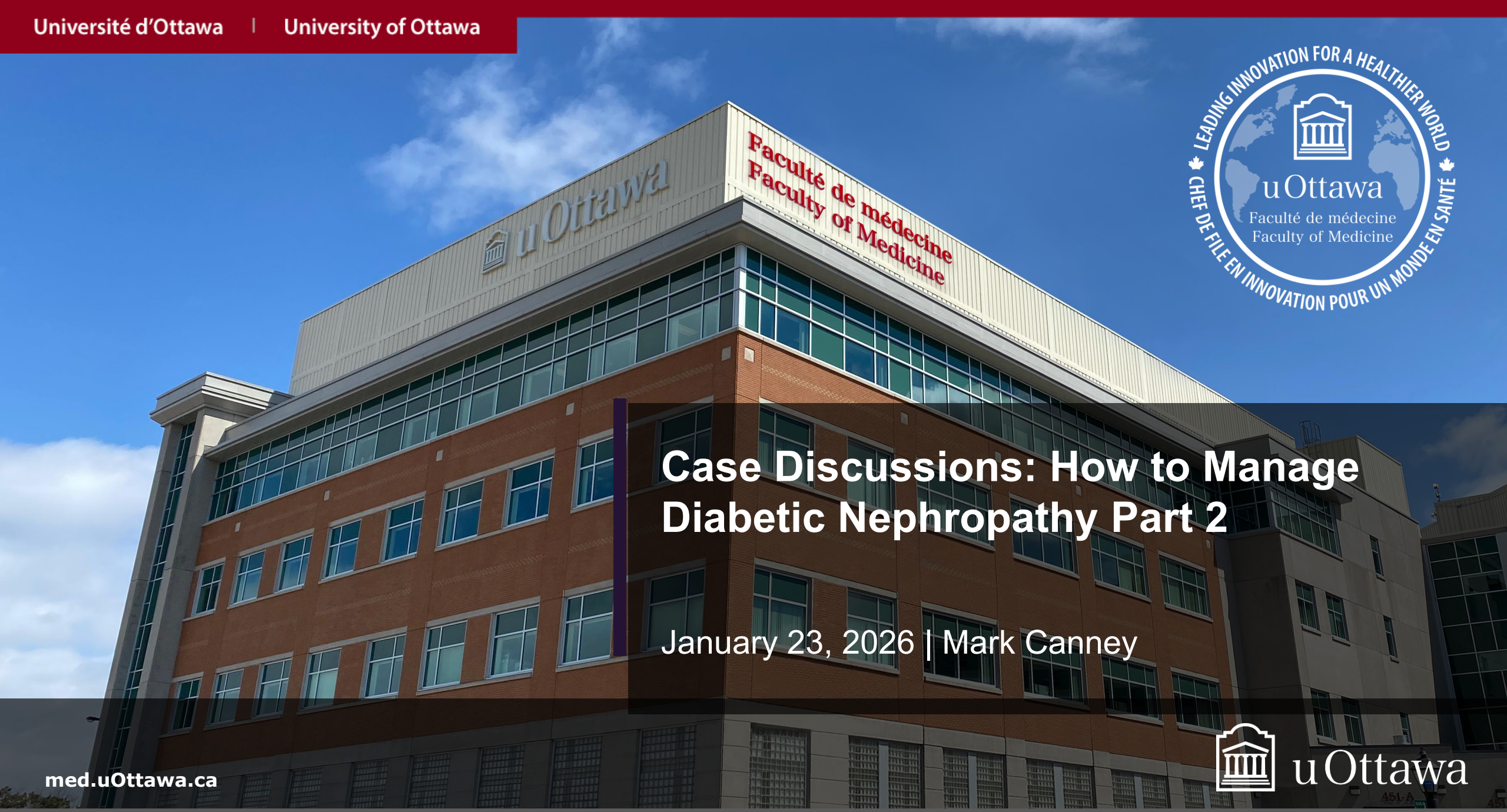

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Case Discussions: How to Manage Diabetic Nephropathy Part 2

January 23, 2026 | Mark Canney

uOttawa

PRESENTER DISCLOSURE

- **Presenter:** Mark Canney

- **Relationships with commercial interests:**
  - **Grants/Research Support:** None
  - **Speakers Bureau/Honoraria:** None
  - **Consulting Fees:** None
  - **Other:** n/a

- I will discuss off-label use of medications

LEARNING OBJECTIVES

1) **Review therapeutic options beyond RAAS inhibition**

2) **Evaluate clinical trial evidence for different approaches**

3) **Discuss future therapeutic options**

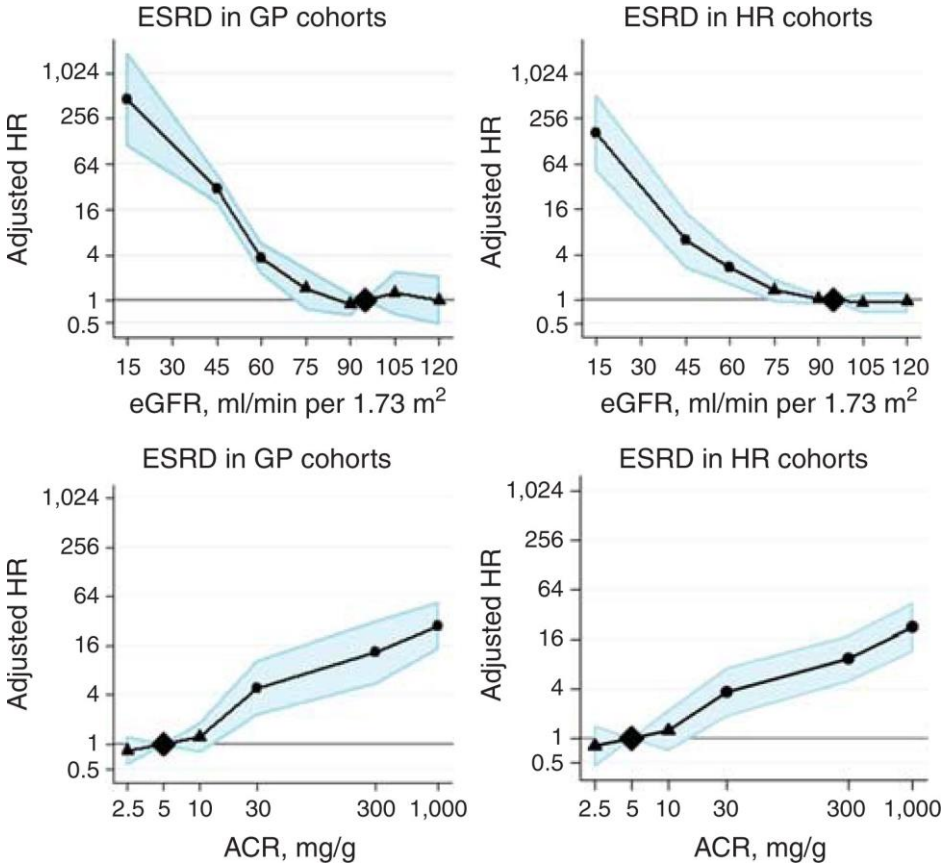
Follow-up visit at your clinic

- Candesartan 16 mg daily
- Metformin 500 mg twice daily
- BP 115/70 mmHg
- HbA1C 6.8%
- Creatinine 80 µmol/L, eGFR 105 mL/min
- ACR 30 mg/mmol

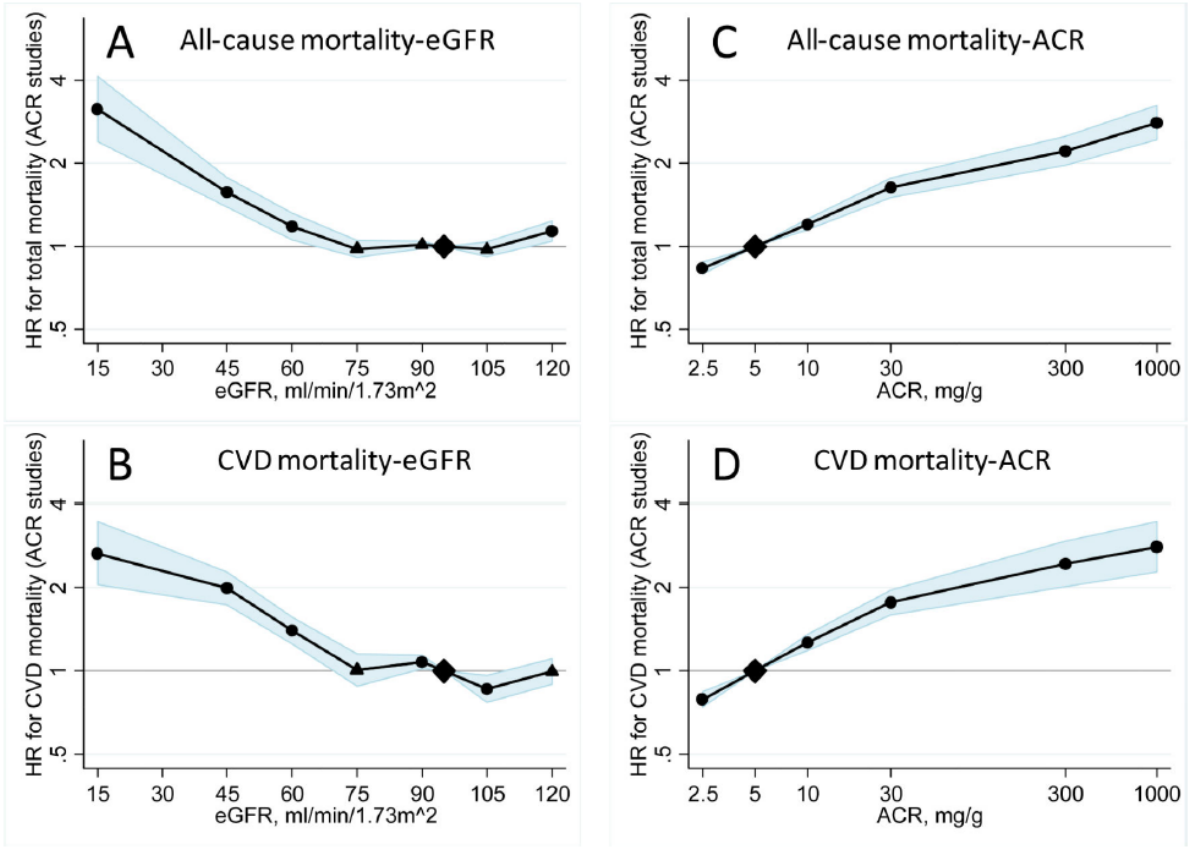
What will you do next?

1. No changes
2. Increase Candesartan
3. Add GLP-1 receptor agonist
4. Add SGLT2 inhibitor
5. Something else

Option 1: No change
Proteinuria predicts bad things



Gansvoort et al. *Kidney International* 2011;80(1):93-104



Matsushita et al. *Lancet* 2010;375(9731):2073-2081

An ACR of 30 represents a high-risk phenotype

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			X
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Option 2: Maximize the ARB

- Reasonable option

- Considerations:
  - How much additional risk reduction will that give you?
  - Will the current BP level allow the increased dose?

Option 3: Add GLP-1 RA

Pros

- Weight reduction
- Glycemic control
- CV health
- Reduce kidney risk

Cons

- Tolerability
- Maybe doesn't need the glycemic control
- Injections
- Cost?

