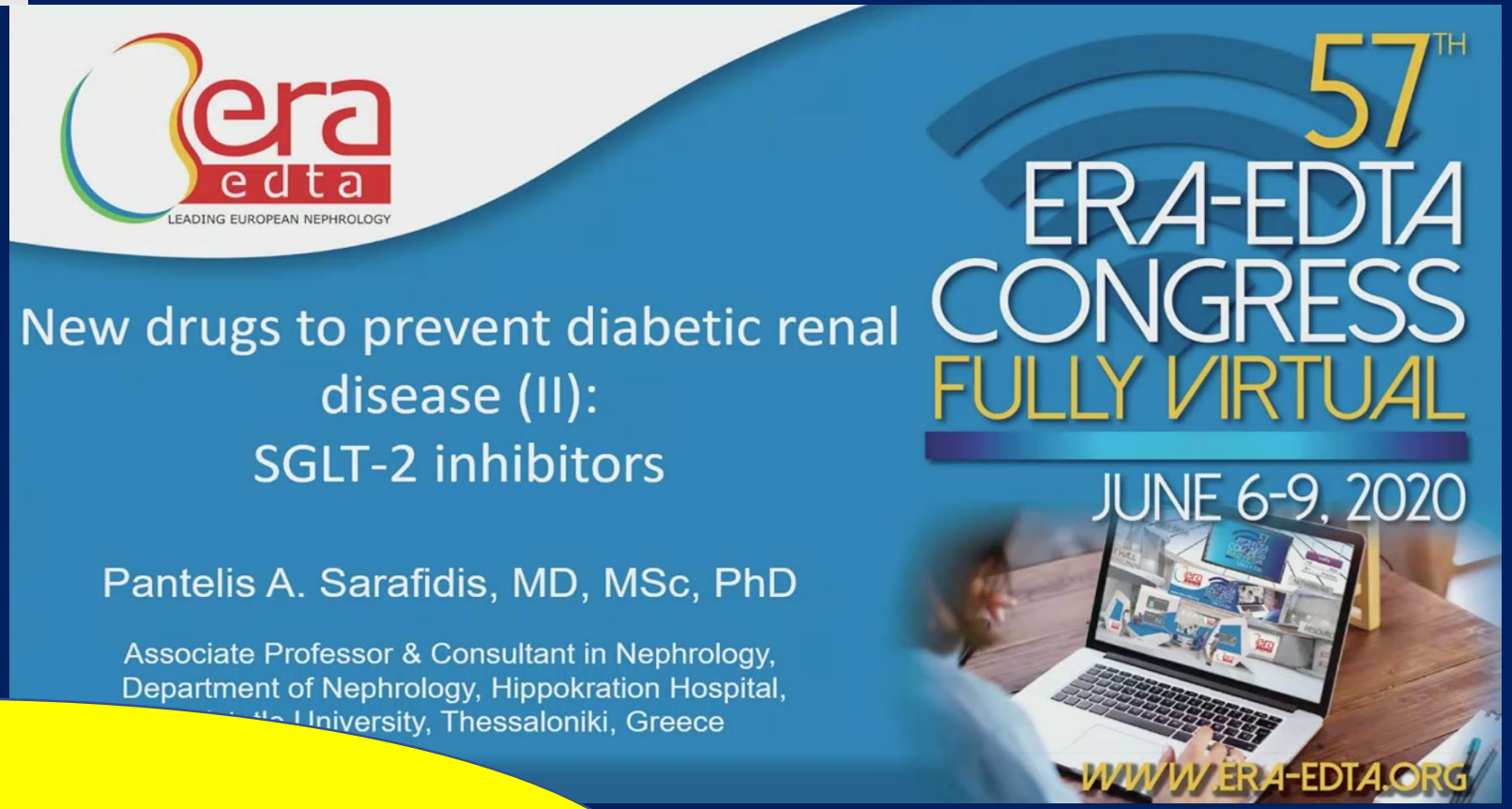
Inn the name of god

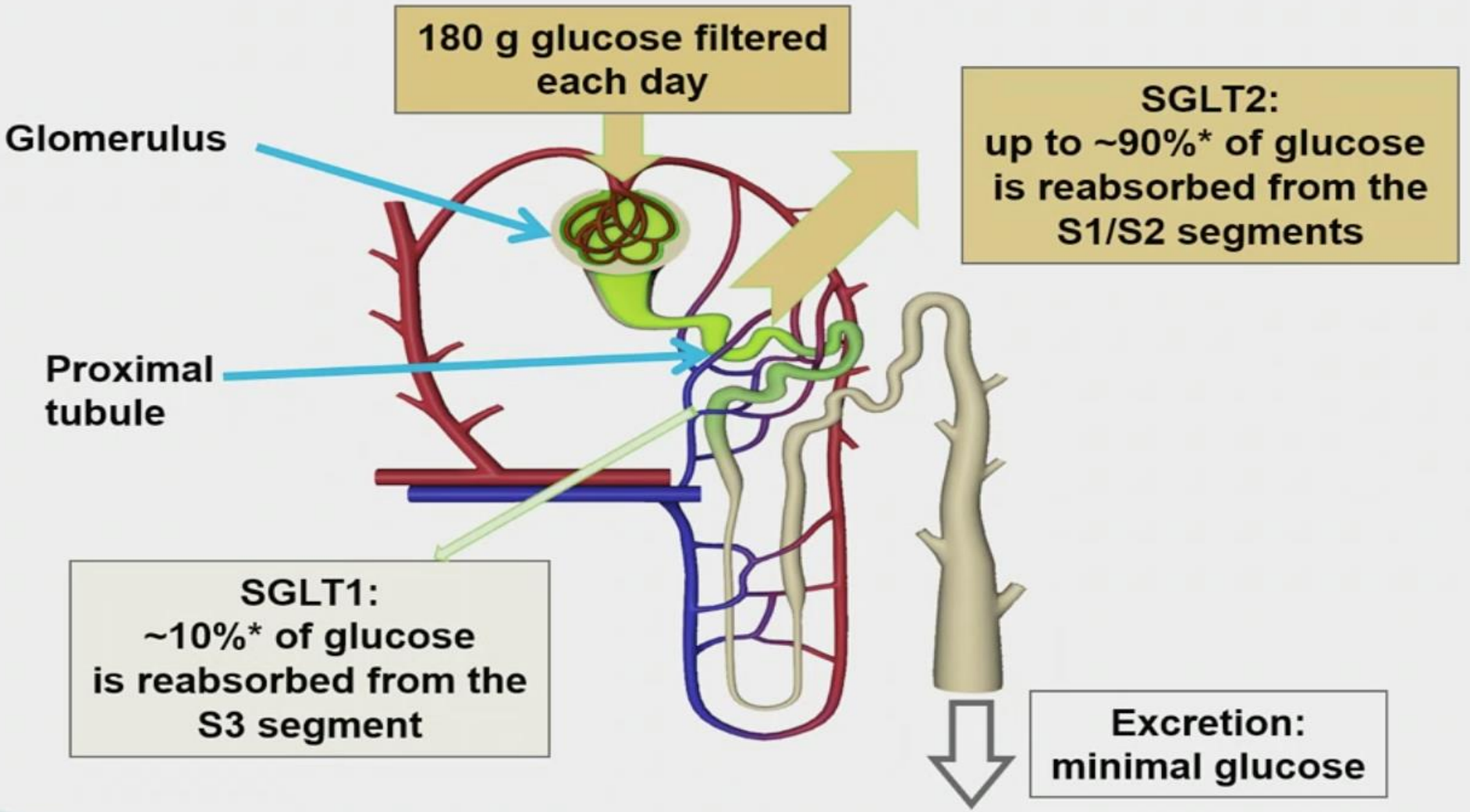


Fariba samadian

