New Renoprotective Approach The Role of SGLT-2 inhibitors, GLP-1 RA & NS MRA

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Nephrology

Burden of CKD

Epidemialogy of chronic kidney disease: an update 2022





Chronic lading, diverse (CND) noous frequently and has deviating consequences. This should prompt in major efforts to develop preventative and therapeutic measures that are effective. The aim of these measures should be lowering the incidence of CKD and slowing its progression.

Caused of CKD



KDIGO Classification

Progin KDIG0	osis of (0 2012	2KD by GFR and Albuminuna Categories:	Persistent albuminaria categories Description and Range						
			A1	A2	A3				
				Normal to mildly increased	Moderately increased	Severely increased			
				<30 mg/g	30-300 mg/g	>300 mg/g			
3 Getegories (miximit), 73 m ³) Description, and Range.	G1	Normal or High	≥90						
	G2	Mildly decreased	60-89						
	G3a	Mildly to moderately decreased	45-59						
	G3b	Moderately to severely decreased	30-44						
	G4	Severely decreased	15-29						
5	G5	Kidney failure	<15						

Green: low risk (if no other markets of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Rec, very high risk;

Goal of treatment



Definition of Outcomes



Plethora of studies



CKD vs CVD



Historic Invention



SGLT2 Inhibitors

OH

SGLT2 Inhibitors

Bexagliflozin (Brenzavvy)
Canagliflozin (Invokana)
Dapagliflozin (Farxiga)
Empagliflozin (Jardiance)
Ertugliflozin (Steglatro)
Sotagliflozin (Inpefa)



Gliflozin



Diuretics mechanism of action





Mechanism of action



Systemic Effects



Diabetic kidney disease

- Increased tubular reabsorption of Na partly from SGLT2 upregulation
 - Resulting in lowering of the [Na] at the macula densa
- Leading to decreased afferent arteriolar tone
- 👗 Eventually increased GFR
- K Hyperfiltration eventually leads to fibrosis within the glomerulus and tubulointerstitium



Mechanism of renoprotection of SGLT-2



Normal physiology

Hyperfiltration in early stages of diabetic nephropathy SGLT-2 inhibition reduces hyperfiltration via TGF

Outcome



CANVAS

Canagliflozin (SGLT2i) for type 2 DM: cardiovascular outcomes

Canagliflezin and Cardiovascular and Renal Events in Type 2 Diabetes. B Neal, V Perkovie, R. W. Mahattey, Dick de Zeeuw CANVAS Program Collaborative Group, NEJM 2017 EPub.





CANVAS

Risk Reductions in Cardiovascular and Kidney Outcomes With Canagliflozin Across KDIGO Risk Categories



CREDENCE



Perkovic, Vlado, et al. Canagillioan and Renal Outcomes in Type 2 Diabetes and Nephropathy. NEJM, 2019, doi:10.1056/nejmoa1811744.

MarioFunesMD

CREDENCE

Canagliflozin and Kidney-Related Adverse Events in Type 2 Diabetes and CKD: Findings From the Randomized CREDENCE Trial

Design	Results								
CREDENCE Multicenter, double-blind,	4,401 people with type 2 diabetes, CKD, and	e 2 Canagliflozin reduces the risk of kidney-related adverse events							
placebo-controlled, randomized trial	UACR >300-5,000 mg/g		Antidoonto exerciper patient y	40 in .000 012					
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690 centers 34 countries	Canagliflozin Placebo			1	n han i finnen	pulle			

CONCLUSION: Canaglifiozin decreased the incidence of kidney-related adverse events, highlighting the renal safety of canagliflozin in patients with type 2 diabetes and CKC.

Hiddo JL Heerspink, Megumi Oshime, Hong Zhang et al. (2021) (QAJKDontne | DOI: 10.1053/j.april.2021.05.005



EMPA-KIDNEY

Empagliflozin in Patients with Chronic Kidney Disease (EMPA-KIDNEY)





Conclusion: among a wide range of patients with chronic kidney disease who were at risk for disease progression, empagificain therapy lad to a lower risk of progression of kidney disease or death from cardiovescular causes than placebo.