Semaglutide for CKD in Patients with Type 2 Diabetes: "FLOW"ing with the Semaglu"TIDE"

#NephJC

METHODS

International, double-blind, placebo-controlled
28 countries

Type 2 DM and CKD:
GFR 50-75 ml/min + ACR 300-5000 mg/g
or
GFR 25-<50 ml/min + ACR 100-5000 mg/g

Median follow-up, 3.4 years

	Major kidney disease events	Death from any causes	Adverse event leading to discontinuation
Major kidney disease events- kidney failure, ≥50% reduction in GFR, death from CV or kidney-related causes			
Placebo n = 1766	7.5 events per 100 patient-years	279(15.8%)	211(11.9%)
	HR 0.76 (95% CI, 0.66-0.88)	HR 0.80 (95% CI, 0.67-0.95)	
Semaglutide n = 1767	5.8 events per 100 patient-years	227(12.8%)	233(13.2%)

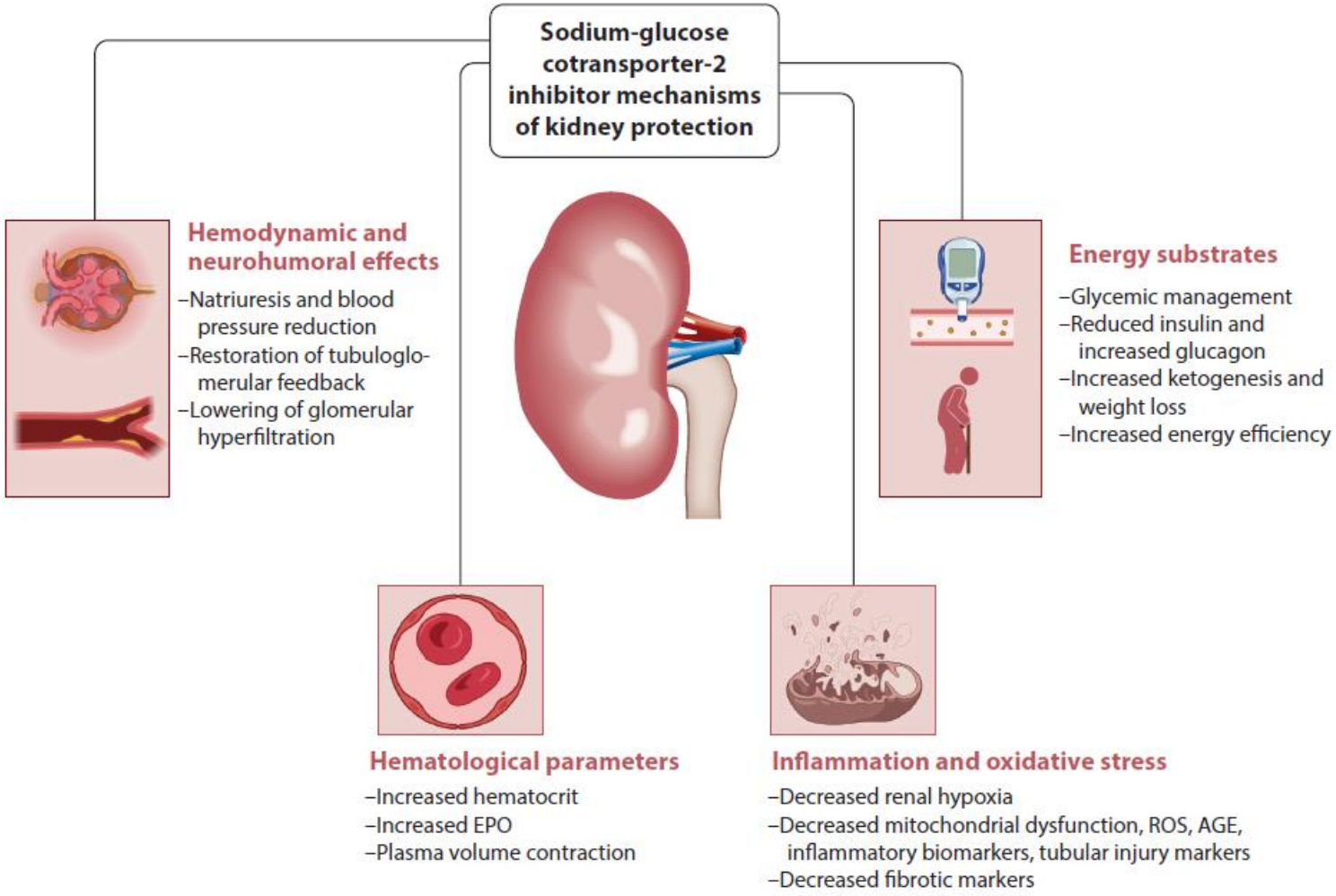
HR= Hazard ratio

Reference: Perkovic,V et al. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. NEJM, May 2024.

VA by Anjana Gopal 𝕏@anjanagopal9

Conclusion: Semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes in patients with type 2 diabetes and chronic kidney disease.

Option 4: Add SGLT2i

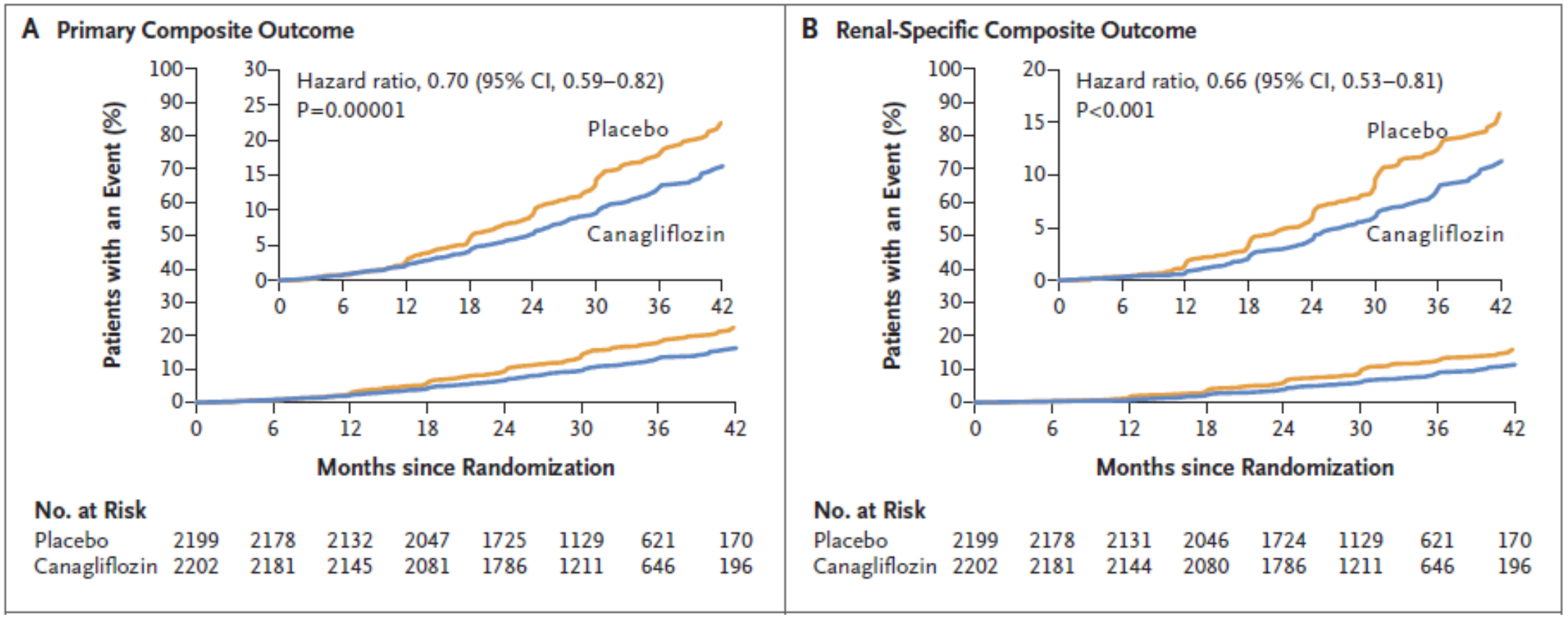


Dharia et al. *Annu Rev Med*. 2023 Jan 27:74:369-384

SGLT2i: The 3 big kidney trials

	CREDENCE	DAPA-CKD	EMPA-CKD
Year	2019	2020	2023
N	4401	4304	6609
Diabetes (%)	100	68	46
eGFR	56 (18)	43 (12)	37 (14)
eGFR <30 (%)	0	15	34
Eligibility	eGFR 30-90 uACR 300-5000	eGFR 25-75 uACR 200-5000	eGFR 20-45 **OR** eGFR 45-90 with uACR >200