Associate professor of shahid Beheshti university of medical science

Labbafinejhad Hospital

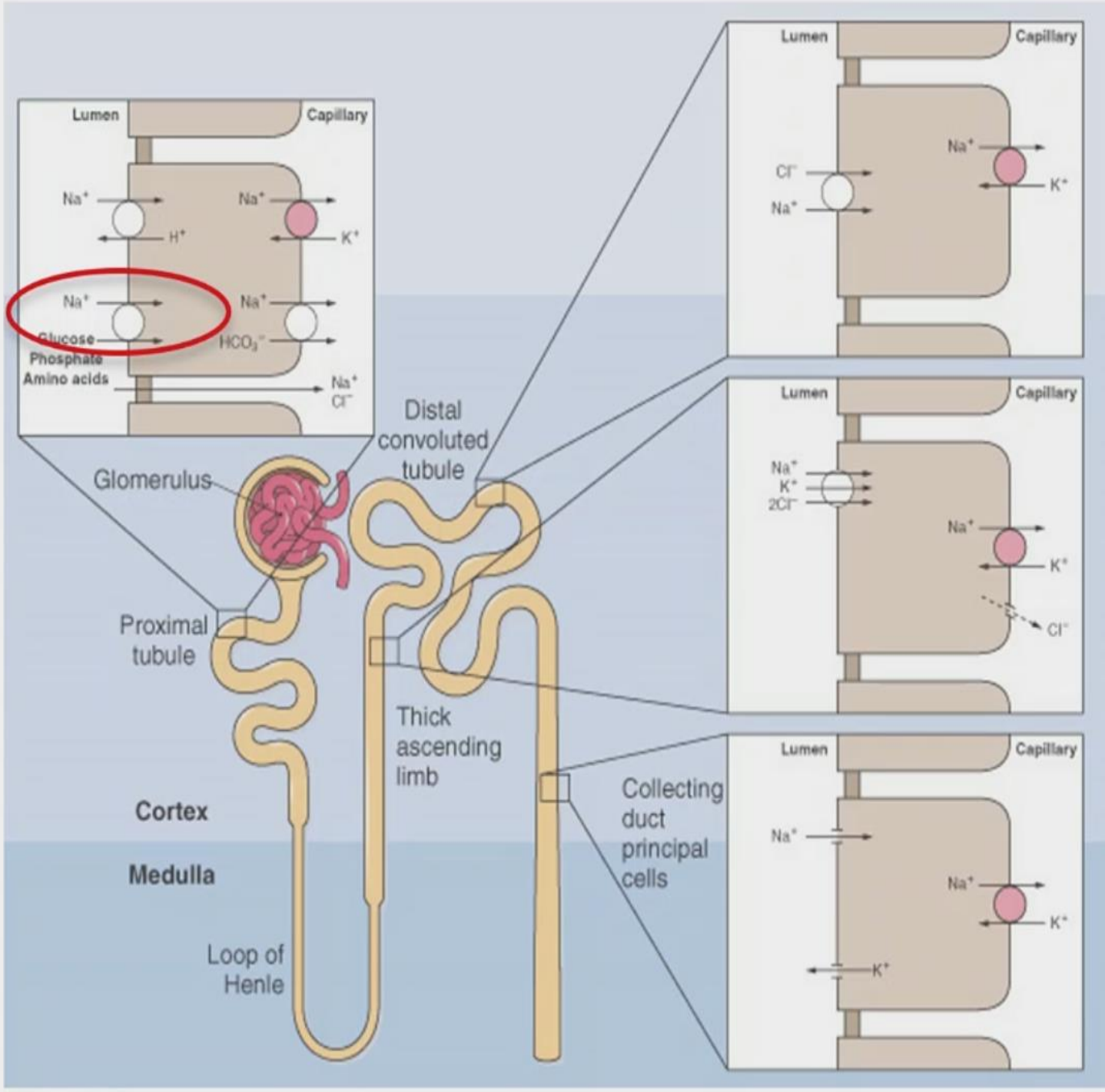
Glucose filtration and reabsorption



*based on animal data

Wright EM. *Am J Physiol Renal Physiol* 2001;280:F10–8
Lee YJ, et al. *Kidney Int Suppl* 2007;106:S27–35

