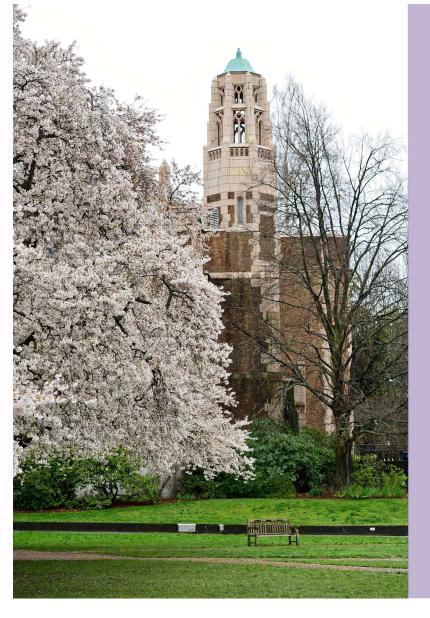
# University of Washington Cardiometabolic ECHO



Cardiometabolic Benefits of Renal Diabetes and Obesity Medications

September 21, 2022

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# Disclosures

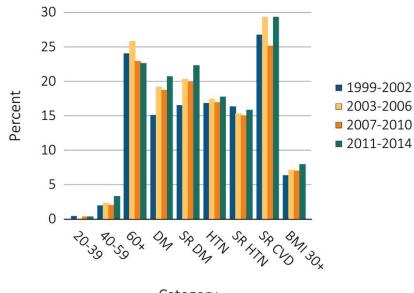
• Consultation from Bayer, Otsuka, Baxter, Quanta

# Learning Objectives

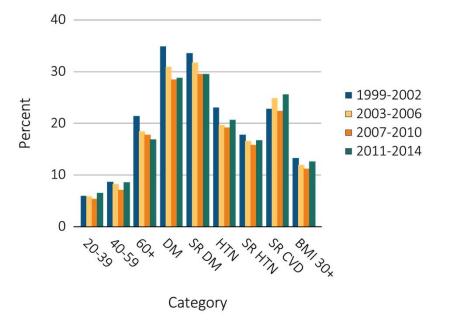
- 1. Pharmacological Interventions to reduce Cardiorenal Risk in Patients with DM2 and/or Chronic Kidney Diseases
- 2. Selecting Patients for Cardiorenal Risk Reduction

## Diabetic CKD (DKD) is common...

 NHANES participants with eGFR <60 ml/min/1.73 m2</li>  NHANES participants with urine albumin/creatinine ratio ≥30 mg/g

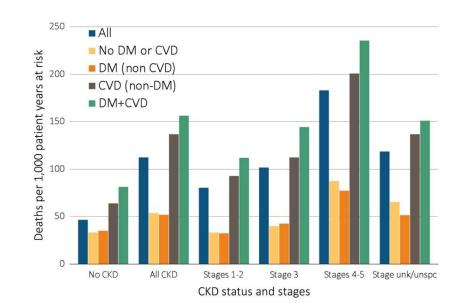


Category



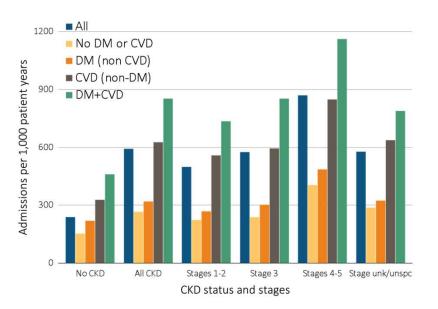
2016 Annual Data Report, Vol 1, CKD, Ch 1

## Diabetic CKD + Cardiovascular Disease = Hospitalization + Death



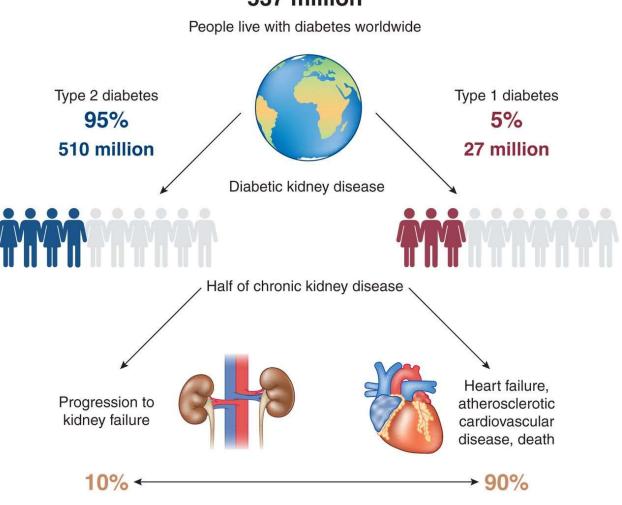
Death

#### 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.

2016 Annual Data Report, Vol 1, CKD, CH 3



537 million

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

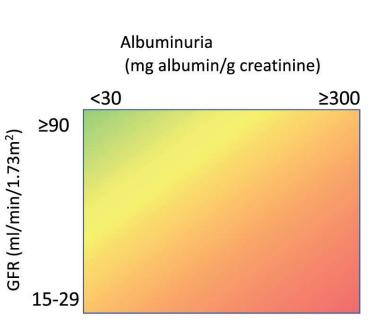
### Both UACR and eGFR must be obtained in clinical practice

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			uria categories Ilbumin/g creat	
	N	Low risk Aoderate risk		A1 Normal to mildly	A2 Moderately increased	A3 Severely increased
	١	High risk /ery high risk		increased <30	30 to <300	≥300
90	G1	High and optimal	≥ 90			
וd ran <sub>(</sub> 3 m²)	G2	Mild	60-89			
FR stages and (mL/min/1.73	G3a	Mild-moderate	45-59			
eGFR stages and range (mL/min/1.73 m <sup>2</sup> )	G3b	Moderate-severe	30-44			
еG	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

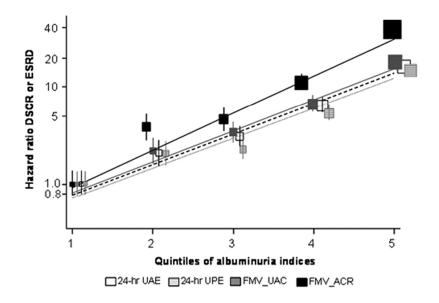


Table 2. Area under the ROC curve and 95% CIs for the prediction of the composite of doubling of serum creatinine or end-stage renal disease based on baseline proteinuria measures

		Doubli	ng of Serum Creati	nine or End-Stage Rer	ial Disease
	Subjects/Events	24-Hou	ır <mark>Urine</mark>	First-Mo	rning 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] <sup>a,b,c</sup>
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] <sup>a,c</sup>
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] <sup>a,b,c</sup>
>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] <sup>a,b</sup>
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] <sup>a,b,c</sup>

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.

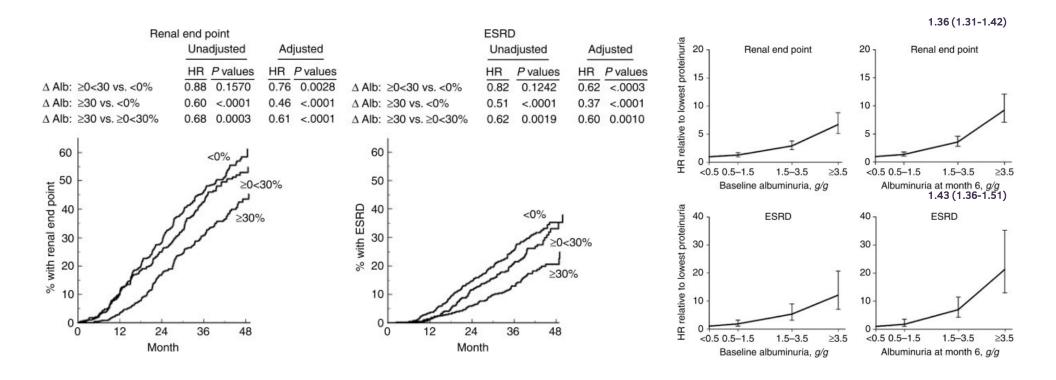
\*P < 0.01 versus UAE.

<sup>b</sup>P < 0.01 versus UPE.

<sup>c</sup>P < 0.01 versus UAC.

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

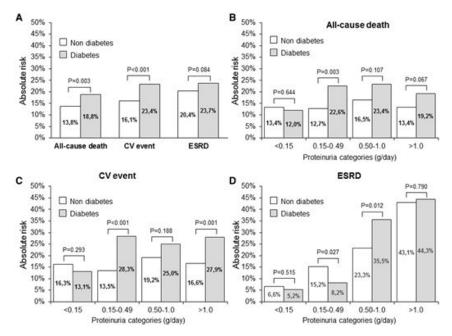
## Residual albuminuria, Albuminuria Dela after ARB predict kidney outcomes



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

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



	Proteinuria categ	ories (g/day)						
	<0.15		0.15-0.49		0.50-1.00		>1.00	
	Events/patients (n/N)	HR (95% CI)	Events/patients ( <i>n/N</i> )	HR (95% CI)	Events/patients ( <i>n/N</i> )	HR (95% CI)	Events/patients ( <i>n/N</i> )	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.

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Nephrol Dial Transplant (2018) 33: 1942-1949



https://www.ajkd.org/article/S0272-6386(21)00924-0/fulltext

 Received: 13 September 2020
 Revised: 28 October 2020
 Accepted: 29 October 2020

 DOI: 10.1002/clc.23508
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REVIEW

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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<sup>1</sup> | Christos Argyropoulos<sup>2</sup>



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Perspective

Are the protective effects of SGLT2 inhibitors a "class-effect" or are there differences between agents?

Darren W. Schmidt, Christos Argyropoulos and Namita Singh Kidney360 February 2021, 10.34067/KID.0000622021; DOI: https://doi.org/10.34067/KID.0000622021

#### **PAYING FOR NEW THERAPIES**

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https://bitbucket.org/chrisarg/sglt2imetanalysis/

