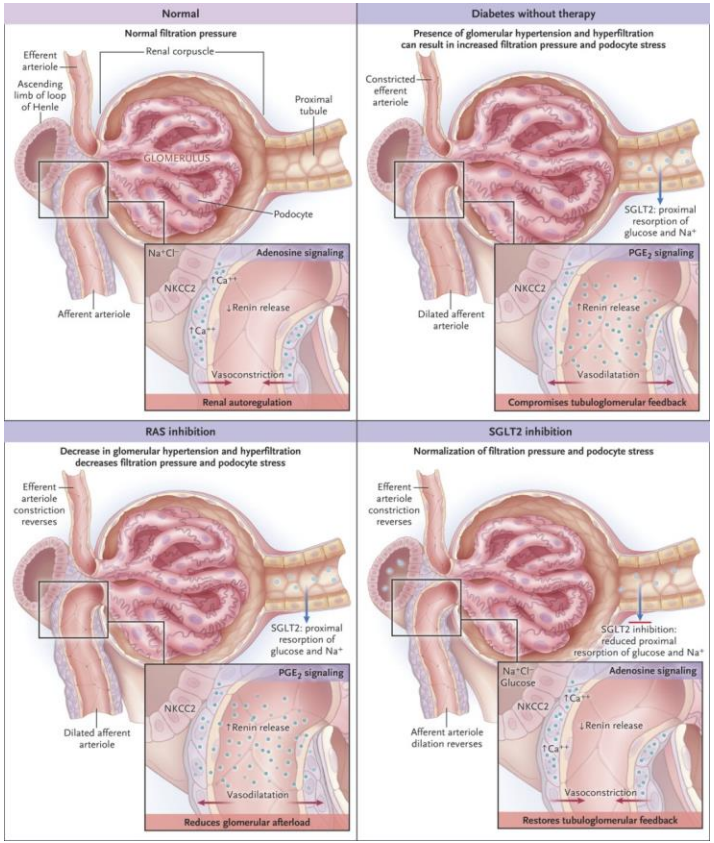
American Diabetes Association Diab Care 2021;44:S111-S124

American Diabetes Association.

adboudumc

EINDE en dank voor jullie aandacht en geduld!

Glomerular Filtration Pressure That Drives Albuminuria, Podocyte Loss, and Glomerulosclerosis in Diabetes.



The NEW ENGLAND JOURNAL of MEDICINE

Radboudumc

Anders H et al. N Engl J Med 2016;375:2096-2098.

Cardiorenal outcomes with SGLT2i across strata of e-GFR and albuminuria

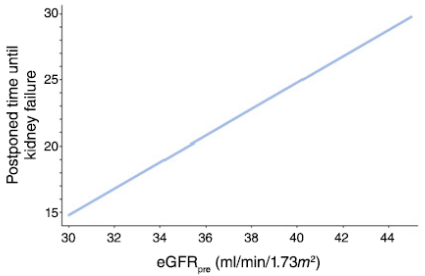
A

MACE - 3			Albuminuria Category: Normal to mildly increased (< 30)	Moderately increased (30-300)	Severely increased (> 300)	
eGFR category (ml/min/1.73m²)	Normal or high	≥ 90	0.89	0.93	0.69	
	Mildly decreased	60-89	0.89	0.93	0.69	
	Mild to moderately decreased	45-59	0.93	0.69	0.88	0.86
	Moderately to severely decreased	30-44	0.69	0.88	0.88	
	Severely decreased	15-29	0.88	0.88	0.88	
	Kidney failure	≤ 15	0.88	0.88	0.88	
						0.86

B

Incident or worsening nephropathy			Albuminuria Category: Normal to mildly increased (< 30)	Moderately increased (30-300)	Severely increased (> 300)	
eGFR category (ml/min/1.73m²)	Normal or high	≥ 90	0.67	0.58	0.52	
	Mildly decreased	60-89	0.67	0.58	0.52	
	Mild to moderately decreased	45-59	0.58	0.52	0.68	0.61
	Moderately to severely decreased	30-44	0.69	0.68	0.68	
	Severely decreased	15-29	0.68	0.68	0.68	
	Kidney failure	≤ 15	0.68	0.68	0.68	
						0.61