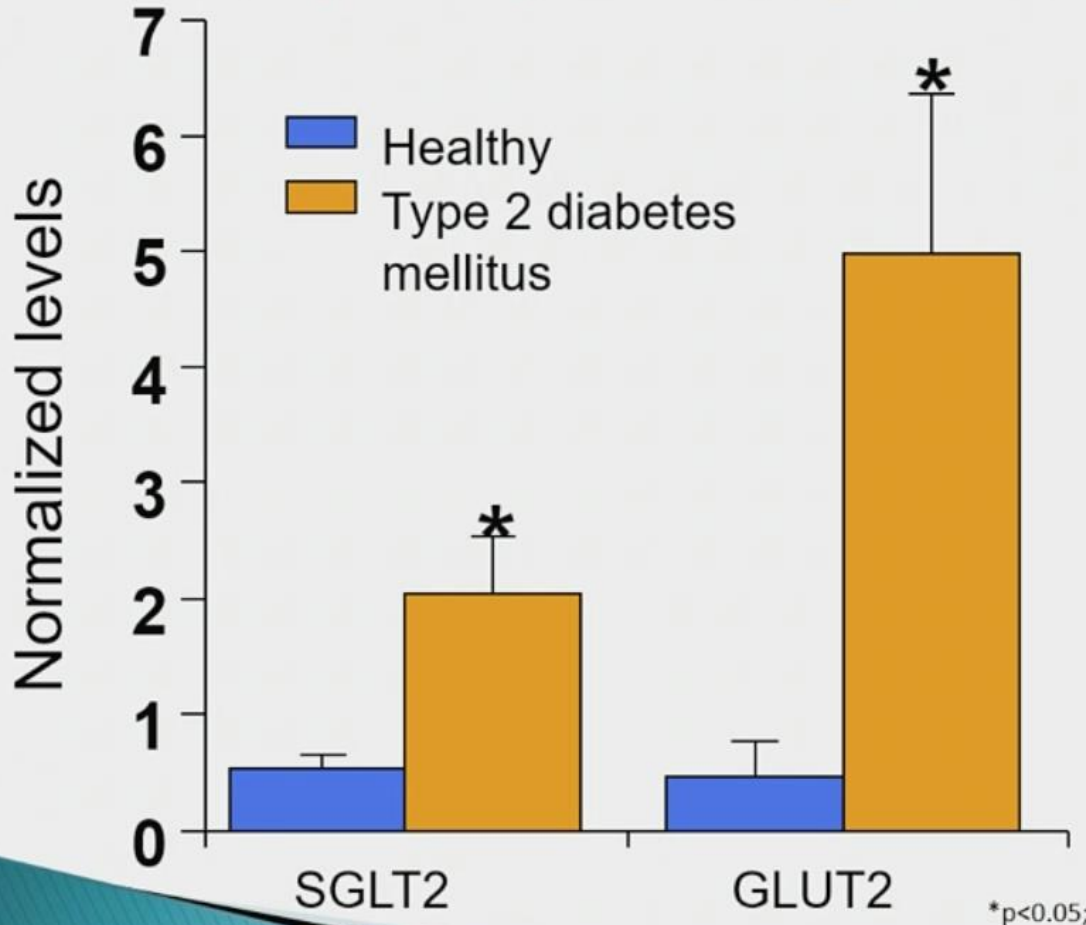
Main tubular Na^+ transport systems



Feehally J, Floege J, Johnson RJ (eds). Comprehensive Clinical Nephrology, 3rd Edn. Mosby Elsevier, Philadelphia, PA, 2007