## Snapshot of the SGLT2i trials pre-2022

	Empagliflozin		Canagliflozir	ı	Dapagliflozin			Ertugliflozin			https://	onlinolih	orary.wiley.co	om/doi/o	ndf/10	1002/cl/	- 22500
	EMPA-REG Outcome <sup>10,14,31</sup>	EMPEROR - REDUCED <sup>16</sup>	CANVAS Program <sup>11</sup>	CREDENCE <sup>17,32</sup>	DECLARE- TIMI 58 <sup>12,33</sup>	DAPA- HF <sup>15</sup>	DAPA- CKD <sup>18</sup>	VERTIS- CV <sup>13</sup>			<u>III(p3.//)</u>	Jiiiiieiib	nary.witey.co		pui/ 10.	1002/ 00	<u>23308</u>
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		Empagliflozin		Canagliflozi	1	Dapagliflozin			Ertugliflozin
Region										EMPA-REG	EMPEROR -	CANVAS		DECLARE-	DAPA- HF <sup>15</sup>	DAPA-	VERTIS-
Europe	2885 (41.1)	1353 (36.3)	NR	864 (19.6)	7629 (44.5)	2154 (45.4)	1233 (28.6)	4637 (56.2)	Renal status	Outcome <sup>10,14,31</sup>	REDUCED <sup>16</sup>	Program <sup>11</sup>	CREDENCE <sup>17,32</sup>	TIMI 58 <sup>12,33</sup>	HF**	CKD <sup>18</sup>	CV <sup>13</sup>
North America	1394 (19.9)	425 (11.4)	NR	1182 (26.9)	5468 (31.9)	677 (14.3)	813 (18.9)	1813 (22)	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
Asia	1347 (19.2)	493 (13.2)	NR	NR	2186 (12.7)	1096 (23.1)	1346 (31.3)	523 (6.3)	eGFR ≥90	1538 (21.9)°	NR	2476 (24.4)	211 (4.8)	8162 (47.6)	8162 (47.6)	None	NR
Latin America Rest of the	1081 (15.4) 313 (4.5)	1286 (34.5) 173 (4.6) <sup>a</sup>	NR NR	941 (21.4) 1414 (32.1)	1877 (10.9) Νοιε	817 (17.2) None	912 (21.2) None	723 (8.8) 550 (6.7) <sup>b</sup>	eGFR 60-90	366 <b>1</b> (52.2) <sup>e</sup>	NR	5625 (55.5)	1558 (35.4)	7732 (45.1)	7732 (45.1)	454 (10.5)	NR
world	5X								eGFR <60	1819 (25.9)°	906 (12.9)	2039	2631 (59.8)	1265 (7.4)	1265 (7.4)	3850 (89.5)	1807 (21.9)
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)	Mild albuminuria	4171 (60.0)°	NR	(20.1) 7007 (69.1)	31 (0.7)	11 644 (69.1)	11 644 (69.1)	NR	NR
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	Moderate	2013 (29.0)°	NR	2266	496 (11.3)	4029 (23.9)	4029 (23.9)	NR	NR
Race/ethnicity									albuminuria Severe	769 (11.1)°	NR	(22.3) 760 (7.5)	3874 (88)	1169 (6.9)	1169 (6.9)	2079 (48.3)	NR
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)	albuminuria	707 (11.1)	INK	700 (7.3)	3074 (00)	1107 (0.7)	1107 (0.7)	2017 (40.3)	INK
Asian	1517 (21.3)	672 (18)	1284 (12.7)	877 (19.9)	2303 (13.4)	<mark>1116</mark> (23.5)	1467 (34.1)	498 (6.0)	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)
Black	357 (5.1)	257 (6.9)	336 (3. <mark>3</mark> )	224 (5.1)	603 (3.5)	226 (4.8)	191 (4.4)	235 (2.8)	Beta-blockers	4554 (64.9)	3533 (94.7)	5421 (53.5)	1770 (40.2)	9030 (52.6)	4558 (96.1)	NR	5692 (69)
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)	Antiplatelet	6293 (89.6)	NR	7466	2624 (59.6)	10 487	NR	NR	6978 (84.6)
Diabetes (%)	100%	49.8%	100%	100%	100%	41.8%	67.7%	100%	agents <sup>f</sup> Statins	5403 (77)	NR	(73.6) 7599	3036 (69)	(61.1) 12 868 (75)	2794 (58.9)	2794 (64.9)	6747 (81.8)
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	Statilis	3403 (77)	INK	(74.9)	3030 (07)	12 000 (7 3)	2774 (30.7)	2/74 (04.7)	0/4/ (01.0)
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	MRA Diuretics	441 (6.3) 3035 (43.2)	2661 (71.3) NR	NR 4490	NR 2057 (46.7)	NR 6967 (40.6)	3370 (71) 4433 (93.4)	NR 1882 (43.7)	674 (8.2) 3542 (43)
Cardiac/cardiovas	cular diseases								ARNI	NR	727 (19.5)	(44.3) NR	NR	NR	508 (10.7)	NR	NR
Coronary artery disease	5308 (75.6)	1929 (51.7)°	5721 (56.4)	1313 (29.8)	5648 (32.9)	2674 (56.4) <sup>c</sup>	1710 (39.7) <sup>d</sup>	6256 (75.9)	Insulin	3387 (48.2)	NR	5095 (50.2)	2884 (65.5)	7013 (40.9)	540 (11.4)	NR	3900 (47.3)
Cerebrovascular disease	1637 (23.3)	NR	1958 (19.3)	700 (15.9)	1301 (7.6)	NR		1889 (22.9)	Metformin	5193 (74.0)	NR	7825 (77.2)	2545 (57.8)	14 068 (82)	1016 (21.4)		6292 (76.3)
Peripheral arterial	1461 (20.8)	NR	7324 (72.2)	47.5 (1.1)	1025 (6)	NR		1541 (18.7)	Sulfonylureas DPP4i	3006 (42.8) 796 (11.3)	NR NR	4361 (43) 1261 (12.4)	1268 (28.8) 751 (17.1)	7322 (42.7) 2888 (16.8)	438 (9.2) 310 (6.5)	NR NR	3390 (41.1) 911 (11)
disease									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%

A								]	В							
Study	Trial	Rate SGLT2i	Rate SGLT2i	CV Death	HR	95%-CI	Weight		Study	Trial	Rate SGLT2i	Rate SGLT2i	All Cause Death	HR	95%-C	l Weight
Drug = Canagliflozin CANVAS Program CREDENCE Random effects model Heterogeneity: $l^2 = 0\%$ , $\tau^2 =$	CVOT CKD = 0, p = 1	17.3 19.0 0.50	19.5 24.4		0.87 [0. 0.78 [0. <b>0.83 [0.</b> ]		13.7% 10.2% <b>23.9%</b>		<b>Drug = Canagliflozin</b> CANVAS Program CREDENCE <b>Random effects model</b> Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0\%$	CVOT CKD = 0, <i>p</i> = 0	11.6 29.0 ).72	12.8 35.0		0.83	0.74; 1.02 0.68; 1.02 <b>0.76; 0.97</b>	j 9.8%
	CKD HFrEF CVOT = 0.003	14.0 65.0 7.0	17.0 79.0 7.1				6.8% 15.2% 15.0% <b>36.9%</b>			CKD HFrEF CVOT = 0.010	22.0 79.0 15.1 2, p = 0.0	31.0 - 95.0 16.4		0.83 0.93	0.54; 0.89 0.71; 0.97 0.83; 1.05 <b>0.72; 0.97</b>	] 13.2% ] 16.7%
Drug = Empagliflozin EMPA-REG OUTCOME EMPEROR-REDUCED Random effects model Heterogeneity: $l^2$ = 85%, $\tau^2$	HFrEF		20.2 81.0		0.62 [0. 0.92 [0. <b>0.76 [0.</b>	49; 0.78] 75; 1.12] <b>51; 1.12]</b>	13.2%		Drug = Empagliflozin EMPA-REG OUTCOME EMPEROR-REDUCED Random effects model Heterogeneity: $l^2$ = 82%, $\tau^2$	HFrEF	19.4 101.0 2, p = 0.0	28.6 107.0		0.92	0.57; 0.82 0.77; 1.10 <b>0.59; 1.06</b>	] 11.4%
Drug = Ertugliflozin VERTIS-CV Random effects model Heterogeneity: not applicab	CVOT le	18.0	19.0			77; 1.10] 7 <b>7; 1.10]</b>			Drug = Ertugliflozin VERTIS-CV Random effects model Heterogeneity: not applicab	CVOT	24.0	26.0			0.83; 1.04 <b>0.83; 1.04</b>	
Random effects model Prediction interval Heterogeneity: $I^2 = 42\%$ , $\tau^2$ Residual heterogeneity: $I^2 = 42\%$			10 <sup>1</sup> 0.	5 1		77; <mark>0.93]</mark> 66; 1.09]	100.0%		Random effects model Prediction interval Heterogeneity: $l^2 = 49\%$ , $r^2$ Residual heterogeneity: $l^2$			06	0.75 1 1.5	0.85	0.78; 0.92 0.68; 1.05	] 100.0% ]

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

Drug	Trial	Rate SGLT2i	Rate PBO	CV Death HHF	HR	95%-CI	Weight (fixed)	
Canagliflozin Dapagliflozin Dapagliflozin Dapagliflozin Empagliflozin	CKD CKD HFrEF CVOT CVOT HFrEF	16.3 31.5 22.0 114.0 12.2 19.7 158.0 23.4	20.8 45.4 30.0 153.0 14.7 30.1 210.0 26.6		0.78 0.69 0.71 0.75 0.83 0.66 0.75 0.88	[0.67; 0.91] [0.57; 0.83] [0.56; 0.92] [0.66; 0.86] [0.73; 0.95] [0.55; 0.79] [0.65; 0.86] [0.75; 1.03]	13.3% 8.8% 4.7% 17.3% 18.0% 9.5% 15.9% 12.4%	13.4% 9.5% 5.4% 16.5% 17.0% 10.1% 15.5% 12.6%
<sup>2</sup> = 0.0014, <i>p</i> =	0.27			.75 1 1.5			100.0% 	100.0%
		Pato	Pata				Weight	Weight
Drug	Trial			HHF	HR	95%-CI	(fixed)	(random)
Canagliflozin Dapagliflozin Dapagliflozin Empagliflozin Empagliflozin	CKD HFrEF CVOT CVOT HFrEF	5.5 15.7 69.0 6.2 9.4 107.0 7.0	8.7 25.3 98.0 8.5 14.5 155.0 11.0		0.67 0.61 0.70 0.73 0.65 0.69 0.70	[0.52; 0.87] [0.47; 0.80] [0.59; 0.83] [0.61; 0.88] [0.50; 0.85] [0.59; 0.81] [0.54; 0.90]	9.3% 8.7% 21.1% 18.3% 8.7% 24.5% 9.4%	9.3% 8.7% 21.1% 18.3% 8.7% 24.5% 9.4%
						[0.64; 0.74] [0.64; 0.74]	100.0%	100.0%
	Canagilflozin Dapagilflozin Dapagilflozin Dapagilflozin Empagilflozin Ertugilflozin <sup>2</sup> = 0.0014, <i>p</i> = <b>Drug</b> Canagilflozin Dapagilflozin Dapagilflozin Empagilflozin Empagilflozin Empagilflozin	Canagliflozin CVOT Canagliflozin CKD Dapagliflozin CKD Dapagliflozin HFrEF Dapagliflozin HFrEF Empagliflozin CVOT Empagliflozin CVOT 2 = 0.0014, p = 0.27 Drug Trial Canagliflozin CKD Dapagliflozin CKD Dapagliflozin CVOT Canagliflozin HFrEF Dapagliflozin CVOT Empagliflozin CVOT	Drug         Trial         SGLT2i           Canagliflozin         CVOT         16.3           Canagliflozin         CKD         31.5           Dapagliflozin         CKD         22.0           Dapagliflozin         HFrEF         114.0           Dapagliflozin         CVOT         19.7           Empagliflozin         CVOT         19.7           Empagliflozin         HFrEF         158.0           Ertugliflozin         CVOT         23.4           2² = 0.0014, p = 0.27         Zanagliflozin         Kate           Drug         Trial         SGLT2i           Canagliflozin         CVOT         5.5           Canagliflozin         CKD         15.7           Dapagliflozin         CVOT         6.2           Empagliflozin         CVOT         9.4           Empagliflozin         CVOT         9.4	Drug         Trial         SGLT2i         PBO           Canagliflozin         CVOT         16.3         20.8           Canagliflozin         CKD         31.5         45.4           Dapagliflozin         CKD         22.0         30.0           Dapagliflozin         CVOT         12.2         14.7           Empagliflozin         CVOT         19.7         30.1           Empagliflozin         CVOT         23.4         26.6           2*         0.0014, p = 0.27         2*         4.7           Prug         Trial         Rate         Rate           Drug         CVOT         5.5         8.7           Canagliflozin         CVOT         5.5         8.7           Canagliflozin         CVOT         5.7         25.3           Dapagliflozin         CVOT         5.5         8.7           Canagliflozin         CVOT         5.5         8.7           Dapagliflozin         CVOT         5.5         8.7           Dapagliflozin         CVOT         5.2         8.5           Empagliflozin         CVOT         6.2         8.5           Empagliflozin         CVOT         6.2         8.5  <	Drug         Trial         SGLT2i         PBO         CV Death HHF           Canagliflozin         CVD         16.3         20.8	Drug         Trial         SGLT2i         PBO         CV Death HHF         HR           Canagliflozin         CVD         16.3         20.8         0.78         0.78           Canagliflozin         CKD         31.5         45.4         0.69         0.71           Dapagliflozin         CKD         22.0         30.0         0.71         0.71           Dapagliflozin         CVOT         12.2         14.7         0.83         0.66           Empagliflozin         CVOT         19.7         30.1         0.75         0.75         0.83           Empagliflozin         CVOT         23.4         26.6         0.88         0.66           2* 0.0014, p = 0.27         0.75         1         1.5         0.76         0.77           0.75         1         1.5         0.77         0.75         1         0.5           2* 0.0014, p = 0.27         0.75         1         1.5         0.76         0.76         0.76           2* 0.0014, p = 0.27         0.75         1         1.5         0.77         0.75         0.75         0.76           2* 0.0014, p = 0.27         0.75         1         1.5         0.76         0.76         0.76      <	Drug         Trial         SGLT2i         PBO         CV Death HHF         HR         95%-CI           Canagliflozin         CVD         16.3         20.8	Drug         Trial         SGLT2i         PBO         CV Death HHF         HR         95%-Cl         (fixed)           Canagliflozin         CVO         16.3         20.8

