Cardiometabolic Benefits of Renal Diabetes and Obesity Medications

University of Washington
Cardiometabolic
ECHO

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Disclosures

- Consultation from Bayer, Otsuka, Baxter, Quanta

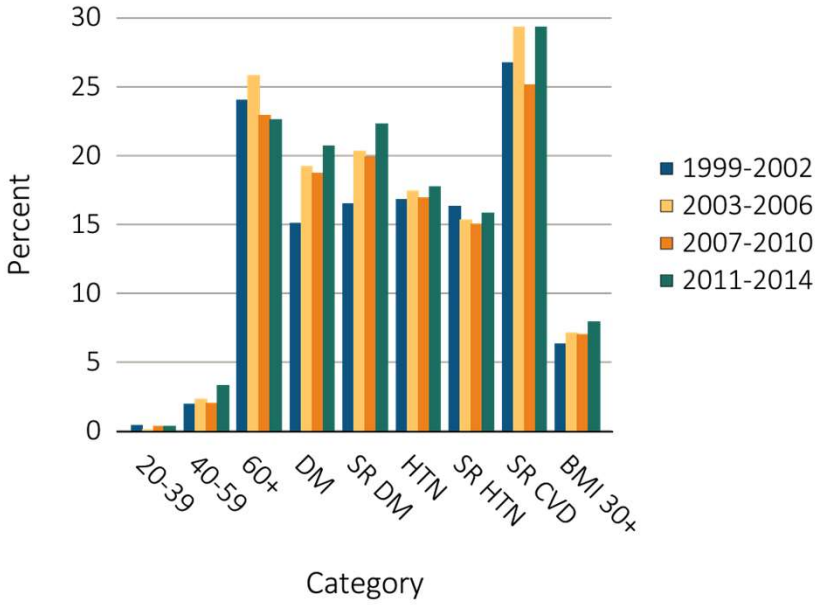
Learning Objectives

1. Pharmacological Interventions to reduce Cardiorenal Risk in Patients with DM2 and/or Chronic Kidney Diseases

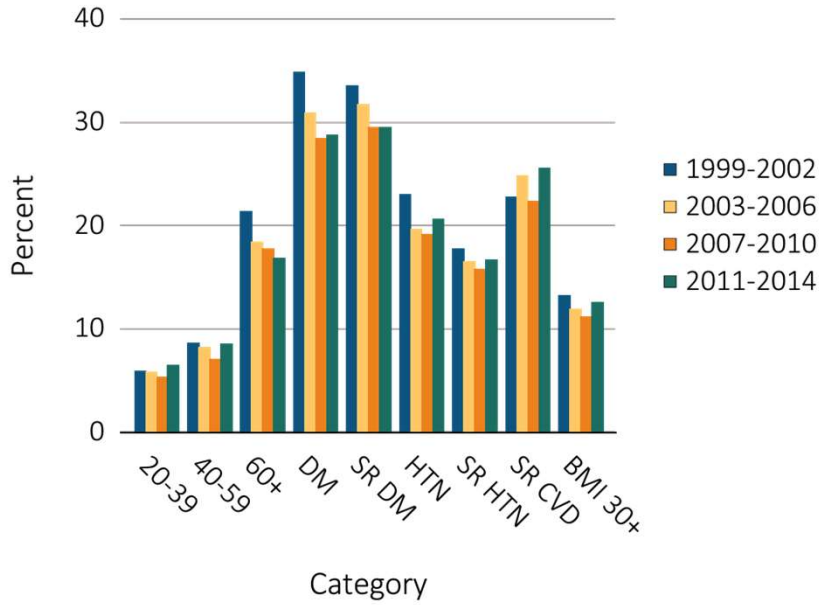
2. Selecting Patients for Cardiorenal Risk Reduction

Diabetic CKD (DKD) is common…

- NHANES participants with eGFR <60 ml/min/1.73 m2

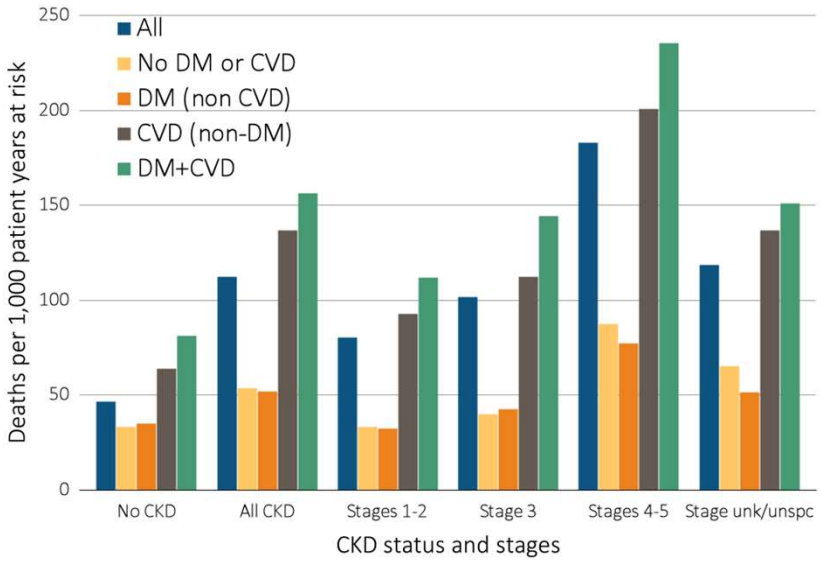


- NHANES participants with urine albumin/creatinine ratio ≥30 mg/g

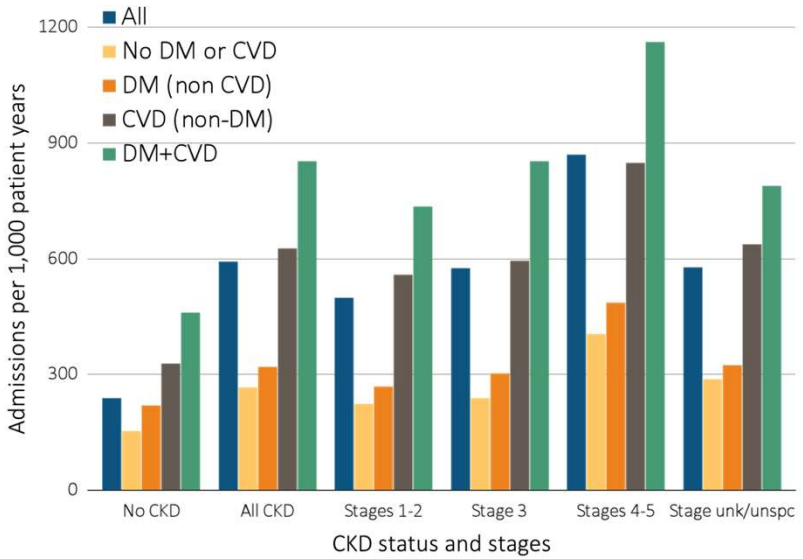


Diabetic CKD + Cardiovascular Disease = Hospitalization + Death

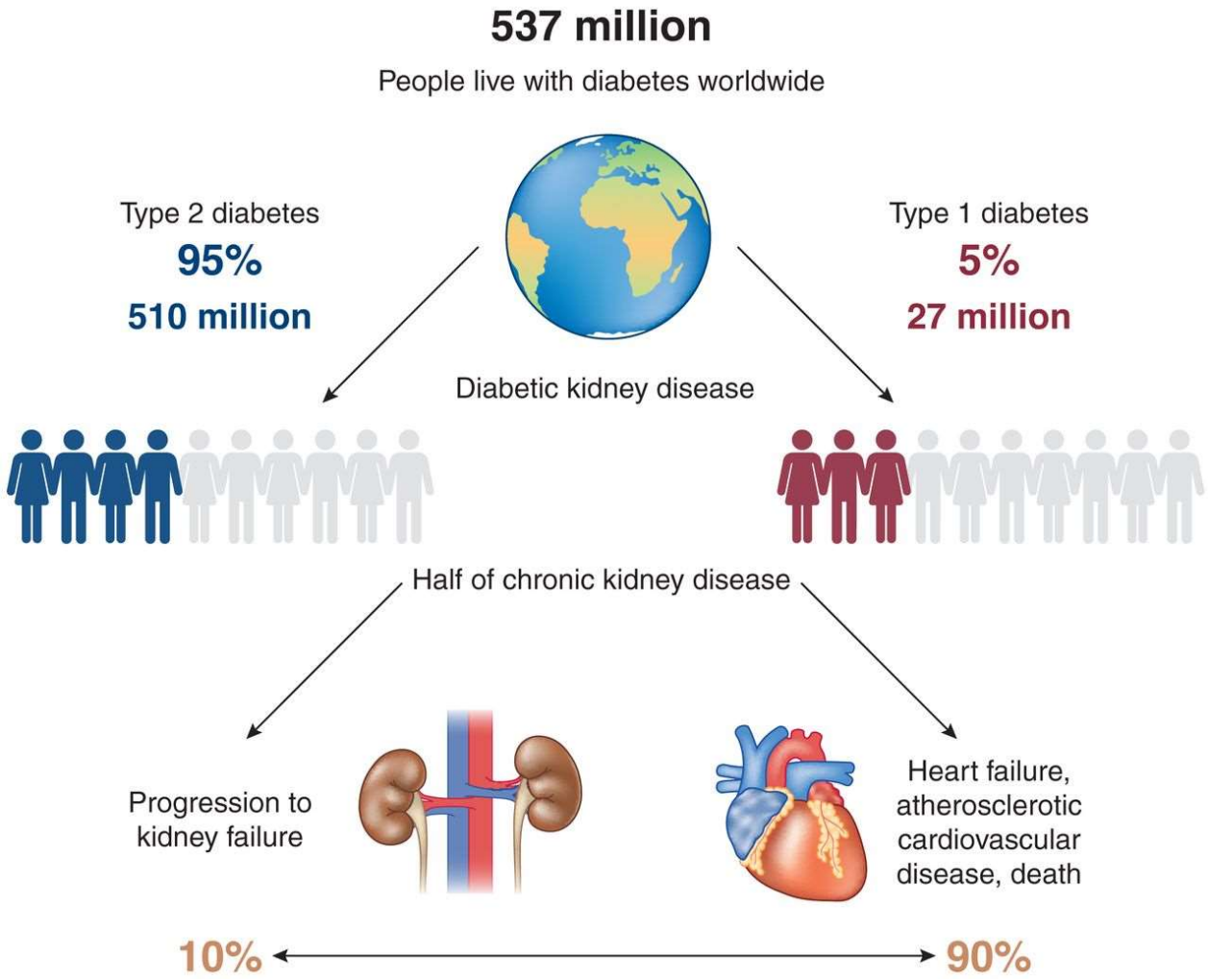
Death



Hospitalization



Data source: Medicare 5 percent sample. January 1, 2014 point prevalent patients aged 66 and older. Adj: age/sex/race. Ref: all patients, 2014. Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus.



https://cjasn.asnjournals.org/content/clinjasn/17/7/1092.full.pdf

Diagnosis of DKD & Cardiovascular Risk Stratification

- Impaired eGFR (<60 ml/min/1.73m2): **kidney function**
- Albuminuria (UACR> 30 mg/g creatinine): **kidney damage**
  - Spot sample to calculate the ratio of Albumin to Creatinine (morning sample preferred)
- Annual screening for DKD
  - 5 years after the diagnosis of Type 1 diabetes
  - Upon diagnosis of Type 2 diabetes

Both UACR and eGFR must be obtained in clinical practice

Am J Kidney Dis. 71(6):884-895,2018

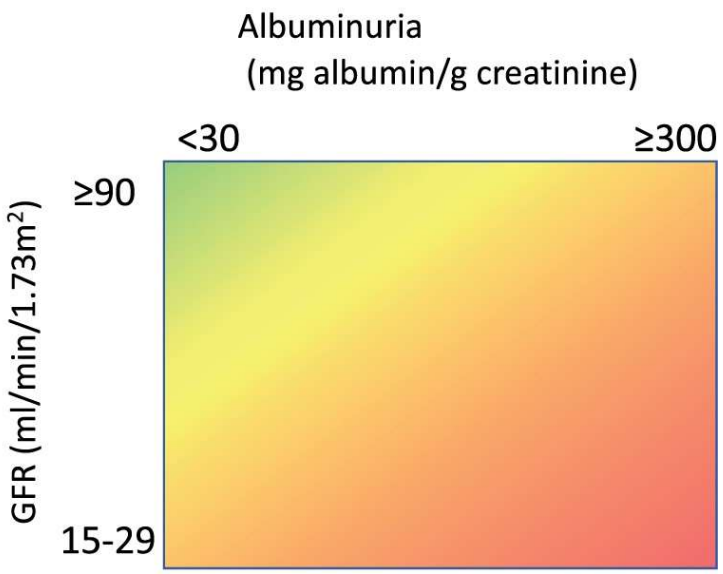
Why one should obtain BOTH eGFR and UACR in clinical practice: ”the kidney cholesterol”

Risk defined in guidelines and trials

KDIGO risk
Low risk
Moderate risk
High risk
Very high risk

eGFR stages and range (mL/min/1.73 m²)				Albuminuria categories and range (mg albumin/g creatinine)		
				A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
				<30	30 to <300	≥300
G1	High and optimal	≥ 90				
G2	Mild	60-89				
G3a	Mild-moderate	45-59				
G3b	Moderate-severe	30-44				
G4	Severe	15-29				

Risk in patients



https://doi.org/10.1093/eurheartj/ehab827

Urine Albumin to Creatinine Ratio: the Piss Prophet of Renal Risk in RENAAL

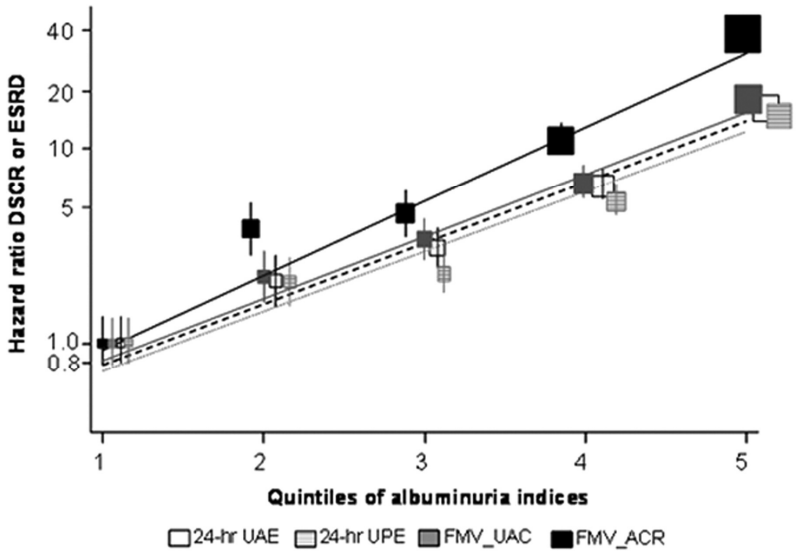


Table 2. Area under the ROC curve and 95% CIs for the prediction of the composite of doubling of serum creatinine or end-stage renal disease based on baseline proteinuria measures

	Subjects/Events	Doubling of Serum Creatinine or End-Stage Renal Disease			
		24-Hour Urine		First-Morning Void	
		UAE (mg/24 h)	UPE (mg/24 h)	UAC (mg/L)	ACR (mg/g)
Overall	701/202	0.78 [0.74, 0.82]	0.78 [0.75, 0.82]	0.79 [0.75 to 0.83]	0.82 [0.79, 0.86][a,b,c]
Subgroups					
Gender					
men	436/107	0.76 [0.71, 0.81]	0.76 [0.70, 0.81]	0.77 [0.72, 0.82]	0.79 [0.73, 0.84]
women	265/95	0.81 [0.76, 0.87]	0.83 [0.77, 0.88]	0.82 [0.77, 0.87]	0.86 [0.82, 0.91][a,c]
Age					
≤61.0 years	351/120	0.78 [0.72, 0.83]	0.79 [0.74, 0.84]	0.80 [0.75, 0.85]	0.84 [0.79, 0.88][a,b,c]
>61.0 years	350/82	0.77 [0.71, 0.83]	0.76 [0.70, 0.83]	0.77 [0.71, 0.83]	0.80 [0.75, 0.86]
Race					
Caucasian	323/75	0.76 [0.70, 0.82]	0.77 [0.71, 0.83]	0.79 [0.73, 0.85]	0.79 [0.74, 0.85]
African American	144/33	0.75 [0.64, 0.86]	0.76 [0.65, 0.86]	0.77 [0.68, 0.87]	0.83 [0.74, 0.91]
Hispanic	192/78	0.78 [0.71, 0.85]	0.78 [0.71, 0.85]	0.78 [0.71, 0.85]	0.82 [0.75, 0.88][a,b]
Gender, age, and race adjusted	701/202	0.79 [0.75, 0.83]	0.79 [0.75, 0.83]	0.80 [0.76 to 0.83]	0.82 [0.79, 0.86][a,b,c]

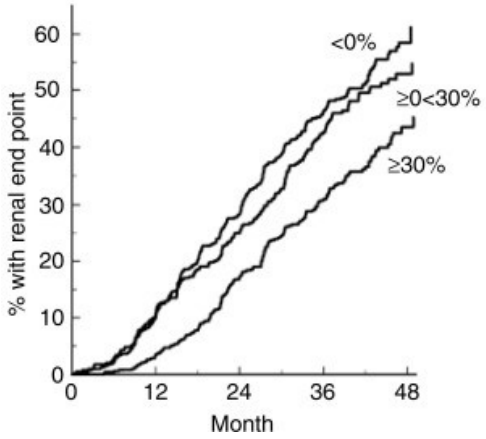
Bonferroni correction was applied in AUC comparison to adjust for multiple testing. ACR, first-morning void albumin:creatinine ratio; AUC, area under the ROC curve; UAE, 24-hour urinary albumin excretion; UPE, 24-hour urinary protein excretion.
[a] $P < 0.01$ *versus* UAE.
[b] $P < 0.01$ *versus* UPE.
[c] $P < 0.01$ *versus* UAC.