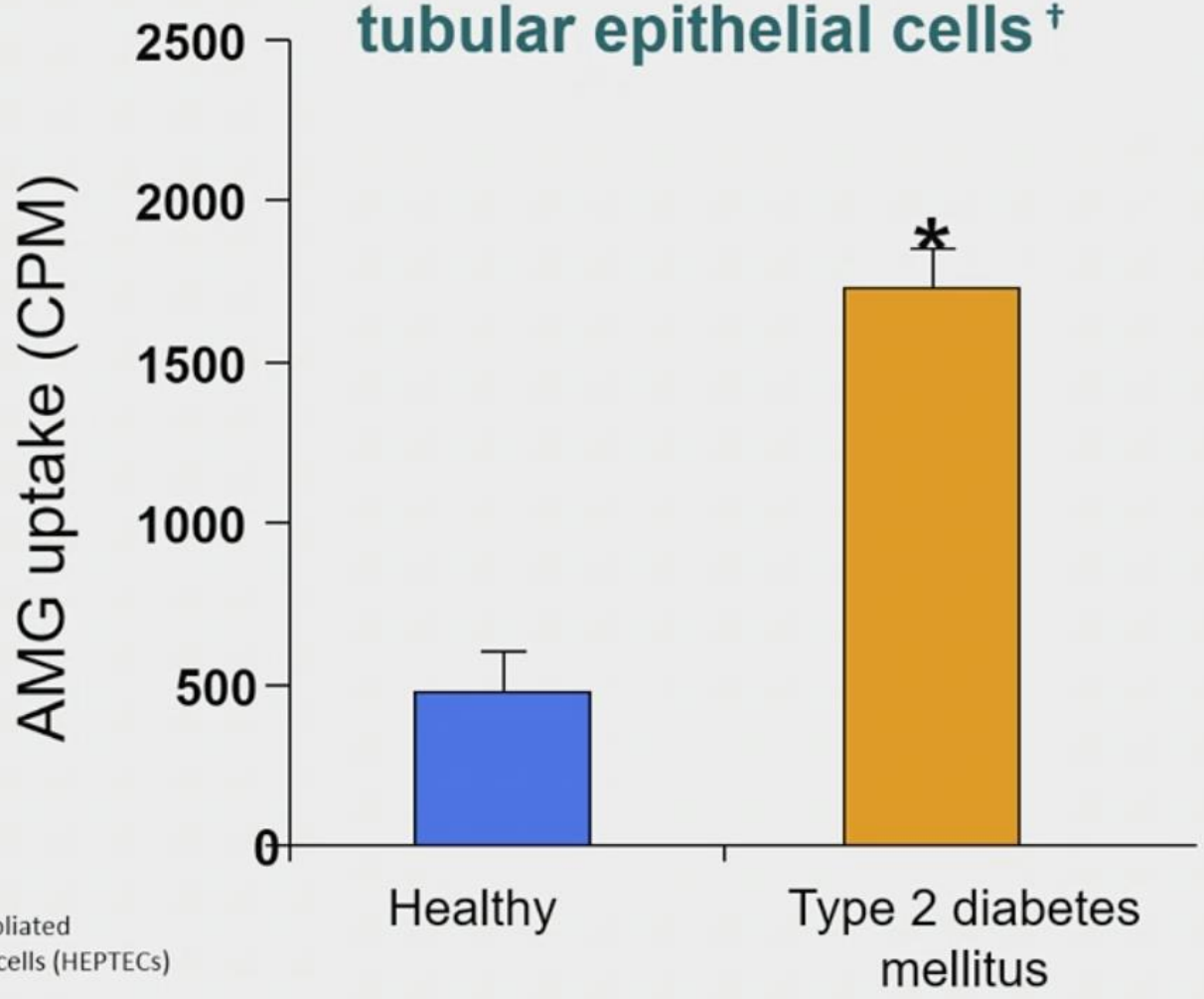
T2DM: SGLT-2 upregulation and increased glucose reabsorption

Transporter protein expression



*p<0.05; †from human exfoliated proximal tubular epithelial cells (HEPTECs)