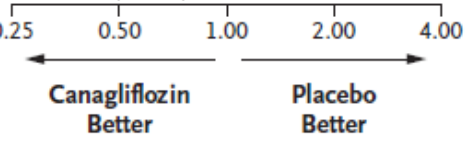
CREDENCE



Perkovic et al. NEJM 2019;380:2295-2306

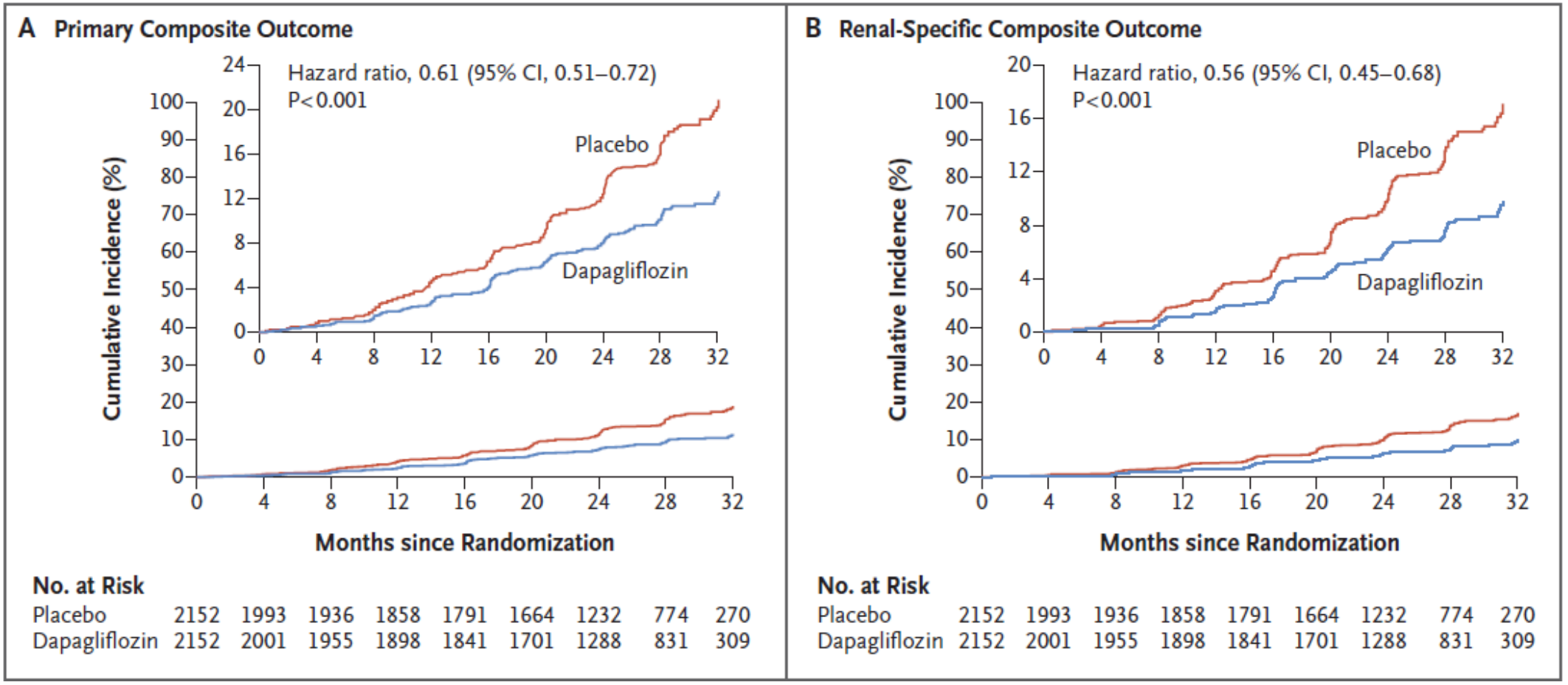
CREDENCE

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



Perkovic et al. NEJM 2019;380:2295-2306

DAPA-CKD

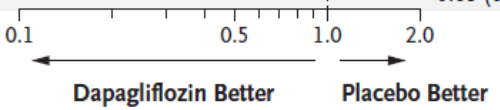


Heerspink et al. NEJM 2020;383:1436-1446

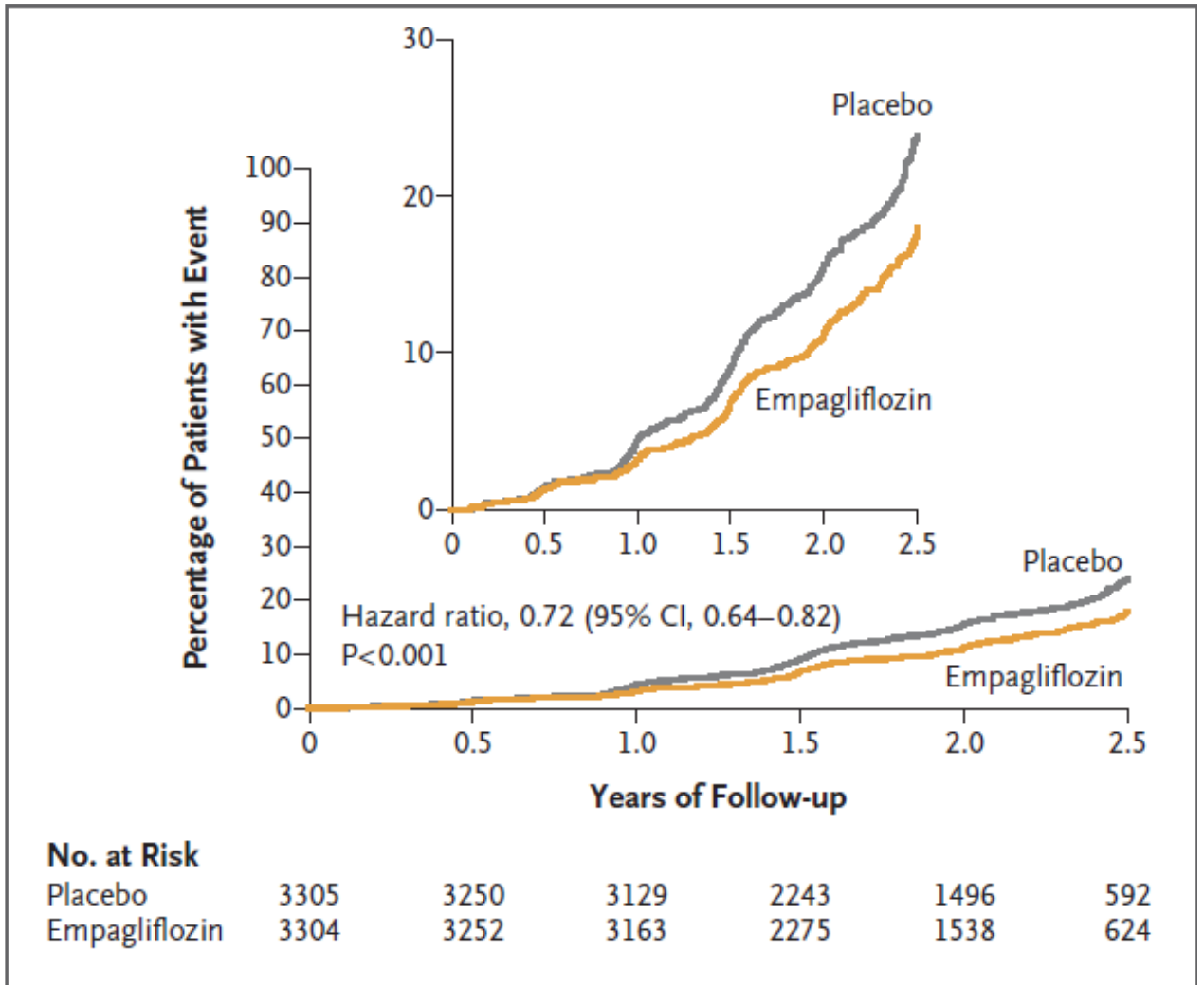
DAPA-CKD

Heerspink et al. NEJM 2020;383:1436-1446

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)



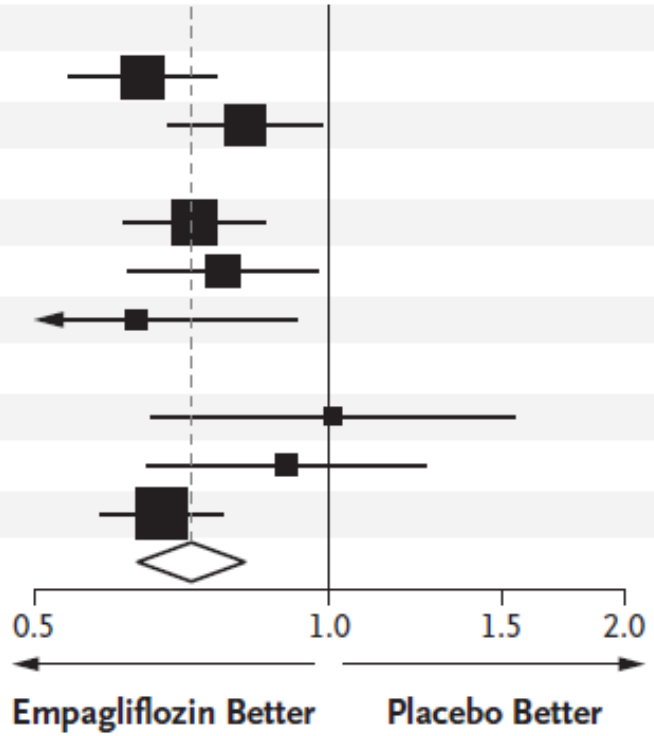
EMPA-CKD



Herrington et al. NEJM 2023;388:117-127

EMPA-CKD

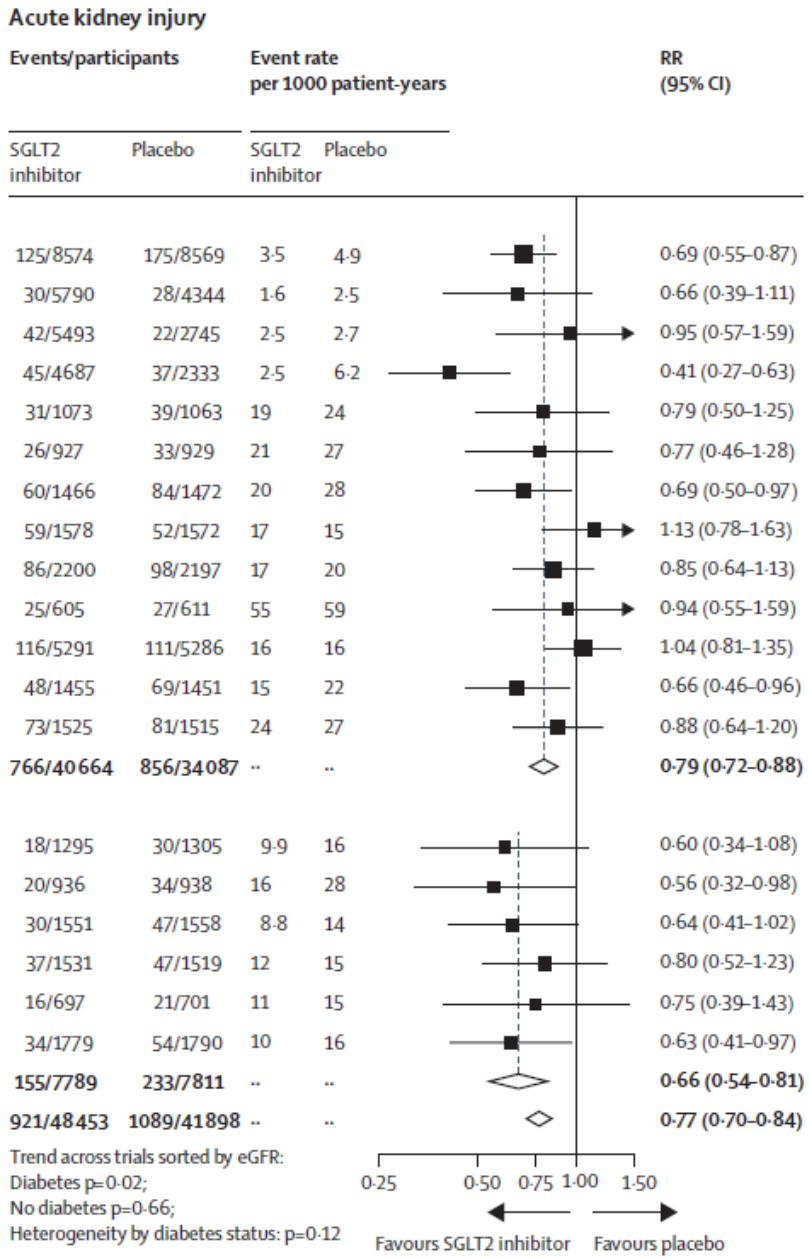
Subgroup	Empagliflozin (no. of patients with event/total no.)	Placebo (no. of patients with event/total no.)	Hazard Ratio for Progression of Kidney Disease or Death from Cardiovascular Causes (95% CI)
Diabetes mellitus			
Present	218/1525	306/1515	0.64 (0.54–0.77)
Absent	214/1779	252/1790	0.82 (0.68–0.99)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



Herrington et al. NEJM 2023;388:117-127

Does it matter which one I use?

- The evidence is strong across the board
- Dapa is available as a generic
- Doses used in the trials:
  - Cana 100 mg daily
  - Empa 10 mg daily
  - Dapa 10 mg daily

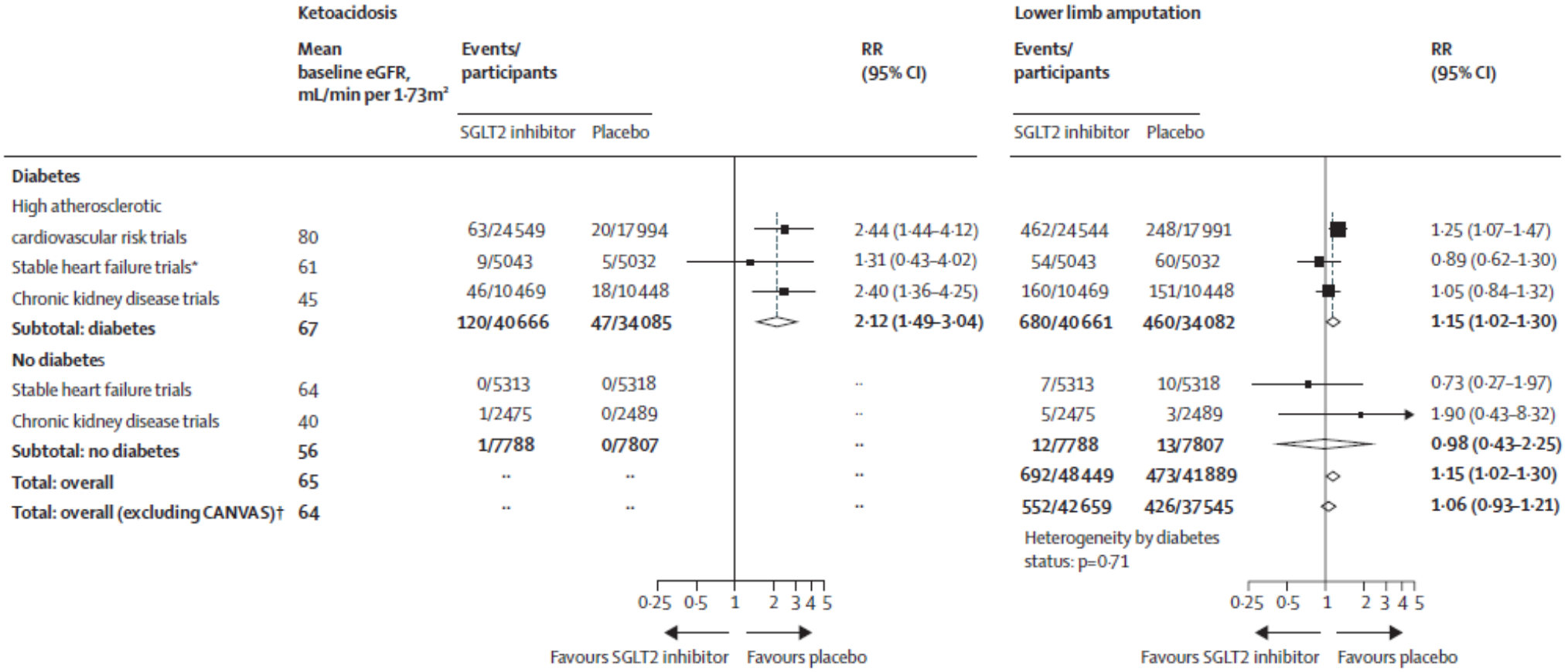


Should I be worried about causing AKI?