https://jasn.asnjournals.org/content/21/8/1355.long

Residual albuminuria, Albuminuria Dela after ARB predict kidney outcomes

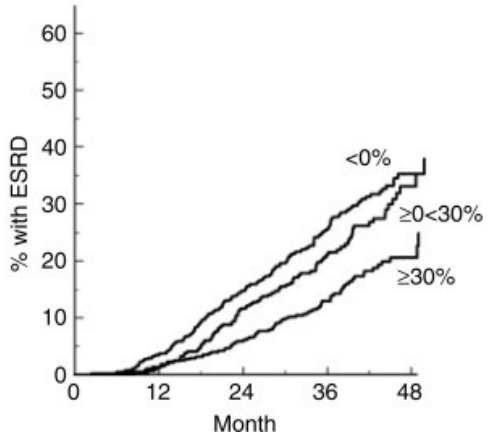
Renal end point

	Unadjusted		Adjusted	
	HR	*P* values	HR	*P* values
Δ Alb: ≥0<30 vs. <0%	0.88	0.1570	0.76	0.0028
Δ Alb: ≥30 vs. <0%	0.60	<.0001	0.46	<.0001
Δ Alb: ≥30 vs. ≥0<30%	0.68	0.0003	0.61	<.0001

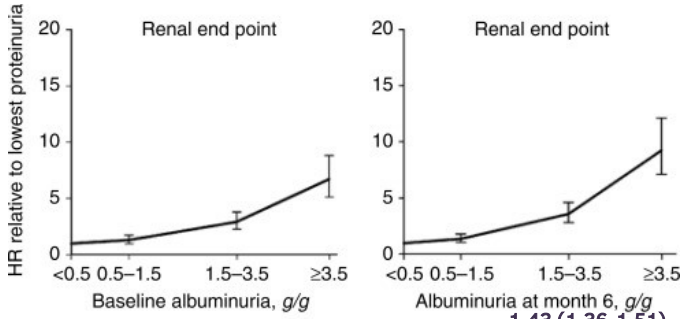


ESRD

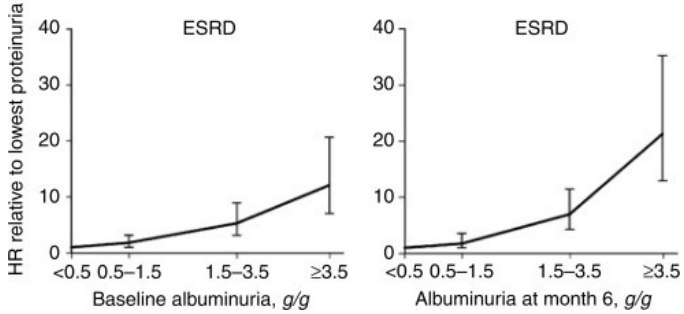
	Unadjusted		Adjusted	
	HR	*P* values	HR	*P* values
Δ Alb: ≥0<30 vs. <0%	0.82	0.1242	0.62	<.0003
Δ Alb: ≥30 vs. <0%	0.51	<.0001	0.37	<.0001
Δ Alb: ≥30 vs. ≥0<30%	0.62	0.0019	0.60	0.0010



1.36 (1.31-1.42)

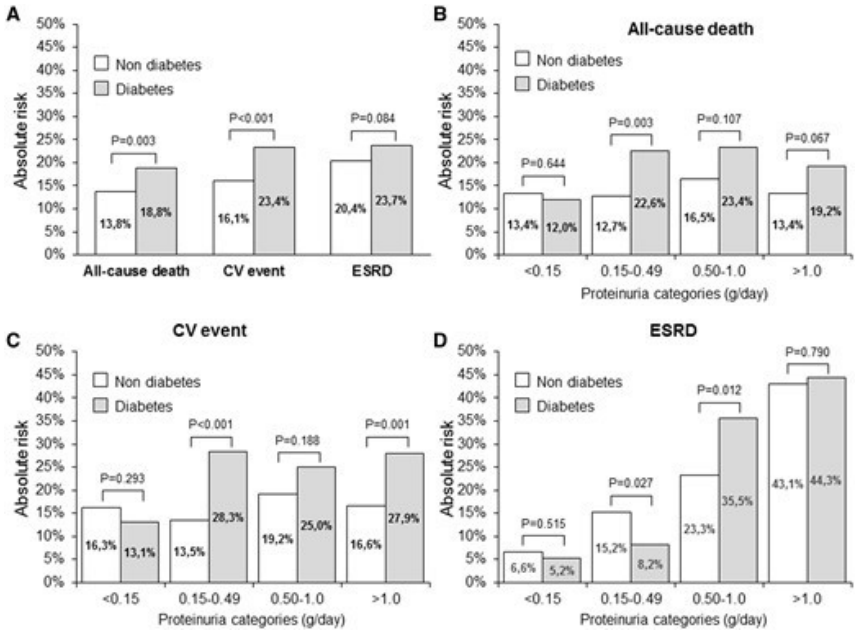


1.43 (1.36-1.51)



https://doi.org/10.1111/j.1523-1755.2004.00653.x

Residual Proteinuria (after RAASi) is associated with increased cardiovascular risk



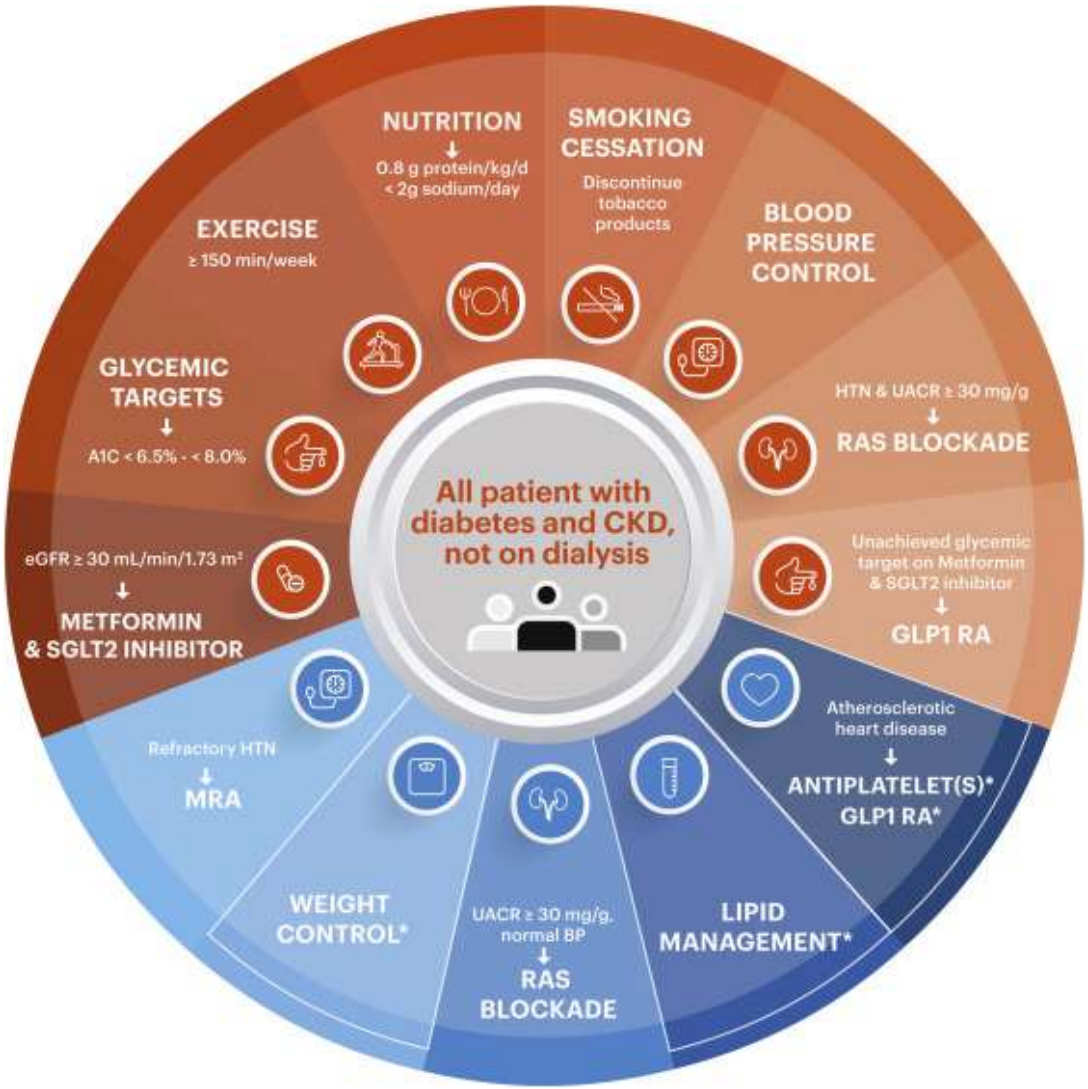
	Proteinuria categories (g/day)							
	<0.15		0.15–0.49		0.50–1.00		>1.00	
	Events/patients (*n*/*N*)	HR (95% CI)	Events/patients (*n*/*N*)	HR (95% CI)	Events/patients (*n*/*N*)	HR (95% CI)	Events/patients (*n*/*N*)	HR (95% CI)
All-cause mortality								
Non-diabetic CKD	63/471	Reference	51/401	1.17 (0.79–1.71)	44/266	**1.60 (1.07–2.40)**	46/343	**1.69 (1.20–2.55)**
Diabetic CKD	23/191	0.81 (0.50–1.32)	36/159	**1.92* (1.25–2.95)**	29/124	**1.99 (1.26–3.15)**	42/219	**1.98 (1.28–3.06)**
CV events								
Non-diabetic CKD	77/471	Reference	54/401	0.95 (0.66–1.35)	51/266	1.33 (0.92–1.92)	57/343	**1.51 (1.04–2.19)**
Diabetic CKD	25/191	0.78 (0.49–1.23)	45/159	**1.80* (1.23–2.63)**	31/124	**1.60 (1.04–2.46)**	61/219	**1.92 (1.32–2.80)**
ESRD								
Non-diabetic CKD	31/471	Reference	61/401	1.31 (0.84–2.04)	62/266	**1.85 (1.18–2.88)**	148/343	**2.69 (1.77–4.10)**
Diabetic CKD	10/191	0.79 (0.38–1.64)	13/159	0.82 (0.43–1.59)	44/124	**1.80 (1.11–2.91)**	97/219	**2.70 (1.75–4.17)**

Cox models were stratified by cohort and adjusted for age, gender, smoking, BMI, history of CV disease, systolic BP, total cholesterol, triglycerides, phosphate, albumin, haemoglobin and GFR.
*P < 0.05 versus non-diabetic CKD. Values in bold indicate significant HRs.

Nephrol Dial Transplant (2018) 33: 1942–1949

KDOQI US Commentary on the KDIGO 2020 Clinical Practice Guideline for Diabetes Management in CKD

Amy K. Mottl, Radica Alicic, Christos Argyropoulos, Frank C. Brosius, Michael Mauer, Mark Molitch, Robert G. Nelson, Leigh Perreault, and Susanne B. Nicholas



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REVIEW

CLINICAL CARDIOLOGY WILEY

The cardiovascular outcomes, heart failure and kidney disease trials tell that the time to use Sodium Glucose Cotransporter 2 inhibitors is now

Michael E. Johansen[1] | Christos Argyropoulos[2]

Payment Coverage and Health Economics of SGLT2 inhibitors

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https://bitbucket.org/chrisarg/sglt2imetanalysis/ https://onlinelibrary.wiley.com/doi/epdf/10.1002/clc.23508

Snapshot of the SGLT2i trials pre-2022

	Empagliflozin		Canagliflozin		Dapagliflozin			Ertugliflozin
	EMPA-REG Outcome[10,14,31]	EMPEROR - REDUCED[16]	CANVAS Program[11]	CREDENCE[17,32]	DECLARE-TIMI 58[12,33]	DAPA-HF[15]	DAPA-CKD[18]	VERTIS-CV[13]
Primary Outcome	MACE-3	CV Death/ HHF	MACE-3	WKD/ESKD/CV Death/Renal Death	MACE-3	WHF / CV Death	WKD/ ESKD/ CV Death/ Renal Death	MACE-3
N of participants	7020	3730	10 142	4401	17 160	4744	4304	8246
Median follow up (y)	3.1	1.3	2.4	2.6	4.2	1.52	2.4	3.0
Region								
Europe	2885 (41.1)	1353 (36.3)	NR	864 (19.6)	7629 (44.5)	2154 (45.4)	1233 (28.6)	4637 (56.2)
North America	1394 (19.9)	425 (11.4)	NR	1182 (26.9)	5468 (31.9)	677 (14.3)	813 (18.9)	1813 (22)
Asia	1347 (19.2)	493 (13.2)	NR	NR	2186 (12.7)	1096 (23.1)	1346 (31.3)	523 (6.3)
Latin America	1081 (15.4)	1286 (34.5)	NR	941 (21.4)	1877 (10.9)	817 (17.2)	912 (21.2)	723 (8.8)
Rest of the world	313 (4.5)	173 (4.6)[a]	NR	1414 (32.1)	None	None	None	550 (6.7)[b]
Women	2004 (28.5)	3730 (23.9)	3633 (35.8)	1494 (33.9)	6422 (37.4)	1109 (23.4)	1425 (33.1)	2477 (30.0)
Age (y)	63.1 ± 8.6	66.8 ± 11	63.3 ± 8.3	63.0 ± 9.2	63.9 ± 6.8	66.3 ± 10.9	61.9 ± 12.1	64.4 ± 8.1
Race/ethnicity								
White	5081 (72.4)	2629 (70.5)	7944 (78.3)	2931 (79.6)	13 653 (79.6)	3333 (70.3)	2290 (53.2)	7240 (87.8)
Asian	1517 (21.3)	672 (18)	1284 (12.7)	877 (19.9)	2303 (13.4)	1116 (23.5)	1467 (34.1)	498 (6.0)
Black	357 (5.1)	257 (6.9)	336 (3.3)	224 (5.1)	603 (3.5)	226 (4.8)	191 (4.4)	235 (2.8)
Other/NA	65 (0.9)	172 (4.6)	587 (5.7)	369 (8.4)	601 (3.5)	69 (1.5)	356 (8.3)	273 (3.3)
Diabetes (%)	100%	49.8%	100%	100%	100%	41.8%	67.7%	100%
Hb A1c	8.1 ± 0.8	NR	8.2 ± 0.9	8.3 ± 1.3	8.3 ± 1.2	NR	NR	8.2 ± 1.0
Duration of diabetes	57% > 10 y	NR	13.5 ± 7.8	15.7 ± 8.7	11.9 ± 7.8	NR	NR	13.0 ± 8.3
Cardiac/cardiovascular diseases								
Coronary artery disease	5308 (75.6)	1929 (51.7)[c]	5721 (56.4)	1313 (29.8)	5648 (32.9)	2674 (56.4)[c]	1710 (39.7)[d]	6256 (75.9)
Cerebrovascular disease	1637 (23.3)	NR	1958 (19.3)	700 (15.9)	1301 (7.6)	NR		1889 (22.9)
Peripheral arterial disease	1461 (20.8)	NR	7324 (72.2)	47.5 (1.1)	1025 (6)	NR		1541 (18.7)

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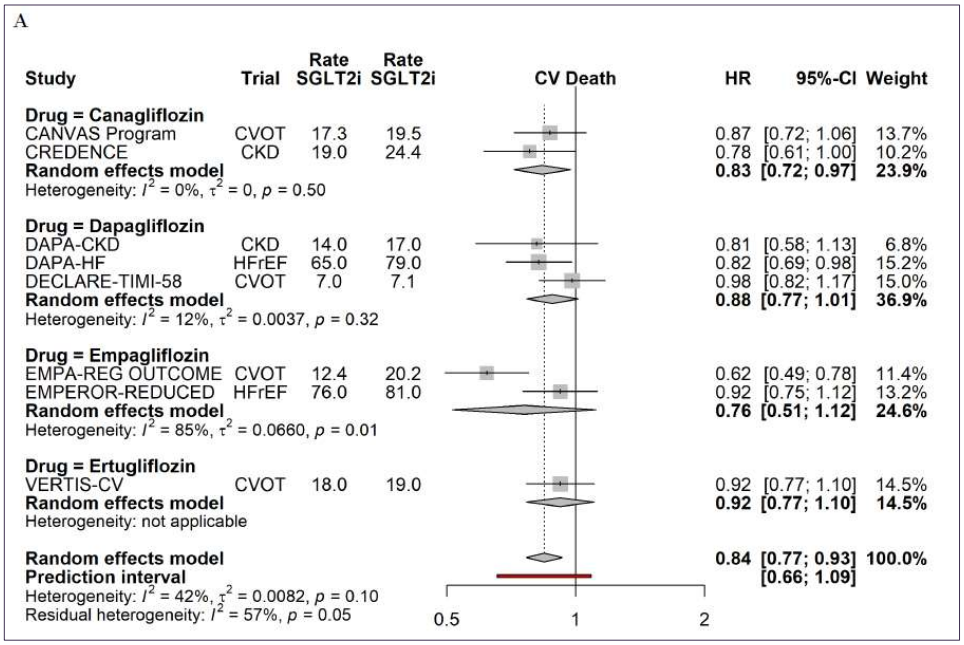
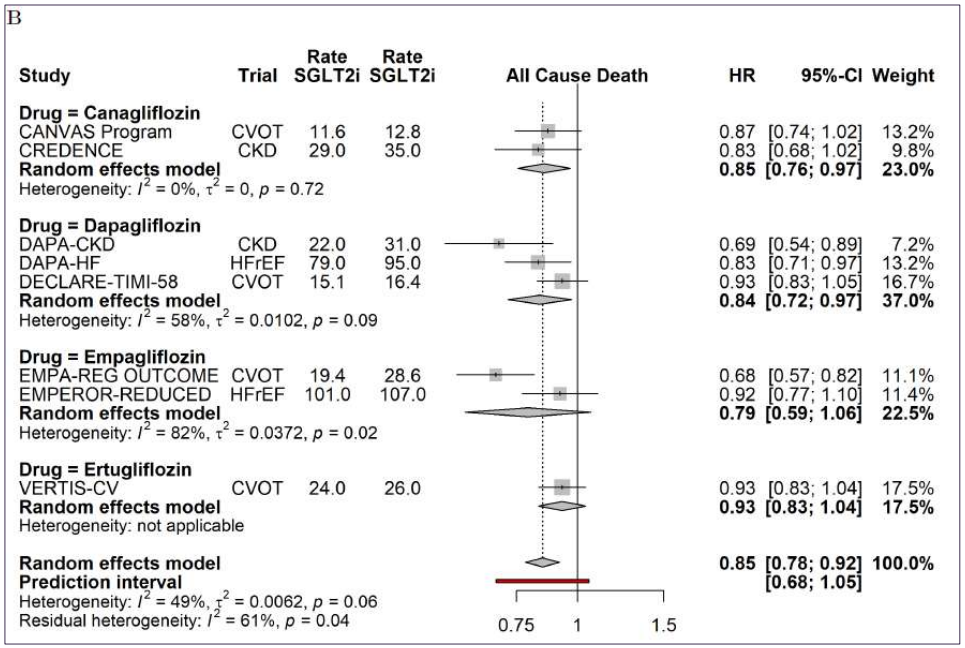
	Empagliflozin		Canagliflozin		Dapagliflozin			Ertugliflozin
	EMPA-REG Outcome[10,14,31]	EMPEROR - REDUCED[16]	CANVAS Program[11]	CREDENCE[17,32]	DECLARE-TIMI 58[12,33]	DAPA-HF[15]	DAPA-CKD[18]	VERTIS-CV[13]
Renal status								
eGFR	74 ± 21.4	62 ± 21.6	76.5 ± 20.5	56.2 ± 18.2	85.3 ± 15.9	65.8 ± 19.5	43.1 ± 12.3	76 ± 20.9
eGFR ≥90	1538 (21.9)[e]	NR	2476 (24.4)	211 (4.8)	8162 (47.6)	8162 (47.6)	None	NR
eGFR 60–90	3661 (52.2)[e]	NR	5625 (55.5)	1558 (35.4)	7732 (45.1)	7732 (45.1)	454 (10.5)	NR
eGFR <60	1819 (25.9)[e]	906 (12.9)	2039 (20.1)	2631 (59.8)	1265 (7.4)	1265 (7.4)	3850 (89.5)	1807 (21.9)
Mild albuminuria	4171 (60.0)[e]	NR	7007 (69.1)	31 (0.7)	11 644 (69.1)	11 644 (69.1)	NR	NR
Moderate albuminuria	2013 (29.0)[e]	NR	2266 (22.3)	496 (11.3)	4029 (23.9)	4029 (23.9)	NR	NR
Severe albuminuria	769 (11.1)[e]	NR	760 (7.5)	3874 (88)	1169 (6.9)	1169 (6.9)	2079 (48.3)	NR
Medications								
RASi	5712 (81.4)	2600 (69.7)	8116 (80)	4395 (99.9)	13 950 (81.3)	3968 (83.6)	4224 (98.1)	6686 (81.1)
Beta-blockers	4554 (64.9)	3533 (94.7)	5421 (53.5)	1770 (40.2)	9030 (52.6)	4558 (96.1)	NR	5692 (69)
Antiplatelet agents[f]	6293 (89.6)	NR	7466 (73.6)	2624 (59.6)	10 487 (61.1)	NR	NR	6978 (84.6)
Statins	5403 (77)	NR	7599 (74.9)	3036 (69)	12 868 (75)	2794 (58.9)	2794 (64.9)	6747 (81.8)
MRA	441 (6.3)	2661 (71.3)	NR	NR	NR	3370 (71)	NR	674 (8.2)
Diuretics	3035 (43.2)	NR	4490 (44.3)	2057 (46.7)	6967 (40.6)	4433 (93.4)	1882 (43.7)	3542 (43)
ARNI	NR	727 (19.5)	NR	NR	NR	508 (10.7)	NR	NR
Insulin	3387 (48.2)	NR	5095 (50.2)	2884 (65.5)	7013 (40.9)	540 (11.4)	NR	3900 (47.3)
Metformin	5193 (74.0)	NR	7825 (77.2)	2545 (57.8)	14 068 (82)	1016 (21.4)	NR	6292 (76.3)
Sulfonylureas	3006 (42.8)	NR	4361 (43)	1268 (28.8)	7322 (42.7)	438 (9.2)	NR	3390 (41.1)
DPP4i	796 (11.3)	NR	1261 (12.4)	751 (17.1)	2888 (16.8)	310 (6.5)	NR	911 (11)
GLP1-RA	196 (2.8)	NR	407 (4)	183 (4.2)	750 (4.4)	21 (0.4)	NR	278 (3.4)