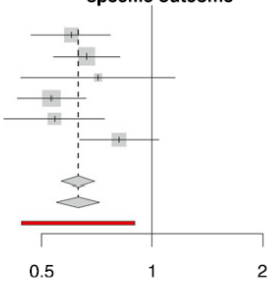
C



D

Study	SGLT2i events /1000 PYs	PBO events /1000 PYs	HR	95%-CI	Weight (fixed)	Weight (random)
CANVAS Program	5.5	9.0	0.60	[0.47; 0.77]	18.1%	18.4%
CREDENCE	27.0	40.4	0.66	[0.53; 0.82]	24.5%	21.7%
DAPA-HF	8.0	12.0	0.71	[0.44; 1.15]	4.7%	6.9%
DECLARE-TIMI-58	3.7	4.0	0.53	[0.43; 0.66]	24.0%	21.5%
EMPA-REG Outcome	6.3	11.5	0.54	[0.39; 0.74]	11.2%	13.5%
VERTIS-CV	9.0	12.0	0.81	[0.63; 1.04]	17.5%	18.1%
Fixed effect model			**0.63**	**[0.56; 0.70]**	**100.0%**	**--**
Random effects model			**0.63**	**[0.55; 0.722]**	**--**	**100.0%**
Prediction interval				**[0.44; 0.90]**		

Heterogeneity: I^2 = 36%, τ^2 = 0.0115, p = 0.17



Cardiorenal outcomes with SGLT2i across strata of e-GFR and albuminuria

Baseline eGFR ranges and UACRs in Cardiovascular and Kidney Outcome Trials (Reported and Ongoing) With SGLT2is

eGFR Categories, mL·min^{-1}·1.73 m^{-2}		UACR Categories, mg/g		
		<30, Normal-MildIncrease (A1)	30–300, ModerateIncrease (A2)	>300, SevereIncrease (A3)
≥90, Normal	G1	DECLARE TIMI-58 CANVASEMPA-REG OUTCOMEVERTIS-CV	DECLARE TIMI-58 CANVASEMPA-REG OUTCOMEVERTIS-CV	
60–89, Mild reduction	G2	DECLARE TIMI-58 CANVASEMPA-REG OUTCOME VERTIS-CV	DECLARE TIMI-58 CANVASEMPA-REG OUTCOME DAPA-CKDEMPA-KIDNEY VERTIS-CV	CREDENCE DAPA-CKD EMPA-KIDNEY VERTIS-CV
45–59, Mild-moderate reduction	G3a	DECLARE TIMI- 58 CANVASEMPA-REG OUTCOMEVERTIS-CV SCORED	DAPA-CKD EMPA-KIDNEY VERTIS-CV	CREDENCE DAPA-CKD EMPA-KIDNEY SCORED VERTIS-CV
30–44, Moderate-severe reduction	G3b	EMPA-KIDNEY VERTIS-CV SCORED	DAPA-CKD EMPA-KIDNEY VERTIS-CV SCORED	CREDENCE DAPA-CKD EMPA-KIDNEY VERTIS-CV SCORED
15–29, Severe reduction	G4	EMPA-KIDNEY SCORED	DAPA-CKDEMPA-KIDNEY SCORED	DAPA-CKDEMPA-KIDNEY SCORED
<15, Kidney failure	G5			

De SGLT-2-remmers zijn al opgenomen in het GVS op bijlage 1A (cluster 0A10BXAO V) en worden vergoed voor specifieke patiëntengroepen. Deze patiëntengroepen zijn per SGLT-2-remmer gedefinieerd in de vergoedingsvoorwaarden op Bijlage 2 van het GVS.
Voor vergoeding van canagliflozine (Invokana®), dapagliflozine (Forxiga®), empagliflozine (Jardiance®) bij de behandeling van volwassenen met diabetes mellitus type 2 met een zeer hoog risico op hart- en vaatziekten gelden de volgende aanvullende bijlage-2 voorwaarden:

•Eerder bewezen hart- en vaatziekten;
en/of
•chronische nierschade met
– eGFR 30-59 ml/min per 1,73m2 met matig verhoogde albuminurie (ACR> 3 mg/mmol/l);
of
– eGFR ≥ 60 ml/min per 1,73m2 met ernstig verhoogde albuminurie (ACR>30 mg/mmol).