Diabetes
RR 0.79 (0.72-0.88)

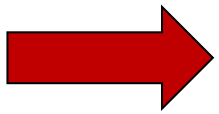
No diabetes
RR 0.77 (0.70-0.84)

Major complications

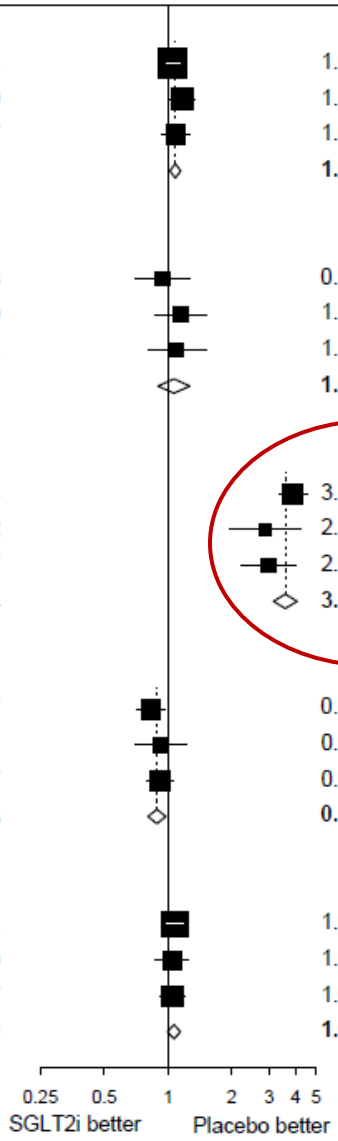


	Mean baseline eGFR, mL/min per 1·73m²	Ketoacidosis: Events/participants SGLT2 inhibitor	Ketoacidosis: Events/participants Placebo	Ketoacidosis: RR (95% CI)	Lower limb amputation: Events/participants SGLT2 inhibitor	Lower limb amputation: Events/participants Placebo	Lower limb amputation: RR (95% CI)
Diabetes							
High atherosclerotic cardiovascular risk trials	80	63/24549	20/17994	2·44 (1·44–4·12)	462/24544	248/17991	1·25 (1·07–1·47)
Stable heart failure trials*	61	9/5043	5/5032	1·31 (0·43–4·02)	54/5043	60/5032	0·89 (0·62–1·30)
Chronic kidney disease trials	45	46/10469	18/10448	2·40 (1·36–4·25)	160/10469	151/10448	1·05 (0·84–1·32)
Subtotal: diabetes	**67**	**120/40666**	**47/34085**	**2·12 (1·49–3·04)**	**680/40661**	**460/34082**	**1·15 (1·02–1·30)**
No diabetes							
Stable heart failure trials	64	0/5313	0/5318	..	7/5313	10/5318	0·73 (0·27–1·97)
Chronic kidney disease trials	40	1/2475	0/2489	..	5/2475	3/2489	1·90 (0·43–8·32)
Subtotal: no diabetes	**56**	**1/7788**	**0/7807**	..	**12/7788**	**13/7807**	**0·98 (0·43–2·25)**
Total: overall	**65**	..	..	..	**692/48449**	**473/41889**	**1·15 (1·02–1·30)**
Total: overall (excluding CANVAS)†	**64**	..	..	..	**552/42659**	**426/37545**	**1·06 (0·93–1·21)**

Heterogeneity by diabetes status: p=0·71



	Mean baseline eGFR (mL/min/1.73m²)	Events/participants SGLT2i	Events/participants Placebo	Relative risk (95% CI)
Urinary tract infections				
High atherosclerotic CV risk trials	80	1938/24549	975/17994	1.05 (0.97, 1.13)
Stable heart failure trials	61	418/7985	358/7979	1.17 (1.02, 1.34)
Chronic kidney disease trials	44	936/12944	878/12937	1.09 (0.93, 1.27)
TOTAL: OVERALL	65	3344/46083	2255/39521	**1.08 (1.02, 1.15)**
Serious urinary tract infections				
High atherosclerotic CV risk trials	75	119/10180	63/5078	0.94 (0.69, 1.27)
Stable heart failure trials	61	106/7985	92/7979	1.15 (0.87, 1.52)
Chronic kidney disease trials	39	81/5453	72/5454	1.10 (0.80, 1.52)
TOTAL: OVERALL	61	306/23618	227/18511	**1.07 (0.90, 1.27)**
Mycotic genital infections				
High atherosclerotic CV risk trials	80	1258/24549	208/17994	3.88 (3.32, 4.53)
Stable heart failure trials	61	98/4859	34/4852	2.87 (1.95, 4.24)
Chronic kidney disease trials	44	179/12944	59/12937	2.98 (2.22, 3.99)
TOTAL: OVERALL	65	1540/42957	302/36394	**3.57 (3.14, 4.06)**
Severe hypoglycaemia				
High atherosclerotic CV risk trials	80	405/18754	281/13647	0.83 (0.71, 0.96)
Stable heart failure trials	62	89/10353	96/10351	0.93 (0.70, 1.23)
Chronic kidney disease trials	44	369/12944	400/12937	0.91 (0.79, 1.05)
TOTAL: OVERALL	64	872/42656	779/37546	**0.89 (0.80, 0.98)**
Bone fracture				
High atherosclerotic CV risk trials	80	1151/24549	811/17994	1.07 (0.98, 1.17)
Stable heart failure trials	63	228/7227	218/7220	1.04 (0.87, 1.25)
Chronic kidney disease trials	44	396/12944	377/12937	1.05 (0.91, 1.21)
TOTAL: OVERALL	65	1787/45325	1415/38762	**1.07 (0.99, 1.14)**



Summary of what we know about flozins

- Consistent kidney and cardiac benefit in all trials
- No effect modification by level of eGFR
- We have efficacy data for eGFRs down to 20 mL/min
- We have safety data for eGFRs below 20 mL/min
- There are some safety concerns but these are small in absolute terms (e.g., 0.2 per 1000 person years for ketoacidosis)

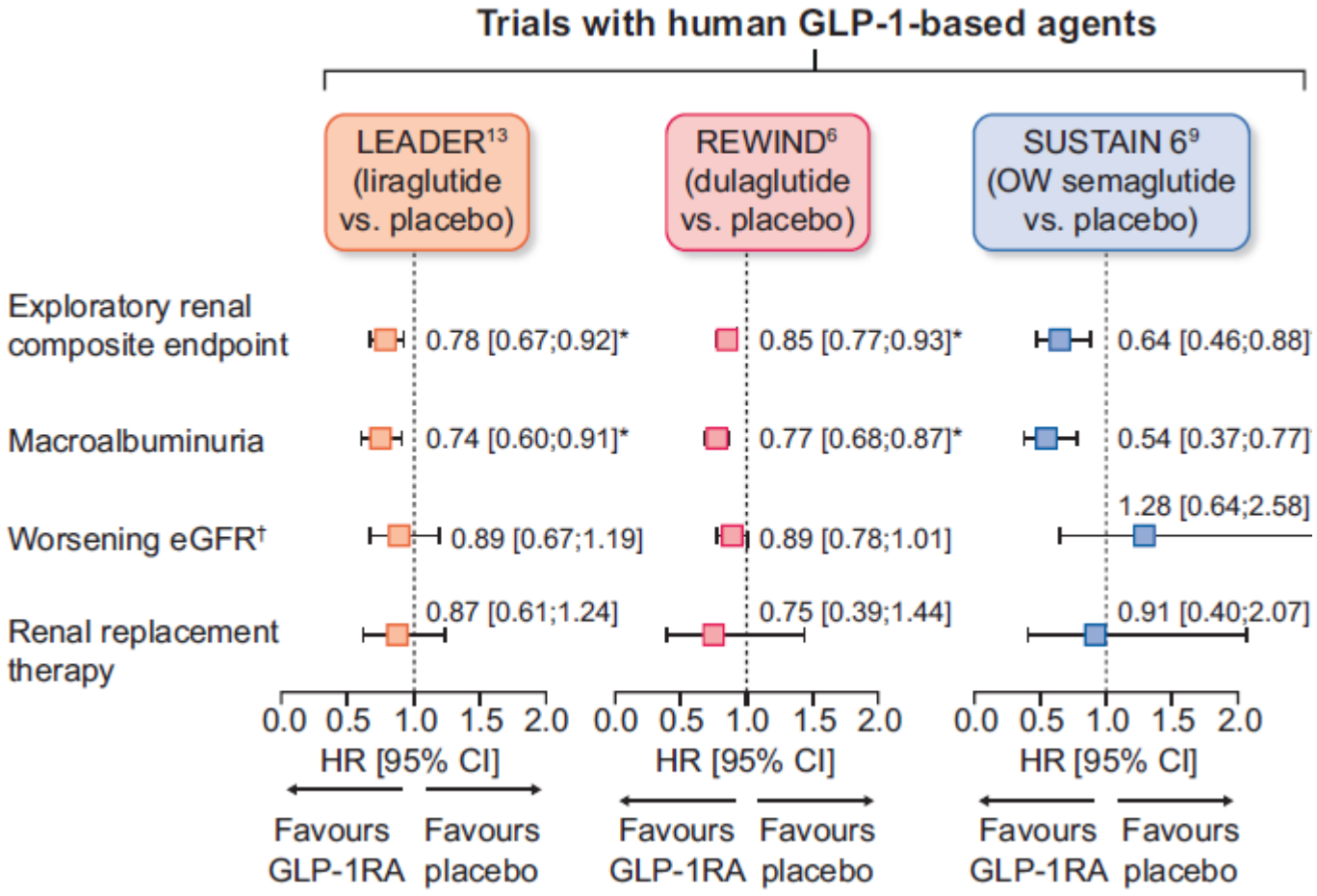
A couple of years later…

- Not doing so great
- Weight gain, not checking sugars
- HbA1C drifting up 8.0%
- ACR now 50 mg/mmol
- BP 135/80 despite Candesartan 32 mg daily
- eGFR 75 mL/min
- Referred to Nephrology – recommended GLP1-RA

Who should prescribe Semaglutide?

1. Nephrologist
2. Family physician
3. Refer to Endocrinology

GLP-1 Receptor Agonists: Kidney benefit observed in CV outcome trials



Benefits not explained by indirect effects e.g., weight loss, lower BP, better glycemic control

Possible direct effects:
Anti-inflammatory
Less oxidative stress
Hemodynamic effects

Rossing et al. NDT 2023;38:2401-2051

The NEW ENGLAND JOURNAL of MEDICINE

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Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D., Peter Rossing, M.D., D.M.Sc., Kenneth W. Mahaffey, M.D., Johannes F.E. Mann, M.D., George Bakris, M.D., Florian M.M. Baeres, M.D., Thomas Idorn, M.D., Ph.D., Heidrun Bosch-Traberg, M.D., Nanna Leonora Lausvig, M.Sc., and Richard Pratley, M.D., for the FLOW Trial Committees and Investigators*

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Semaglutide (N=1767)	Placebo (N=1766)	Total (N=3533)
Age — yr	66.6±9.0	66.7±9.0	66.6±9.0
Female sex — no. (%)	519 (29.4)	550 (31.1)	1069 (30.3)
Geographic region — no. (%)			
Asia	478 (27.1)	434 (24.6)	912 (25.8)
Europe	472 (26.7)	491 (27.8)	963 (27.3)
North America	423 (23.9)	442 (25.0)	865 (24.5)
Other	394 (22.3)	399 (22.6)	793 (22.4)
Race or ethnic group — no. (%)†			
White	1155 (65.4)	1168 (66.1)	2323 (65.8)
Asian	439 (24.8)	407 (23.0)	846 (23.9)
Black	78 (4.4)	82 (4.6)	160 (4.5)
Other	95 (5.4)	109 (6.2)	204 (5.8)
Hispanic or Latinx ethnic group — no. (%)†			
Yes	273 (15.4)	283 (16.0)	556 (15.7)
No	1421 (80.4)	1411 (79.9)	2832 (80.2)
Not reported	73 (4.1)	72 (4.1)	145 (4.1)
Glycated hemoglobin level — %	7.8±1.3	7.8±1.3	7.8±1.3
Body-mass index‡	31.9±6.1	32.0±6.5	32.0±6.3
Body weight — kg	89.5±19.8	89.8±21.2	89.6±20.5
Systolic blood pressure — mm Hg	138.9±16.1	138.4±15.4	138.6±15.8
Diastolic blood pressure — mm Hg	76.8±10.0	76.1±10.0	76.4±10.0
Diabetes duration — no. (%)			
<15 yr	774 (43.8)	753 (42.6)	1527 (43.2)
≥15 yr	992 (56.1)	1013 (57.4)	2005 (56.8)
Previous myocardial infarction or stroke — no. (%)	405 (22.9)	403 (22.8)	808 (22.9)

Mean age 66 years
Mostly white or Asian
HbA1C 7.8%
BMI 32
Long duration of diabetes