Glucose uptake into tubular epithelial cells †

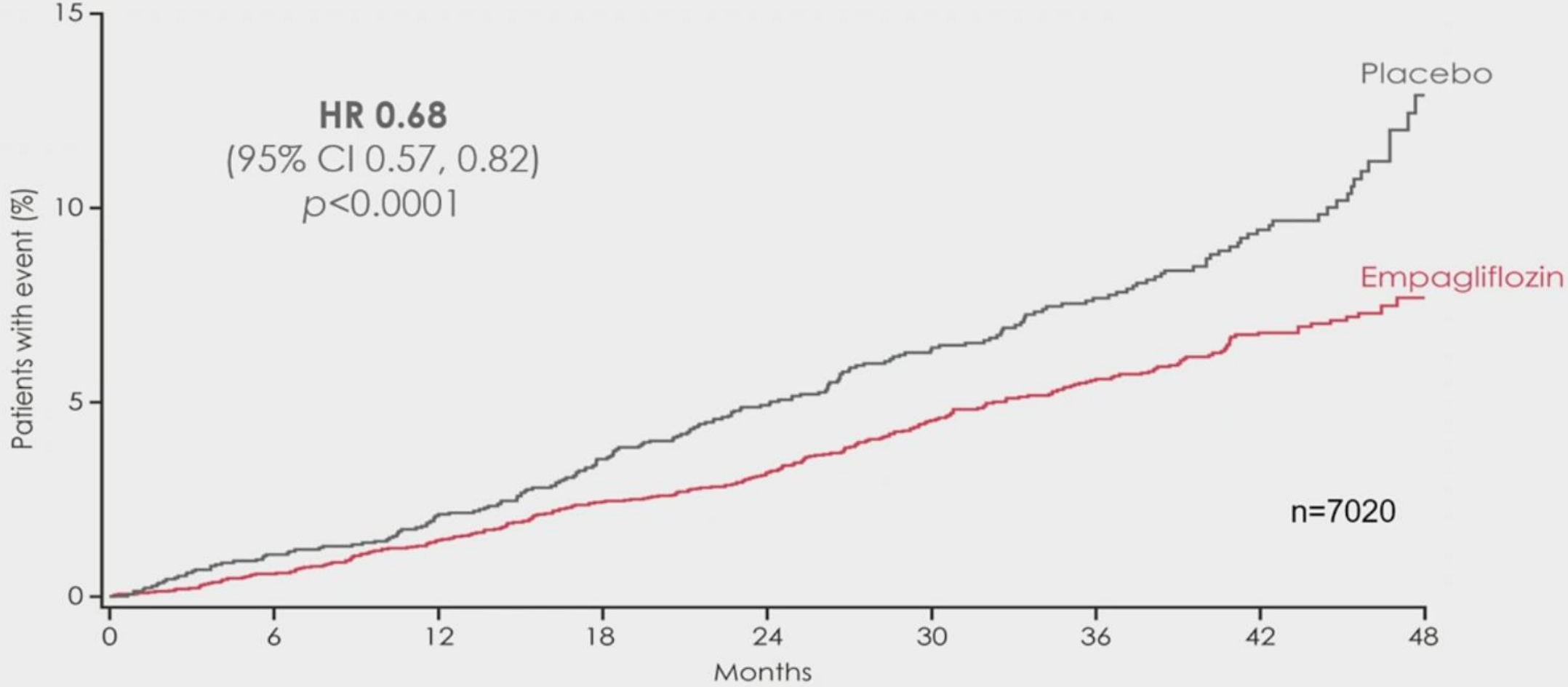


Rahmoune H, et al. *Diabetes* 2005;54:3427–34.

SGLT-2 inhibitors

Effects on cardiovascular outcomes

EMPA-REG OUTCOME: All-cause mortality



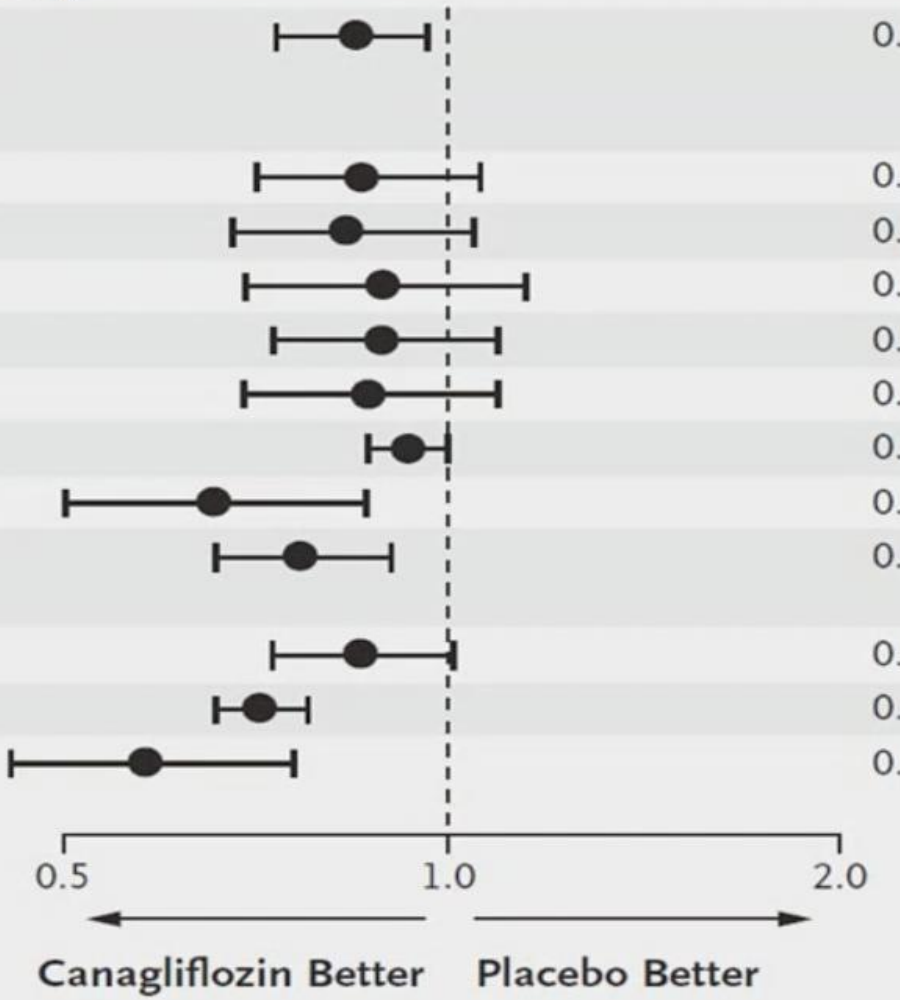
No. of patients									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Kaplan-Meier estimate. HR, hazard ratio