Reference: EVER 5005 (Y Cellaboradae: Group: (1921)
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EMPA-KIDNEY

Effects of empagliflozin in patients with chronic kidney disease who are at risk for disease progression



Conclusions Among a wide range of patients with chronic kidney disease who were at risk for disease progression, empagifican therapy led to a lower risk of progression of kidney disease or death from cardiovascular couses than placebo. EMPA-KIDNEY Collaborative Group. Empagilillozin in Patients with Chronic Kidney Disease. N Engl J Med. 2022 Nov 4. doi: 10.1056/NEJMce2204233 Visual Abstract by Edgar Lenna, WD, FASN

KIDNE

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Does Dapagliflozin compared to placebo reduce the risk of kidney failure and CV events in CKD patients with and without T2DM?



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CONCLUSION: Repainflown sophics of y reduces the risk of know feiture CV death on respitation on for this shall be sense to by in patients with CKC with one without T2DM compared to piece so. Dapagificzin was well to erated, in keeping with its established safety profile.

DAPA-CKD

presented by Professer Hebrapirk at the BEO Congress -August 50, 2000

DAPA-CKD

You, 1 Area all by Art. Names MD

Could dapagliflozin improve kidney and

cardiovascular outcomes in patients with CKD?



Conclusion: Among patients with chronic kidney disease, the risk of any composite kidney or cardiovascular outcomes or death was significantly lower with dapagliflozin than with placebo.

Reference: Heatspirk Hill er of Capagi Horistic Parlenss with Chronic Cidney Disease: N Engl J Micd. 2000 Sep 24. DOI: 10.1056/NDIMea2024846



NephJC

Maual abstract: Den bas Arei area, MD 😏 @dani se jarri

DAPA-CKD – by Geography

Efficacy and Safety of Dapagliflozin in Patients with Chronic Kidney Disease Across Major Geographic Regions



DAPA-CKD Multicenter



Double-blinded



eGFR 25-75 millinii 75.09



UACR 200-5000 $m_{\rm eff}$



± Diabetes On stable measurely tolerated ACEI or ARE doso



Primary composite endpoint		Sustained decline in eGFR > 50% End-stage Kidney Disease (ESKD) Dech from litchey disease-related or GV cause					
		Relative risk of the primery composite endpoint in patients on depagtificatin (as placebo)	Occurience of serious adverse events Depoglification van Piecebo				
	31.3% Asia	HR 0.70 (80% Ci 0.48-1.00)	21.9% - 26.8%				
4	28.6% Europe	HR 0.60 (85% CI 0.43-0.85)	34.1% 38.6%				
7	21.2% Latin America	HR 0.61 (87% CI 0.43-0.85)	29.8% - 31.5%				
Ħ	18.9%	HR 0.51 (95% C10.34-0.78)	34.9% vs 41.0%				

War1 P; 2022 Charge allowinged by: Edget Lenne, MD Conclusion Dapagliflozin reduced kidney and cardiovascular events, and prolonged survival in patients with CKD, with and without type 2 diabetes, with no apparent. effect modification by geographic region.

🐭 (notparelement)

Effect of dapagliflozin on kidney and cardiovascular outcomes by baseline KDIGO risk categories – a post-hoc analysis of the DAPA-CKD trial



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Exception's Better - Fixedo Better

Metanalysis



Conclusion: SGLT2 inhibitors reduce the risk of cardio renal outcomes in patients with T2DV and CKD, without clear evidence of additional safety concerns beyond these already known for the class.