ARTSENVERKLARING

Ingevuld formulier is bestemd voor apotheek

GLIFLOZINE

(hoog risico op hart- en vaatziekten of hartfalen)

NB: Uitsluitend de **laatste versie** van de (artsen)verklaring wordt geaccepteerd door de zorgverzekeraar. Controleer dit op http://www.znformulieren.nl

VERSIE: 2.1
INGANGSDATUM: 01-09-2021
NUMMER: 130

A VERZEKERDEGEGEVENS

vul de gevraagde gegevens volledig in

naam:

geboortedatum:

verzekerdenummer:

adres:

ruimte voor patiëntenetiket/ponsplaatje

B IN TE VULLEN DOOR DE VOORSCHRIJVEND ARTS

doorloop onderstaande criteria en kruis aan, teken dit formulier bij 'C', toevoegingen/correcties maken dit formulier ongeldig.

Ondergetekende, huisarts, cardioloog of (vasculair) internist, schrijft dapagliflozine aan deze verzekerde voor ter behandeling van:			kolom 1*	kolom 2*
1	De indicatie Diabetes Mellitus type 2 *(zonder een zeer hoog risico op hart- en vaatziekten* OF *hartfalen)*-> ga naar de apotheekinstructie, er is geen artsenverklaring nodig.	☐ *JA* ☐ *NEE, ga naar 2*		
2	Een verzekerde van 18 jaar of ouder,	☐ *JA, ga naar 3* ☐ *NEE*		XO
3	Met diabetes mellitus type 2 en eerder bewezen hart- en vaatziekten,	☐ *JA* ☐ *NEE, ga naar 4*	36	
4	Met diabetes mellitus type 2 en chronische nierschade: - eGFR 30-59 ml/min per 1,73m2 met matig verhoogde albuminurie (ACR> 3mg/mmol) of - eGFR ≥ 60 ml/min per 1,73m² met ernstig verhoogde albuminurie (ACR>30 mg/mmol).	☐ *JA* ☐ *NEE, ga naar 5*	36	
5	met symptomatisch (NYHA II-IV) chronisch hartfalen met een verminderde ejectiefractie (LVEF <40%).	☐ *JA* ☐ *NEE*	36	XO

***Een zeer hoog risico op hart- en vaatziekten is gedefinieerd als:**

- **Eerder bewezen hart- en vaatziekten; en/of**
- **Chronische nierschade met**
  - **eGFR 30-59 ml/min per 1,73m2 met matig verhoogde albuminurie (ACR> 3 mg/mmol) of**
  - **eGFR ≥ 60 ml/min per 1,73m2 met ernstig verhoogde albuminurie (ACR>30 mg/mmol).**

C HANDTEKENING ARTS

zorg voor juiste, leesbare en gedateerde handtekening

Deze artsenverklaring is naar waarheid ingevuld

naam:

praktijkadres:

telefoon:

datum:

handtekening arts:

D IN TE VULLEN DOOR APOTHEEKHOUDENDE

De apotheekhoudende verklaart dat het voorgeschreven geneesmiddel o.b.v deze artsenverklaring en de bijbehorende apotheekinstructie is:

☐ *a) afgeleverd, ten laste van de zorgverzekeraar*
☐ *b) afgeleverd, NIET ten laste van de zorgverzekeraar*
☐ *c) NIET afgeleverd*

AGB code apotheekhoudende:

datum:

handtekening apotheekhoudende:

*

1. Indicaties eindigend in kolom 1 voldoen **wel** aan de vergoedingsvoorwaarden zoals vastgelegd in **nr 130** van Bijlage 2 van de Regeling zorgverzekering.
2. Indicaties eindigend in kolom 2 voldoen hier **niet** aan.
3. Een verklarende lijst voor de vergoedingscodes in kolom 1 en 2 kunt u vinden op www.znformulieren.nl.