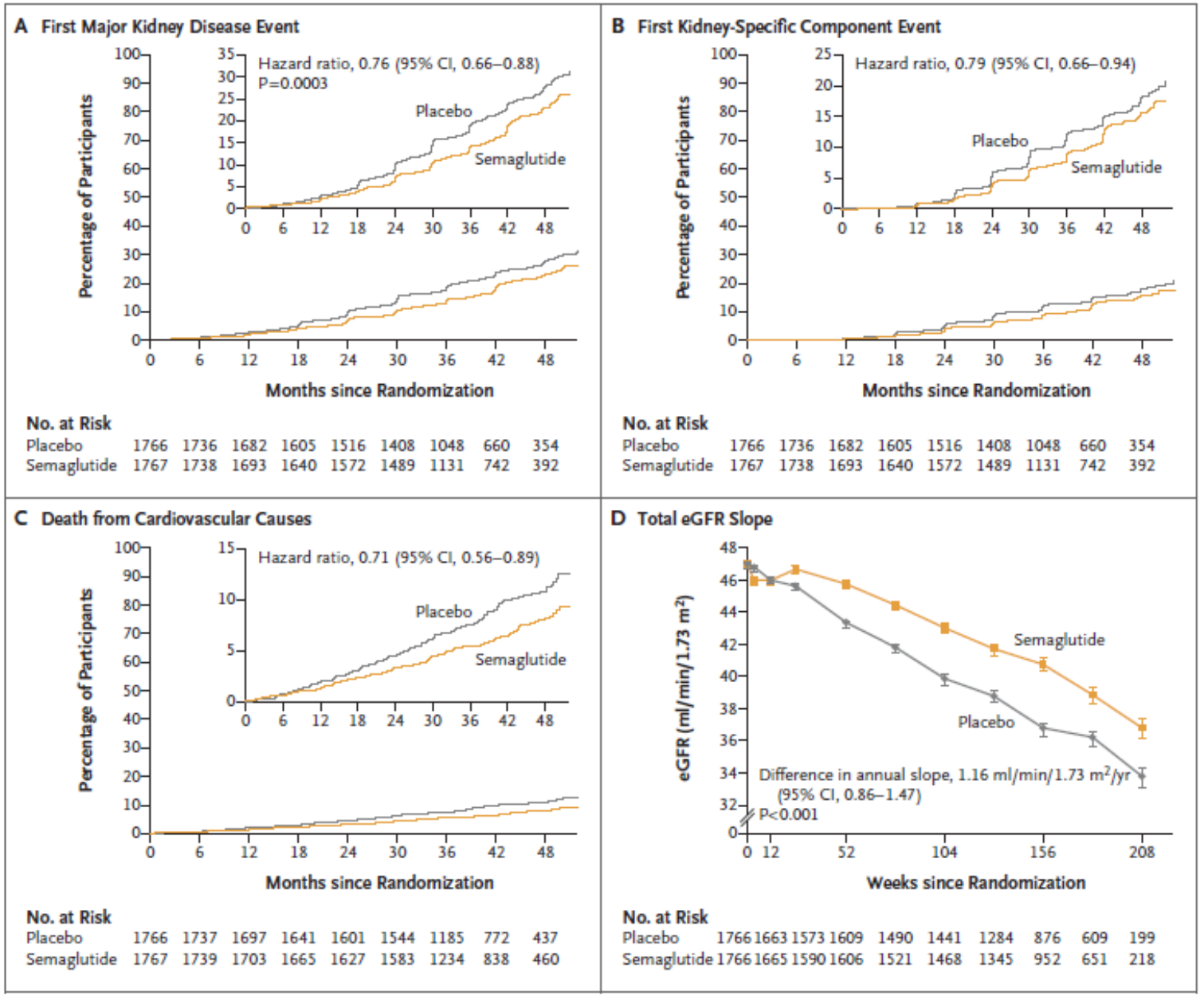
eGFR — ml/min/1.73 m²¶	46.9±15.6	47.1±14.7	47.0±15.2
eGFR distribution — no. (%)¶			
≥60 ml/min/1.73 m²	366 (20.7)	353 (20.0)	719 (20.4)
≥45 to <60 ml/min/1.73 m²	515 (29.1)	540 (30.6)	1055 (29.9)
≥30 to <45 ml/min/1.73 m²	667 (37.7)	691 (39.1)	1358 (38.4)
<30 ml/min/1.73 m²	218 (12.3)	182 (10.3)	400 (11.3)
Median urinary albumin-to-creatinine ratio‖	582.3	557.8	567.6
Category of albuminuria — no. (%)**			
A1, normoalbuminuria	52 (2.9)	57 (3.2)	109 (3.1)
A2, microalbuminuria	509 (28.8)	495 (28.0)	1004 (28.4)
A3, macroalbuminuria	1205 (68.2)	1214 (68.7)	2419 (68.5)

Mean eGFR 47 mL/min
50% under 45 mL/min
High grade albuminuria

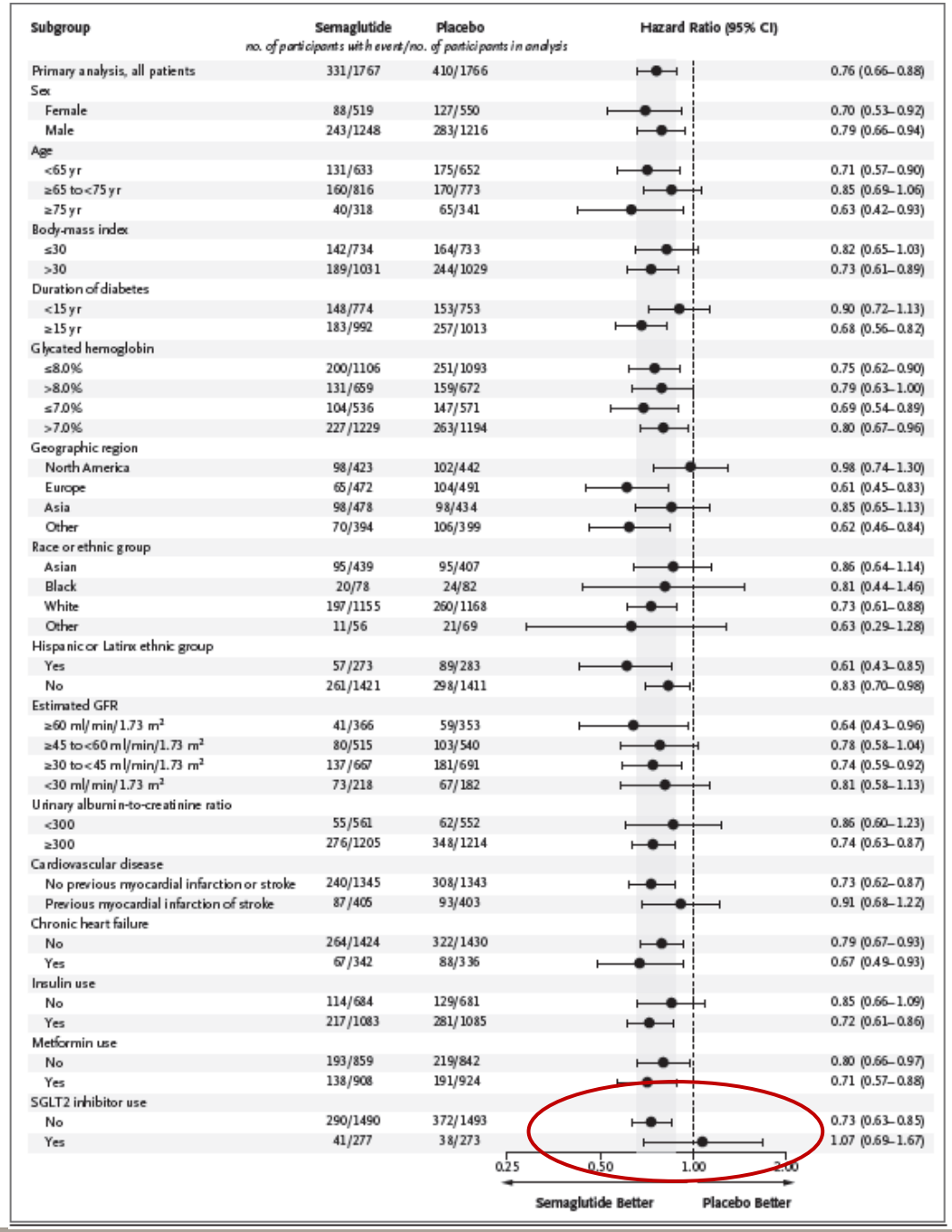
Table 1. (Continued.)

Characteristic	Semaglutide (N=1767)	Placebo (N=1766)	Total (N=3533)
Medication use — no. (%)			
SGLT2 inhibitor	277 (15.7)	273 (15.5)	550 (15.6)
ACE inhibitor	625 (35.4)	615 (34.8)	1240 (35.1)
ARB	1066 (60.3)	1061 (60.1)	2127 (60.2)
Lipid-lowering drug	1418 (80.2)	1416 (80.2)	2834 (80.2)
Diuretic agent	870 (49.2)	910 (51.5)	1780 (50.4)
Insulin	1083 (61.3)	1085 (61.4)	2168 (61.4)

95% on ACEi/ARB
15% on SGLT2i


A First Major Kidney Disease Event
Hazard ratio, 0.76 (95% CI, 0.66–0.88)
P=0.0003
Placebo
Semaglutide
Percentage of Participants
Months since Randomization
No. at Risk
Placebo 1766 1736 1682 1605 1516 1408 1048 660 354
Semaglutide 1767 1738 1693 1640 1572 1489 1131 742 392
B First Kidney-Specific Component Event
Hazard ratio, 0.79 (95% CI, 0.66–0.94)
Placebo
Semaglutide
Percentage of Participants
Months since Randomization
No. at Risk
Placebo 1766 1736 1682 1605 1516 1408 1048 660 354
Semaglutide 1767 1738 1693 1640 1572 1489 1131 742 392
C Death from Cardiovascular Causes
Hazard ratio, 0.71 (95% CI, 0.56–0.89)
Placebo
Semaglutide
Percentage of Participants
Months since Randomization
No. at Risk
Placebo 1766 1737 1697 1641 1601 1544 1185 772 437
Semaglutide 1767 1739 1703 1665 1627 1583 1234 838 460
D Total eGFR Slope
Semaglutide
Placebo
Difference in annual slope, 1.16 ml/min/1.73 m²/yr
(95% CI, 0.86–1.47)
P<0.001
eGFR (ml/min/1.73 m²)
Weeks since Randomization
No. at Risk
Placebo 1766 1663 1573 1609 1490 1441 1284 876 609 199
Semaglutide 1766 1665 1590 1606 1521 1468 1345 952 651 218