Another metanalysis



Outcome: Regardless of A1C control

	SGLT2 inhibitors			DPP4 inhibitors			20202000000	2010/03/22 Providence (2020)
	Patients DØ	Events	Events per 1000 patient yrs	Patients (%)	Events	Events per 1000 patient yrs	Hazard ratio (95% CI)	P value Hazard ratio for (95% CI) Interaction
Total population	29.887 (7.00)	111:	2.6	29 887 (100)	360	6.2		0.42 (0.34 to 0.53)
Sex	10: 10:00 M							0.704
Mett	181290612	8.9	27	18:129-0510	232	5.0	+	0.41 (0.31 to 0.54)
Women	11 758 (39)	42	2.4	11.758 (39)	128	5.6		0.45 (0.32 to 0.54)
Age								0.985
35-64 years	17 954 6600	45	1.7	17.984-(60)	145	4.2		0.42 00.30 to 0.591
65-84 years	11,903 (40)	66	4.0	11 903 (40)	212	9.4		0.43 (0.32 to 0.56)
Major cardiovase	ular disease		100000	CONTRACTOR OUT				0.022
Yes	5 659 (19)	36	4.6	5 449 (18)	155	14.8		0.30 00.21 to 0.44/
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Chronic kidney d	isease .	200	10182.15	2012/03/2012/07		59433		<0.001
Yes	987(30	14	9.2	287 (3)	97	51.3 -		0.18 00.10 to 0.311
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Outcome: Regardless of A1C control



Safety: Overall summary

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TREAM AND COMPANY TRANSPORT

Safety: Severe hypoglycemia


Safety: EuDKA



Safety: Hypotension

FDA warning on all SGLT2 class relating to assessment of volume status prior to initiation of, and during, therapy:

- Meta-analysis of data from >5,000 individuals showing significantly lower SBP & DBP with SGLT2 inhibitor (RR, 1.48; 95% CI, 0.94–2.32)
- Lower blood pressure may, however, be beneficial in many people with T2DM

Decrease salt-induced hypertension



Safety: Diuretic Effect

What are the acute and intermediate effects of empagliflozin on natriuresis, volume status and neurohormonal activation in patients with heart failure?

Cohort N=20 Study Design Outcomes. 600k Randomized, double blind, placebo-Male 75% 5 controlled crossover study FENa **CGFR** Blood volume **& Body Weight** BMI 37 ± 7 Empagliflozin 10mg -208 ml 2.4 1.3 kg -5.2 ± loop diuretic Age 60 ± 12 IOR -586 to 153 16.5 12.638 2 2wkwesheut 2 Crossower p×0.04 0-0.11 p=0.035 For Bit daws p=0.005 1 HbA1c 7.1 1.6 -1.2 -14 mL 0.1 kg Placebo ± 7.6 108-282 to 335 $\pm 1.6\%$ LVEF 45%

Summary: There was a sustained natriuretic effect of Empagificzin over a 14-day period with volume optimization and weight loss without significant RAAS activation or eGFR decline. There was a synergistic effect with loop diuretics.

Reference: Griffin & Rao et al. Empagiflozin in Heart Failure: Diuretic and Cardio-Renal Effects. *Circulation*. 2020 May 15.

Visual Abstract by 💓 @docanjuyadav

#Nech00

Safety: AKI

Characterization and implications of the initial estimated glomerular filtration rate 'dip' upon sodium-glucose co-transporter-2 inhibition with empaglificzin in the EMPA-REG OUTCOME trial.



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Safety: AKI

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Safety: AKI



Combining RAAS Inhibitor & SGLT2 Inhibior



Conclusion: Each DAAS inhibitions & SGLT2 inhibitions reduce in coplements: pressure This reduces pressure within the glomorulus and kidney function is better preserved over time, as shown in numerous trials. Indices of glomeru anti-tracion rise when initiating these chuga. It is important to be aware that these drops are expected to reduce glomerular filtration rate (GER); it is a sign that they are protecting the kidney.

Reference: Meraphylinda et al. ISSER deckta after SGL72 inhibitor Lottations the fortake and the home taking and 2021. 10.01067/1410.0001172021

Visual Abstract by Carlo Trinidad, MD



Safety: GU Infection

K GU infections were the most prevalent

- Candida species was 3–4 x higher than in the control group
- The risk factors include:
 - Female sex
 - Past GU infections
- Higher AIC were not associated with a higher incidence of the infection
- A high rate of treatment discontinuation in patients who had UTI
- Adequate intimate hygiene is crucial as it allows a considerable reduction in infections:
 - 40.8% in the control group vs.
 - 4.8% in the group instructed about hygiene