SGLT2i reduce all cause and cardiovascular death by 15%





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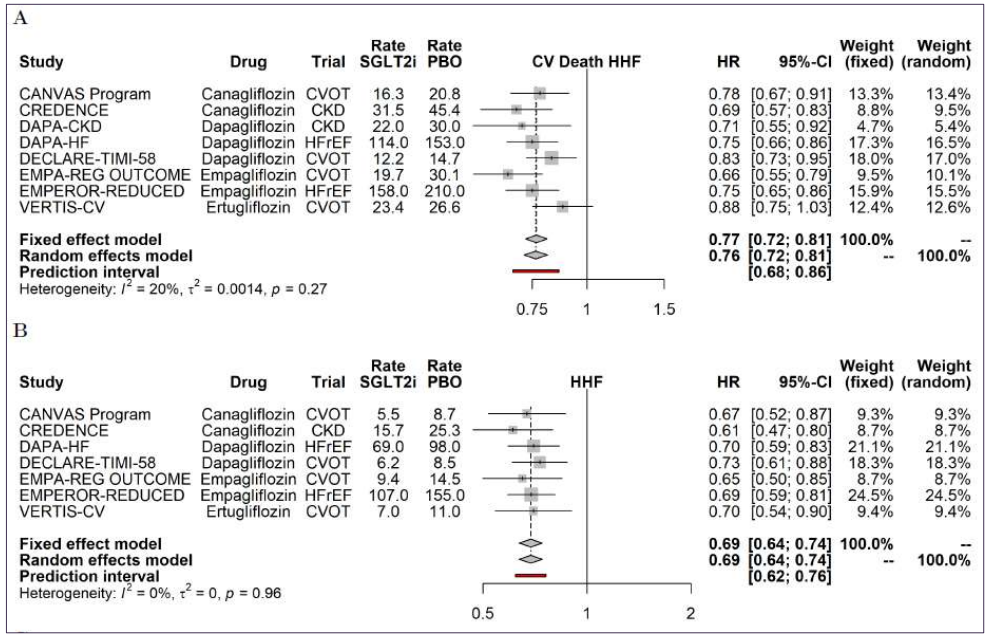
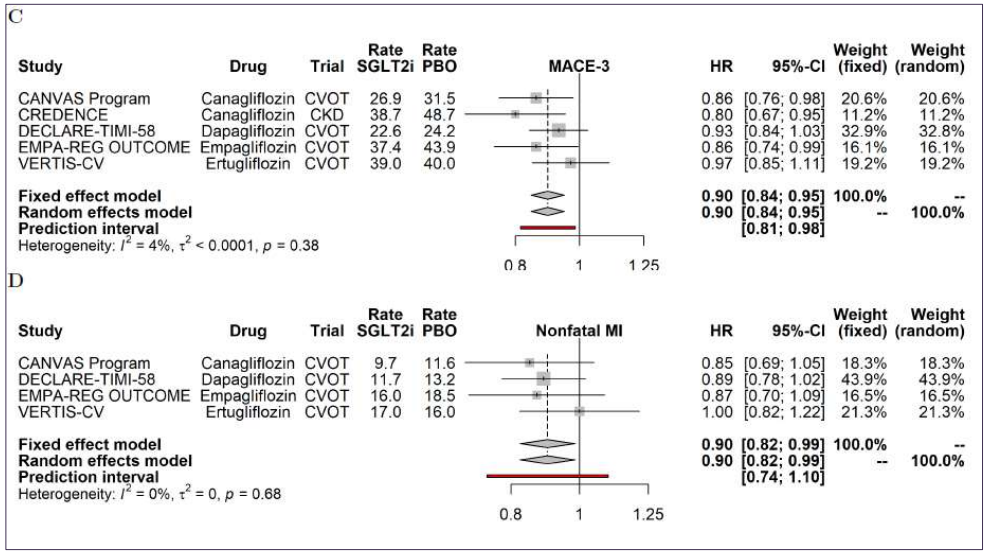
SGLT2i reduce major cardiovascular events by 10% and heart failure events by 30%





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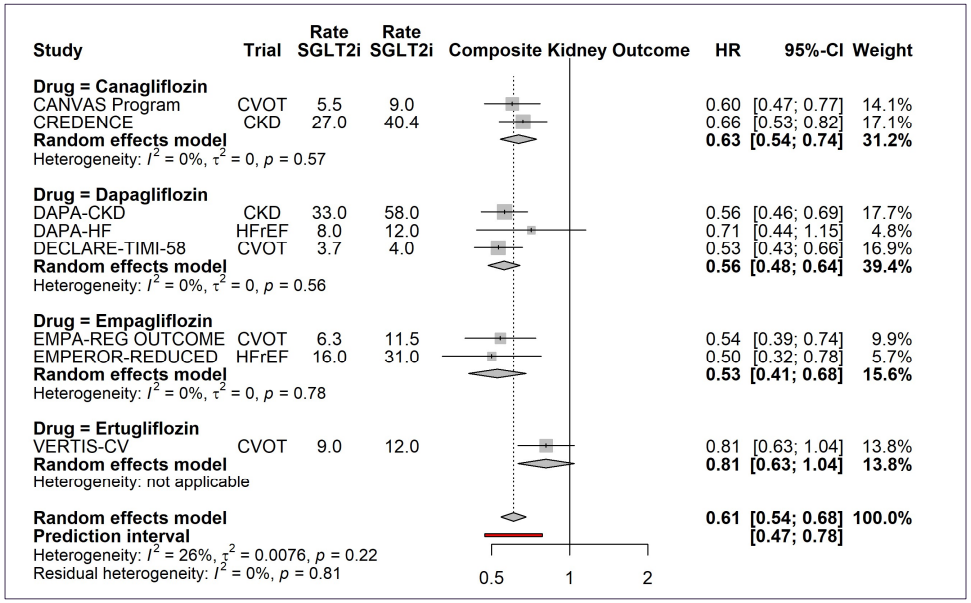
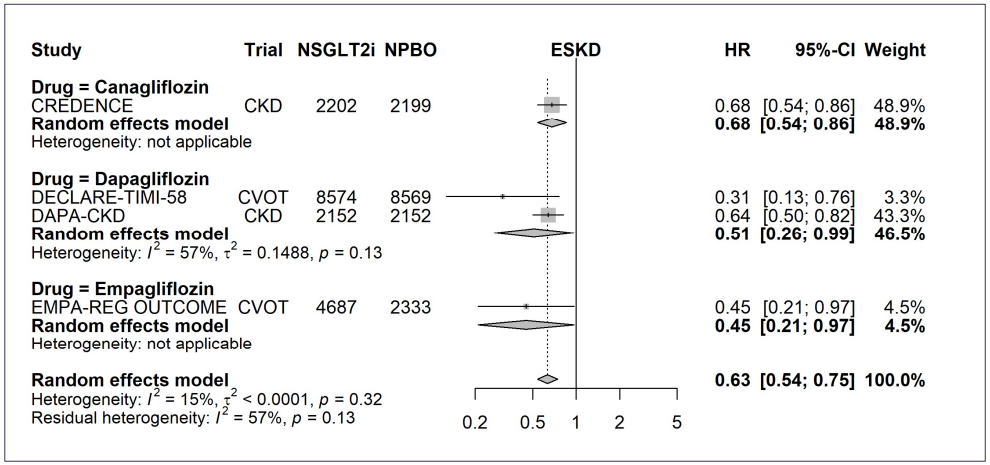
SGLT2i reduced rates of ESKD by 37% and the composite kidney outcome of worsening kidney function/ESKD by 39%





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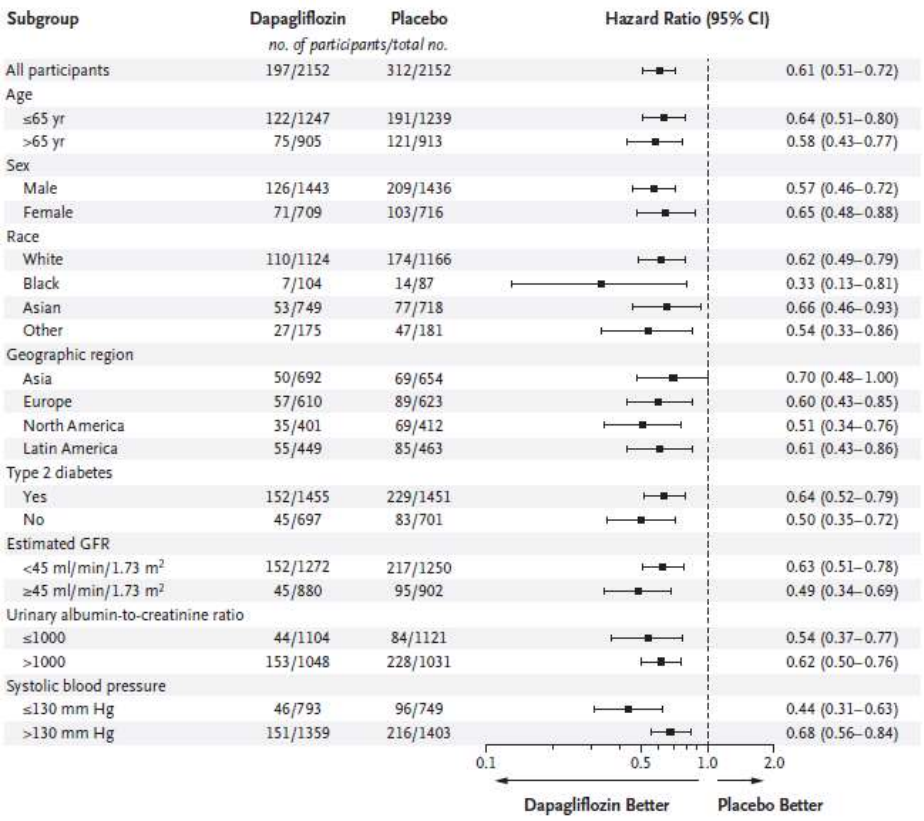
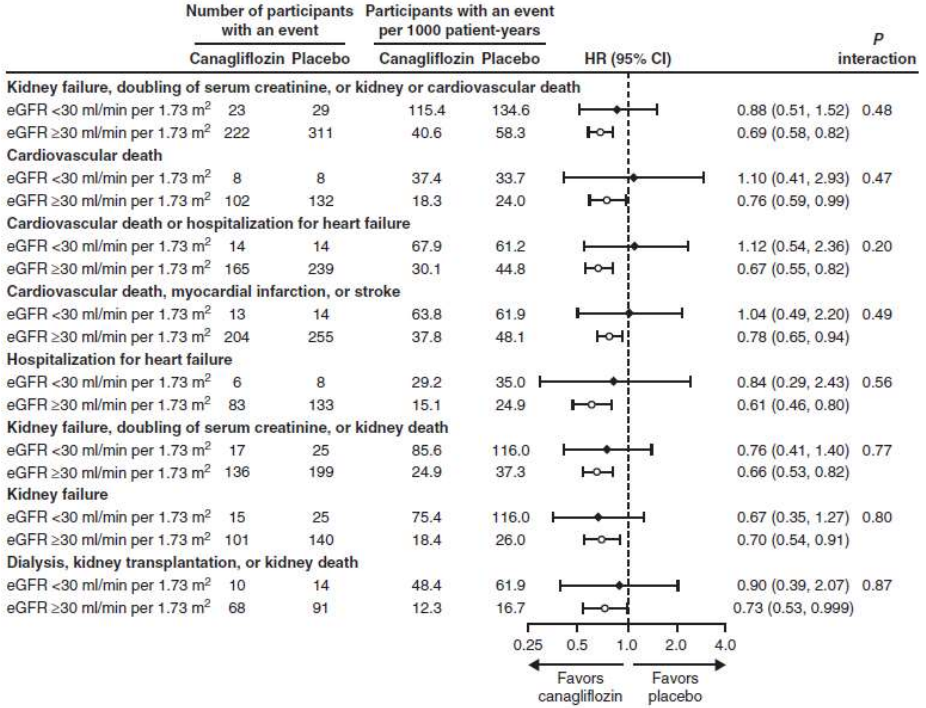
Renal benefits of SGLT2i are observed across demographics and levels of eGFR



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)