Study	Drug	Trial	Rate SGLT2i	Rate PBO	MAÇE-3	HR	95%-CI	Weight (fixed)	Weigh (random
CANVAS Program CREDENCE DECLARE-TIMI-58 EMPA-REG OUTCOME VERTIS-CV	Canagliflozin Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	CKD CVOT	26.9 38.7 22.6 37.4 39.0	31.5 48.7 — 24.2 43.9 40.0		0.86 0.80 0.93 0.86 0.97	[0.76; 0.98] [0.67; 0.95] [0.84; 1.03] [0.74; 0.99] [0.85; 1.11]	20.6% 11.2% 32.9% 16.1% 19.2%	20.6% 11.2% 32.8% 16.1% 19.2%
Fixed effect model Random effects model Prediction interval						0.90 0.90	[0.84; 0.95] [0.84; 0.95] [0.81; 0.98]	100.0%	- 100.0%
Heterogeneity: $I^2 = 4\%$ , $\tau^2$	< 0.0001, p = 0	.38			0.8 1 125		[0.0.1, 0.00]		
Heterogeneity: / <sup>2</sup> = 4%, τ <sup>2</sup> ) Study	< 0.0001, p = 0 Drug		Rate SGLT2i	Rate PBO	0.8 1 1.25 Nonfatal MI	HR	95%-CI	Weight (fixed)	Weigh (random
)		Trial CVOT CVOT CVOT				HR 0.85 0.89 0.87 1.00			

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

Study	Trial	Rate SGLT2i	Rate SGLT2i	Composite Kidney	y Outcome	HR	95%-CI	Weight
<b>Drug = Canagliflozin</b> CANVAS Program CREDENCE <b>Random effects model</b> Heterogeneity: / <sup>2</sup> = 0%, τ <sup>2</sup>		27.0	9.0 40.4			0.66	[0.47; 0.77] [0.53; 0.82] <b>[0.54; 0.74]</b>	17.1%
Drug = Dapagliflozin DAPA-CKD DAPA-HF DECLARE-TIMI-58 Random effects model Heterogeneity: / <sup>2</sup> = 0%, τ <sup>2</sup>		3.7	58.0 12.0 4.0	+ + +		0.71 0.53	[0.46; 0.69] [0.44; 1.15] [0.43; 0.66] <b>[0.48; 0.64]</b>	4.8% 16.9%
Drug = Empagliflozin EMPA-REG OUTCOME EMPEROR-REDUCED Random effects model Heterogeneity: $I^2$ = 0%, $\tau^2$	HFrEF	16.0	11.5 31.0			0.50	[0.39; 0.74] [0.32; 0.78] <b>[0.41; 0.68]</b>	5.7%
Drug = Ertugliflozin VERTIS-CV Random effects model Heterogeneity: not applica		9.0	12.0				[0.63; 1.04] <b>[0.63; 1.04]</b>	
Random effects model Prediction interval Heterogeneity: $l^2 = 26\%$ , $\tau$ Residual heterogeneity: $l^2$	<sup>2</sup> = 0.00	76, <i>p</i> = 0.2 = 0.81	22	0.5 1	2	0.61	[0.54; 0.68] [0.47; 0.78]	100.0%

Study	Trial	NSGLT2i	NPBO	ESKD	HR	95%-CI	Weight
Drug = Canagliflozin CREDENCE Random effects model Heterogeneity: not applicate	CKD	2202	2199	÷.		[0.54; 0.86] <b>[0.54; 0.86]</b>	48.9% <b>48.9%</b>
<b>Drug = Dapagliflozin</b> DECLARE-TIMI-58 DAPA-CKD <b>Random effects model</b> Heterogeneity: / <sup>2</sup> = 57%, τ <sup>2</sup>	CVOT CKD <sup>2</sup> = 0.14	8574 2152 88, <i>p</i> = 0.13	8569 2152		0.64	[0.13; 0.76] [0.50; 0.82] <b>[0.26; 0.99]</b>	3.3% 43.3% <b>46.5%</b>
Drug = Empagliflozin EMPA-REG OUTCOME Random effects model Heterogeneity: not applicat		4687	2333			[0.21; 0.97] <b>[0.21; 0.97]</b>	4.5% <b>4.5%</b>
Random effects model Heterogeneity: $l^2 = 15\%$ , $\tau^2$ Residual heterogeneity: $l^2$	² < 0.00 = 57%,	01, p = 0.32 p = 0.13		0.2 0.5 1 2 5	0.63	[0.54; 0.75]	100.0%

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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 participa	ints/total no.		
All participants	197/2152	312/2152	<b>⊢</b> ∎-1	0.61 (0.51-0.72)
Age			1	
≤65 yr	122/1247	191/1239	F-8-4	0.64 (0.51-0.80)
>65 yr	75/905	121/913	<b>⊢_</b> ∎i i	0.58 (0.43-0.77)
Sex				
Male	126/1443	209/1436	, <b>⊢</b> ∎→(	0.57 (0.46-0.72)
Female	71/709	103/716	·	0.65 (0.48-0.88)
Race			1	
White	110/1124	174/1166		0.62 (0.49-0.79)
Black	7/104	14/87 ⊢	<b></b>	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	P	0.60 (0.43-0.85)
North America	35/401	69/412	P	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 <sup>2</sup>	152/1272	217/1250		0.63 (0.51-0.78)
≥45 ml/min/1.73 m <sup>2</sup>	45/880	95/902		0.49 (0.34-0.69)
Urinary albumin-to-creatinine r	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	i i i i i i i i i i i i i i i i i i i	0.44 (0.31-0.63)
>130 mm Hg	151/1359	216/1403	<b>⊢</b> ∎→	0.68 (0.56-0.84)

Dapagliflozin Better Placebo Better

	with an e	vent	per 1000 pat	ient-years			P
Ca	nagliflozin	Placebo	Canagliflozi	n Placebo	HR (95% CI)	iı	teraction
Kidney failure, doubling of s	erum crea	tinine, or k	didney or cardio	ovascular de	eath		
eGFR <30 ml/min per 1.73 m <sup>2</sup>	23	29	115.4	134.6	<b>⊢+</b> ∔−1	0.88 (0.51, 1.52)	0.48
eGFR ≥30 ml/min per 1.73 m <sup>2</sup>	222	311	40.6	58.3	ы	0.69 (0.58, 0.82	
Cardiovascular death							
eGFR <30 ml/min per 1.73 m <sup>2</sup>	8	8	37.4	33.7	→ <b>→</b> →	1.10 (0.41, 2.93	0.47
eGFR ≥30 ml/min per 1.73 m <sup>2</sup>	102	132	18.3	24.0	<b>⊢</b> ⊶i	0.76 (0.59, 0.99)	
Cardiovascular death or hos	pitalizatio	n for heart	failure		i		
eGFR <30 ml/min per 1.73 m <sup>2</sup>	14	14	67.9	61.2	<b>⊢</b> ∔•−−1	1.12 (0.54, 2.36	0.20
eGFR ≥30 ml/min per 1.73 m <sup>2</sup>	165	239	30.1	44.8	юн	0.67 (0.55, 0.82)	
Cardiovascular death, myoc	ardial infa	rction, or s	troke				
eGFR <30 ml/min per 1.73 m <sup>2</sup>	13	14	63.8	61.9		1.04 (0.49, 2.20)	0.49
eGFR ≥30 ml/min per 1.73 m <sup>2</sup>	204	255	37.8	48.1	юч	0.78 (0.65, 0.94	
Hospitalization for heart fail	ure						
eGFR <30 ml/min per 1.73 m <sup>2</sup>	6	8	29.2	35.0 H		0.84 (0.29, 2.43	0.56
eGFR ≥30 ml/min per 1.73 m <sup>2</sup>	83	133	15.1	24.9	Here I	0.61 (0.46, 0.80	
Kidney failure, doubling of s	erum crea	tinine, or k	idney death				
eGFR <30 ml/min per 1.73 m <sup>2</sup>	17	25	85.6	116.0	<b>⊢</b> •∔•	0.76 (0.41, 1.40)	0.77
eGFR ≥30 ml/min per 1.73 m <sup>2</sup>	136	199	24.9	37.3	юч	0.66 (0.53, 0.82)	100000
Kidney failure					1		
eGFR <30 ml/min per 1.73 m <sup>2</sup>	15	25	75.4	116.0	<b>⊢</b> •∔ı	0.67 (0.35, 1.27)	0.80
eGFR ≥30 ml/min per 1.73 m <sup>2</sup>	101	140	18.4	26.0	Hora I	0.70 (0.54, 0.91	1000
Dialysis, kidney transplantat	tion, or kic	Iney death					
eGFR <30 ml/min per 1.73 m <sup>2</sup>	10	14	48.4	61.9	<b>⊢_</b> •	0.90 (0.39, 2.07	0.87
eGFR ≥30 ml/min per 1.73 m <sup>2</sup>	68	91	12.3	16.7	⊢⊶i	0.73 (0.53, 0.999	)
					- +	7	
				0.25	0.5 1.0 2.0	4.0	
					Favors Favors		