Zorgverzekeraars Nederland

SGLT2 inhibitors

Benefits

- ↓ MACEs
- ↓ CV mortality
- ↓ Total mortality
- ↓ Heart failure
- ↓ CKD
- ↓ NAFLD

Risks

- Genital infections (x 3-6)
- UTIs (marginal, x 1-1.5)
- Volume depletion (rare)
- AKI (rare, if precitipants)
- Euglycemic DKA (x 2, rare)
- Bone fractures (TBC)
- LLA (canagliflozin ?)
- Fournier gangrene (TBC)


Pee
Rinse
Wipe

Sick Day Medication List

Instructions for Healthcare Professionals:

- If patients become ill and are unable to maintain adequate fluid intake, or have an acute decline in renal function (e.g. due to gastrointestinal upset of dehydration), they should be instructed to hold medications which will:

A/ Increase risk for a decline in kideny function:

- Angiotensin-converting enzyme inhibitor
- Angiotensin receptor blockers
- Direct renin inhibitors
- Non-steroidal anti-inflammatory drugs
- Diuretics
- SGLT2 inhibitors

B/ Have reduced clearance and increase risk for adverse effects:

- Metformin
- Sulfonylureas (gliclazide, glimepiride, glyburide)

S	sulfonylureas
A	ACE-inhibitors
D	diuretics, direct renin inhibitors
M	metformin
A	angiotensin receptor blockers
N	non-steroidal anti-inflammatory
S	SGLT2 inhibitors

GLP-1 RA THERAPY

ADVERSE EVENTS

GI disorders:
- Most frequent: Nausea, diarrhoea, vomiting, constipation, abdominal pain and dyspepsia
- GI AEs gradually subside with time depending on the type of GLP-1 RA

Other AEs:
Hypoglycaemia, hypersensitivity, pre-renal acute kidney injury, injection site reactions, increased heart rate, pancreatitis

MANAGEMENT OF ADVERSE EVENTS

For GI AEs:
- **Counselling:** Mild and transient nature of symptoms
- **Monitoring:** Clinical lab based if required
- **Empowerment on management of AEs:**

  Pharmacological management:
  - Start slow go slow: Dose titration
  - Centrally-acting anti-emetics (ondansetron and PPIs)
  - Probiotics: Indirectly stimulate GIP secretion and increase lactobacilli population in the gut

  Non-pharmacological management:
  - Intake of frequent small meals
  - Avoiding food rich in fats or spicy and strongly flavoured food
  - Munching amla and ginger

For other AEs: Regular contact with HCP (F2F or telephonic)

UNREALITIC EXPECTATIONS

- Drastic weight loss
- Immediate glycaemic control

COUNSELLING

- Realistic expectation setting: goal setting
- Difference between insulin and GLP-1 RA
- Focus on lifestyle modification

Kalra S et al., Diabetes Therapy 2019

SGLT2 INHIBITORS ADDITIONALLY IMPROVE KIDNEY AND CV OUTCOMES IN NON-DIABETIC PATIENTS WITH CKD

There were no statistically significant differences in DAPA-CKD in the primary endpoint between diabetics and non-diabetics, however, the HR was 22% lower for non-diabetics.

Thus the kidney benefit afforded by dapagliflozin was at least as large in patients with non-DKD (including ischaemic/hypertensive nephropathy, IgA nephropathy and focal segmental glomerulosclerosis, among others) than in DKD.

Additionally, dapagliflozin reduced all three secondary endpoints compared with placebo: worsening renal function or death from kidney failure [HR 0.56 (95% CI 0.45–0.68)], hospitalization for HF or CV death [HR 0.71 (95% CI 0.55–0.92)] and all-cause mortality [HR 0.69 (95% CI 0.53–0.88)].

Results on albuminuria and proteinuria for non-diabetic patients enrolled in DAPA-CKD are awaited, as this may provide clues as to the mechanism of nephroprotection afforded by SGLT2 inhibitors.

GLP-1 exerts its main effect by **stimulating glucose-dependent insulin release from the pancreatic islets**. It has also been shown to slow gastric emptying, inhibit inappropriate post-meal glucagon release, and reduce food intake .