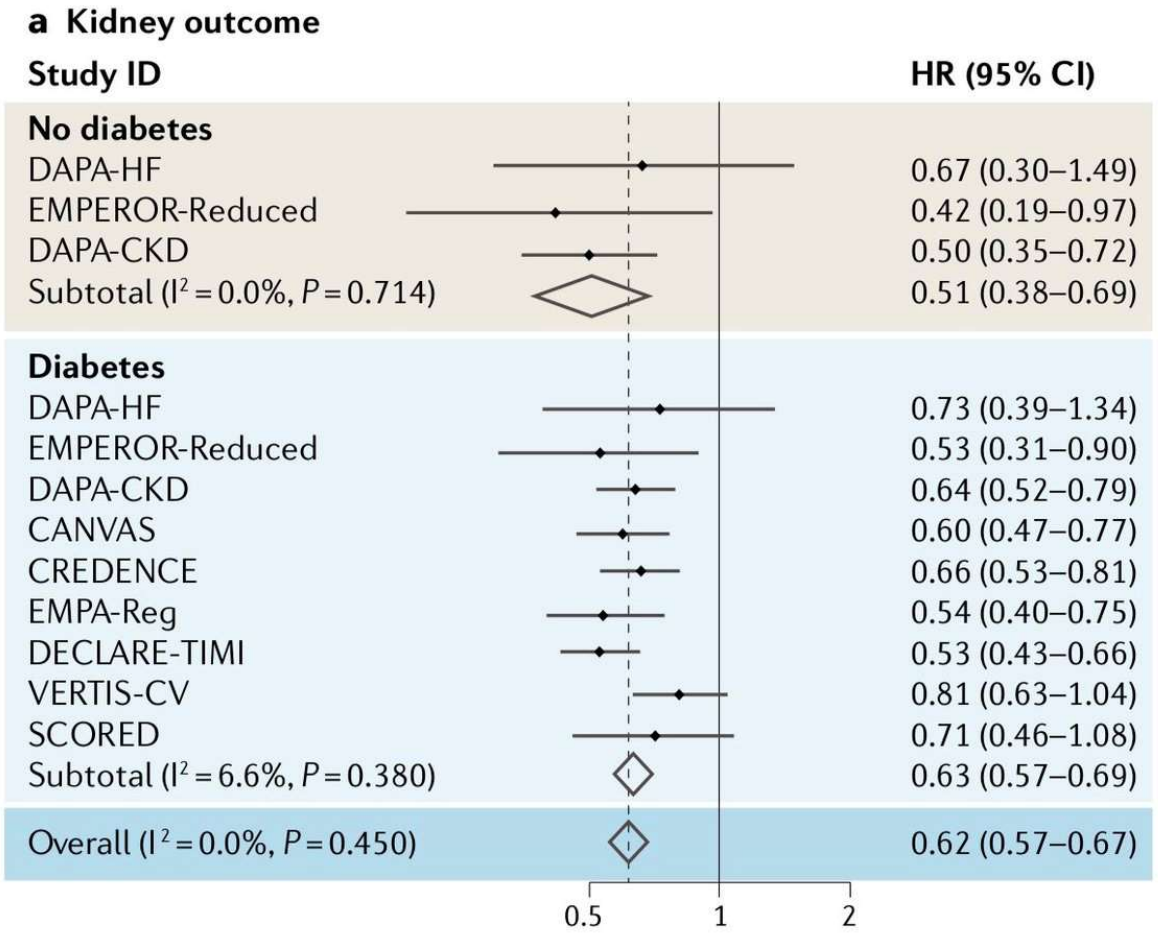


	Number of participants with an event		Participants with an event per 1000 patient-years			*P* interaction
	Canagliflozin	Placebo	Canagliflozin	Placebo	HR (95% CI)	
Kidney failure, doubling of serum creatinine, or kidney or cardiovascular death						
eGFR <30 ml/min per 1.73 m^2	23	29	115.4	134.6	0.88 (0.51, 1.52)	0.48
eGFR ≥30 ml/min per 1.73 m^2	222	311	40.6	58.3	0.69 (0.58, 0.82)	
Cardiovascular death						
eGFR <30 ml/min per 1.73 m^2	8	8	37.4	33.7	1.10 (0.41, 2.93)	0.47
eGFR ≥30 ml/min per 1.73 m^2	102	132	18.3	24.0	0.76 (0.59, 0.99)	
Cardiovascular death or hospitalization for heart failure						
eGFR <30 ml/min per 1.73 m^2	14	14	67.9	61.2	1.12 (0.54, 2.36)	0.20
eGFR ≥30 ml/min per 1.73 m^2	165	239	30.1	44.8	0.67 (0.55, 0.82)	
Cardiovascular death, myocardial infarction, or stroke						
eGFR <30 ml/min per 1.73 m^2	13	14	63.8	61.9	1.04 (0.49, 2.20)	0.49
eGFR ≥30 ml/min per 1.73 m^2	204	255	37.8	48.1	0.78 (0.65, 0.94)	
Hospitalization for heart failure						
eGFR <30 ml/min per 1.73 m^2	6	8	29.2	35.0	0.84 (0.29, 2.43)	0.56
eGFR ≥30 ml/min per 1.73 m^2	83	133	15.1	24.9	0.61 (0.46, 0.80)	
Kidney failure, doubling of serum creatinine, or kidney death						
eGFR <30 ml/min per 1.73 m^2	17	25	85.6	116.0	0.76 (0.41, 1.40)	0.77
eGFR ≥30 ml/min per 1.73 m^2	136	199	24.9	37.3	0.66 (0.53, 0.82)	
Kidney failure						
eGFR <30 ml/min per 1.73 m^2	15	25	75.4	116.0	0.67 (0.35, 1.27)	0.80
eGFR ≥30 ml/min per 1.73 m^2	101	140	18.4	26.0	0.70 (0.54, 0.91)	
Dialysis, kidney transplantation, or kidney death						
eGFR <30 ml/min per 1.73 m^2	10	14	48.4	61.9	0.90 (0.39, 2.07)	0.87
eGFR ≥30 ml/min per 1.73 m^2	68	91	12.3	16.7	0.73 (0.53, 0.999)	

http://www.nejm.org/doi/10.1056/NEJMoa2024816

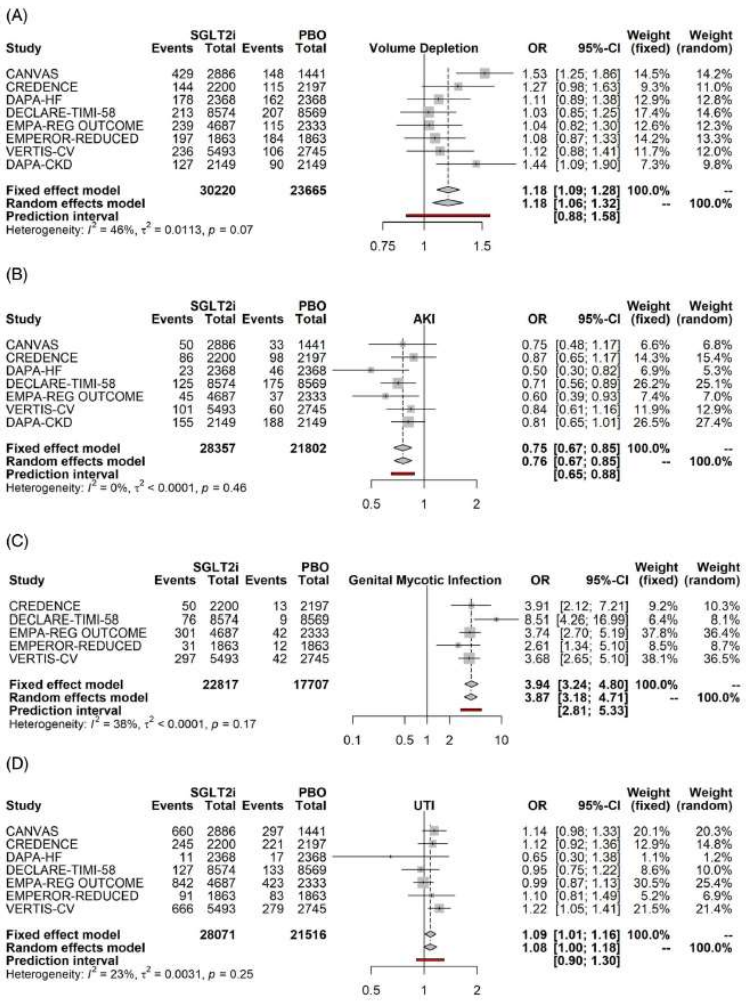
https://doi.org/10.2215/CJN.10140620

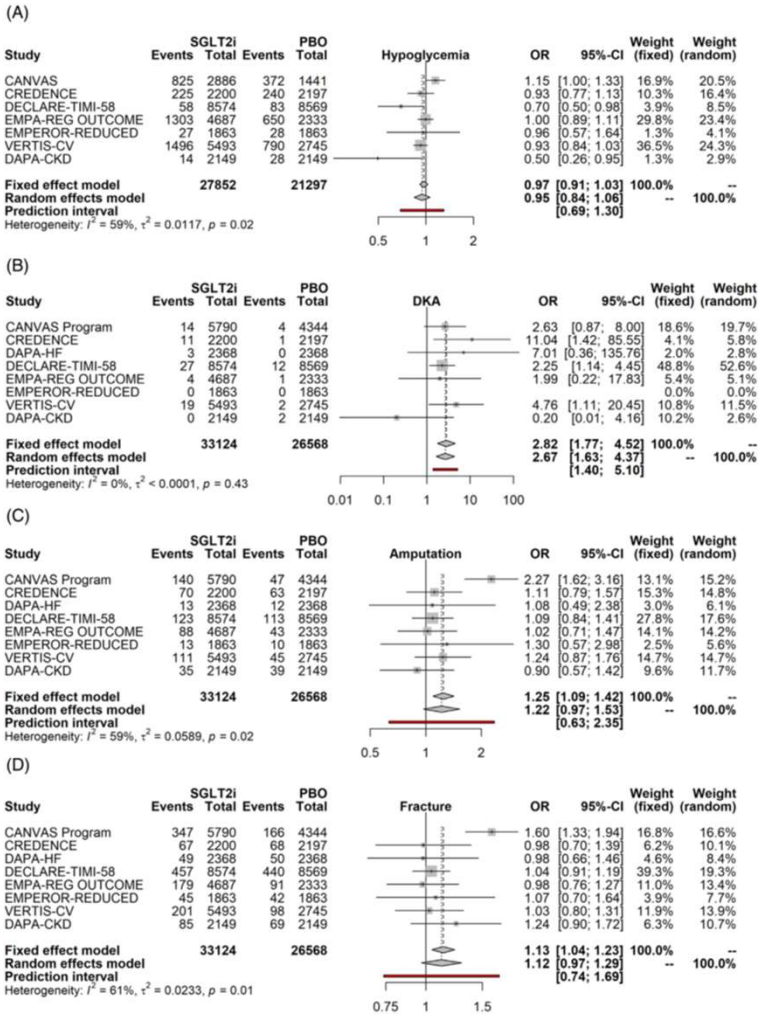
Renal benefits of SGLT2i are observed irrespective of the presence of diabetes type 2



https://doi.org/10.1038/s41581-020-00391-2

Safety events in SGLT2i trials





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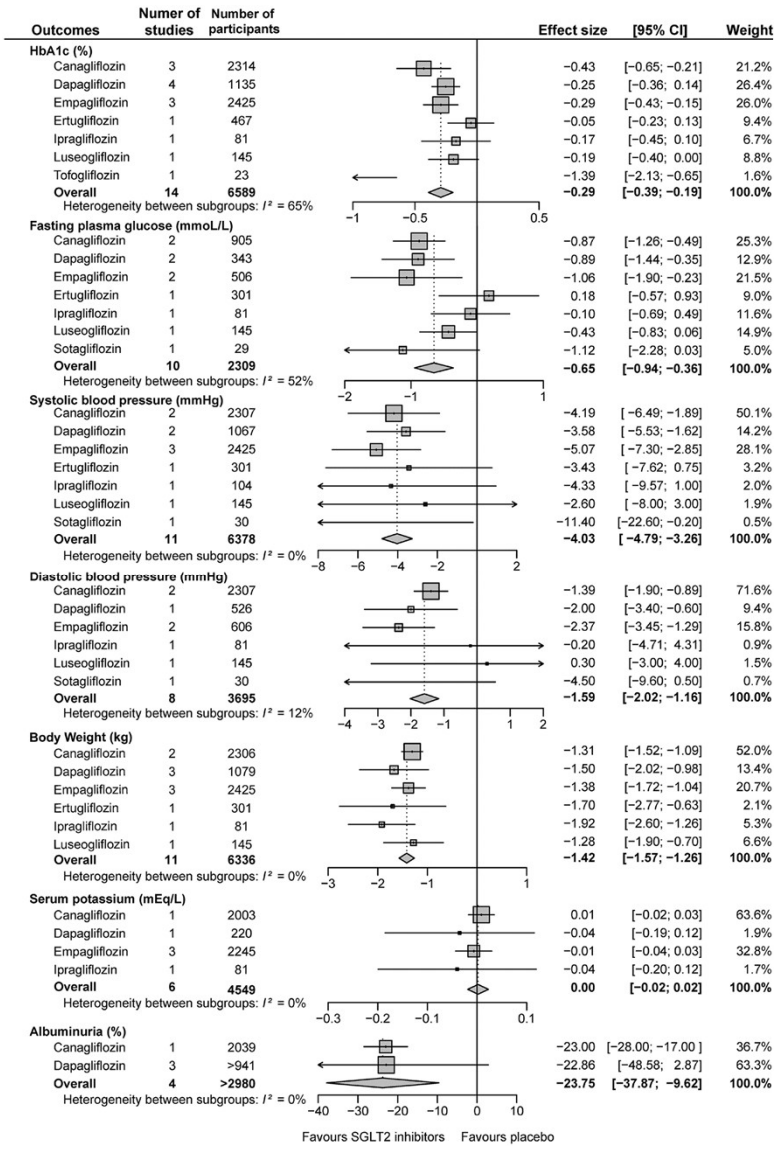
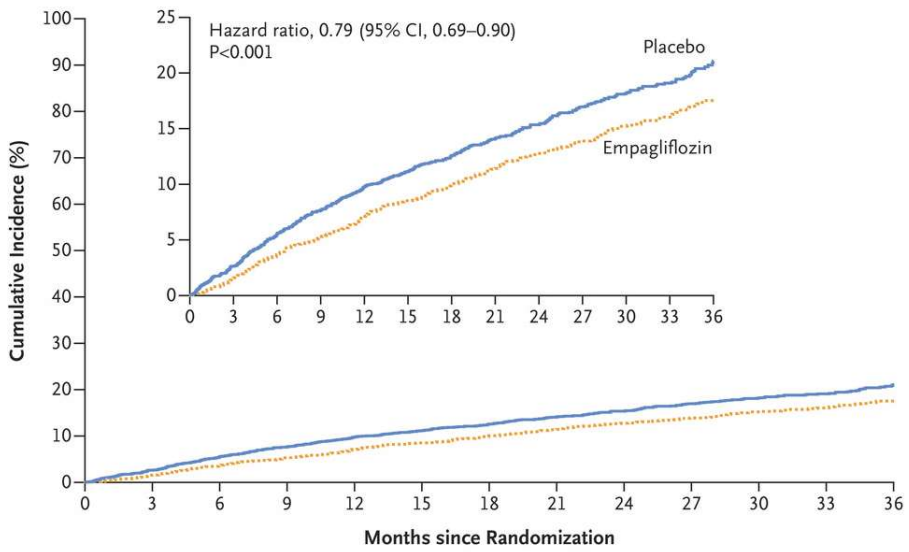


Effects of SGLT2i on biomarkers and clinical variables (meta-analysis)

DOI: 10.1111/dom.13648

SGLT2i DELIVER in HFpEF and become the EMPEROR of this Final Frontier

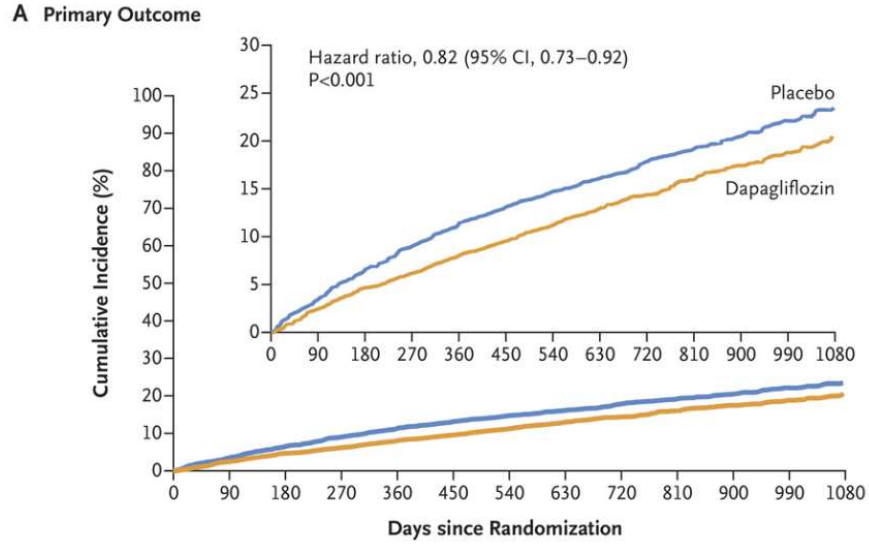
- EMPEROR-PRESERVED



No. at Risk													
Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

N Engl J Med 2021; 385:1451-1461

- DELIVER



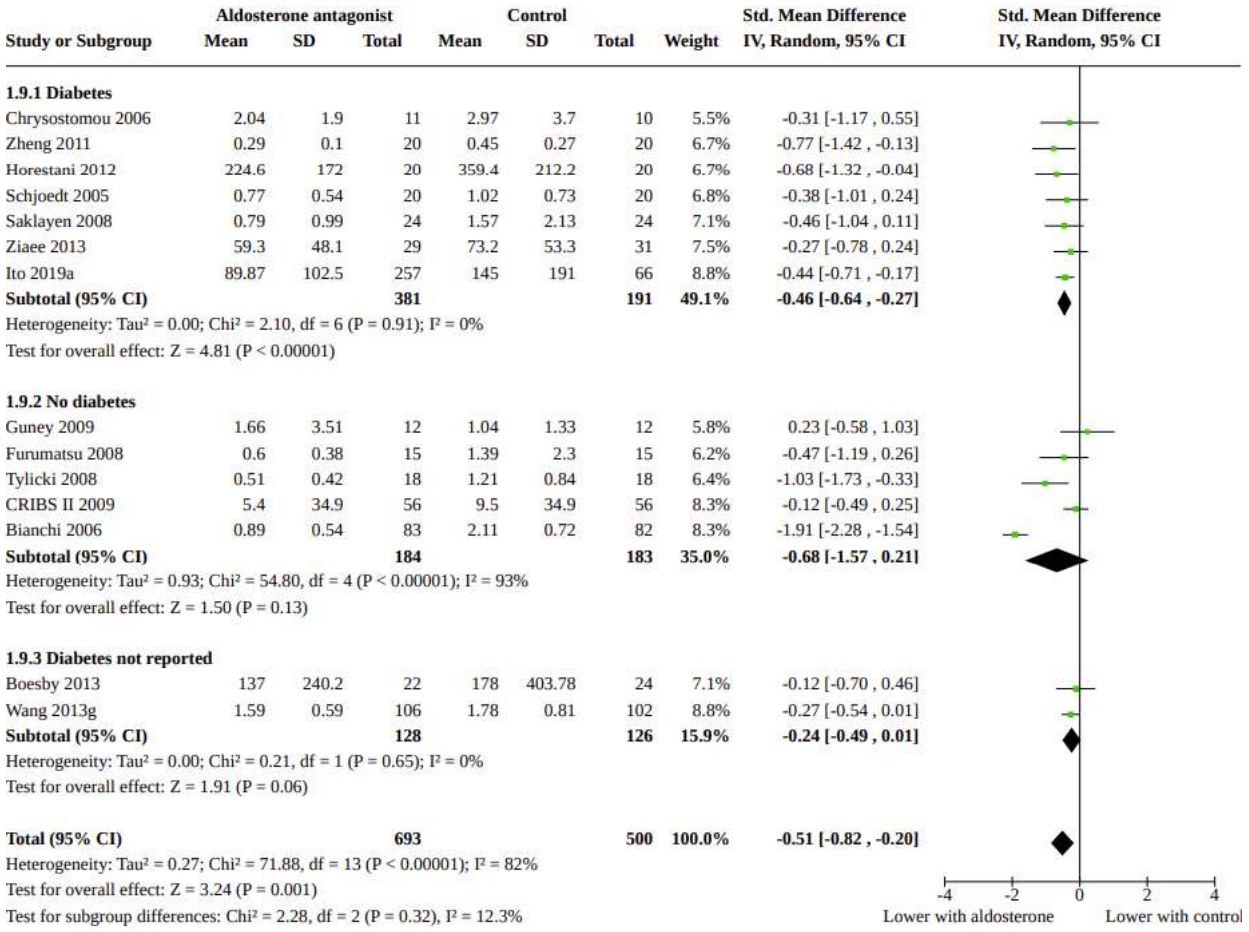
No. at Risk													
Placebo	3132	3007	2896	2799	2710	2608	2318	2080	1923	1554	1140	772	383
Dapagliflozin	3131	3040	2949	2885	2807	2716	2401	2147	1982	1603	1181	801	389