Number of participants Participants with an event

canagliflozin placebo

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

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

a Runey outcome		
Study ID		HR (95% CI)
No diabetes DAPA-HF EMPEROR-Reduced DAPA-CKD Subtotal (I <sup>2</sup> = 0.0%, P = 0.714)		- 0.67 (0.30–1.49) 0.42 (0.19–0.97) 0.50 (0.35–0.72) 0.51 (0.38–0.69)
Diabetes DAPA-HF EMPEROR-Reduced DAPA-CKD CANVAS CREDENCE EMPA-Reg DECLARE-TIMI VERTIS-CV SCORED Subtotal (I <sup>2</sup> = 6.6%, P = 0.380)		$\begin{array}{c} 0.73 \ (0.39-1.34) \\ 0.53 \ (0.31-0.90) \\ 0.64 \ (0.52-0.79) \\ 0.60 \ (0.47-0.77) \\ 0.66 \ (0.53-0.81) \\ 0.54 \ (0.40-0.75) \\ 0.53 \ (0.43-0.66) \\ 0.81 \ (0.63-1.04) \\ 0.71 \ (0.46-1.08) \\ 0.63 \ (0.57-0.69) \end{array}$
Overall ( $I^2 = 0.0\%$ , $P = 0.450$ )	$\diamond$	0.62 (0.57–0.67)
	0.5 1	2

a Kidnev outcome

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

# Safety events in SGLT2i trials

Study	S Events	GLT2i Total	Events	PBO Total	Volume Depletion	OR	95%-CI	Weight (fixed)	Weight (random)
CANVAS CREDENCE DAPA-HF DECLARE-TIMI-58 EMPA-REG OUTCOME EMPEROR-REDUCED VERTIS-CV DAPA-CKD	429 144 178 213 239 197 236 127	2886 2200 2368 8574 4687 1863 5493 2149	148 115 162 207 115 184 106 90	1441 2197 2368 8569 2333 1863 2745 2149		1.53 1.27 1.11 1.03 1.04 1.08 1.12 1.44	[1.25, 1.86] [0.98, 1.63] [0.89, 1.38] [0.85, 1.25] [0.82, 1.30] [0.87, 1.33] [0.88, 1.41] [1.09, 1.90]	14.5% 9.3% 12.9% 17.4% 12.6% 14.2% 11.7% 7.3%	14.2% 11.0% 12.8% 14.6% 12.3% 13.3% 12.0% 9.8%
Fixed effect model Random effects model Prediction interval Heterogeneity: / <sup>2</sup> = 46%, τ		<b>30220</b> 3, p = 0	.07	23665	0.75 1 1.5	1.18 1.18	[1.09; 1.28] [1.06; 1.32] [0.88; 1.58]	100.0%	100.0%
(B)									
Study	S Events	GLT2i Total	Events	PBO Total	AKI	OR	95%-CI	Weight (fixed)	Weigh (random
CANVAS CREDENCE DAPA-HF DECLARE-TIMI-58 EMPA-REG OUTCOME VERTIS-CV DAPA-CKD	50 86 23 125 45 101 155	2886 2200 2368 8574 4687 5493 2149	33 98 46 175 37 60 188	1441 2197 2368 8569 2333 2745 2149		0.75 0.87 0.50 0.71 0.60 0.84 0.81	[0.48; 1.17] [0.65; 1.17] [0.30; 0.82] [0.56; 0.89] [0.39; 0.93] [0.61; 1.16] [0.65; 1.01]	6.6% 14.3% 6.9% 26.2% 7.4% 11.9% 26.5%	6.89 15.49 5.39 25.19 7.09 12.99 27.49
Fixed effect model Random effects model Prediction interval Heterogeneity: $I^2 = 0\%$ , $\tau^2$		28357 p = 0.4	6	21802	0.5 1 2	0.75 0.76	[0.67; 0.85] [0.67; 0.85] [0.65; 0.88]	100.0%	100.09
(C)									
Study		GLT2i Total	Events	PBO Total	Genital Mycotic Infection	OR	95%-C	Weigh I (fixed	t Weig ) (rando
CREDENCE DECLARE-TIMI-58 EMPA-REG OUTCOME EMPEROR-REDUCED VERTIS-CV	50 76 301 31 297	2200 8574 4687 1863 5493	9 42 12	8569 2333 1863		3.91 8.51 3.74 2.61 3.68	[4.26; 16.99 [2.70; 5.19 [1.34; 5.10	6.49 37.89 8.59	6 8.1 6 36.4 6 8.7
	E.	22817		17707	•••	3.94 3.87		] 100.0% ] ]	6 - 100.0
Fixed effect model Random effects model Prediction interval Heterogeneity: 1 <sup>2</sup> = 38%, 1	<sup>2</sup> < 0.000	1, <i>p</i> = 0	.17		0.1 0.5 1 2 10				
Random effects model Prediction interval	r <sup>2</sup> < 0.000	1, ρ = 0	.17		0.1 0.5 1 2 10				
Random effects model Prediction interval Heterogeneity: <i>t</i> <sup>2</sup> = 38%, 1		GLT2i	Events	PBO Total	0.1 0.5 1 2 10 עדו	OR	95%-CI	Weight (fixed)	Weigh (random
Random effects model Prediction interval Heterogeneity: / <sup>2</sup> = 38%, 1 (D)	s	GLT2i				1.14 1.12 0.65 0.95	<b>95%-CI</b> [0.98; 1.33] [0.92; 1.36] [0.30; 1.38] [0.75; 1.22] [0.87; 1.13] [0.81; 1.49] [1.05; 1.41]	Weight (fixed) 20.1% 12.9% 1.1% 8.6% 30.5% 5.2% 21.5%	

Study	S Events	GLT2i Total	Events	PBO Total	Hypoglycemia	OR	95%-CI	Weight (fixed)	Weight (random)
CANVAS CREDENCE DECLARE-TIMI-58 EMPA-REG OUTCOME EMPEROR-REDUCED VERTIS-CV DAPA-CKD	825 225 58 1303 27 1496 14	2886 2200 8574 4687 1863 5493 2149	372 240 83 650 28 790 28	1441 2197 8569 2333 1863 2745 2149		1.15 0.93 0.70 1.00 0.96 0.93 0.50	[1.00; 1.33] [0.77; 1.13] [0.50; 0.98] [0.89; 1.11] [0.57; 1.64] [0.84; 1.03] [0.26; 0.95]	16.9% 10.3% 3.9% 29.8% 1.3% 36.5% 1.3%	20.5% 16.4% 8.5% 23.4% 4.1% 24.3% 2.9%
Fixed effect model Random effects model Prediction interval Heterogeneity: $l^2 = 59\%$ , $\tau$		<b>27852</b> 7, <i>p</i> = 0.	02	21297	0.5 1 2	0.97 0.95	[0.91; 1.03] [0.84; 1.06] [0.69; 1.30]	100.0%	100.0%
(B)									
Study		GLT2i Total	Events	PBO Total	DKA	OF	R 95%	Weig -CI (fix	ght Weight ed) (random)
CANVAS Program CREDENCE DAPA-HF DECLARE-TIMI-58 EMPA-REG OUTCOME EMPEROR-REDUCED VERTIS-CV DAPA-CKD	14 11 3 27 4 0 19 0	5790 2200 2368 8574 4687 1863 5493 2149	4 1 12 12 2	4344 2197 2368 8569 2333 1863 2745 2149		2.63 11.04 7.01 2.25 1.99 4.76 0.20	4 [1.42; 85. [0.36; 135. 5 [1.14; 4. 9 [0.22; 17. 6 [1.11; 20.	76] 2. 45] 48. 83] 5. 0. 45] 10.	1% 5.8% 0% 2.8% 8% 52.6% 4% 5.1% 0% 0.0% 8% 11.5%
Fixed effect model Random effects model Prediction interval Heterogeneity: $I^2 = 0\%$ , $\tau^2$		<b>33124</b>		26568		2.82		37]	0% 100.0%
(C)				C	0.01 0.1 1 10 10	00			
Study	S Events	GLT2i Total		PBO Total	Amputation	OR	95%-CI	Weight (fixed)	Weight (random)
CANVAS Program CREDENCE DAPA-HF DECLARE-TIMI-58 EMPA-REG OUTCOME EMPEROR-REDUCED VERTIS-CV DAPA-CKD	140 70 123 88 13 111 35	5790 2200 2368 8574 4687 1863 5493 2149	47 63 12 113 43 10 45 39	4344 2197 2368 8569 2333 1863 2745 2149		- 2.27 1.11 1.08 1.09 1.02 1.30 1.24 0.90	[1.62; 3.16] [0.79; 1.57] [0.49; 2.38] [0.84; 1.41] [0.71; 1.47] [0.57; 2.98] [0.87; 1.76] [0.57; 1.42]	13.1% 15.3% 3.0% 27.8% 14.1% 2.5% 14.7% 9.6%	15.2% 14.8% 6.1% 17.6% 14.2% 5.6% 14.7% 11.7%
Fixed effect model Random effects model Prediction interval Heterogeneity: $I^2 = 59\%$ , $\tau$		33124	02	26568	\$.	1.25 1.22	[1.09; 1.42] [0.97; 1.53] [0.63; 2.35]	100.0%	100.0%
(D)	- 0.0000	ν, μ = 0.			0.5 1 2				
Study	S Events	GLT2i Total	Events	PBO Total	Fracture	OR	95%-CI	Weight (fixed)	Weight (random)
CANVAS Program CREDENCE DAPA-HF DECLARE-TIMI-58 EMPA-REG OUTCOME EMPEROR-REDUCED VERTIS-CV DAPA-CKD	347 67 49 457 179 45 201 85	5790 2200 2368 8574 4687 1863 5493 2149	166 68 50 440 91 42 98 69	4344 2197 2368 8569 2333 1863 2745 2149		- 1.60 0.98 0.98 1.04 0.98 1.07 1.03 1.24	[1.33; 1.94] [0.70; 1.39] [0.66; 1.46] [0.91; 1.19] [0.76; 1.27] [0.70; 1.64] [0.80; 1.31] [0.90; 1.72]	16.8% 6.2% 4.6% 39.3% 11.0% 3.9% 11.9% 6.3%	16.6% 10.1% 8.4% 19.3% 13.4% 7.7% 13.9% 10.7%
Fixed effect model Random effects model Prediction interval Heterogeneity: $I^2 = 61\%$ , $\tau$		<b>33124</b> 3, <i>p</i> = 0.	.01	26568		1.13 1.12	[1.04; 1.23] [0.97; 1.29] [0.74; 1.69]	100.0%	100.0%
					0.75 1 1.5				