Consistent benefit across all subgroups

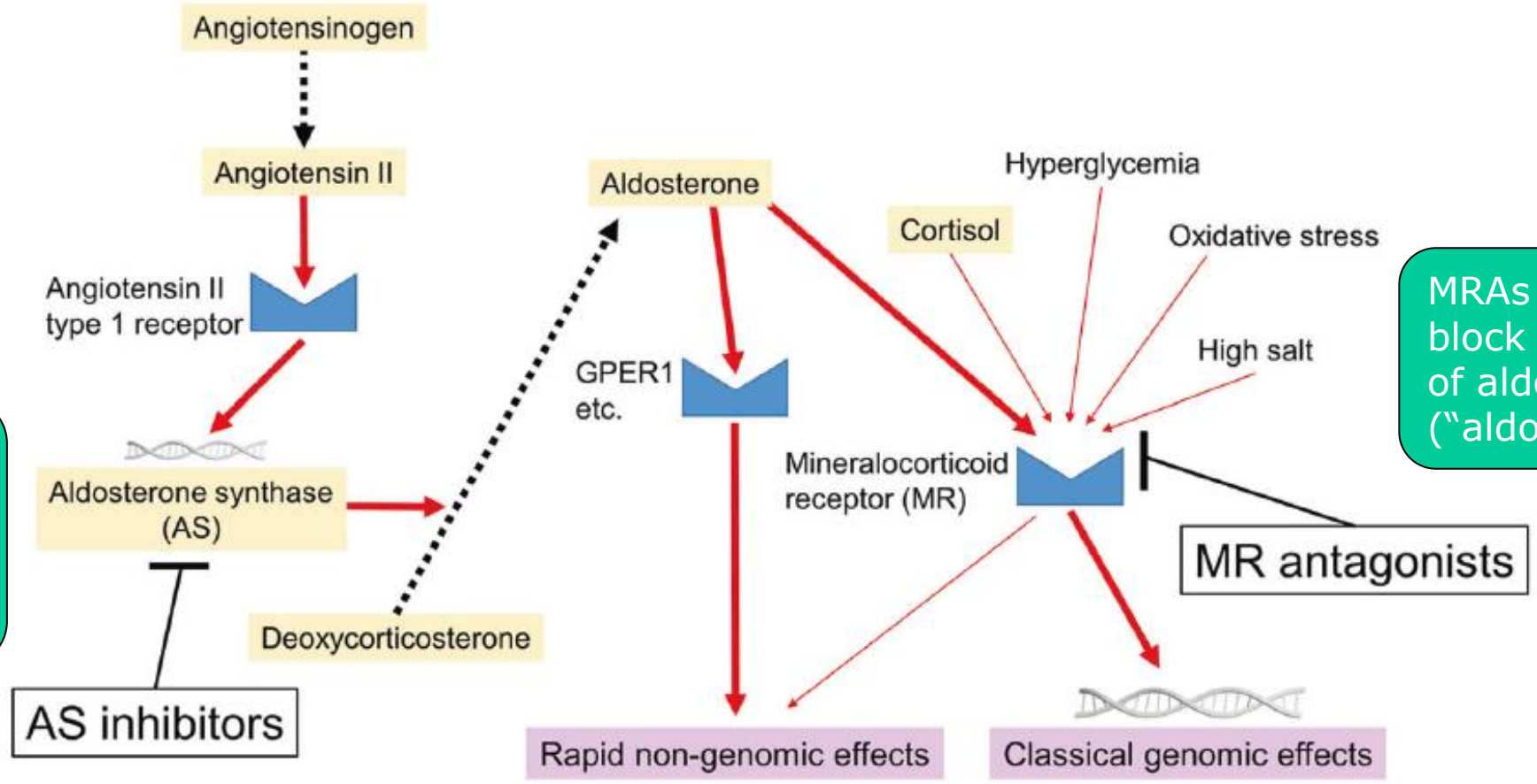


Subgroup	Semaglutide	Placebo	Hazard Ratio (95% CI)
	no. of participants with event/no. of participants in analysis		
Primary analysis, all patients	331/1767	410/1766	0.76 (0.66–0.88)
Sex			
Female	88/519	127/550	0.70 (0.53–0.92)
Male	243/1248	283/1216	0.79 (0.66–0.94)
Age			
<65 yr	131/633	175/652	0.71 (0.57–0.90)
≥65 to<75 yr	160/816	170/773	0.85 (0.69–1.06)
≥75 yr	40/318	65/341	0.63 (0.42–0.93)
Body-mass index			
≤30	142/734	164/733	0.82 (0.65–1.03)
>30	189/1031	244/1029	0.73 (0.61–0.89)
Duration of diabetes			
<15 yr	148/774	153/753	0.90 (0.72–1.13)
≥15 yr	183/992	257/1013	0.68 (0.56–0.82)
Glycated hemoglobin			
≤8.0%	200/1106	251/1093	0.75 (0.62–0.90)
>8.0%	131/659	159/672	0.79 (0.63–1.00)
≤7.0%	104/536	147/571	0.69 (0.54–0.89)
>7.0%	227/1229	263/1194	0.80 (0.67–0.96)
Geographic region			
North America	98/423	102/442	0.98 (0.74–1.30)
Europe	65/472	104/491	0.61 (0.45–0.83)
Asia	98/478	98/434	0.85 (0.65–1.13)
Other	70/394	106/399	0.62 (0.46–0.84)
Race or ethnic group			
Asian	95/439	95/407	0.86 (0.64–1.14)
Black	20/78	24/82	0.81 (0.44–1.46)
White	197/1155	260/1168	0.73 (0.61–0.88)
Other	11/56	21/69	0.63 (0.29–1.28)
Hispanic or Latinx ethnic group			
Yes	57/273	89/283	0.61 (0.43–0.85)
No	261/1421	298/1411	0.83 (0.70–0.98)
Estimated GFR			
≥60 ml/min/1.73 m²	41/366	59/353	0.64 (0.43–0.96)
≥45 to<60 ml/min/1.73 m²	80/515	103/540	0.78 (0.58–1.04)
≥30 to<45 ml/min/1.73 m²	137/667	181/691	0.74 (0.59–0.92)
<30 ml/min/1.73 m²	73/218	67/182	0.81 (0.58–1.13)
Urinary albumin-to-creatinine ratio			
<300	55/561	62/552	0.86 (0.60–1.23)
≥300	276/1205	348/1214	0.74 (0.63–0.87)
Cardiovascular disease			
No previous myocardial infarction or stroke	240/1345	308/1343	0.73 (0.62–0.87)
Previous myocardial infarction or stroke	87/405	93/403	0.91 (0.68–1.22)
Chronic heart failure			
No	264/1424	322/1430	0.79 (0.67–0.93)
Yes	67/342	88/336	0.67 (0.49–0.93)
Insulin use			
No	114/684	129/681	0.85 (0.66–1.09)
Yes	217/1083	281/1085	0.72 (0.61–0.86)
Metformin use			
No	193/859	219/842	0.80 (0.66–0.97)
Yes	138/908	191/924	0.71 (0.57–0.88)
SGLT2 inhibitor use			
No	290/1490	372/1493	0.73 (0.63–0.85)
Yes	41/277	38/273	1.07 (0.69–1.67)

Emerging therapies

Different ways to target Aldosterone

Aldosterone synthase has a high AA sequence similarity to that of cortisol synthase



MRAs do not fully block the effects of aldosterone ("aldo escape")

Ando. *Hypertension Research* 2023;46:1056-1057

Phase 2 data for BI 690517 (Vicadrostat)

Efficacy and safety of aldosterone synthase inhibition with and without empagliflozin for chronic kidney disease: a randomised, controlled, phase 2 trial

Katherine R Tuttle, Sibylle J Hauske*, Maria Eugenia Canziani, Maria Luiza Caramori, David Cherney, Lisa Cronin, Hiddo J L Heerspink, Christian Hugo, Masaomi Nangaku, Ricardo Correa Rotter, Arnold Silva, Shimoli V Shah, Zhichao Sun, Dorothea Urbach, Dick de Zeeuw, Peter Rossing*, on behalf of the ASi in CKD group†*

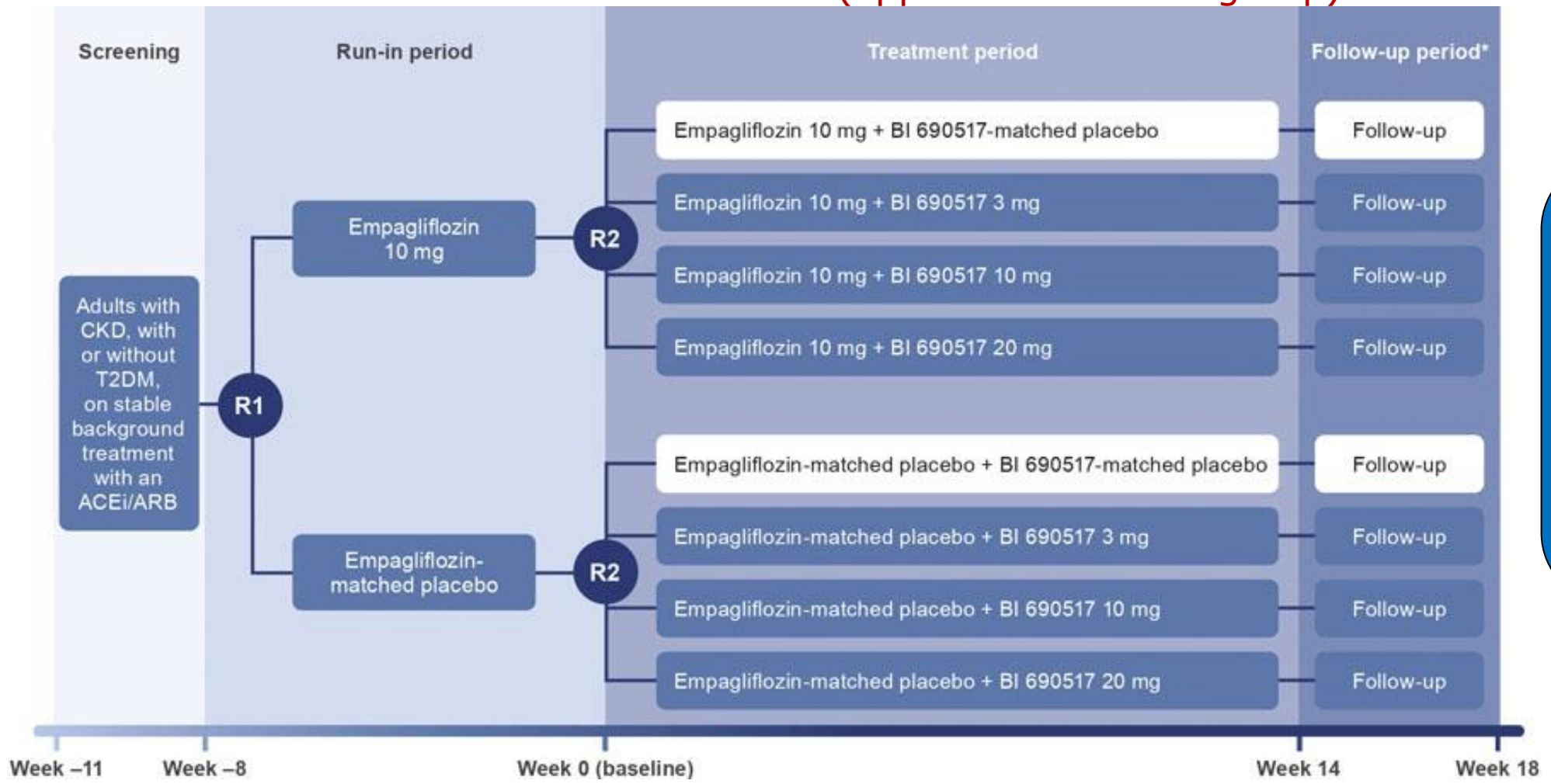
Summary

Background Excess aldosterone accelerates chronic kidney disease progression. This phase 2 clinical trial assessed BI 690517, an aldosterone synthase inhibitor, for efficacy, safety, and dose selection.

Lancet 2024; 403: 379–90

Published Online December 15, 2023

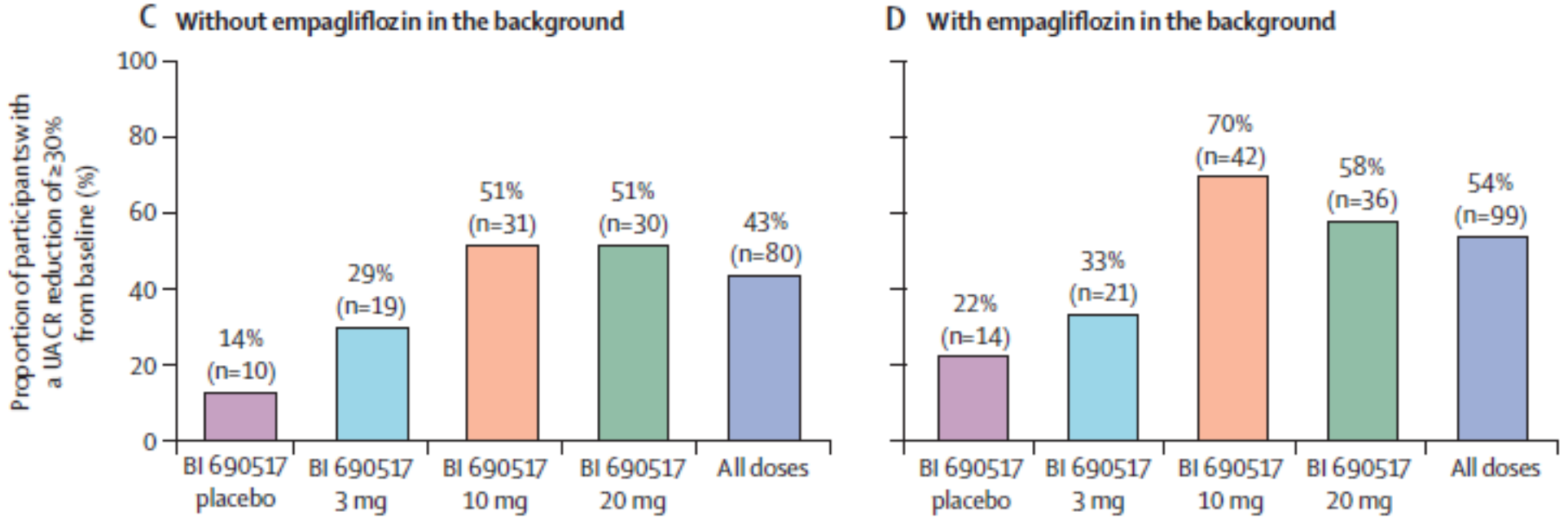
N = 714 N = 586 (approx. 75 in each group)