Safety: GU Infection - Fournier's gangrene

- Kerious type of GU infection is Fournier's gangrene
 - Extremely rare but potentially fatal condition characterized by necrotizing fasciitis of the perineal soft tissues
 - Historically affected J ? = 40 : 1
 - SGLT2 & Fournier's gangrene was reported in 55 cases over 6-yr J ? = 2.4:1
 - FDA included a warning about the risk of Fournier's gangrene



Safety: Limb amputation

- CANVAS trial, a significantly higher incidence of limb amputations with canagliflozin compared to the placebo:
 - 6.3 vs. 3.37 per 1000 person-years. [HR], 1.97 (95% CI, 1.41–2.75)
 - Pt w risk factors for limb ischemia were most at risk for amputation
 - Boxed warning was added by the FDA for canagliflozin in 2017
 - ADA guidelines recommend:
 - Feet of all patients with DM should be evaluated at least annually
 - Patients with evidence of claudication or who have a reduced or absent pedal pulses should be referred for assessment of ABI

Safety: Limb amputation - ABI







Contraindication of SGLT2

Hypersensitivity reaction to SGLT2 inhibitors
 ESRD
 eGFR < 20 ml/min/m2
 Type 1 Diabetes

Diabetes management in CKD



Reference: 18 or four et al.: SDGO guardine on dialeties in CKB; Killing Informational (2020)

VA is Prit Merz, V.D. 😏 #Pritings -

KDIGO Guidelines 2020



Kenney Previous 2020 985 T-S1150CB (10:1015), cm.2020.0031



CC: 58 yo male presents for routine follow-up PMHx:

- DM II x 20 yrs
- HTN
- CKD IIIb: Cr 1.5, eGFR 45 ml/min/1.73m2
- 👗 Med:
 - Atorvastatin 10 mg PO QD
 - Lisinopril 20 mg PO QD
 - Carvedilol 12.5 mg PO BID
 - HCTZ 12.5 mg PO QD
 - Metformin 1000 mg BID
- Kertinent PE:
 - VS: BMI 37, BP 155/94, HR 80
 - Decreased sensation in both feet without foot ulcers
- 💺 Labs: eGFR 49, A1C 8.9, K 5.1, urine albumin/Cr ratio 760 mg/g.

Initiation of SGLT2

Practical provider guide to initiating SGLT2 inhibitors in patients with type 2 diabetes and CKD



Non-Steroidal Mineralocorticoid Antagonist

 H_2N

MRA structure



More NS-MRA to follow



Steroidal MRA



The second se

Mechanism of action of NS MRA



Mechanism of action



MRA: steroidal vs non steriodal



Finerenone



NS MRA Indications: 2 studies & 1 pooled analysis

- FIDELIO-DKD investigated the efficacy & safety of finerenone in delaying CKD progression in advanced CKD
- **FIGARO-DKD** evaluated the efficacy & safety of finerenone in reducing CV morbidity & mortality in earlier stages of CKD
- **FIDELITY** prespecified individual patient analysis of both trials
- K The primary outcomes were defined as:
 - CV endpoints
 - Renal endpoints including:
 - Doubling of serum creatinine
 - Time to ESKD

Indication for MRA



FIDELIO-DKD Prespecified

What's the Design of the "Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease" Trial (FIDELIO-DKD)?





Conclosion: The countrie of FEEE IS-DXD will determine whether an optimally traded cohort of TZD partents with CKD at high risk of progression of their regai discours and CV regists will experience cardiomical benefits with the addition of Energodone to their treatment regiment. Results are expected to 2020. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Nowack C, Kolkhof P, Ferreira AC, Schloemer P, Filippatos G: Design and Baseline Characteristics of the Finecemone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease Trial. Am J Nephrol DOI: 10.1159/000503718