https://onlinelibrary.wiley.com/doi/epdf/10.1002/clc.23508

#### (A)

Outcomes		Number of				
outcomes	studies	Number of participants	,	Effect size	[95% CI]	Weight
HbA1c (%)	Studies	participanto		-11661 3120		weight
Canagliflozin	3	2314		-0.43	[-0.65; -0.21]	21.2%
Dapagliflozin	4	1135		-0.25	[-0.36; 0.14]	26.4%
Empagliflozin	3	2425		-0.29	[-0.43; -0.15]	26.0%
Ertugliflozin	1	467		-0.05	[-0.23; 0.13]	9.4%
Ipragliflozin	1	81		-0.17	[-0.45; 0.10]	6.7%
Luseogliflozin	1	145		-0.19	[-0.40; 0.00]	8.8%
Tofogliflozin	1	23	<u> </u>	-1.39	[-2.13; -0.65]	1.6%
Overall	14	6589	· •	-0.29	[-0.39; -0.19]	100.0%
Heterogenei	ty between s	subgroups: $I^2 = 6$	5% -1 -0.5 0.4	-		
Fasting plasma g			-1 -0.5 0.3		1 1 00 0 101	05.00/
Canagliflozin	2	905 343		-0.87	[-1.26; -0.49]	25.3%
Dapagliflozin				-0.89	[-1.44; -0.35]	12.9%
Empagliflozin	2	506		-1.06	[-1.90; -0.23]	21.5%
Ertugliflozin	1	301		0.18	[-0.57; 0.93]	9.0%
Ipragliflozin	1	81 145		-0.10	[-0.69; 0.49]	11.6%
Luseogliflozin	1			-0.43	[-0.83; 0.06]	14.9%
Sotagliflozin	10	29 2309		-1.12	[-2.28; 0.03]	5.0%
Overall Heterogenei		2309 subgroups: /2 = 5	~	-0.65	[-0.94; -0.36]	100.0%
Systolic blood pr			-21			
Canagliflozin	2	2307		-4.19	[-6.49; -1.89]	50.1%
Dapagliflozin	2	1067		-3.58	[-5.53; -1.62]	14.2%
Empagliflozin	3	2425		-5.07	[-7.30; -2.85]	28.1%
Ertugliflozin	1	301		-3.43	[-7.62; 0.75]	3.2%
Ipragliflozin	1	104	<	-4.33	[-9.57; 1.00]	2.0%
Luseogliflozin	1	145	<→	-2.60	[-8.00; 3.00]	1.9%
Sotagliflozin	1	30	<u> </u>	-11.40	[-22.60; -0.20]	0.5%
Overall	11	6378	$\diamond$	-4.03	[-4.79; -3.26]	100.0%
Heterogenei	ty between s	subgroups: $I^2 = 0$	%			
Diastolic blood p	ressure (mn	nHg)	-8 -6 -4 -2 2			
Canagliflozin	2	2307		-1.39	[-1.90; -0.89]	71.6%
Dapagliflozin	1	526		-2.00	[-3.40; -0.60]	9.4%
Empagliflozin	2	606		-2.37	[-3.45; -1.29]	15.8%
Ipragliflozin	1	81	<>	-0.20	[-4.71; 4.31]	0.9%
Ipragliflozin Luseogliflozin	1	81 145	· · · · · ·	-0.20	[-4.71; 4.31] [-3.00; 4.00]	0.9% 1.5%
Luseogliflozin Sotagliflozin Overall	1 1 8	145 30 <b>3695</b>		0.30	[-3.00; 4.00]	1.5%
Luseogliflozin Sotagliflozin Overall	1 1 8	145 30		0.30 -4.50 -1.59	[-3.00; 4.00] [-9.60; 0.50]	1.5% 0.7%
Luseogliflozin Sotagliflozin Overall Heterogenei	1 1 8 ty between s	145 30 <b>3695</b>		0.30 -4.50 -1.59	[-3.00; 4.00] [-9.60; 0.50] <b>[-2.02; -1.16]</b>	1.5% 0.7% <b>100.0%</b>
Luseogliflozin Sotagliflozin Overall Heterogenei	1 1 8 ty between s	145 30 <b>3695</b>		0.30 -4.50 -1.59 -1.31	[-3.00; 4.00] [-9.60; 0.50] <b>[-2.02; -1.16]</b> [-1.52; -1.09]	1.5% 0.7% <b>100.0%</b> 52.0%
Luseogliflozin Sotagliflozin Overall Heterogenei Body Weight (kg) Canagliflozin Dapagliflozin	1 1 ty between s 2 3	145 30 <b>3695</b> subgroups: /² = 1: 2306 1079		-0.30 -4.50 -1.59 -1.31 -1.50	[-3.00; 4.00] [-9.60; 0.50] [-2.02; -1.16] [-1.52; -1.09] [-2.02; -0.98]	1.5% 0.7% <b>100.0%</b> 52.0% 13.4%
Luseogliflozin Sotagliflozin Overall Heterogenei Body Weight (kg) Canagliflozin	1 1 8 ty between s	145 30 <b>3695</b> subgroups: /² = 1: 2306		- 0.30 -4.50 -1.59 -1.31 -1.50 -1.38	[-3.00; 4.00] [-9.60; 0.50] [-2.02; -1.16] [-2.02; -0.98] [-1.72; -1.04]	1.5% 0.7% <b>100.0%</b> 52.0% 13.4% 20.7%
Luseogliflozin Sotagliflozin Overall Heterogenei Body Weight (kg) Canagliflozin Dapagliflozin	1 1 ty between s 2 3	145 30 <b>3695</b> subgroups: /² = 1: 2306 1079		- 0.30 -4.50 -1.59 -1.31 -1.50 -1.38 -1.70	[-3.00; 4.00] [-9.60; 0.50] [-2.02; -1.16] [-1.52; -1.09] [-2.02; -0.98] [-1.72; -1.04] [-2.77; -0.63]	1.5% 0.7% <b>100.0%</b> 52.0% 13.4% 20.7% 2.1%
Luseogliflozin Sotagliflozin Overall Heterogenei Body Weight (kg) Canagliflozin Dapagliflozin Empagliflozin	1 8 ty between s 2 3 3	145 30 <b>3695</b> subgroups: /² = 1: 2306 1079 2425		-1.31 -1.50 -1.31 -1.50 -1.38 -1.70 -1.92	[-3.00; 4.00] [-9.60; 0.50] [-2.02; -1.16] [-2.02; -0.98] [-1.72; -1.04] [-2.77; -0.63] [-2.60; -1.26]	1.5% 0.7% <b>100.0%</b> 52.0% 13.4% 20.7% 2.1% 5.3%
Luseogliflozin Sotagliflozin Overall Heterogenei Body Weight (kg) Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	1 8 ty between s 2 3 3 1 1 1	145 30 <b>3695</b> subgroups: /² = 1: 2306 1079 2425 301		- 0.30 -4.50 -1.59 -1.31 -1.50 -1.38 -1.70 -1.92 -1.28	[-3.00; 4.00] [-9.60; 0.50] [-2.02; -1.16] [-2.02; -0.98] [-1.72; -1.04] [-2.77; -0.63] [-2.60; -1.26] [-1.90; -0.70]	1.5% 0.7% <b>100.0%</b> 52.0% 13.4% 20.7% 2.1% 5.3% 6.6%
Luseogliflozin Sotagliflozin Overall Heterogenei Body Weight (kg) Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin Ipragliflozin Luseogliflozin Overall	1 8 8 2 3 3 1 1 1 1 1	145 30 <b>3695</b> Jubgroups: /² = 1: 2306 1079 2425 301 81 145 <b>6336</b>		-1.31 -1.50 -1.31 -1.50 -1.38 -1.70 -1.92	[-3.00; 4.00] [-9.60; 0.50] [-2.02; -1.16] [-2.02; -0.98] [-1.72; -1.04] [-2.77; -0.63] [-2.60; -1.26]	1.5% 0.7% <b>100.0%</b> 52.0% 13.4% 20.7% 2.1% 5.3%
Luseogliflozin Sotagliflozin Overall Heterogenei Body Weight (kg) Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin Ipragliflozin Luseogliflozin Overall	1 8 8 2 3 3 1 1 1 1 1	145 30 <b>3695</b> :ubgroups: /² = 1: 2306 1079 2425 301 81 145		- 0.30 -4.50 -1.59 -1.31 -1.50 -1.38 -1.70 -1.92 -1.28	[-3.00; 4.00] [-9.60; 0.50] [-2.02; -1.16] [-2.02; -0.98] [-1.72; -1.04] [-2.77; -0.63] [-2.60; -1.26] [-1.90; -0.70]	1.5% 0.7% <b>100.0%</b> 52.0% 13.4% 20.7% 2.1% 5.3% 6.6%
Luseogliflozin Sotagliflozin Overall Heterogenei Sody Weight (kg) Canagliflozin Dapagliflozin Ertugliflozin Ipragliflozin Luseogliflozin Verall Heterogenei Serum potassium	1 8 8 2 3 3 1 1 1 1 1 1 1 1 1 1 1 1 1	145 30 3695 2306 1079 2425 301 81 145 6336 ubgroups: /² = 0		-1.31 -1.59 -1.59 -1.50 -1.38 -1.70 -1.92 -1.28 -1.28 -1.42	[-3.00; 4.00] [-9.60; 0.50] [-2.02; -1.16] [-1.52; -1.09] [-1.72; -1.04] [-1.72; -1.04] [-2.77; -0.63] [-1.90; -0.70] [-1.57; -1.26]	1.5% 0.7% 100.0% 52.0% 13.4% 20.7% 2.7% 5.3% 6.6% 100.0%
Luseogliflozin Sotagliflozin Overall Heterogenei Body Weight (kg) Canagliflozin Dapagliflozin Ertugliflozin Ipragliflozin Ipragliflozin Useogliflozin Heterogenei	1 8 8 2 3 3 1 1 1 1 1 1 1 1 1 1 1 1 1	145 30 3695 subgroups: /² = 1: 2306 1079 2425 301 81 145 6336 subgroups: /² = 0 2003		- 0.30 -4.50 -1.59 -1.59 -1.31 -1.50 -1.38 -1.70 -1.38 -1.70 -1.28 -1.42	[-3.00; 4.00] [-9.60; 0.50] [-2.02; -1.6] [-1.52; -1.09] [-2.02; -0.80] [-1.72; -1.04] [-2.77; -0.63] [-2.60; -1.26] [-1.90; -0.70] [-1.57; -1.26]	1.5% 0.7% 100.0% 52.0% 13.4% 20.7% 2.1% 5.3% 6.6% 100.0%
Luseogliflozin Sotagliflozin Overall Heterogenei Sody Weight (kg) Canagliflozin Dapagliflozin Ertugliflozin Ipragliflozin Luseogliflozin Verall Heterogenei Serum potassium	1 8 8 2 3 3 1 1 1 1 1 1 5 0 (mEq/L) 1 1	145 30 3695 2306 1079 2425 301 81 145 6336 subgroups: /² = 0 2003 220		0.30 -4.50 -1.59 -1.59 -1.31 -1.50 -1.38 -1.70 -1.38 -1.70 -1.28 -1.28 -1.42	[-3.00; 4.00] [-9.60; 0.50] [-2.02; -1.16] [-1.52; -1.09] [-1.72; -1.04] [-1.72; -1.04] [-2.77; -0.63] [-1.90; -0.70] [-1.57; -1.26]	1.5% 0.7% 100.0% 52.0% 13.4% 20.7% 2.1% 5.3% 6.6% 100.0% 63.6% 1.9%
Luseogliflozin Sotagliflozin Overall Heterogenei Body Weight (kg) Canagliflozin Dapagliflozin Ertugliflozin Ipragliflozin Luseogliflozin Overall Heterogenei Serum potassium Canagliflozin	1 8 8 9 2 3 1 1 1 1 1 1 1 1 1 1 1 1 1 3	145 30 3695 2306 1079 2425 301 81 145 6336 12 = 0 2003 220 2245		- 0.30 -4.50 -1.59 -1.59 -1.31 -1.50 -1.38 -1.70 -1.92 -1.28 -1.42 0.01 -0.04 -0.01	[-3.00; 4.00] [-9.60; 0.50] [-2.02; -1.16] [-1.52; -1.04] [-2.02; -0.98] [-1.72; -1.04] [-2.77; -0.63] [-2.60; -1.26] [-1.90; -0.70] [-1.57; -1.26] [-0.02; 0.03] [-0.19; 0.12] [-0.04; 0.03]	1.5% 0.7% 100.0% 52.0% 13.4% 20.7% 2.1% 5.3% 6.6% 100.0% 63.6% 1.9% 32.8%
Luseogliflozin Sotagliflozin Overall Heterogenei Bady Weight (kg) Canagliflozin Dapagliflozin Ertugliflozin Ipragliflozin Verall Heterogenei Serum potassium Canagliflozin Dapagliflozin Empagliflozin Ipragliflozin	1 8 8 2 3 3 1 1 1 1 1 1 0 (mEq/L) 1 1 3 1	145 30 3695 2306 1079 2425 301 81 145 6336 subgroups: /² = 0 2003 220		0.30 -4.50 -1.59 -1.59 -1.59 -1.31 -1.50 -1.38 -1.70 -1.92 -1.28 -1.42 0.01 -0.04 -0.01 -0.04	[-3.00; 4.00] [-9.60; 0.50] [-2.02; -1.16] [-1.52; -1.09] [-2.02; -0.80] [-1.72; -1.04] [-2.77; -0.63] [-2.60; -1.26] [-1.90; -0.70] [-1.57; -1.26] [-0.02; 0.03] [-0.19; 0.12] [-0.04; 0.03] [-0.20; 0.12]	1.5% 0.7% 100.0% 52.0% 13.4% 20.7% 2.1% 5.3% 6.6% 100.0% 63.6% 1.9% 32.8% 1.7%
Luseogliflozin Sotagliflozin Overall Heterogenei Body Weight (Kg) Canagliflozin Dapagliflozin Ertugliflozin Ipragliflozin Useogliflozin Overall Meterogenei Serum potassium Canagliflozin Empagliflozin Ipragliflozin Dapagliflozin Overall	1 8 8 2 3 1 1 1 1 1 1 1 1 1 1 1 1 3 1 3 6	145 30 3695 2306 1079 2425 301 81 145 6336 ubgroups: /² = 0 2003 220 2245 81 4549		- 0.30 -4.50 -1.59 -1.59 -1.31 -1.50 -1.38 -1.70 -1.92 -1.28 -1.42 0.01 -0.04 -0.01	[-3.00; 4.00] [-9.60; 0.50] [-2.02; -1.16] [-1.52; -1.04] [-2.02; -0.98] [-1.72; -1.04] [-2.77; -0.63] [-2.60; -1.26] [-1.90; -0.70] [-1.57; -1.26] [-0.02; 0.03] [-0.19; 0.12] [-0.04; 0.03]	1.5% 0.7% 100.0% 52.0% 13.4% 20.7% 2.1% 5.3% 6.6% 100.0% 63.6% 1.9% 32.8%
Luseogliflozin Sotagliflozin Overall Heterogenei Body Weight (Kg) Canagliflozin Dapagliflozin Ertugliflozin Ipragliflozin Useogliflozin Overall Meterogenei Serum potassium Canagliflozin Empagliflozin Ipragliflozin Dapagliflozin Overall	1 8 8 2 3 1 1 1 1 1 1 1 1 1 1 1 3 1 3 6	145 30 3695 2306 1079 2425 301 81 145 6336 2003 220 2245 81		0.30 -4.50 -1.59 -1.59 -1.59 -1.31 -1.50 -1.38 -1.70 -1.92 -1.28 -1.42 0.01 -0.04 -0.01 -0.04	[-3.00; 4.00] [-9.60; 0.50] [-2.02; -1.16] [-1.52; -1.09] [-2.02; -0.80] [-1.72; -1.04] [-2.77; -0.63] [-2.60; -1.26] [-1.90; -0.70] [-1.57; -1.26] [-0.02; 0.03] [-0.19; 0.12] [-0.04; 0.03] [-0.20; 0.12]	1.5% 0.7% 100.0% 52.0% 13.4% 20.7% 2.1% 5.3% 6.6% 100.0% 63.6% 1.9% 32.8% 1.7%
Luseogliflozin Sotagliflozin Overali Heterogenei Body Weight (kg) Canagliflozin Dapagliflozin Erugaliflozin Ipragliflozin Uverali Heterogenei Serum potassium Canagliflozin Dapagliflozin Ipragliflozin Ipragliflozin Ipragliflozin Bargaliflozin Ipragliflozin Ipragliflozin Ipragliflozin Ipragliflozin Ipragliflozin Ipragliflozin Overali	1 8 8 2 3 1 1 1 1 1 1 1 1 1 1 1 3 1 3 6	145 30 3695 2306 1079 2425 301 81 145 6336 ubgroups: /² = 0 2003 220 2245 81 4549		0.30 -4.50 -1.59 -1.59 -1.59 -1.31 -1.50 -1.38 -1.70 -1.92 -1.28 -1.42 0.01 -0.04 -0.01 -0.04	[-3.00; 4.00] [-9.60; 0.50] [-2.02; -1.16] [-1.52; -1.09] [-2.02; -0.80] [-1.72; -1.04] [-2.77; -0.63] [-2.60; -1.26] [-1.90; -0.70] [-1.57; -1.26] [-0.02; 0.03] [-0.19; 0.12] [-0.04; 0.03] [-0.20; 0.12]	1.5% 0.7% 100.0% 52.0% 13.4% 20.7% 2.1% 5.3% 6.6% 100.0% 63.6% 1.9% 32.8% 1.7%
Luseogliflozin Sotagliflozin Overall Heterogenei Body Weight (kg) Canagliflozin Empagliflozin Ertugliflozin Ipragliflozin Overall Heterogenei Canagliflozin Dapagliflozin Dapagliflozin Dreasliflozin Overall Heterogenei Albuminuria (%)	1 8 2 3 3 1 1 1 1 1 1 1 1 5 (mEq/L) 1 3 1 6 5 ty between s	145 30 3695 2306 1079 2425 301 81 45 6336 2003 220 2203 220 2245 81 4549 4549 4549 4549 1 <sup>2</sup> = 0		- 0.30 -4.50 -1.59 -1.59 -1.31 -1.50 -1.38 -1.70 -1.92 -1.92 -1.92 -1.42 0.01 -0.04 -0.01 -0.04 0.00	[-3.00; 4.00] [-9.60; 0.50] [-2.02; -1.6] [-1.52; -1.09] [-2.02; -0.8] [-1.72; -1.04] [-2.77; -0.63] [-2.60; -1.26] [-1.90; -0.70] [-1.57; -1.26] [-0.02; 0.03] [-0.19; 0.12] [-0.04; 0.03] [-0.02; 0.02] [-0.02; 0.02]	1.5% 0.7% 100.0% 52.0% 13.4% 20.7% 2.1% 5.3% 6.6% 100.0% 63.6% 1.9% 32.8% 1.7% 100.0%
Luseogliflozin Sotagliflozin Overall Heterogenei Body Weight (kg) Canagliflozin Dapagliflozin Ertugliflozin Luseogliflozin Luseogliflozin Noverall Heterogenei Serum potassium Canagliflozin Dapagliflozin Dapagliflozin Dapagliflozin Overall Heterogenei Albuminuria (%) Canagliflozin	1 8 1 2 3 3 1 1 1 1 1 1 1 1 1 1 5 6 5 1 1	145 30 3695 2306 1079 2425 301 81 145 6336 cubgroups: /² = 0 2003 220 2245 81 4549 12 = 0 2003 220 2245 81 4549 12 = 0 2039		- 0.30 -4.50 -1.59 -1.59 -1.31 -1.50 -1.38 -1.70 -1.38 -1.42 -0.01 -0.04 -0.01 -0.04 0.00 -23.00	[-3.00; 4.00] [-3.00; 4.00] [-2.02; -1.16] [-2.02; -0.16] [-1.72; -1.04] [-2.77; -0.63] [-2.60; -1.26] [-1.90; -0.70] [-1.57; -1.26] [-0.02; 0.03] [-0.49; 0.12] [-0.04; 0.03] [-0.20; 0.12] [-0.02; 0.02]	1.5% 0.7% 100.0% 52.0% 13.4% 20.7% 2.1% 5.3% 6.6% 100.0% 63.6% 1.9% 32.8% 1.7% 100.0%
Luseogliflozin Sotagliflozin Overall Heterogenei Body Weight (kg) Canagliflozin Dapagliflozin Ertugliflozin Ipragliflozin Overall Heterogenei Serum potassium Canagliflozin Dapagliflozin Dreagliflozin Overall Heterogenei Albuminuria (%)	1 8 2 3 3 1 1 1 1 1 1 1 1 5 (mEq/L) 1 3 1 6 5 ty between s	145 30 3695 2306 1079 2425 301 81 45 6336 2003 220 2203 220 2245 81 4549 4549 4549 4549 1 <sup>2</sup> = 0		- 0.30 -4.50 -1.59 -1.59 -1.31 -1.50 -1.38 -1.70 -1.92 -1.92 -1.92 -1.42 0.01 -0.04 -0.01 -0.04 0.00	[-3.00; 4.00] [-9.60; 0.50] [-2.02; -1.6] [-1.52; -1.09] [-2.02; -0.8] [-1.72; -1.04] [-2.77; -0.63] [-2.60; -1.26] [-1.90; -0.70] [-1.57; -1.26] [-0.02; 0.03] [-0.19; 0.12] [-0.04; 0.03] [-0.02; 0.02] [-0.02; 0.02]	1.5% 0.7% 100.0% 52.0% 13.4% 20.7% 2.1% 5.3% 6.6% 100.0% 63.6% 1.9% 32.8% 1.7% 100.0%