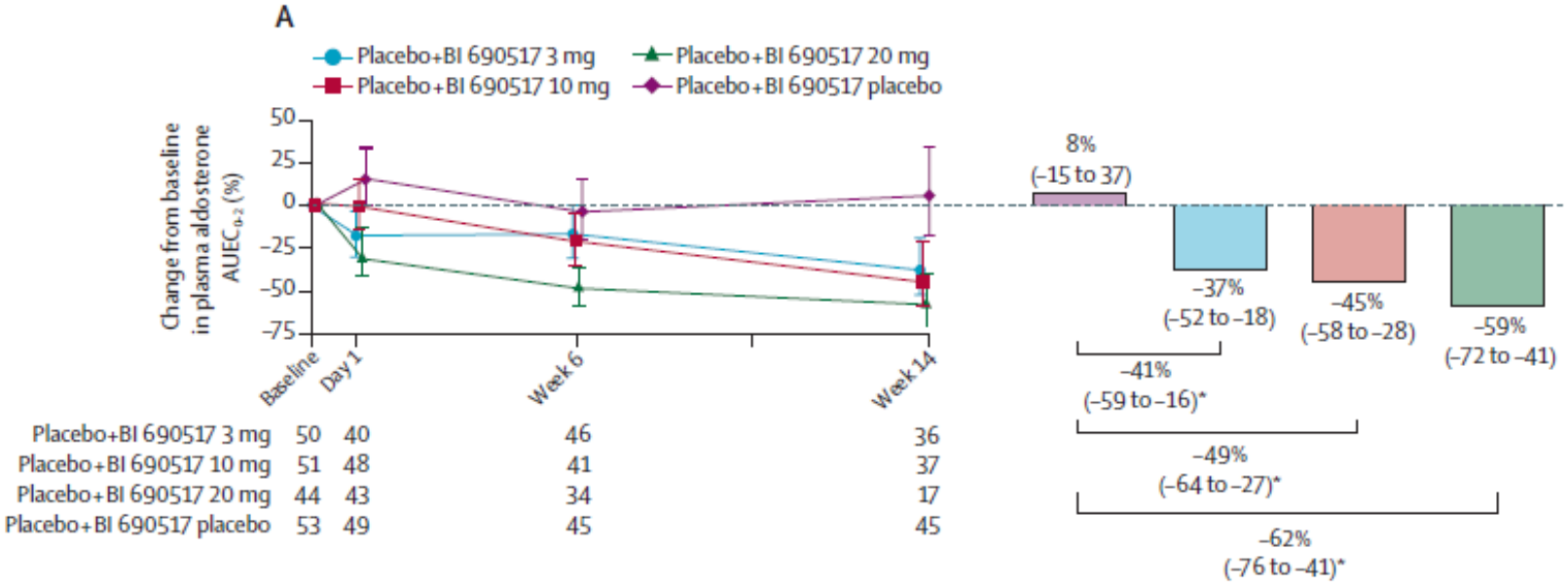
At Baseline:

- 33% female
- Age 63.8 years
- 71% T2DM
- SBP 133.8 mmHg
- K 4.3 mmol/L
- GFR 52 mL/min
- ACR 426 mg/g

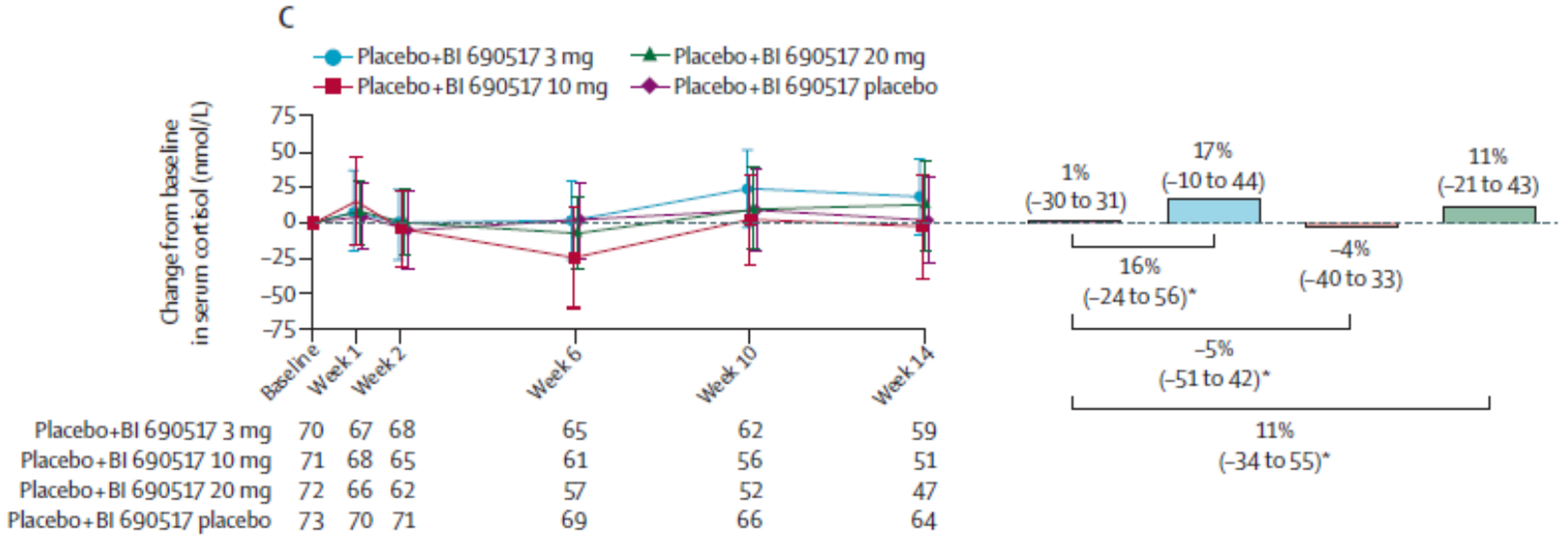
Tuttle et al. *Am J Nephrol* 2024;55(2):262-272