DOI: 10.1056/NEJMoa2206286

NYHA II-IV, EF>40%

MRA improves proteinuria in CKD

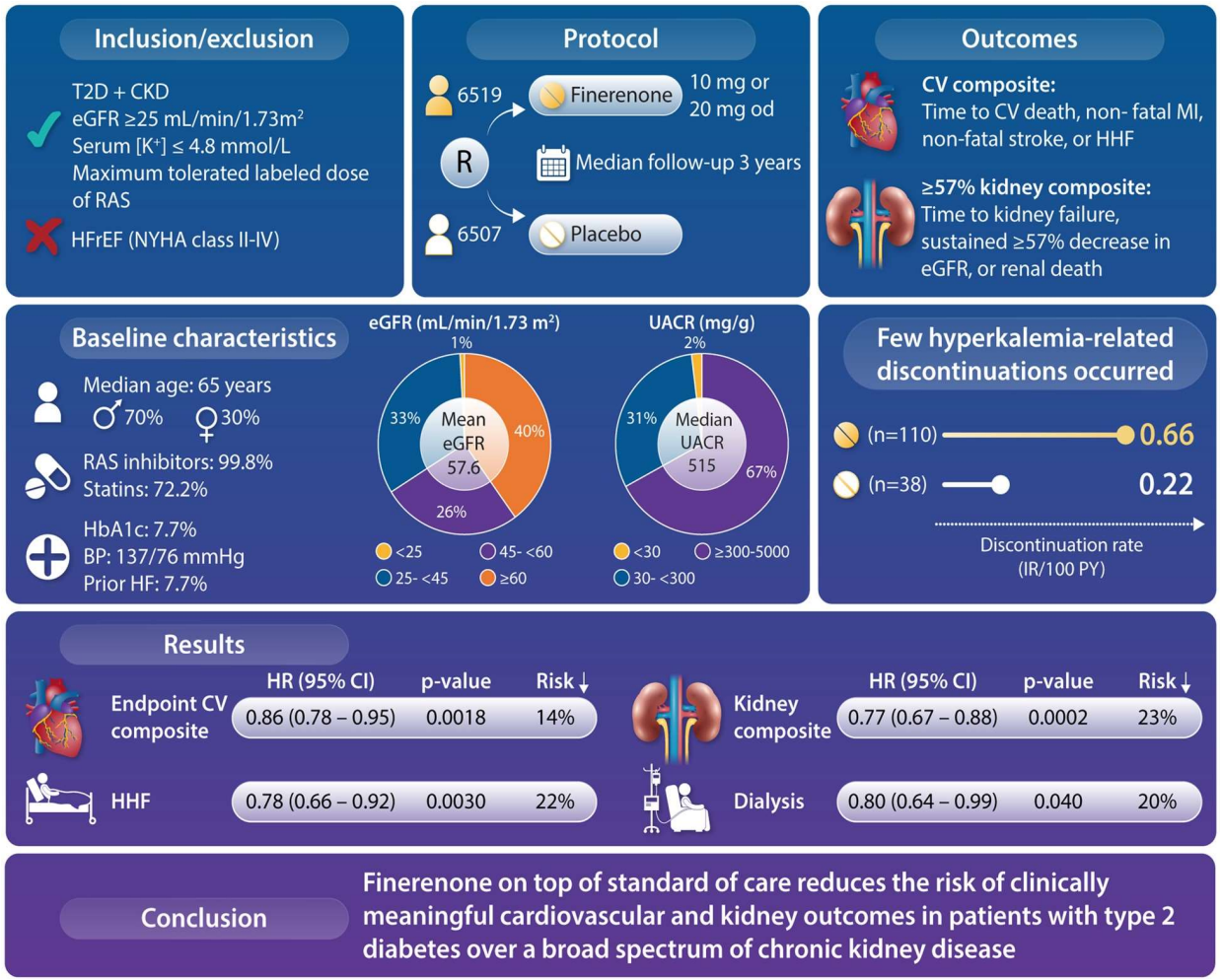
- Uncertain effects on:
  1. Kidney failure
  2. Death
  3. CV events
- MRA may decrease blood pressure: MD -4.98 mmHg, 95% CI -8.22 to -1.75, I2 = 87%

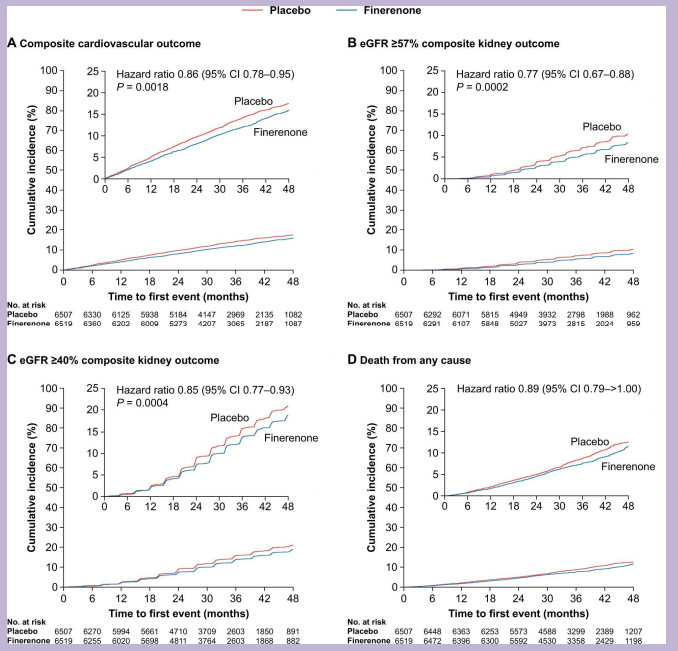


Study or Subgroup	Aldosterone antagonist Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.9.1 Diabetes								
Chrysostomou 2006	2.04	1.9	11	2.97	3.7	10	5.5%	-0.31 [-1.17 , 0.55]
Zheng 2011	0.29	0.1	20	0.45	0.27	20	6.7%	-0.77 [-1.42 , -0.13]
Horestani 2012	224.6	172	20	359.4	212.2	20	6.7%	-0.68 [-1.32 , -0.04]
Schjoedt 2005	0.77	0.54	20	1.02	0.73	20	6.8%	-0.38 [-1.01 , 0.24]
Saklayen 2008	0.79	0.99	24	1.57	2.13	24	7.1%	-0.46 [-1.04 , 0.11]
Ziaee 2013	59.3	48.1	29	73.2	53.3	31	7.5%	-0.27 [-0.78 , 0.24]
Ito 2019a	89.87	102.5	257	145	191	66	8.8%	-0.44 [-0.71 , -0.17]
Subtotal (95% CI)			**381**			**191**	**49.1%**	**-0.46 [-0.64 , -0.27]**
Heterogeneity: Tau² = 0.00; Chi² = 2.10, df = 6 (P = 0.91); I² = 0%								
Test for overall effect: Z = 4.81 (P < 0.00001)								
1.9.2 No diabetes								
Guney 2009	1.66	3.51	12	1.04	1.33	12	5.8%	0.23 [-0.58 , 1.03]
Furumatsu 2008	0.6	0.38	15	1.39	2.3	15	6.2%	-0.47 [-1.19 , 0.26]
Tylicki 2008	0.51	0.42	18	1.21	0.84	18	6.4%	-1.03 [-1.73 , -0.33]
CRIBS II 2009	5.4	34.9	56	9.5	34.9	56	8.3%	-0.12 [-0.49 , 0.25]
Bianchi 2006	0.89	0.54	83	2.11	0.72	82	8.3%	-1.91 [-2.28 , -1.54]
Subtotal (95% CI)			**184**			**183**	**35.0%**	**-0.68 [-1.57 , 0.21]**
Heterogeneity: Tau² = 0.93; Chi² = 54.80, df = 4 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 1.50 (P = 0.13)								
1.9.3 Diabetes not reported								
Boesby 2013	137	240.2	22	178	403.78	24	7.1%	-0.12 [-0.70 , 0.46]
Wang 2013g	1.59	0.59	106	1.78	0.81	102	8.8%	-0.27 [-0.54 , 0.01]
Subtotal (95% CI)			**128**			**126**	**15.9%**	**-0.24 [-0.49 , 0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%								
Test for overall effect: Z = 1.91 (P = 0.06)								
Total (95% CI)			**693**			**500**	**100.0%**	**-0.51 [-0.82 , -0.20]**
Heterogeneity: Tau² = 0.27; Chi² = 71.88, df = 13 (P < 0.00001); I² = 82%								
Test for overall effect: Z = 3.24 (P = 0.001)								
Test for subgroup differences: Chi² = 2.28, df = 2 (P = 0.32), I² = 12.3%								

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8094274

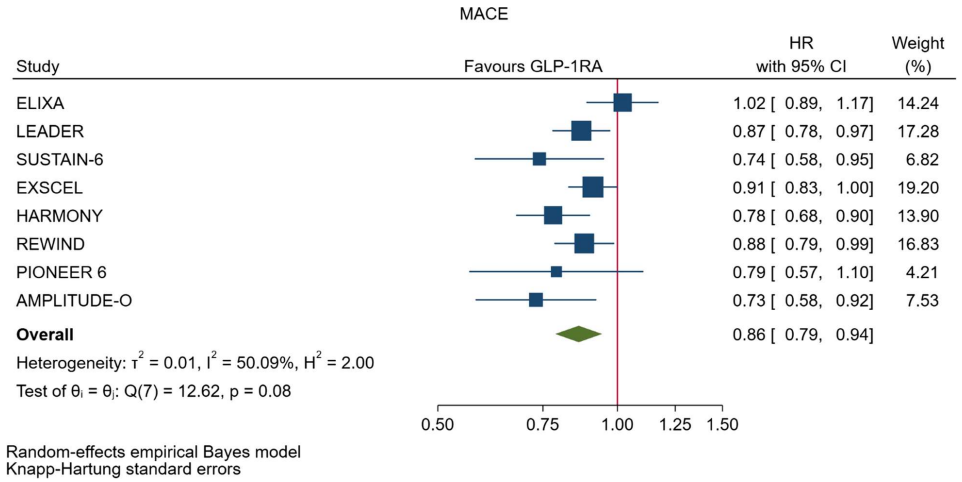
Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis





https://doi.org/10.1093/eurheartj/ehab777

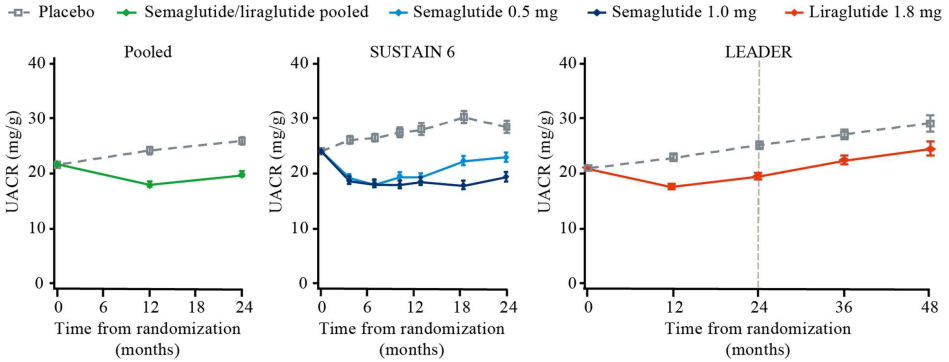
GLP1 RA improve Cardiovascular Outcomes in patients with DM2



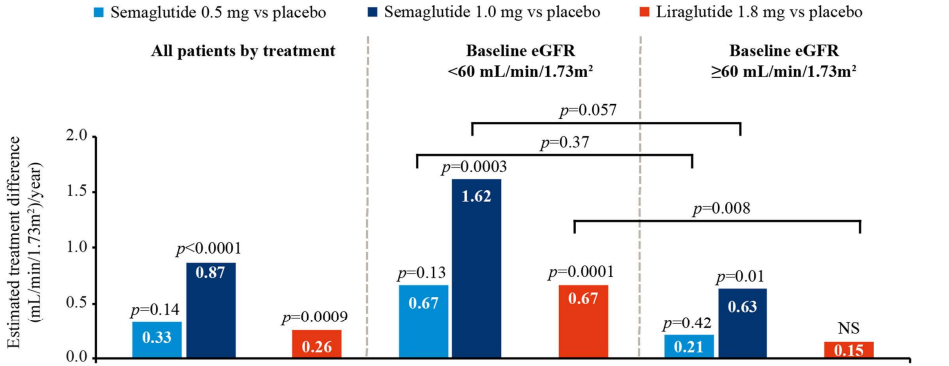
Outcome	Trials (n)	Estimate (HR)	95% CI	P value of HR	I^2 (%)	P value of I^2
MACE						
All	8	0.86	0.79–0.94	0.006	50.0	0.080
Prior CVD	6	0.84	0.79–0.90	< 0.001	6.1	0.370
No prior CVD	6	0.94	0.83–1.06	0.330	0.0	0.420
CV mortality	8	0.87	0.78–0.96	0.016	18.7	0.330
Non-fatal MI	8	0.91	0.81–1.01	0.078	34.6	0.170
Non-fatal stroke	8	0.84	0.76–0.94	0.007	0.0	0.580
Heart failure	8	0.90	0.83–0.98	0.023	0.0	0.670
All-cause mortality	8	0.88	0.80–0.96	0.012	26.3	0.350
Renal endpoints	6	0.83	0.73–0.94	< 0.012	36.5	0.280
New macro	6	0.74	0.67–0.82	< 0.001	11.0	0.370

https://cardiab.biomedcentral.com/articles/10.1186/s12933-021-01366-8

GLP1 RA may decrease rate of loss of kidney function & markers of kidney damage



Estimated treatment ratio at 2 years (treatment vs placebo) [95% CI]; *p* value*			
Overall pooled trial population	**SUSTAIN 6**		**LEADER**
	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Liraglutide 1.8 mg
0.76 [0.73, 0.80]; $p<0.001$	0.80 [0.72, 0.90]; $p<0.001$	0.67 [0.60, 0.76]; $p<0.001$	0.77 [0.73, 0.82]; $p<0.001$
Estimated treatment ratio at 2 years (by-treatment comparisons) [95% CI]; *p* value			
Liraglutide 1.8 mg vs semaglutide 0.5 mg	0.96 [0.85, 1.09]; $p=0.53$	Liraglutide 1.8 mg vs semaglutide 1.0 mg	1.15 [1.02, 1.31]; $p=0.024$



Annual eGFR change (mL/min/ 1.73m²)/year	**Estimate [95% CI]**				
	SUSTAIN 6			**LEADER**	
	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo	Liraglutide 1.8 mg	Placebo
All patients by treatment	n=825 −1.59 [−1.95, −1.23]	n=821 −1.05 [−1.41, −0.69]	n=1648 −1.92 [−2.18, −1.67]	n=4512 −1.72 [−1.84, −1.61]	n=4498 −1.98 [−2.10, −1.87]
<60 mL/min/ 1.73m² at baseline	n=212 −1.20 [−1.90, −0.49]	n=204 −0.25 [−0.97, 0.48]	n=427 −1.87 [−2.37, −1.36]	n=968 −1.44 [−1.68, −1.19]	n=905 −2.11 [−2.37, −1.85]
≥60 mL/min/ 1.73m² at baseline	n=613 −1.73 [−2.15, −1.32]	n=617 −1.31 [−1.72, −0.90]	n=1221 −1.94 [−2.24, −1.64]	n=3544 −1.80 [−1.92, −1.67]	n=3593 −1.95 [−2.08, −1.83]

https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.121.055459

GLP1/GIP dual agonists and kidney disease in SURPASS-4

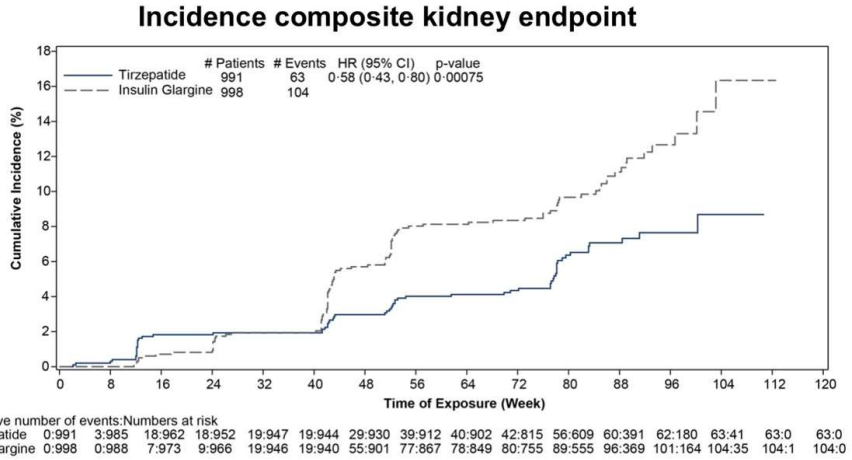


Table. Kidney endpoints in pooled tirzepatide (5, 10, 15 mg) and insulin glargine treatment arms of SURPASS-4.