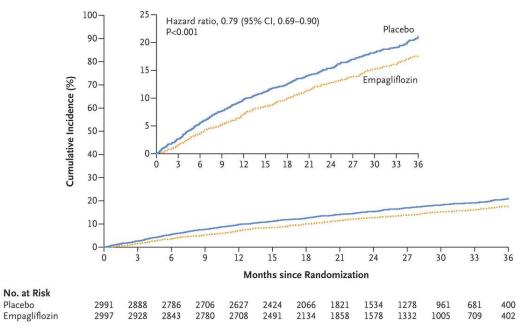
Favours SGLT2 inhibitors Favours placebo

# Effects of SGLT2i on biomarkers and clinical variables (metaanalysis)

DOI: 10.1111/dom.13648

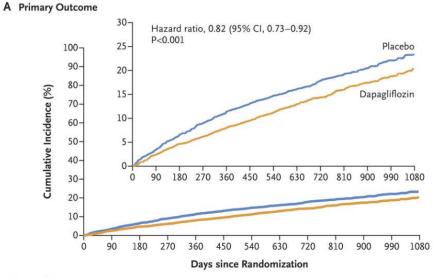
## SGLT2i DELIVER in HFpEF and become the EMPEROR of this Final Frontier

#### EMPEROR-PRESERVED



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

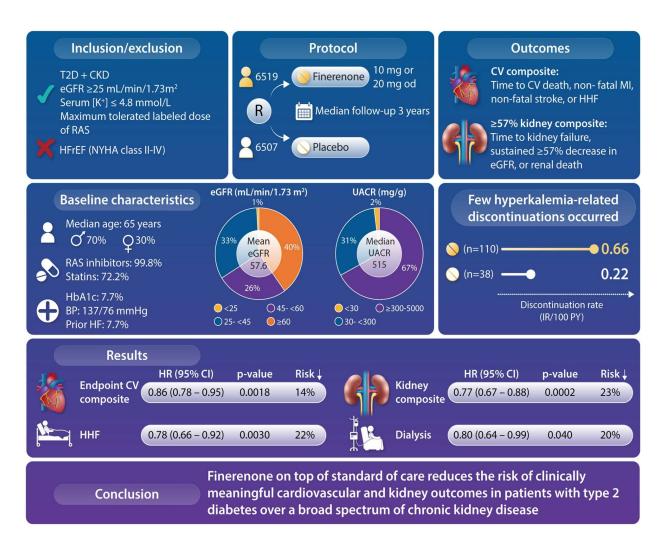
   -4.98 mmHg, 95% CI -8.22 to -1.75,
   I2 = 87%