Tuttle et al. *Lancet* 2024;403:379-390

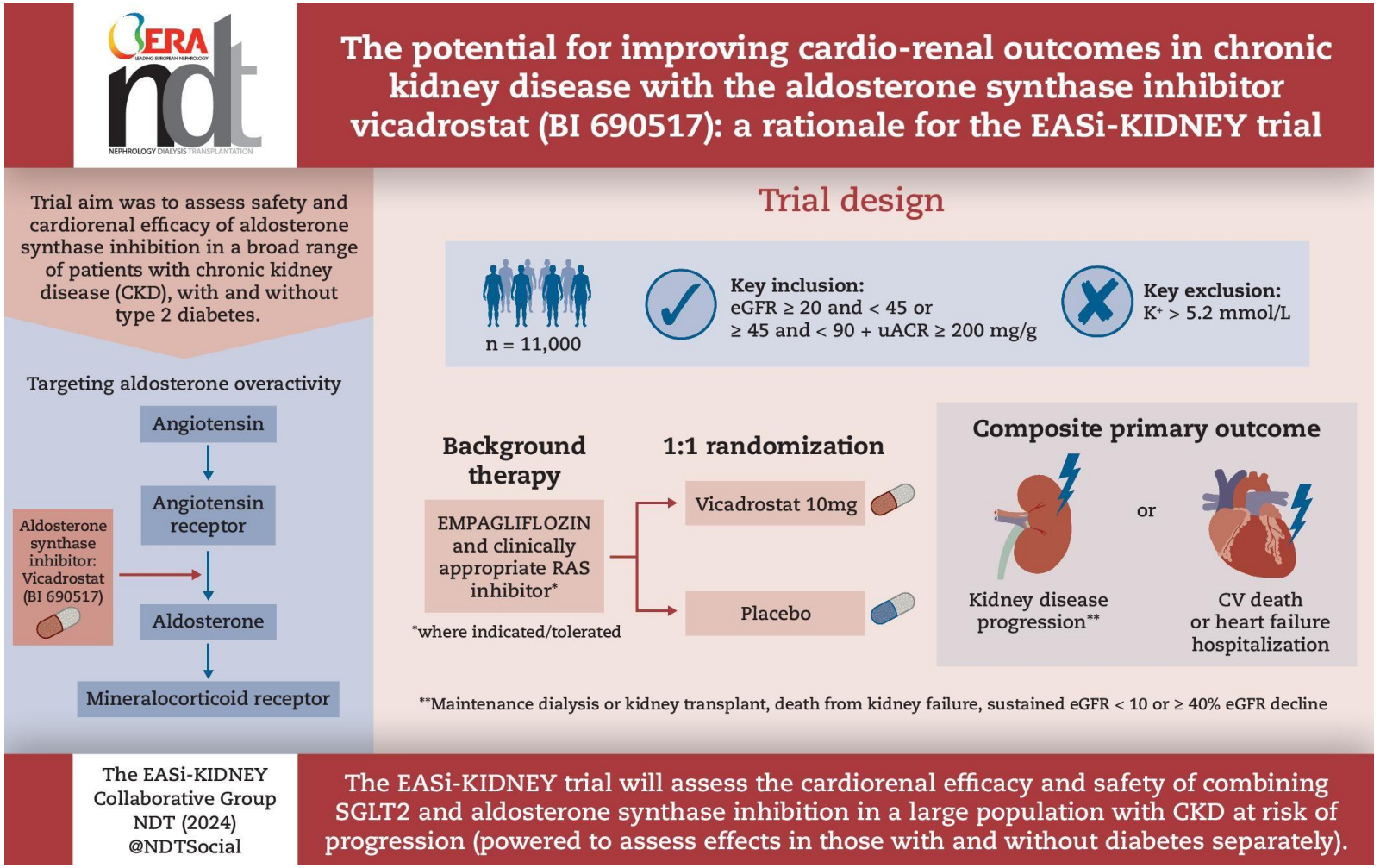


Dose-dependent reduction in plasma aldosterone



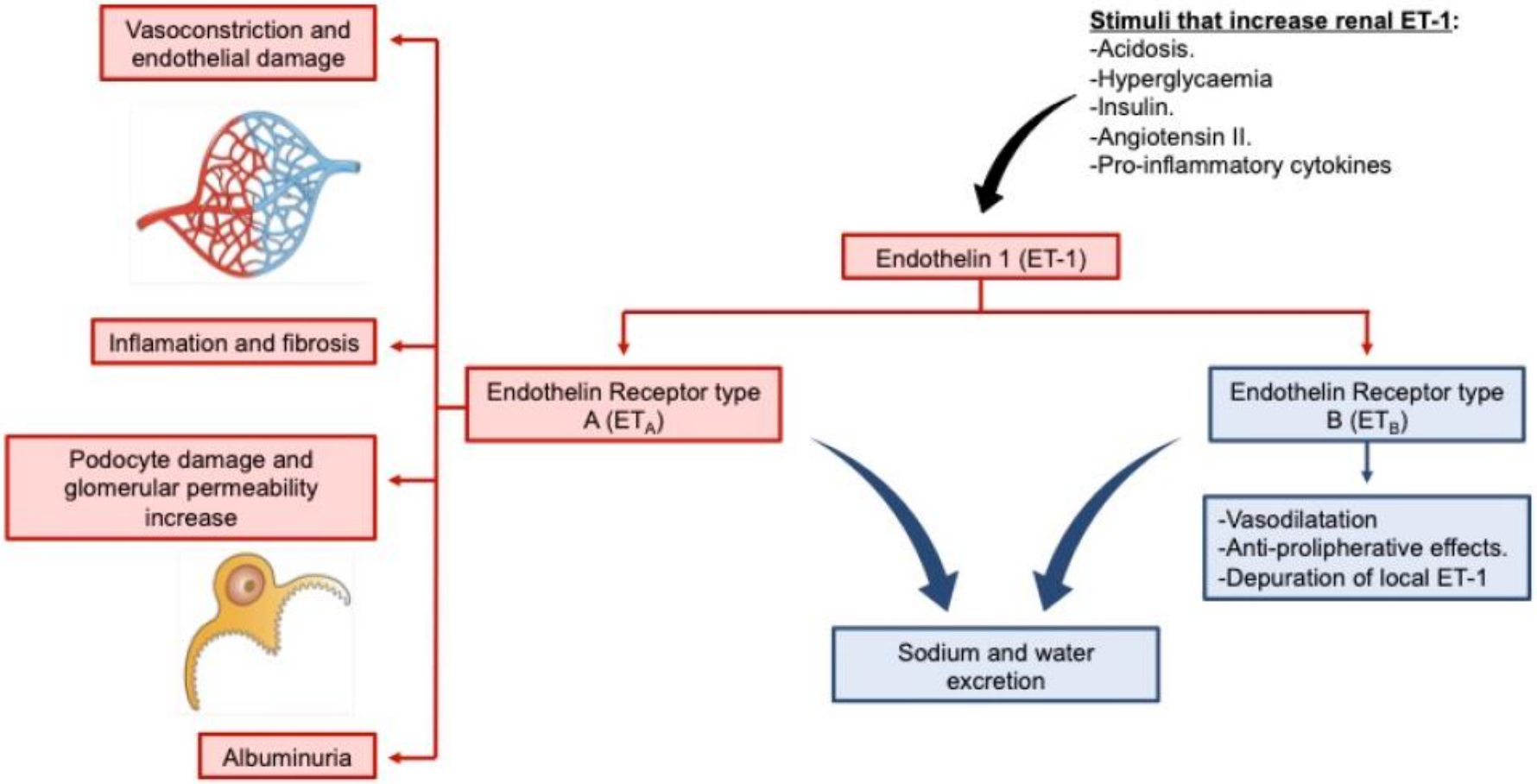
Without suppressing cortisol production

uOttawa



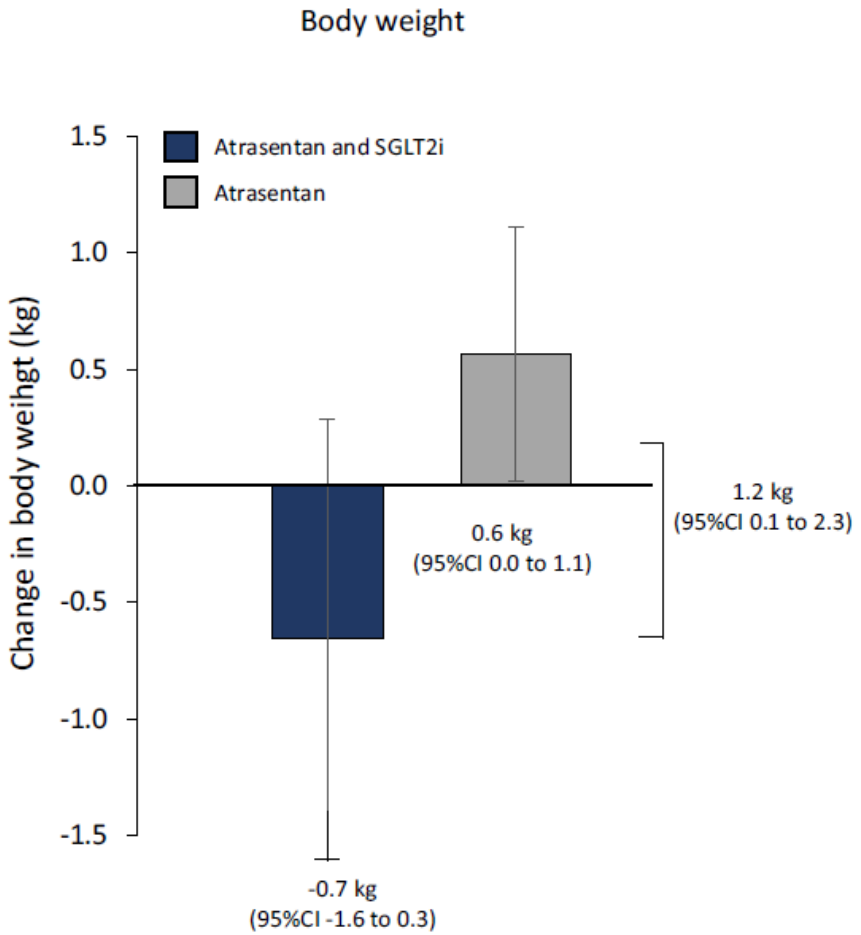
Judge et al. *NDT* 2024 (Online ahead of print)

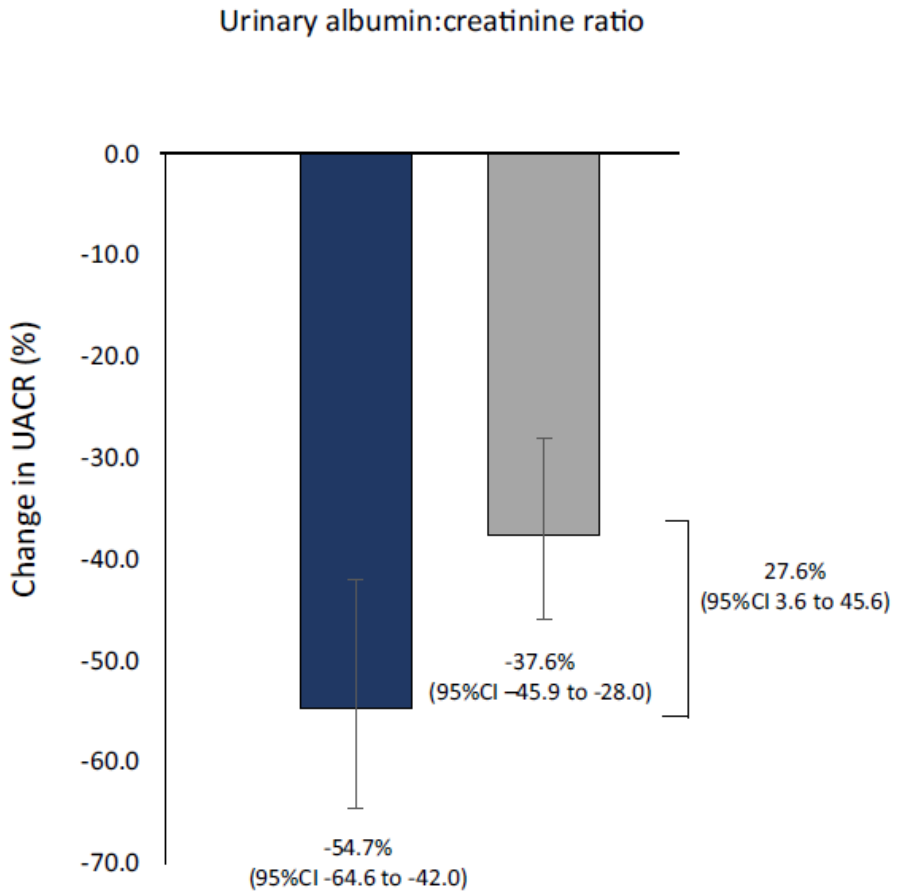
Role of Endothelin in CKD progression



Martinez-Diaz et al. *Int. J. Mol. Sci*. 2023;24:3427

Post-hoc analysis from the SONAR trial





Heerspink et al. *Kidney International*. 2021;99:346-349

Zibotentan: Highly selective ET-A antagonist

Zibotentan in combination with dapagliflozin compared with dapagliflozin in patients with chronic kidney disease (ZENITH-CKD): a multicentre, randomised, active-controlled, phase 2b, clinical trial

Hiddo J L Heerspink, Arihiro Kiyosue, David C Wheeler, Min Lin, Emma Wijkmark, Glenn Carlson, Anne-Kristina Mercier, Magnus Åstrand, Sebastian Ueckert, Peter J Greasley, Phil Ambery

Lancet 2023; 402: 2004–17

Published Online November 3, 2023

https://doi.org/10.1016/

Summary

Background In patients with chronic kidney disease, SGLT2 inhibitors and endothelin A receptor antagonists (ERAs) can reduce albuminuria and glomerular filtration rate (GFR) decline. We assessed the albuminuria-lowering efficacy and safety of the ERA zibotentan combined with the SGLT2 inhibitor dapagliflozin.

Is Zibotentan Safe and Efficacious in Retarding Chronic Kidney Disease Progression? (ZENITH-CKD)

#NephJC

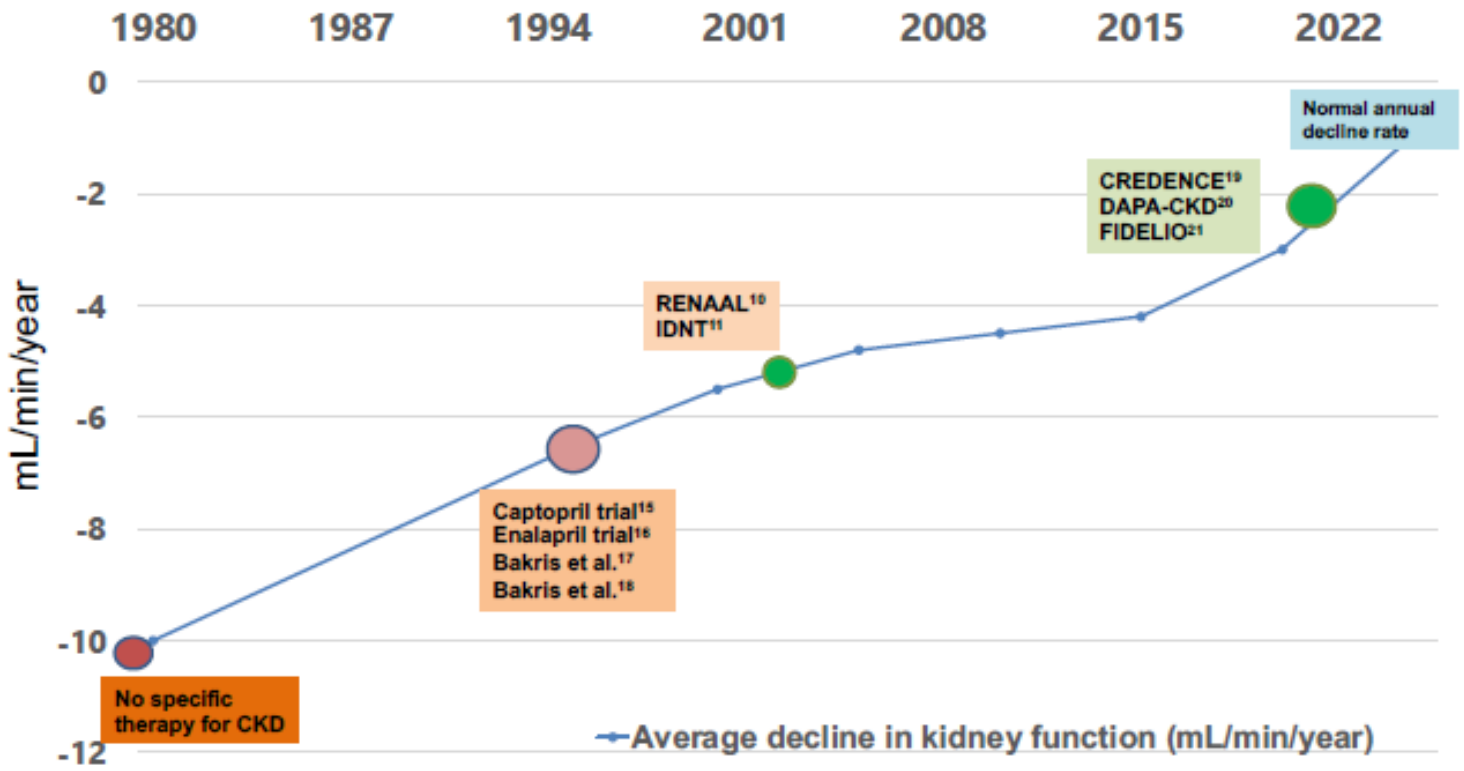
- 18 countries
- Randomized, Double blinded
- Age ≥ 18 to ≤ 90 (Median age 62.8 years)
- eGFR ≥ 20 ml/min
- UACR 150-5000 mg/g (Median – 565 mg/g)
- April 2021 – Jan 2023
- Stable dose of ACEi or ARBs for 4 weeks

Randomized into three groups 2:1:2	All were on Dapagliflozin 10 mg		
	Zibotentan 1.5 mg	Zibotentan 0.25 mg	Placebo
Number of patients	179	91	177
% Mean change in UACR (baseline to 12 weeks)	-52.5% (-59 to -44.9) (P<0.0001)	-47.7% (-55.7 to -38.2) (P=0.0022)	-28.3% (-37.8 to -17.4) (ref)
Fluid retention events	18%	9%	8%

Conclusion: Zibotentan reduced albuminuria with an acceptable tolerability and safety profile in chronic kidney disease patients already receiving currently recommended therapy

Heerspink HJL et al, Lancet 2023
VA by
Dr Sabarinath S MD DM FASN
@sabarivenus

Reasons to be hopeful



Naaman & Bakris. 2021 In: Chronic Kidney Disease and Type 2 Diabetes

Thank you for your attention

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