		Composite endpoint 1[a]		Composite endpoint 2[b]		eGFR decline ≥40% from baseline		Renal death		Progression to ESRD		New onset macroalbuminuria	
Population	Treatment	n (%)	HR (95% CI)	n (%)	HR (95% CI)	n (%)	HR (95% CI)	n (%)	HR (95% CI)	n (%)	HR (95% CI)	n (%)	HR (95% CI)
SURPASS-4 population	TZP N=995	64 (6.4)	**0.59 (0.43,0.80)***	39 (3.9)	0.80 (0.53,1.22)	38 (3.8)	0.86 (0.56,1.33)	1 (0.1)	0.99 (0.06,15.80)	0 (0.0)	-	25 (2.5)	**0.41 (0.26,0.66)***
	iGlar N=1000	105 (10.5)		48 (4.8)		45 (4.5)		1 (0.1)		5 (0.5)		61 (6.1)	
SGLT2i use at baseline	TZP N=245	15 (6.1)	0.66 (0.34,1.26)	7 (2.9)	0.90 (0.33,2.47)	7 (2.9)	0.93 (0.34,2.55)	0 (0.0)	-	0 (0.0)	-	8 (3.3)	0.54 (0.23,1.27)
	iGlar N=256	23 (9.0)		8 (3.1)		8 (3.1)		0 (0.0)		1 (0.4)		15 (5.9)	
No SGLT2i use at baseline	TZP N=750	49 (6.5)	0.57 (0.40,0.81)*	32 (4.3)	0.78 (0.49,1.23)	31 (4.1)	0.85 (0.53,1.37)	1 (0.1)	0.98 (0.06,15.64)	0 (0.0)	-	17 (2.3)	0.37 (0.21,0.65)*
	iGlar N=744	82 (11.0)		40 (5.4)		37 (5.0)		1 (0.1)		4 (0.5)		46 (6.2)	
Albuminuria ≥30 mg/g	TZP N=358	35 (9.8)	0.47 (0.31,0.71)*	20 (5.6)	0.70 (0.39,1.25)	19 (5.3)	0.75 (0.41,1.37)	1 (0.3)	0.96 (1.06,15.31)	0 (0.0)	-	15 (4.2)	0.33 (0.18,0.61)*
	iGlar N=349	65 (18.6)		27 (7.7)		24 (6.9)		1 (0.3)		3 (0.9)		39 (11.2)	
Albuminuria <30 mg/g	TZP N=621	27 (4.3)	0.70 (0.43,1.14)	19 (3.1)	0.92 (0.49,1.71)	19 (3.1)	0.97 (0.52,1.80)	0 (0.0)	-	0 (0.0)	-	8 (1.3)	0.42 (0.18,0.94)*
	iGlar N=630	39 (6.2)		21 (3.3)		21 (3.3)		0 (0.0)		2 (0.3)		21 (3.3)	
Moderate or severely reduced kidney function[c]	TZP N=176	12 (6.8)	0.46 (0.23,0.93)*	5 (2.8)	0.37 (0.13,1.02)	4 (2.3)	0.40 (0.13,1.27)	1 (0.6)	-	0 (0.0)	-	7 (4.0)	0.68 (0.26,1.74)
	iGlar N=166	24 (14.5)		13 (7.8)		11 (6.6)		0 (0.0)		2 (1.2)		11 (6.6)	
High risk for kidney related outcomes[d]	TZP N=92	10 (10.9)	0.59 (0.27,1.29)	6 (6.5)	0.51 (0.19,1.35)	5 (5.4)	0.62 (0.21,1.84)	1 (1.1)	1.05 (0.07,16.85)	0 (0.0)	-	4 (4.3)	0.91 (0.24,3.38)
	iGlar N=94	17 (18.1)		12 (12.8)		9 (9.6)		1 (1.1)		2 (2.1)		5 (5.3)	

Data are from the mITT population (efficacy analysis set), including on treatment data prior to the use of rescue therapy. Cox proportional-hazards model was used to estimate the HR and 95% CI for pooled TZP compared with iGlar for the endpoints. HR estimate with CI is not calculated when either the TZP or iGlar arm has no event. [a]eGFR decline ≥40% from baseline, renal death, progression to ESRD, and new onset macroalbuminuria. [b]eGFR decline ≥40% from baseline, renal death, and progression to ESRD. [c]eGFR <60 CKD-EPI mL/min per 1.73 m^2. [d]eGFR <75 CKD-EPI mL/min per 1.73 m^2 and macroalbuminuria, or eGFR<45 CKD-EPI mL/min per 1.73 m^2. TZP 5 mg, 10 mg, and 15 mg arms pooled for analysis.*P<.05 versus iGlar. CI=confidence interval; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; ESRD=end stage renal disease; eGFR=estimated glomerular filtration rate; HR=hazard ratio; iGlar=insulin glargine; mITT=modified intention-to-treat; N=number of patients in population; n=number of patients with event; SGLT2i=sodium-glucose co-transporter 2 inhibitors; TZP=tirzepatide; UACR=urine albumin-creatinine ratio.

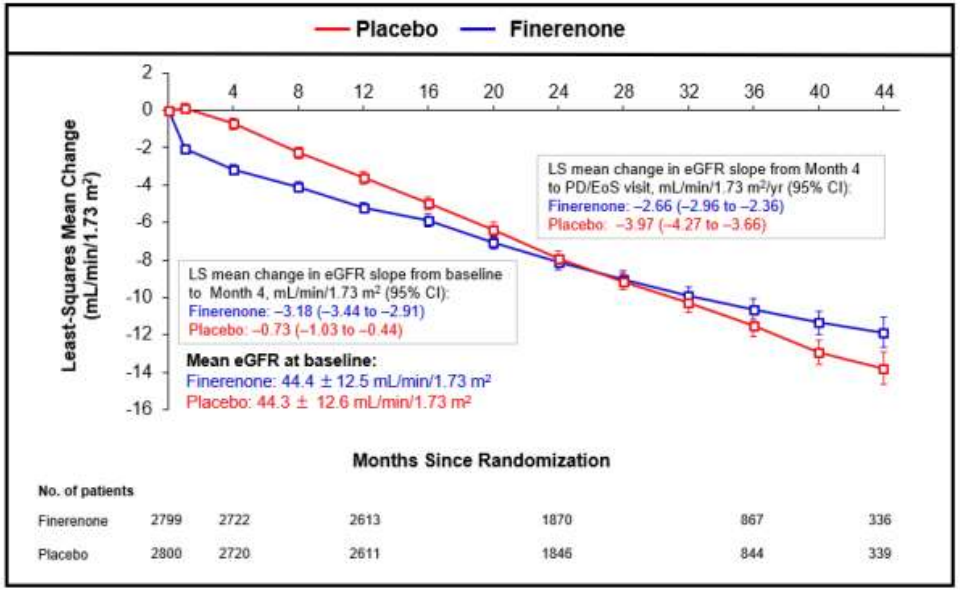
https://doi.org/10.2337/db22-17-OR

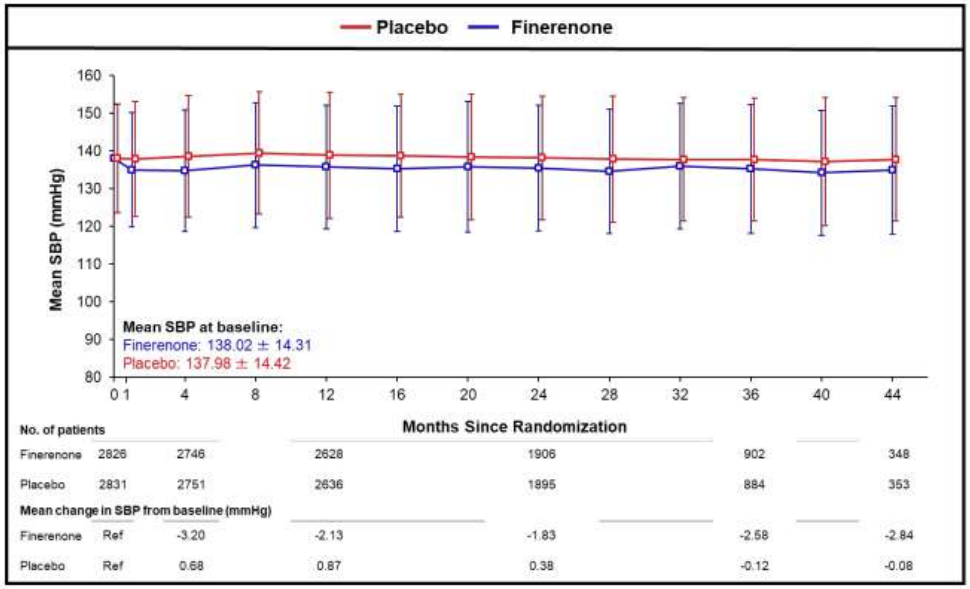
If you are only going to retain one slide...

1. Patients may be selected for further therapies based on UACR
2. SGLT2i have broad cardiovascular, renal and heart failure benefits
3. Cardiorenal benefits of SGLT2i are likely to be class, rather than agent specific
4. Effects of SGLT2i on CKD don't differ between diabetic and non-diabetic forms of CKD
5. Selective, non-steroidal MRAs have the same effects on cardiorenal outcomes as SGLT2i
6. Associate the letter "G" with the GLP1 (/GIP1) rather than Glipizide
7. We still don't know if we have to aim for the trifecta: SGLT2i/MRA/GLP1(/GIP1) on our patients

Backup

Effects of Finerenone reduced loss of eGFR and had modest effects on BP

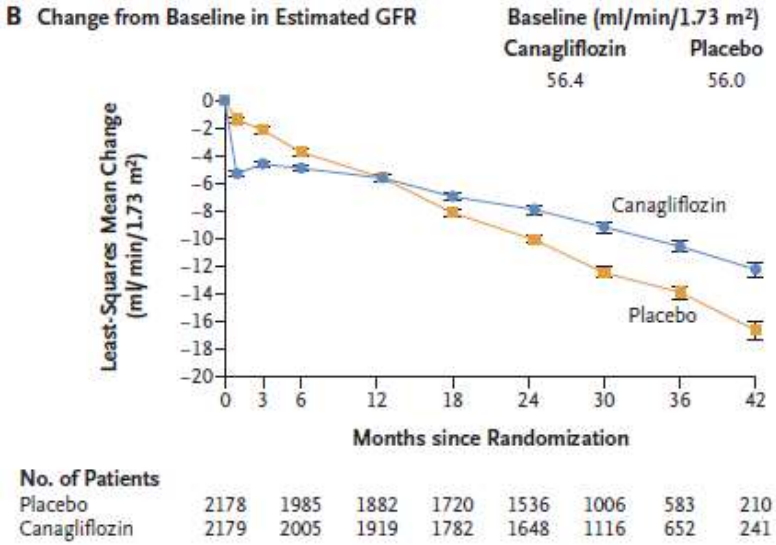




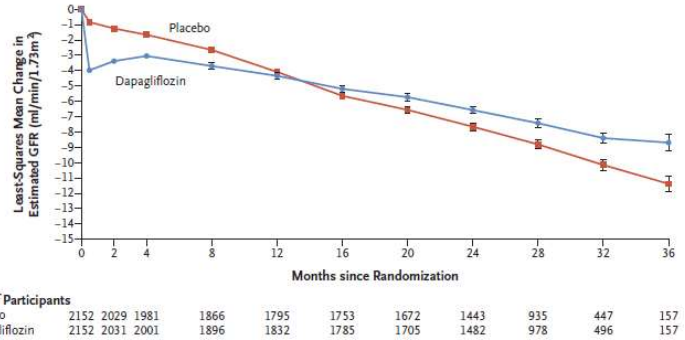
Change in SBP < 3 mmHg throughout FIDELIO-CKD

https://www.nejm.org/doi/10.1056/NEJMoa2025845

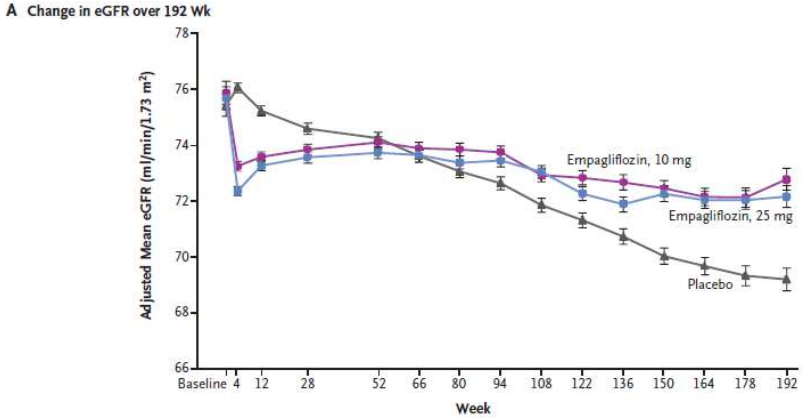
Canagliflozin (CREDENCE)



Empagliflozin (EMPA-REG)



Dapagliflozin (DAPA-CKD)

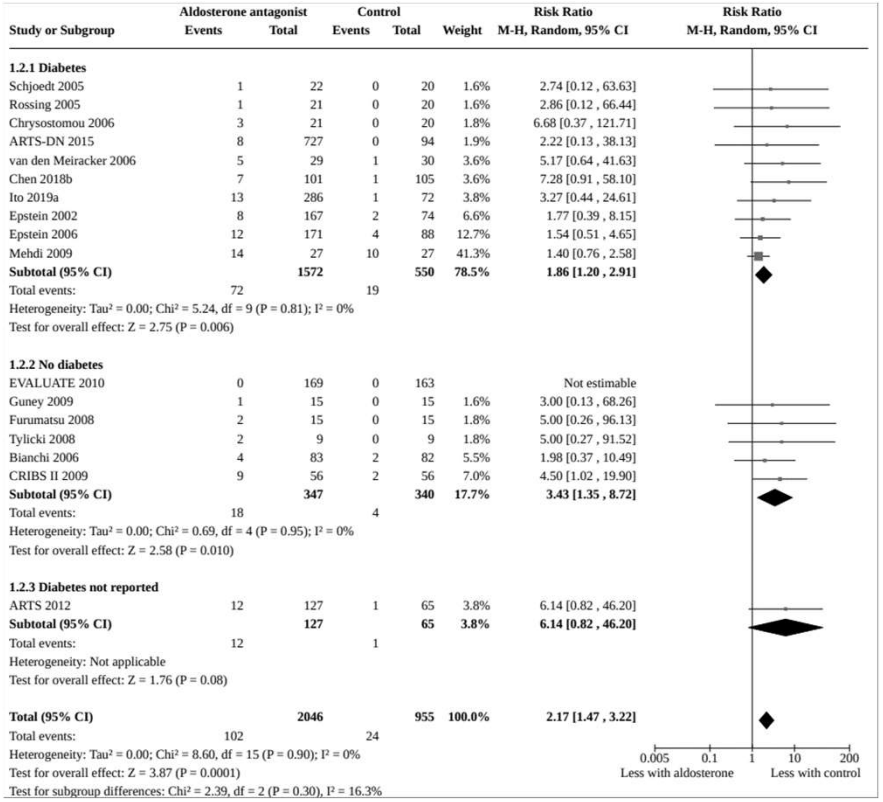


EMPA-REG: https://www.nejm.org/doi/full/10.1056/nejmoa1515920
DAPA-CKD: https://www.nejm.org/doi/full/10.1056/NEJMoa2024816
CREDENCE: https://www.nejm.org/doi/full/10.1056/NEJMoa1811744

Biphasic eGFR changes upon initiation of SGLT2i

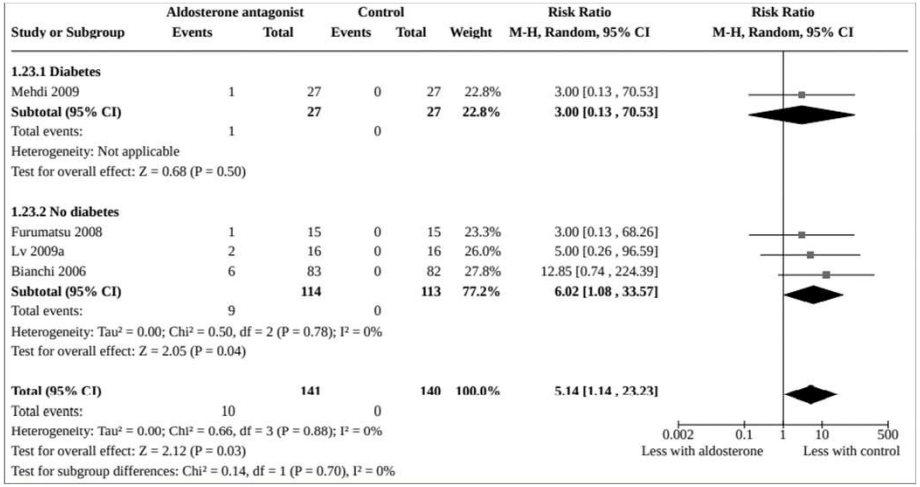
Nonselective MRA is associated with hyperkalemia and gynecomastia

Hyperkalemia



Study or Subgroup	Aldosterone antagonist Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Diabetes						
Schjoedt 2005	1	22	0	20	1.6%	2.74 [0.12 , 63.63]
Rossing 2005	1	21	0	20	1.6%	2.86 [0.12 , 66.44]
Chrysostomou 2006	3	21	0	20	1.8%	6.68 [0.37 , 121.71]
ARTS-DN 2015	8	727	0	94	1.9%	2.22 [0.13 , 38.13]
van den Meiracker 2006	5	29	1	30	3.6%	5.17 [0.64 , 41.63]
Chen 2018b	7	101	1	105	3.6%	7.28 [0.91 , 58.10]
Ito 2019a	13	286	1	72	3.8%	3.27 [0.44 , 24.61]
Epstein 2002	8	167	2	74	6.6%	1.77 [0.39 , 8.15]
Epstein 2006	12	171	4	88	12.7%	1.54 [0.51 , 4.65]
Mehdi 2009	14	27	10	27	41.3%	1.40 [0.76 , 2.58]
Subtotal (95% CI)		**1572**		**550**	**78.5%**	**1.86 [1.20 , 2.91]**
Total events:	72		19			
Heterogeneity: Tau² = 0.00; Chi² = 5.24, df = 9 (P = 0.81); I² = 0%						
Test for overall effect: Z = 2.75 (P = 0.006)						
1.2.2 No diabetes						
EVALUATE 2010	0	169	0	163		Not estimable
Guney 2009	1	15	0	15	1.6%	3.00 [0.13 , 68.26]
Furumatsu 2008	2	15	0	15	1.8%	5.00 [0.26 , 96.13]
Tylicki 2008	2	9	0	9	1.8%	5.00 [0.27 , 91.52]
Bianchi 2006	4	83	2	82	5.5%	1.98 [0.37 , 10.49]
CRIBS II 2009	9	56	2	56	7.0%	4.50 [1.02 , 19.90]
Subtotal (95% CI)		**347**		**340**	**17.7%**	**3.43 [1.35 , 8.72]**
Total events:	18		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.69, df = 4 (P = 0.95); I² = 0%						
Test for overall effect: Z = 2.58 (P = 0.010)						
1.2.3 Diabetes not reported						
ARTS 2012	12	127	1	65	3.8%	6.14 [0.82 , 46.20]
Subtotal (95% CI)		**127**		**65**	**3.8%**	**6.14 [0.82 , 46.20]**
Total events:	12		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.76 (P = 0.08)						
Total (95% CI)		**2046**		**955**	**100.0%**	**2.17 [1.47 , 3.22]**
Total events:	102		24			
Heterogeneity: Tau² = 0.00; Chi² = 8.60, df = 15 (P = 0.90); I² = 0%						
Test for overall effect: Z = 3.87 (P = 0.0001)						
Test for subgroup differences: Chi² = 2.39, df = 2 (P = 0.30), I² = 16.3%						