	Aldoste	rone anta	gonist	10	Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	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: Tau <sup>2</sup> = 0	).00; Chi <sup>2</sup> = 2.1	10, $df = 6$	(P = 0.91);	$I^2 = 0\%$					•
Test for overall effect: 2	Z = 4.81 (P < 0)	0.000 <mark>01</mark> )							
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]	1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-
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: Tau <sup>2</sup> = 0	).93; Chi² = 54	.80, df = 4	4 (P < 0.00	001); I <sup>2</sup> = 93	3%				
Test for overall effect: 2	Z = 1.50 (P = 0)	).13 <mark>)</mark>							
1.9.3 Diabetes not repo	orted								
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: $Tau^2 = 0$	).00; Chi <sup>2</sup> = 0.2	21, df = 1	(P = 0.65);	$I^2 = 0\%$					
Test for overall effect: 2	Z = 1.91 (P = 0)	0.06)							
Total (95% CI)			693			500	100.0%	-0.51 [-0.82 , -0.20]	•
Heterogeneity: Tau <sup>2</sup> = 0	).27; Chi <sup>2</sup> = 71	.88, df = 1	13 (P < 0.0	0001); I <sup>2</sup> = 1	82%				· · · · · · · · · · · · · · · · · · ·
Test for overall effect: 2									-4 -2 0 2
	The second second		20022 - V 2020	01012200 000000	22.5			290 mound	

Test for subgroup differences: Chi<sup>2</sup> = 2.28, df = 2 (P = 0.32), I<sup>2</sup> = 12.3%

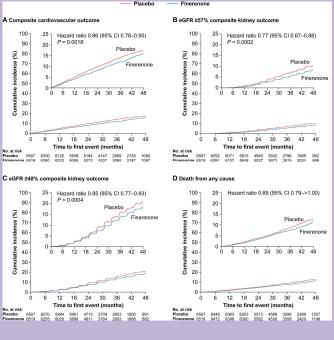
Lower with aldosterone Lower with control

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

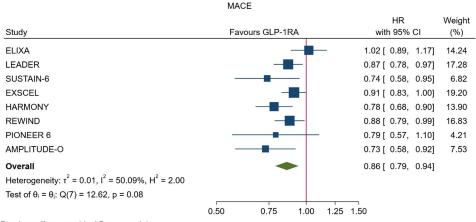


https://doi.org/10.1093/eurheartj/ehab777

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



## GLP1 RA improve Cardiovascular Outcomes in patients with DM2



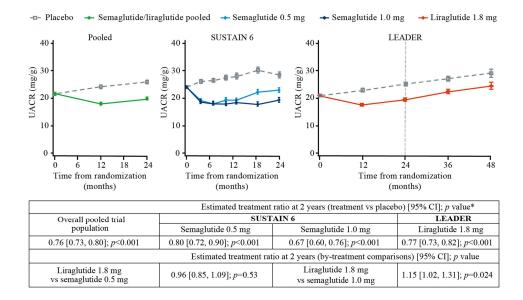
Outcome	Trials (n)	Estimate (HR)	95% CI	P value of HR	l <sup>2</sup> (%)	P value of I <sup>2</sup>
MACE						
All	8	0.86	0.79–0.94	0.006	50.0	0.080
Prior CVD	6	0.84	0.79–0.90	< 0.001	6.1	0.370
No prior CVD	6	0.94	0.83-1.06	0.330	0.0	0.420
CV mortality	8	0.87	0.78-0.96	0.016	18.7	0.330
Non-fatal MI	8	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

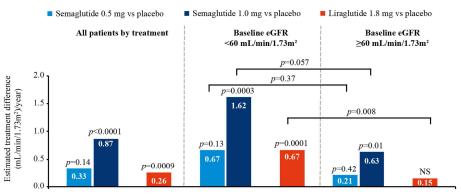
Random-effects empirical Bayes model Knapp-Hartung standard errors

25

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

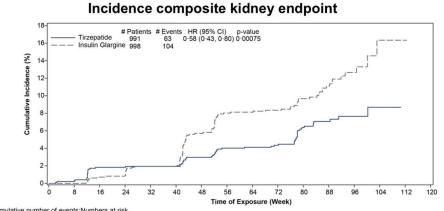




Annual eGFR		E	stimate [95% CI]				
change		SUSTAIN 6		LEADER			
(mL/min/ 1.73m²)/year	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo	Liraglutide 1.8 mg	Placebo		
All patients	n=825	n=821	n=1648	n=4512	n=4498		
by treatment	-1.59 [-1.95, -1.23]	-1.05 [-1.41, -0.69]	-1.92 [-2.18, -1.67]	-1.72 [-1.84, -1.61]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



 Cumulative number of events:Numbers at risk
 Tirzepatide
 0:991
 3:985
 18:962
 19:947
 19:944
 29:930
 39:912
 40:902
 42:815
 56:609
 60:391
 62:180
 63:41
 63:0
 63:0

 nsulin Glargine
 0:998
 7:973
 9:966
 19:940
 55:901
 77:867
 78:849
 80:755
 89:555
 96:369
 101:164
 104:0

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

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

Data are from the mTT population (efficacy analysis set), including on treatment data prior to the use of rescue therapy. Cox proportional-hazards model was used to estimate the IR and 95% CT for pooled TZP compared with iolar for the endpoints. HR estimate with CI is not calculated when either the TZP or iolar am has no event. \*eGFR decline ≥40% from baseline, renal death, and progression to ESRD, \*eGFR =60 CKD-EPI mL/min per 1.73 m<sup>3</sup>. #GFR <75 CKD-EPI mL/min per 1.73 m<sup>3</sup>. #GFR <75 CKD-EPI mL/min per 1.73 m<sup>3</sup>. Interval to the set provide the set provide the set of the endpoints. HR estimates with CI is not calculated when either the TZP or iolar am has no event. \*eGFR decline ≥40% from baseline, renal death, and progression to ESRD. \*eGFR <60 CKD-EPI mL/min per 1.73 m<sup>3</sup>. #GFR <75 CKD-EPI mL/min per 1.73 m<sup>3</sup>. IZP 5 mg, 10 mg, and 15 mg arms pooled for analysis.\*P<.05 versus IGAr. CT=confidence interval; CKD-EPI mL/min per 1.73 m<sup>3</sup>. IZP 5 mg, 20 mg, and 15 mg arms pooled for analysis.\*P<.05 versus IGAr. CT=confidence interval; CKD-EPI mL/min per 1.73 m<sup>3</sup>. IZP 5 mg, 20 mg, and 15 mg arms pooled for analysis.\*P<.05 versus IGAr. CT=confidence interval; CKD-EPI mL/min ret.178 m<sup>3</sup>. TZP 5 mg, 20 mg, and 15 mg arms pooled for analysis.\*P<.05 versus IGAr. CT=confidence interval; CKD-EPI mL/min ret.178 m<sup>3</sup>. TZP 5 mg, 20 mg, and 15 mg arms pooled for analysis.\*P<.05 versus IGAr. CT=confidence interval; CKD-EPI mL/min ret.178 m<sup>3</sup>. TZP 5 mg, 20 mg, and 15 mg arms pooled for analysis.\*P<.05 versus IGAr. CT=confidence interval; CKD-EPI mL/min ret.178 m<sup>3</sup>. TZP 5 mg, 20 mg, 20

## 27

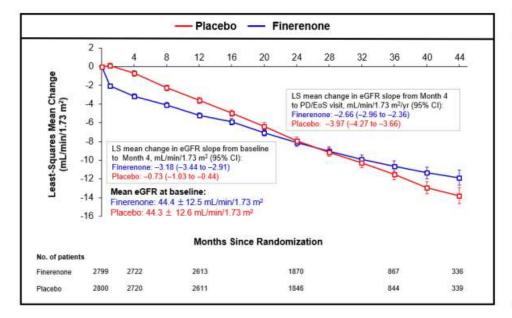
#### https://doi.org/10.2337/db22-17-OR

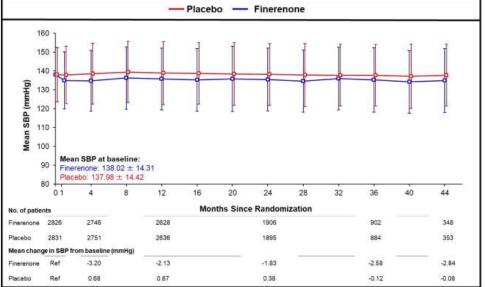
# If you are only going to retain one slide...

- 1. Patients may be selected for further therapies based on UACR
- 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
- Associate the letter "G" with the GLP1 (/GIP1) rather than Glipizide
- We still don't know if we have to aim for the trifecta: SGLT2i/MRA/GLP1(/GIP1) on our patients

# Backup

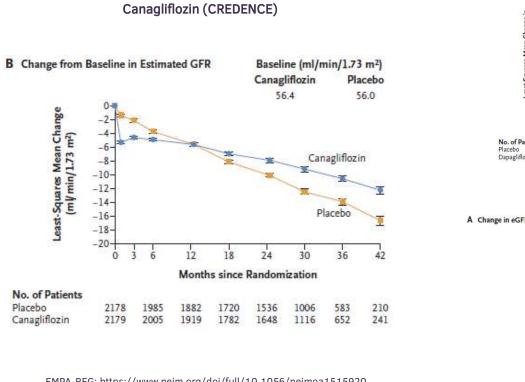
# Effects of Finerenone reduced loss of eGFR and had modest effects on BP



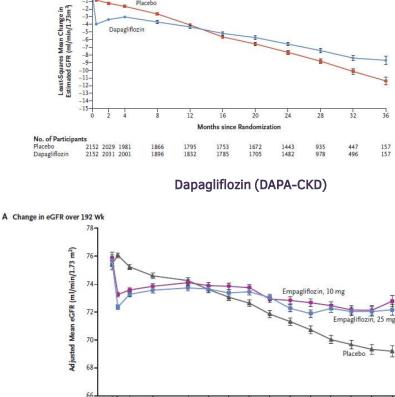


Change in SBP < 3 mmHg throughout FIDELIO-CKD

Empagliflozin (EMPA-REG)



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



Baseline 4 12

28

52 66 80 94 Week 108 122 136 150 164 178 192

31

## Biphasic eGFR changes upon initiation of SGLT2i

# Nonselective MRA is associated with hyperkalemia and gynecomastia

#### Hyperkalemia

	Aldosterone a	ntagonist	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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: Tau <sup>2</sup> = 0.00; C	hi <sup>2</sup> = 5.24, df = 9	(P = 0.81); I <sup>2</sup>	= 0%				
Test for overall effect: Z = 2.7	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: Tau <sup>2</sup> = 0.00; C	hi <sup>2</sup> = 0.69, df = 4	(P = 0.95); I <sup>2</sup>	= 0%				
Test for overall effect: Z = 2.5	8 (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 = 1.7	6 (P = 0.08)						
Total (95% CI)		2046		955	100.0%	2.17 [1.47 , 3.22]	•
Total events:	102		24				•
Heterogeneity: Tau <sup>2</sup> = 0.00; C	hi <sup>2</sup> = 8.60, df = 1	5 (P = 0.90); I				0.0	05 0.1 1 10 200
Test for overall effect: Z = 3.8							ith aldosterone Less with contro
Test for subgroup differences:	Chi <sup>2</sup> = 2.39, df =	2 (P = 0.30).	$I^2 = 16.3\%$				

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#### Gynecomastia

	Aldosterone a	ntagonist	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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 appli	icable						
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: Tau <sup>2</sup> = 0.	00; Chi <sup>2</sup> = 0.50, df	= 2 (P = 0.78	B); I <sup>2</sup> = 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: Tau <sup>2</sup> = 0.	00; Ch1 <sup>2</sup> = 0.66, df	= 3 (P = 0.8	8); I <sup>2</sup> = 0%			0.0	02 0.1 1 10 500
Test for overall effect: Z	= 2.12 (P = 0.03)					Less w	ith aldosterone Less with contro
Test for subgroup differe	ences: Chi <sup>2</sup> = 0.14,	df = 1 (P = 0)	.70), 12 = 04	%			