FIDELIO-DKD

Does finerenone slow progression of CKD and reduce cardiovascular mortality in patients with type 2 diabetes? #NeohIC PHASE 3, DOUBLE-BLIND, MULTICENTER, RANDOMIZED, CONTROLLED TRIAL Placebo 5074 Finerenone (10 mg nr 20mg daily) n = 2833Patients with type 2 6.4.6.4.6. 2.6 year median follow up diahetes and CKD Primary Composite Outcome: HR 0.82 21.1% Kidney Pailure with >40% decrease 17.8% (a.73 - a.93) in eGPR over 4-week period or death (504/2833) (600/28(1) p = 0.001from renal causes Secondary Composite Outcome: HR 0.86 13.0% I4.8% Death from cardiovascular causes or (0.75-0.99) (367/2833) (420(2847) hospitalization for any cause p = 0.03

In patients with CKD and type 2 diabetes, treatment with finerenone resulted in lower risk of CKD progression and cardiovascular events than placebo.

Refrience: Baleris G1, Augusted R, Anker S, Fitt B, et al. Effect of Finemanne on Chronic Sidney Disease O accurses in Town Disjocks, NEIM

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FIGARO

Figure 2. FIGARO-DKD

Does finerenone improve cardiovascular outcomes in type 2 diabetes and CKD?



Conclusion among rations with type 2 diabetes and stage 2 to a tist with moder stoly elevants achorizonic or stage 1 or 21 KS with reversing elevanded electricula, five anone therapy improved cardiovascular succomes as compared with placebo. For T. et al.: EdisBO-DED Investigations: Cardinascon an events in this entropy in branch discuss and type 2 resources in Equilibrium these structure shared of parts. August 18, 2021 (cost 40, 100-Mig Visu21) (costs Was for home by Michael and METER: CETE

FIDELITY pooled analysis

The FIDELITY¹ prespecified pooled analysis of FIDELIO-DKD² and FIGARO-DKD³ showed significant risk reductions in CV and kidney outcomes with finerenone



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FIDELITY pooled analysis

Kidney Outcomes with Finerenone in Patients with Type 2 Diabetes and Chronic Kidney Disease: The FIDELITY Pre-Specified Pooled Analysis



м	lethods and Cohort	Key Outcomes					
	Dec enceitied sealed			Placebo	Finerenone	HR (95% CI)	
0	efficacy and safety analysis	Kidney efficacy	composite / outcome	7.1%	5.5%	0.77 (0.67-0.88)	
	FIDELIO and FIGARO RCT	ß	Sustained eGFR reduction ≥57%	5.5%	3.9%	0.70 (0.60-0.83) p=0.0001	
e ma	cohorts (n= 13 026)	2	Kidney failure*	4.6%	3.9%	0.84 (0.71-0.99) pr:0.03	
1	Age ≥18 years Type 2 DM and CKD • mean eSFR 57.6mL/min/1.7m2	R	Renal death	<0.1%	0.1%	0.53 (0.10-2.91)	
1	 median UACR 515 mg/g on maximum tolerated RASi 	Safety					
		Δ	SAE*	33.7%	31.6%	"Odrey (billore = and-stope history disease (3382) as a sustained decrease in a 628 to	
۰	Finerenone vs placebo	8	Hyperkalemia	5.9%	12.0%	 Smil/min/1.75 m2 Sectors scheme event 	

Conclusion: Finerenone reduced the risk of clinically important kidney outcomes vs. placebo across the spectrum of CKD in patients with type 2 diabetes. Agarwel et al., Europeon Heart Journal, (2022)

supported by an unrestricted educational grant from Bayer AG

by Dilushi Wijayaratne MD MRCP @Dilushiwijay

Finerenone in CKD: Meta-Analysis of RCT

- **Objective:** validate efficacy & safety of finerenone in CKD
- **Results:** 5 trials (n = 13,078) were included. Finerenone significantly:
 - Lower UACR from baseline [MD -0.30 (95% CI -0.32, -0.28), p < 0.00001]
 - Decrease eGFR from baseline [MD -2.44 (95% CI -2.82, -2.05), p < 0.00001]
 - Proportion of patients with decreased eGFR (≥40%) was lower [**RR 0.85** (95% CI 0.78, 0.93), *p* = 0.0002]
 - Lower ESKD [**RR 0.80** (95% CI 0.65, 0.99), *p* = 0.04]
 - Lower CVs [RR 0.88 (95% CI 0.80, 0.95), p < 0.003]
- 🖊 Safety:
 - Increase in the [K] [MD 0.17 (95% CI 0.10, 0.24), p < 0.00001]
 - Higher incidence of hyperkalemia [**RR 2.03** (95% CI 1.83, 2.26), *p* < 0.00001]