Gynecomastia



Study or Subgroup	Aldosterone antagonist Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.23.1 Diabetes						
Mehdi 2009	1	27	0	27	22.8%	3.00 [0.13 , 70.53]
Subtotal (95% CI)		**27**		**27**	**22.8%**	**3.00 [0.13 , 70.53]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
1.23.2 No diabetes						
Furumatsu 2008	1	15	0	15	23.3%	3.00 [0.13 , 68.26]
Lv 2009a	2	16	0	16	26.0%	5.00 [0.26 , 96.59]
Bianchi 2006	6	83	0	82	27.8%	12.85 [0.74 , 224.39]
Subtotal (95% CI)		**114**		**113**	**77.2%**	**6.02 [1.08 , 33.57]**
Total events:	9		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 2 (P = 0.78); I² = 0%						
Test for overall effect: Z = 2.05 (P = 0.04)						
Total (95% CI)		**141**		**140**	**100.0%**	**5.14 [1.14 , 23.23]**
Total events:	10		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 3 (P = 0.88); I² = 0%						
Test for overall effect: Z = 2.12 (P = 0.03)						
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.70), I² = 0%						

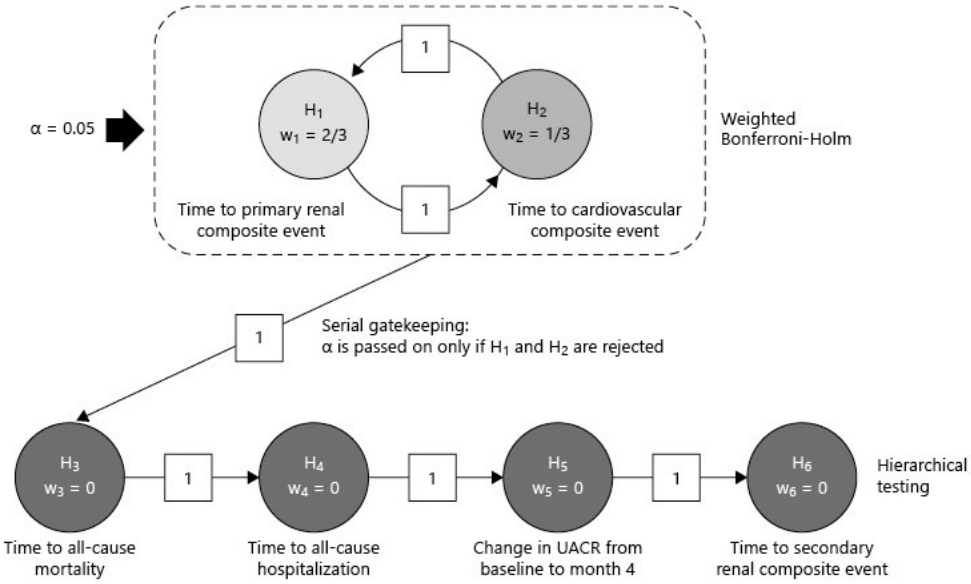
Numbers Needed To Harm

Hyperkalemia	Gynecomastia
41	14.1

Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD007004.
DOI: 10.1002/14651858.CD007004.pub3.

FIDELIO CKD: Inclusion, exclusion, & statistical analysis

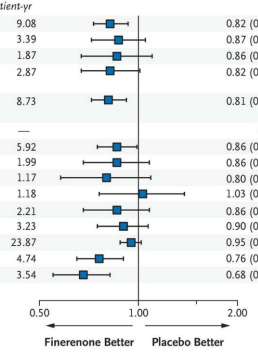
- Pts with T2D and CKD :
  - UACR > 300 mg/g & eGFR in 25-75 ml/min/1.73m2
  - UACR in 30-300 mg/g & eGFR in 25-60 ml/min/1.73m2
- Serum potassium level ≤ 4.8 meq/l
- Prior treatment with ACEi or ARB
- Excluded pts currently receiving eplerenone/spironolactone/renin inhibitor/K-sparing diuretic
- Excluded A1c > 12% or UACR >5,000 mg/g
- Dialysis dependent AKI within 12 wks of study run-in visit
- Poorly controlled hypertension (BP > 170/110 mmHg)
- NYHA Class II-IV or indication 1A for MRA

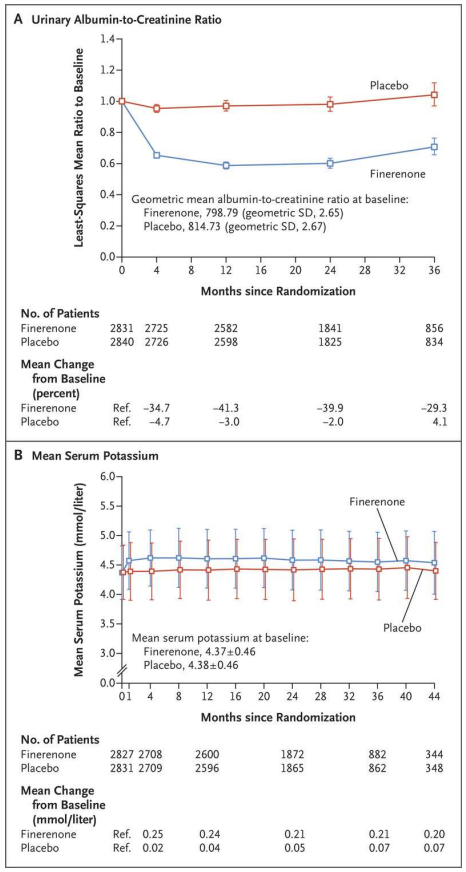


https://www.karger.com/Article/FullText/503713

Finerenone reduces hard kidney and cardiovascular outcomes in moderate DKD

Outcome	Finerenone (N=2833) no. of patients with event (%)	Placebo (N=2841) no. of patients with event (%)	Finerenone (N=2833) no. of patients with event per 100 patient-yr	Placebo (N=2841) no. of patients with event per 100 patient-yr	Hazard Ratio (95% CI)	P Value
Primary composite outcome	504 (17.8)	600 (21.1)	7.59	9.08	0.82 (0.73–0.93)	0.001
Kidney failure	208 (7.3)	235 (8.3)	2.99	3.39	0.87 (0.72–1.05)	—
End-stage kidney disease	119 (4.2)	139 (4.9)	1.60	1.87	0.86 (0.67–1.10)	—
Sustained decrease in eGFR to <15 ml/min/1.73 m²	167 (5.9)	199 (7.0)	2.40	2.87	0.82 (0.67–1.01)	—
Sustained decrease of ≥40% in eGFR from baseline	479 (16.9)	577 (20.3)	7.21	8.73	0.81 (0.72–0.92)	—
Death from renal causes	2 (<0.1)	2 (<0.1)	—	—	—	—
Key secondary composite outcome	367 (13.0)	420 (14.8)	5.11	5.92	0.86 (0.75–0.99)	0.03
Death from cardiovascular causes	128 (4.5)	150 (5.3)	1.69	1.99	0.86 (0.68–1.08)	—
Nonfatal myocardial infarction	70 (2.5)	87 (3.1)	0.94	1.17	0.80 (0.58–1.09)	—
Nonfatal stroke	90 (3.2)	87 (3.1)	1.21	1.18	1.03 (0.76–1.38)	—
Hospitalization for heart failure	139 (4.9)	162 (5.7)	1.89	2.21	0.86 (0.68–1.08)	—
Death from any cause	219 (7.7)	244 (8.6)	2.90	3.23	0.90 (0.75–1.07)	—
Hospitalization for any cause	1263 (44.6)	1321 (46.5)	22.56	23.87	0.95 (0.88–1.02)	—
Secondary composite kidney outcome	252 (8.9)	326 (11.5)	3.64	4.74	0.76 (0.65–0.90)	—
Sustained decrease of ≥57% in eGFR from baseline	167 (5.9)	245 (8.6)	2.41	3.54	0.68 (0.55–0.82)	—



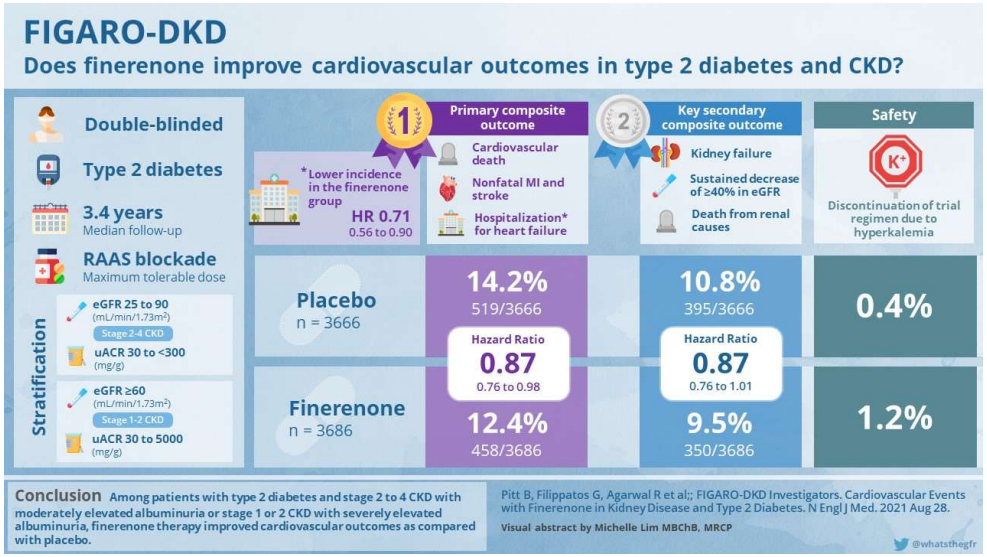


Event	Finerenone (N=2827)	Placebo (N=2831)
	no. of patients (%)	
Any adverse event	**2468 (87.3)**	**2478 (87.5)**
Adverse event related to trial regimen	**646 (22.9)**	**449 (15.9)**
Adverse event leading to discontinuation of trial regimen	207 (7.3)	168 (5.9)
Any serious adverse event	902 (31.9)	971 (34.3)
Serious adverse event related to trial regimen	48 (1.7)	34 (1.2)
Serious adverse event leading to discontinuation of trial regimen	75 (2.7)	78 (2.8)
Investigator-reported hyperkalemia	**516 (18.3)**	**255 (9.0)**
Hyperkalemia related to trial regimen	**333 (11.8)**	**135 (4.8)**
Serious hyperkalemia	**44 (1.6)**	**12 (0.4)**
Hospitalization due to hyperkalemia	**40 (1.4)**	**8 (0.3)**
Permanent discontinuation of trial regimen due to hyperkalemia	**64 (2.3)**	**25 (0.9)**
Investigator-reported hypokalemia	28 (1.0)	61 (2.2)
Investigator-reported renal-related adverse events		
Acute kidney injury	**129 (4.6)**	**136 (4.8)**
Hospitalization due to acute kidney injury	53 (1.9)	47 (1.7)
Discontinuation of trial regimen due to acute kidney injury	5 (0.2)	7 (0.2)
Hospitalization due to acute renal failure	70 (2.5)	71 (2.5)
Discontinuation of trial regimen due to acute renal failure	31 (1.1)	36 (1.3)
Adverse events affecting ≥5% of patients in either group		
Hyperkalemia	**446 (15.8)**	**221 (7.8)**
Nasopharyngitis	241 (8.5)	250 (8.8)
Hypertension	212 (7.5)	273 (9.6)
Anemia	209 (7.4)	191 (6.7)
Peripheral edema	186 (6.6)	304 (10.7)
Diarrhea	184 (6.5)	189 (6.7)
Upper respiratory tract infection	181 (6.4)	189 (6.7)
Glomerular filtration rate decreased	179 (6.3)	133 (4.7)
Urinary tract infection	179 (6.3)	192 (6.8)
Back pain	175 (6.2)	175 (6.2)
Hypoglycemia	151 (5.3)	194 (6.9)
Dizziness	146 (5.2)	153 (5.4)
Arthralgia	142 (5.0)	149 (5.3)
Bronchitis	134 (4.7)	151 (5.3)
Constipation	131 (4.6)	163 (5.8)
Pneumonia	128 (4.5)	181 (6.4)

https://www.nejm.org/doi/10.1056/NEJMoa2025845

Cardiovascular Outcomes of Finerenone in less severe Diabetic Kidney Disease: the FIGARO-DKD trial

- Pts with T2D and CKD :
  - UACR > 300 mg/g & eGFR > 60ml/min/1.73m2
  - UACR in 30-300 mg/g & eGFR in 25-90 ml/min/1.73m2
- Serum potassium level ≤ 4.8 meq/l
- Prior treatment with ACEi or ARB
- Excluded pts currently receiving eplerenone/spironolactone/renin inhibitor/K-sparing diuretic
- Excluded A1c > 12% or UACR >5,000 mg/g
- Dialysis dependent AKI within 12 wks of study run-in visit
- Poorly controlled hypertension (BP > 170/110 mmHg)
- NYHA Class II-IV or indication 1A for MRA



- SAE: 31.4% (Finerenone) vs 33.2% (placebo)
- Incidence of hyperkalemia was higher with finerenone than with placebo (10.8% vs. 5.3%)

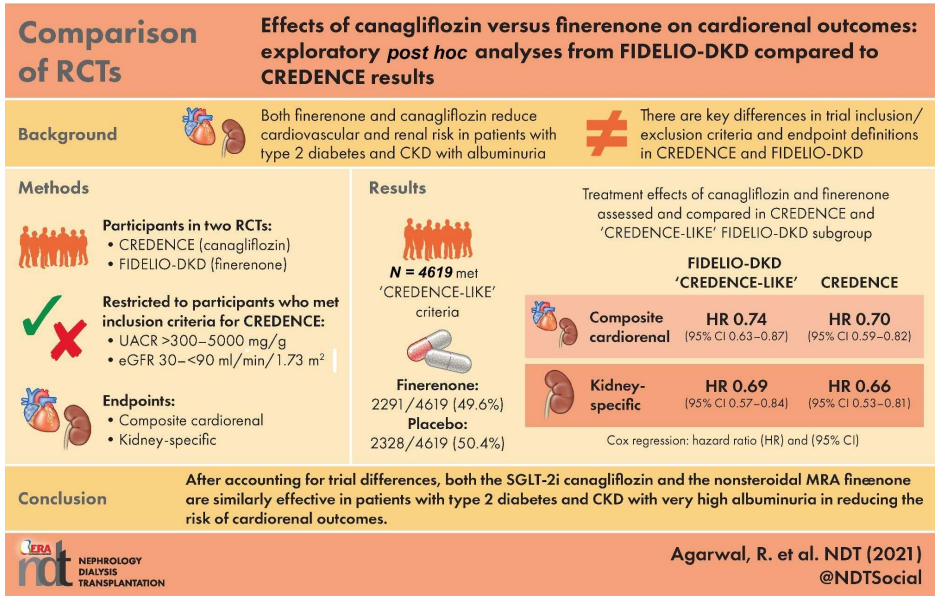
https://www.nejm.org/doi/full/10.1056/NEJMoa2110956

MRA v.s. SGLT2i in the management of CKD

ARE MRAS LESS POTENT?

- Eye-balling HRs
- Network meta-analysis (statistical eye-balling) SGLT2i vs MRA:
  1. Kidney Failure Progression: HR 0.78, 95% CI 0.67–0.90
  2. HHF: HR 0.71, 95% CI 0.55–0.92
  3. MACE: HR 0.95, 95% CI 0.71–1.27

OR DID THE TRIALS JUST RECRUIT PATIENTS WITH SOMEWHAT DIFFERENT RISK PROFILES ?

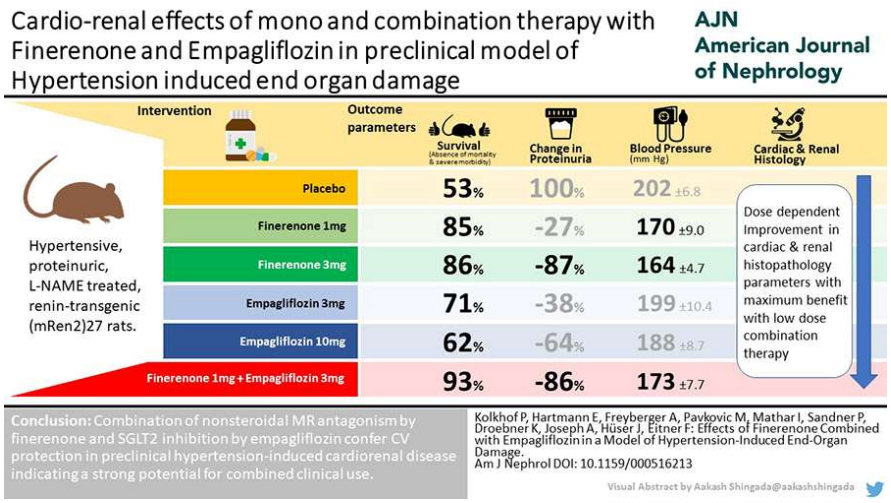


https://www.frontiersin.org/articles/10.3389/fphar.2021.751496/

https://doi.org/10.1093/ndt/gfab336

Role of combination MRA/SGLT2i in CKD?

Of Rodents…



And Humans…

A Study to Learn How Well the Treatment Combination of Finerenone and Empagliflozin Works and How Safe it is Compared to Each Treatment Alone in Adult Participants With Long-term Kidney Disease (Chronic Kidney Disease) and Type 2 Diabetes (CONFIDENCE)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT05254002

Recruitment Status : Not yet recruiting
First Posted : February 24, 2022
Last Update Posted : April 8, 2022

See Contacts and Locations

Sponsor:
Bayer

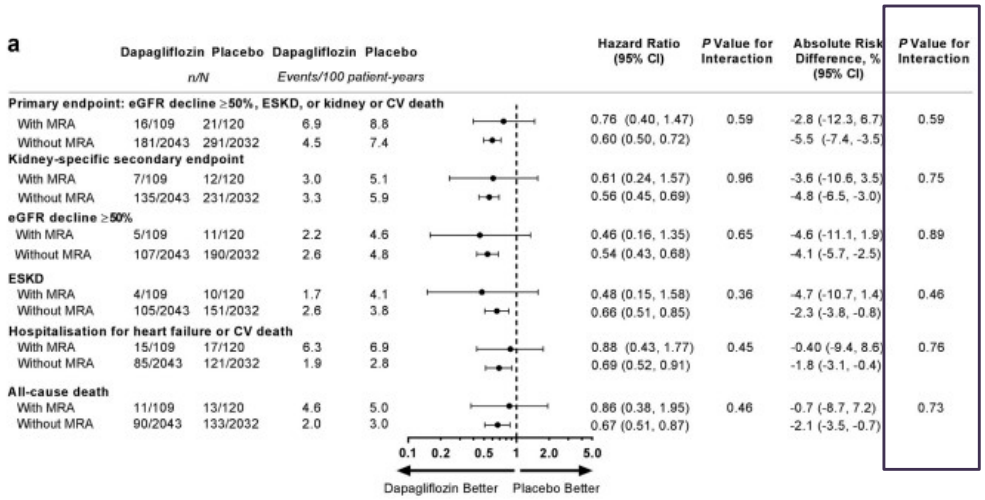
Information provided by (Responsible Party):
Bayer

Empa vs
Finerenone vs
Empa+Finerenone

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8619789/

Do MRA/SGLT2i interfere with each other?