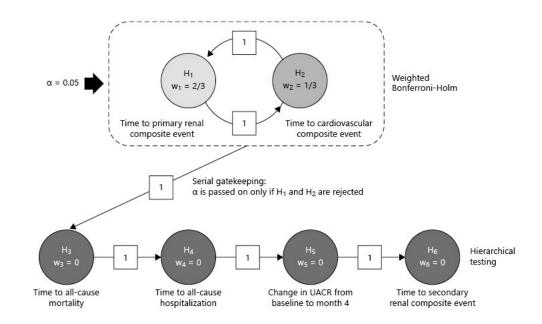
#### Numbers Needed To Harm

Hyperkalemia	Gynecomastia
41	14.1

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

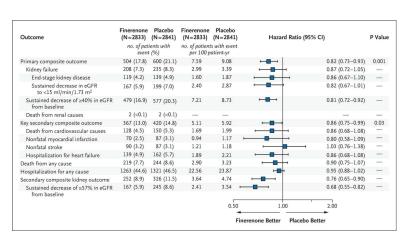
## FIDELIO CKD: Inclusion, exclusion, & statistical analysis

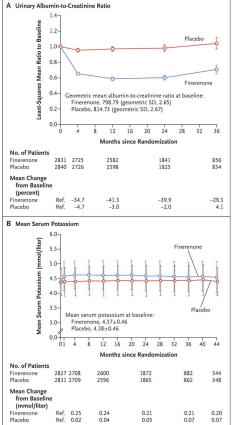
- Pts with T2D and CKD :
  - UACR > 300 mg/g & eGFR in 25-75 ml/min/1.73m2
  - UACR in 30-300 mg/g & eGFR in 25-60 ml/min/1.73m2
- Serum potassium level ≤ 4.8 meq/l
- Prior treatment with ACEi or ARB
- Excluded pts currently receiving eplerenone/spironolactone/renin inhibitor/K-sparing diuretic
- Excluded 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





Event	Finerenone	Placebo
	(N=2827)	(N=2831)
	no. of p	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		- ( )
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 ei	ther 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

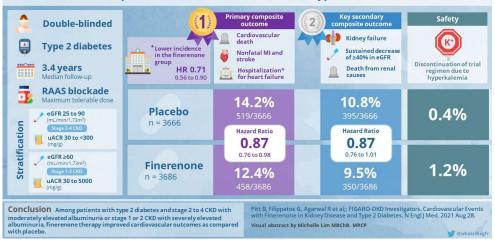
## Cardiovascular Outcomes of Finerenone in less severe Diabetic Kidney Disease: the FIGARO-DKD trial

- 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  $\leq$  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

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#### **FIGARO-DKD**

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



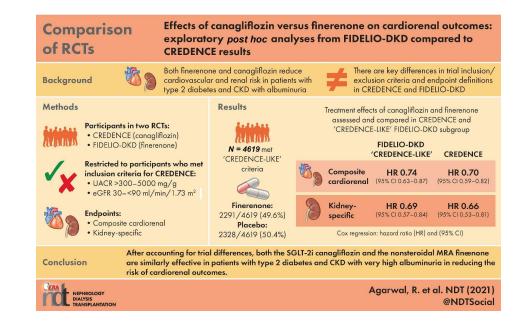
- SAE: 31.4% (Finerenone) vs 33.2% (placebo)
- Incidence of hyperkalemia was higher with finerenone than with placebo (10.8% vs. 5.3%)

## MRA v.s. SGLT2i in the management of CKD

#### ARE MRAS LESS POTENT?

- Eye-balling HRs
- Network meta-analysis (statistical eyeballing) SGLT2i vs MRA:
  - 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 ?



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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...

Cardio-renal effects of mono and combination therapy with Finerenone and Empagliflozin in preclinical model of Hypertension induced end organ damage

AJN American Journal of Nephrology

Intervent	Nerris States and States	meters	Change in Proteinuria	Blood Pressure (mm Hg)	Cardiac & Renal Histology
	Placebo	53%	100%	202 ±6.8	$\bigcap$
	Finerenone 1mg	85%	-27%	170 ±9.0	Dose dependent Improvement in
Hypertensive, proteinuric, NAME treated, renin-transgenic (mRen2)27 rats.	Finerenone 3mg	86%	-87%	<b>164</b> ±4.7	cardiac & renal histopathology parameters with
	Empagliflozin 3mg	71%	-38%	<b>199</b> ±10.4	maximum benefit with low dose
	Empagliflozin 10mg	62%	-64%	<b>188</b> ±8.7	combination
Fineren	one 1mg + Empagliflozin 3mg	93%	-86%	173 ±7.7	

Kolkhof P, Hartmann E, Freyberger A, Pavkovic M, Mathar I, Sandner P, Droebner K, Joseph A, Huser J, Eitner F: Effects of Finerenone Combined with Empagliflozin in a Model of Hypertension-Induced End-Organ Damage. Am J Nephrol DOI: 10.1159/000516213 Visual Abstract by Aakash Shingada@aakashshingada 🏻 🧺

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)



Information provided by (Responsible Party):

Sponsor: Bayer

Bayer

ClinicalTrials.gov Identifier: NCT05254002

Recruitment Status () : Not yet recruiting First Posted 1: February 24, 2022 Last Update Posted () : April 8, 2022

See Contacts and Locations

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

#### SGLT2I IN THE FIDELIO-DKD TRIAL

Events/100 patient-; iKD, or kidney or C 6.9 8.8 4.5 7.4		0.76 (0.40, 1.47)	0.59	(95% CI)	
6.9 8.8 4.5 7.4		0.76 (0.40, 1.47)	0.50		
4.5 7.4		0.76 (0.40, 1.47)	0.50		
	H++ :		0.59	-2.8 (-12.3, 6.7)	0.59
		0.60 (0.50, 0.72)		-5.5 (-7.4, -3.5)	
3.0 5.1		0.61 (0.24, 1.57)	0.96	-3.6 (-10.6, 3.5)	0.75
3.3 5.9	H++	0.56 (0.45, 0.69)		-4.8 (-6.5, -3.0)	
				13 I. D. 13	
2.2 4.6	+	0.46 (0.16, 1.35)	0.65	-4.6 (-11.1, 1.9)	0.89
2.6 4.8	H +	0.54 (0.43, 0.68)		-4.1 (-5.7, -2.5)	
1.7 4.1		0.48 (0.15, 1.58)	0.36	-4.7 (-10.7, 1.4)	0.46
2.6 3.8	H+++	0.66 (0.51, 0.85)		-2.3 (-3.8, -0.8)	
ith					
6.3 6.9	, <b></b> ,	0.88 (0.43, 1.77)	0.45	-0.40 (-9.4, 8.6)	0.76
1.9 2.8	H+++	0.69 (0.52, 0.91)		-1.8 (-3.1, -0.4)	
4.6 5.0		0.86 (0.38, 1.95)	0.46	-0.7 (-8.7, 7.2)	0.73
2.0 3.0	Here i	0.67 (0.51, 0.87)		-2.1 (-3.5, -0.7)	
	0.1 0.2 0.5 1 2.0	5.0			
	2.0 3.0	2.0 3.0	2.0 3.0 0.67 (0.51, 0.87) 0.1 0.2 0.5 1 2.0 5.0	2.0 3.0 0.67 (0.51, 0.87) 0.1 0.2 0.5 1 2.0 5.0	2.0 3.0 0.67 (0.51, 0.87) -2.1 (-3.5, -0.7) 0.1 0.2 0.5 1 2.0 5.0

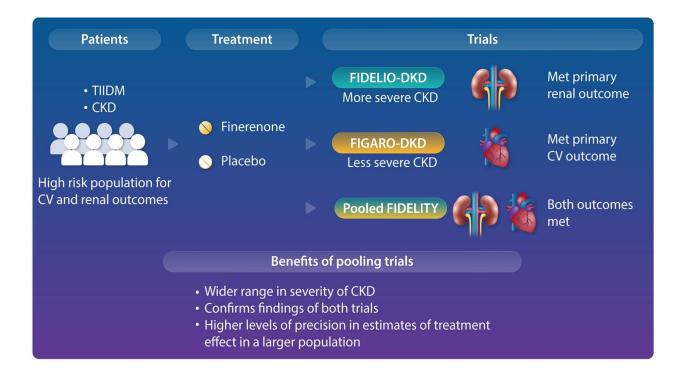
	Finerenone ( <i>n</i> = 2833)		Placebo (n = 2841)						
Outcome	n/N of patients with events (%)	No. of patients with event per 100 patient-years	n/N of patients with events (%)	No. of patients with event per 100 patient-years	-	На	zard rati	o (95% CI)	P value
Primary composite kidney outcome									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 outco	me								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	۲			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)	
				0.0625	0.250	1.00	4.00		
	← → → Favors finerenone Favors placebo							cebo	

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



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

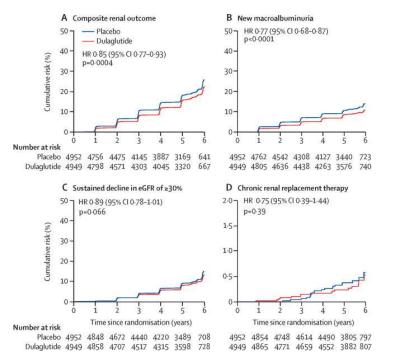
Potential strategies to manage the hyperkalemia risk by any RAASi are:

- 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

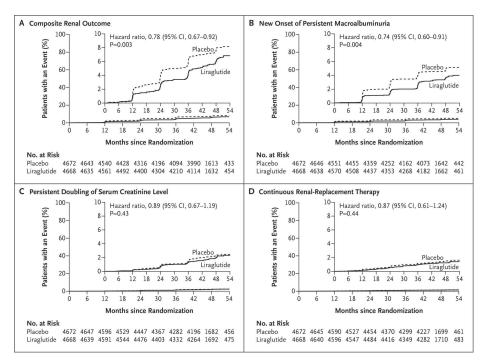
#### Duaglutide



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

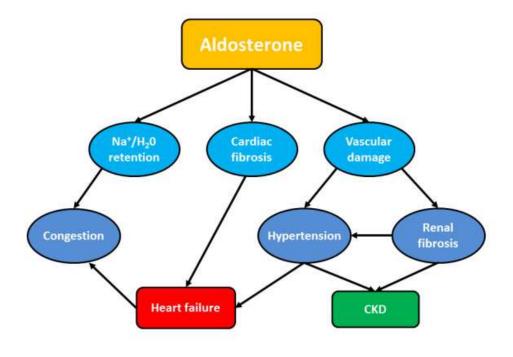
#### Liraglutide

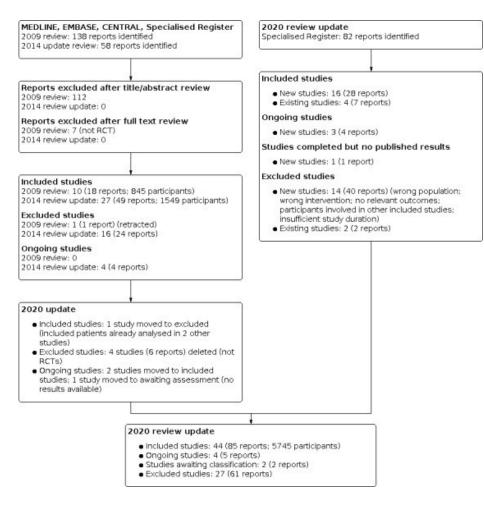


#### Semaglutide:

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)

# Are MRAs our next weapon in managing cardiorenal risk?





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