Conclusion: finerenone confers significant renal & CV benefits in patients with CKD. While higher risk of hyperkalemia

Combining NS MRA & SGLT2

Finerenone in Predominantly Advanced CKD in Type 2 Diabetes With or Without SGLT-2i Therapy





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Conclusion UACR improvement was observed with finerenone in patients with CKD and T2D already receiving SGLT-2i at baseline and benefits on kidney and cardiovascular outcomes appear consistent irrespective of SGLT-2i use.

Cochrane Central Register: Hyperkalemia & AKI

Aldosterone entagonist sensus placebo or standard care for proteineric CKD

Patient or populations are taxen in CK2 Interest tions in a system entrager is: Comparisonapi soebo or viandard care

BMC Cardiovasc Disord 2016 Dec 1;16(1):246

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Conclusion

In patients with T2D and DKD, finerenone reduced albuminuria with a lower risk of hyperkaliemia than observed with steroidal MRAs

Approved by the FDA to reduce the risk of kidney function decline, kidney failure, CV death, non-fatal heart attacks and hospitalization for CHF in patients with T2D
Glucagon-like peptide-1 receptor agonist

.OMe

NH

GLP-1 Receptor & GLP-RA



GLP-1 agonists

- Logical (Crulicity) (weekly)
- K Exenatide extended release (Bydureon bcise) (weekly)
- Kenatide (Byetta) (BID)
- Kemaglutide (Ozempic) (weekly)
- 👗 Liraglutide (Victoza, Saxenda) (QD)
- Lixisenatide (Adlyxin) (QD)
- Semaglutide (Rybelsus) (PO QD)
 Semaglutide (Wegovy) (weekly)



Some combined with Insulin



Summary of utilization in CKD

- Phase 2-3 trials, show that GLP-1 RAs are safe & effective in reducing glycemia and body weight, including in patients with eGFR > 15 mL/min/1.73 m2
- As the **therapeutic options** for patients with CKD **limited**
- K Data are lacking regarding the safety and efficacy of GLP-1 RAs in patients with ESKD
- **K** Limited data on the effects in kidney transplant
- K GLP-1 RAs have beneficial CV effects in patients w & wo CKD
 - Probably even greater in patients with CKD
- Kernel Most consistent finding is reduction of new **macroalbuminuria**
- K Risk to develop ESKD have yet to be demonstrated

DKD treatment: FLOW

FLOW trial is the first long-term kidney outcome trial, studying the effects of the GLP-1 RA, semaglutide, on kidney outcomes



DKD treatment: FLOW



eGFR categories (mL/min/1.73 m²)

Putting all together: 13 different drug classes



Benefits & harms of drug treatment for T2D: meta-analysis

Eligibility criteria for selecting studies:

- Eligible RCT compared drugs of interest in adults with DM-II
- F/U > 24 wk

尾 Results:

- 816 trials with 471 038 patients, evaluating 13 different drug classes
 - SGLT-2 inhibitors (OR 0.88, 95% CI 0.83 to 0.94) & GLP-1 RA (0.88, 0.82 to 0.93) reduce all cause death
 - NS MRA (only with **finerenone**) probably reduce **mortality** (**OR 0.89**, 0.79 to 1.00)
 - SGLT-2 inhibitors and GLP-1 RA reduce CV death, non-fatal MI, admission to hospital for CHF, & ESRD
 - Finerenone probably reduces admissions to hospital for CHF, & possibly CV death
 - Only GLP-1 RA reduce non-fatal stroke
 - Tirzepatide probably results in the largest reduction in body weight (mean difference -8.57 kg)
 - Basal insulin (difference 2.15 kg) & thiazolidinediones (difference 2.81 kg) probably result in the largest increases in body weight BMJ 2023 Apr 6;381

Protect the beans!



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