MRA IN DAPA-CKD



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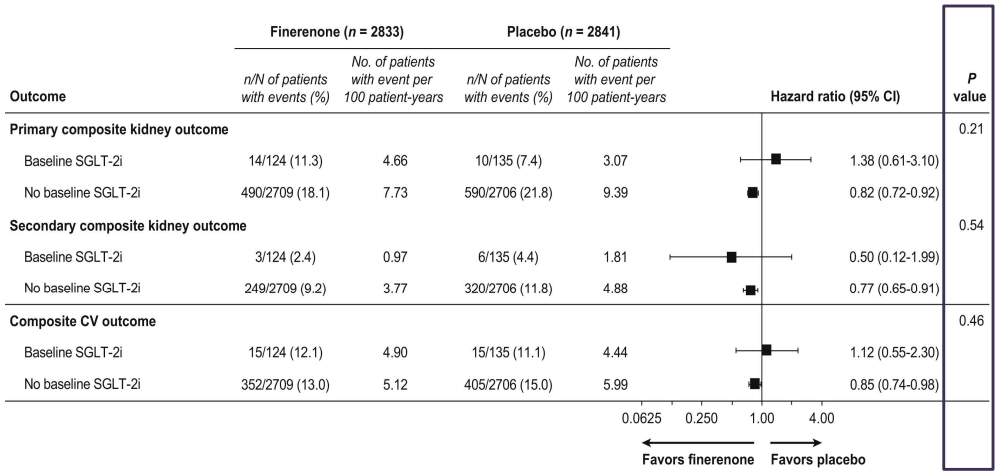
	Dapagliflozin n/N	Placebo n/N	Dapagliflozin Events/100 patient-years	Placebo Events/100 patient-years	Hazard Ratio (95% CI)	P Value for Interaction	Absolute Risk Difference, % (95% CI)	P Value for Interaction
Primary endpoint: eGFR decline ≥50%, ESKD, or kidney or CV death								
With MRA	16/109	21/120	6.9	8.8	0.76 (0.40, 1.47)	0.59	-2.8 (-12.3, 6.7)	0.59
Without MRA	181/2043	291/2032	4.5	7.4	0.60 (0.50, 0.72)		-5.5 (-7.4, -3.5)	
Kidney-specific secondary endpoint								
With MRA	7/109	12/120	3.0	5.1	0.61 (0.24, 1.57)	0.96	-3.6 (-10.6, 3.5)	0.75
Without MRA	135/2043	231/2032	3.3	5.9	0.56 (0.45, 0.69)		-4.8 (-6.5, -3.0)	
eGFR decline ≥50%								
With MRA	5/109	11/120	2.2	4.6	0.46 (0.16, 1.35)	0.65	-4.6 (-11.1, 1.9)	0.89
Without MRA	107/2043	190/2032	2.6	4.8	0.54 (0.43, 0.68)		-4.1 (-5.7, -2.5)	
ESKD								
With MRA	4/109	10/120	1.7	4.1	0.48 (0.15, 1.58)	0.36	-4.7 (-10.7, 1.4)	0.46
Without MRA	105/2043	151/2032	2.6	3.8	0.66 (0.51, 0.85)		-2.3 (-3.8, -0.8)	
Hospitalisation for heart failure or CV death								
With MRA	15/109	17/120	6.3	6.9	0.88 (0.43, 1.77)	0.45	-0.40 (-9.4, 8.6)	0.76
Without MRA	85/2043	121/2032	1.9	2.8	0.69 (0.52, 0.91)		-1.8 (-3.1, -0.4)	
All-cause death								
With MRA	11/109	13/120	4.6	5.0	0.86 (0.38, 1.95)	0.46	-0.7 (-8.7, 7.2)	0.73
Without MRA	90/2043	133/2032	2.0	3.0	0.67 (0.51, 0.87)		-2.1 (-3.5, -0.7)	

SGLT2I IN THE FIDELIO-DKD TRIAL

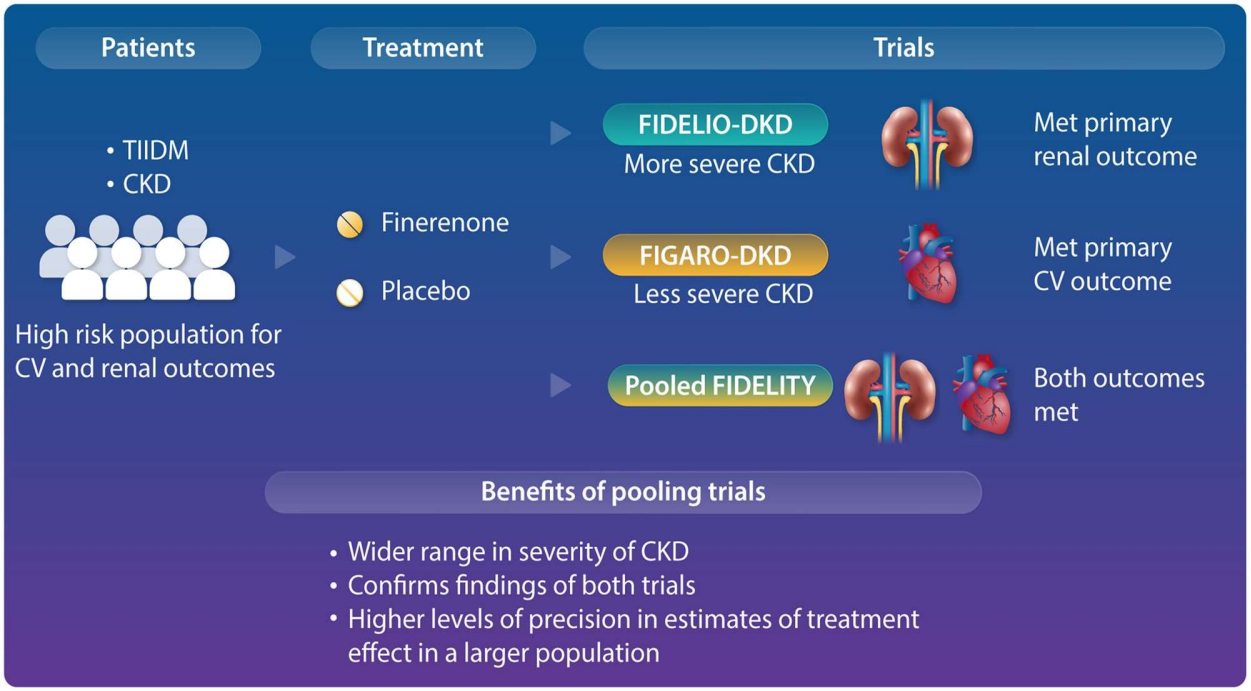


Outcome	Finerenone (*n* = 2833) *n/N of patients with events (%)*	Finerenone (*n* = 2833) *No. of patients with event per 100 patient-years*	Placebo (*n* = 2841) *n/N of patients with events (%)*	Placebo (*n* = 2841) *No. of patients with event per 100 patient-years*	Hazard ratio (95% CI)	*P* value
Primary composite kidney outcome						0.21
Baseline SGLT-2i	14/124 (11.3)	4.66	10/135 (7.4)	3.07	1.38 (0.61-3.10)	
No baseline SGLT-2i	490/2709 (18.1)	7.73	590/2706 (21.8)	9.39	0.82 (0.72-0.92)	
Secondary composite kidney outcome						0.54
Baseline SGLT-2i	3/124 (2.4)	0.97	6/135 (4.4)	1.81	0.50 (0.12-1.99)	
No baseline SGLT-2i	249/2709 (9.2)	3.77	320/2706 (11.8)	4.88	0.77 (0.65-0.91)	
Composite CV outcome						0.46
Baseline SGLT-2i	15/124 (12.1)	4.90	15/135 (11.1)	4.44	1.12 (0.55-2.30)	
No baseline SGLT-2i	352/2709 (13.0)	5.12	405/2706 (15.0)	5.99	0.85 (0.74-0.98)	

No evidence of effect modification based on limited and subject to selection effect post hoc subgroup data

https://doi.org/10.1016/j.ekir.2021.12.013 https://www.kireports.org/article/S2468-0249(21)01467-4/fulltext

Aldosteronism Antagonism (MRA) for the reduction of cardiorenal risk across the spectrum of DKD



https://doi.org/10.1093/eurheartj/ehab827

Hypekalemia will occur with ACEi/ARB and MRAs

Hyperkalemia will occur irrespective of the the diabetic (or not) nature of CKD

Management of hyperkalemia will allow the safe use of ACEi/ARB/MRAs

Continued use of these agents is required to deliver their cardiovascular and kidney benefits

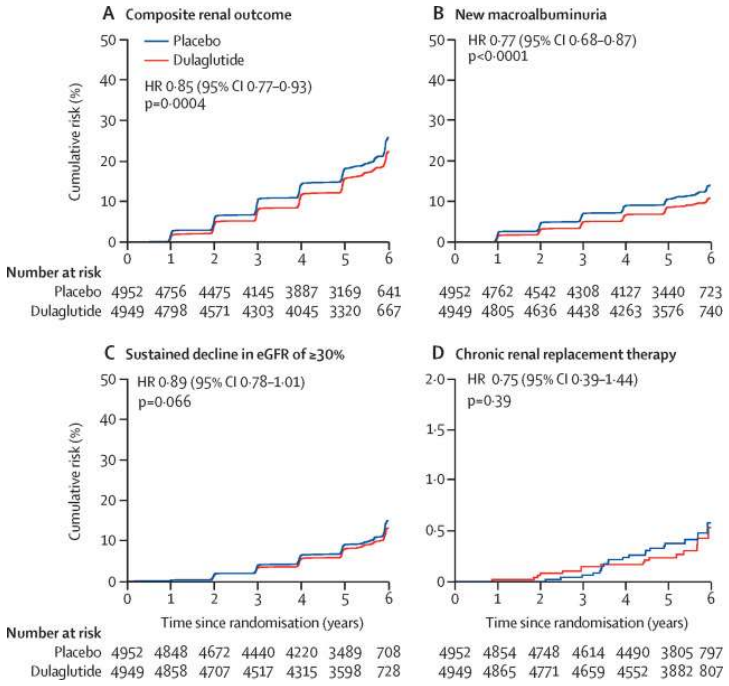
Potential strategies to manage the hyperkalemia risk by *any* RAASi are:

- Measure the potassium (it never makes sense to “stop the count”)
- Stop the RAASi or reduce the dose (temporarily)
- “Convince” the kidneys to get rid of potassium (diuretics/SGLT2 inhibitors)
- Use a potassium binder (patiromer/ZS9)

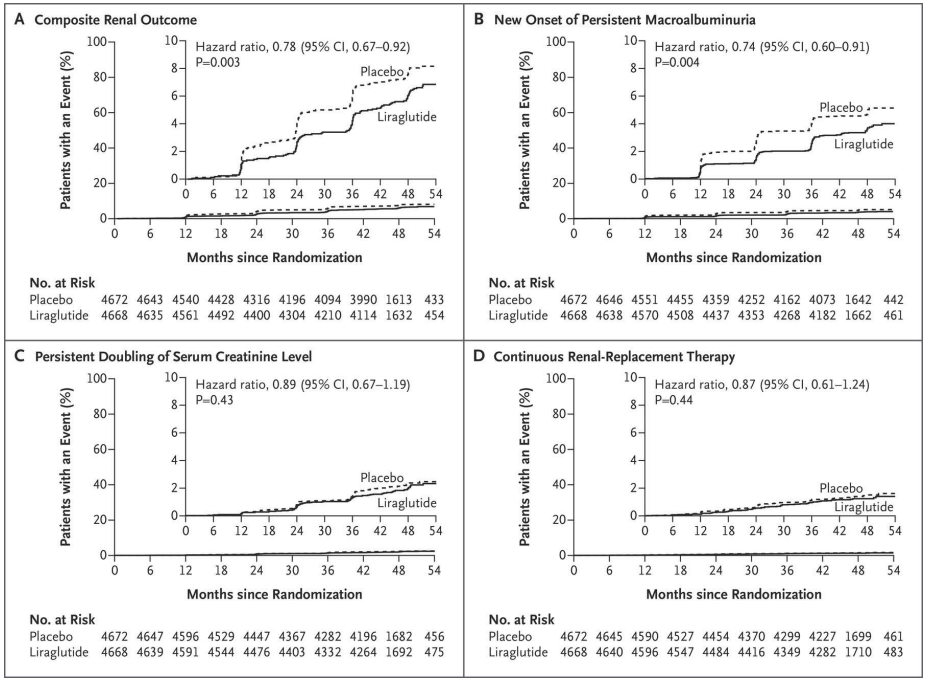
Management of hyperkalemia for diabetic and non-diabetic CKD

GLP1RA in Diabetic Kidney Disease

Duaglutide



Liraglutide



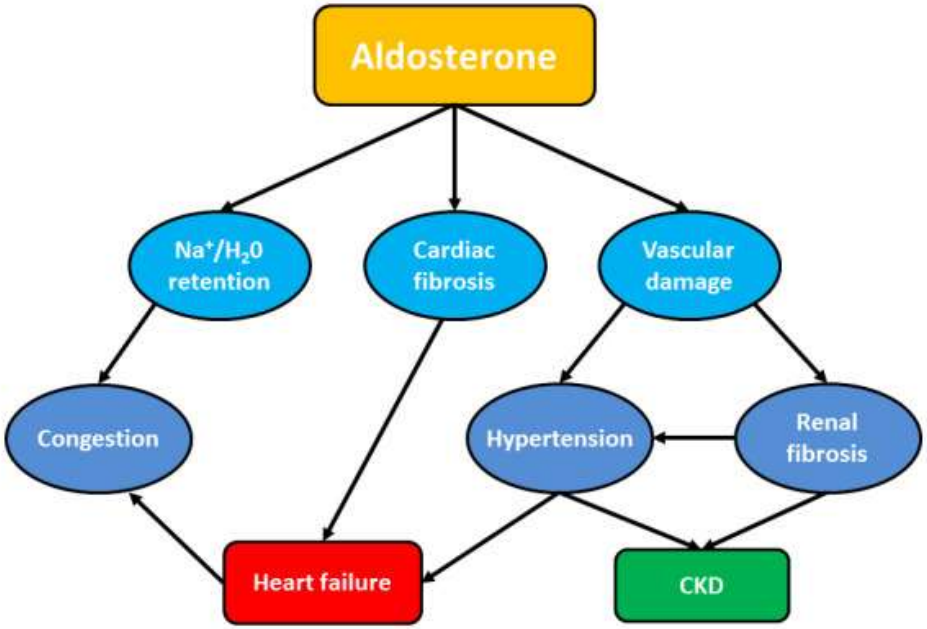
Semaglutide:
Composite Kidney HR 0.64 (95% CI 0.46 – 0.88) mostly driven by progression to macroalbuminuria: HR 0.54 95% CI (0.37 – 0.77)

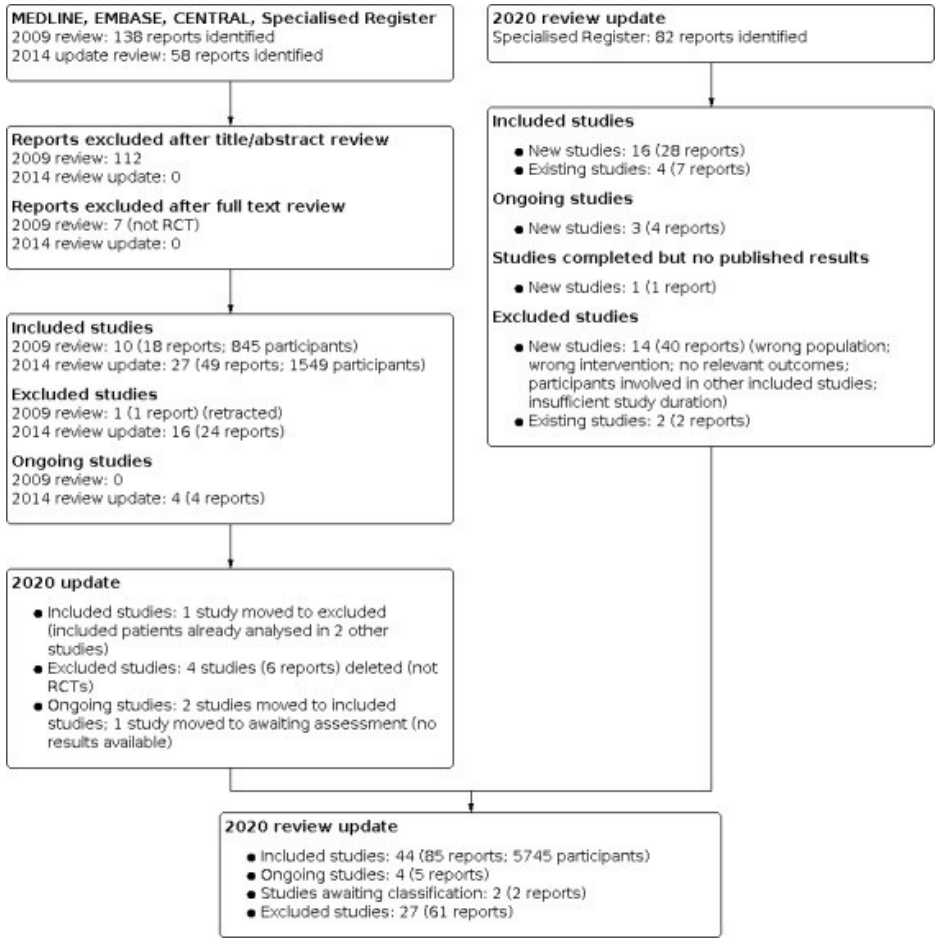
Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial - The Lancet

Liraglutide and Renal Outcomes in Type 2 Diabetes | NEJM

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes | NEJM

Are MRAs our next weapon in managing cardiorenal risk?





https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8094274