Zinman et al, N Engl J Med 2015

Canagliflozin and CV outcomes: CANVAS Program

Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)

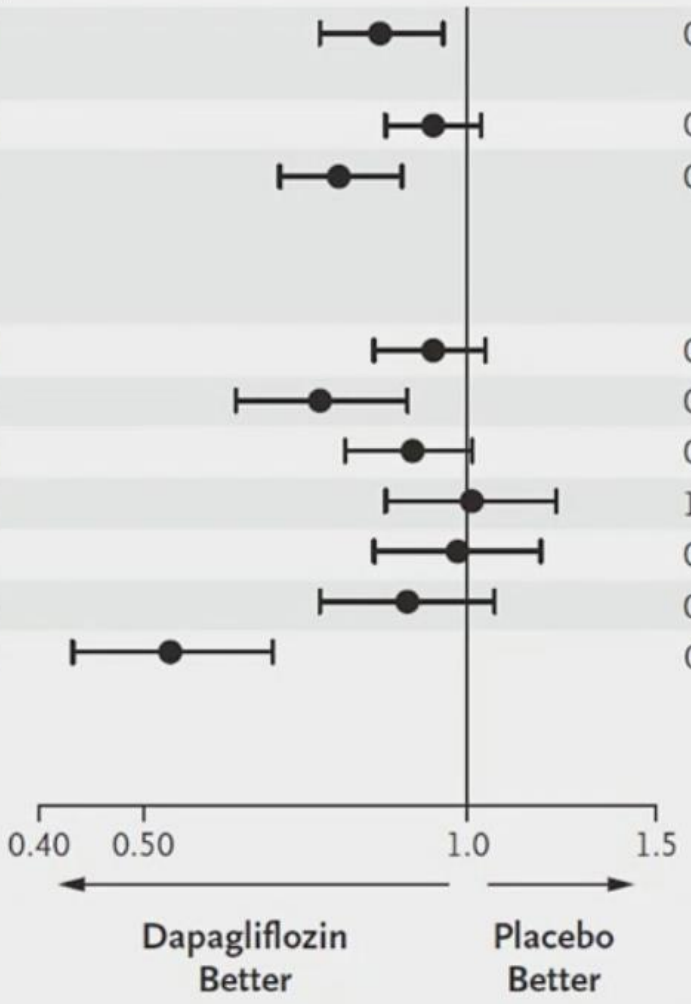


n=10,142

Neal B, et al. *N Engl J Med* 2016

Dapagliflozin and CV outcomes: DECLARE–TIMI 58

Outcome	Dapagliflozin (N=8582) no. (%)	Dapagliflozin (N=8582) rate/1000 patient-yr	Placebo (N=8578) no. (%)	Placebo (N=8578) rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Cardiovascular death or hospitalization for heart failure	417 (4.9)	12.2	496 (5.8)	14.7	0.83 (0.73–0.95)	0.005
MACE	756 (8.8)	22.6	803 (9.4)	24.2	0.93 (0.84–1.03)	0.17
≥40% decrease in eGFR to <60 ml/min/1.73 m^2, ESRD, or death from renal or cardiovascular cause	370 (4.3)	10.8	480 (5.6)	14.1	0.76 (0.67–0.87)	
Death from any cause	529 (6.2)	15.1	570 (6.6)	16.4	0.93 (0.82–1.04)	
Hospitalization for heart failure	212 (2.5)	6.2	286 (3.3)	8.5	0.73 (0.61–0.88)	
Myocardial infarction	393 (4.6)	11.7	441 (5.1)	13.2	0.89 (0.77–1.01)	
Ischemic stroke	235 (2.7)	6.9	231 (2.7)	6.8	1.01 (0.84–1.21)	
Death from cardiovascular cause	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82–1.17)	
Death from noncardiovascular cause	211 (2.5)	6.0	238 (2.8)	6.8	0.88 (0.73–1.06)	
≥40% decrease in eGFR to <60 ml/min/1.73 m^2, ESRD, or death from renal cause	127 (1.5)	3.7	238 (2.8)	7.0	0.53 (0.43–0.66)	



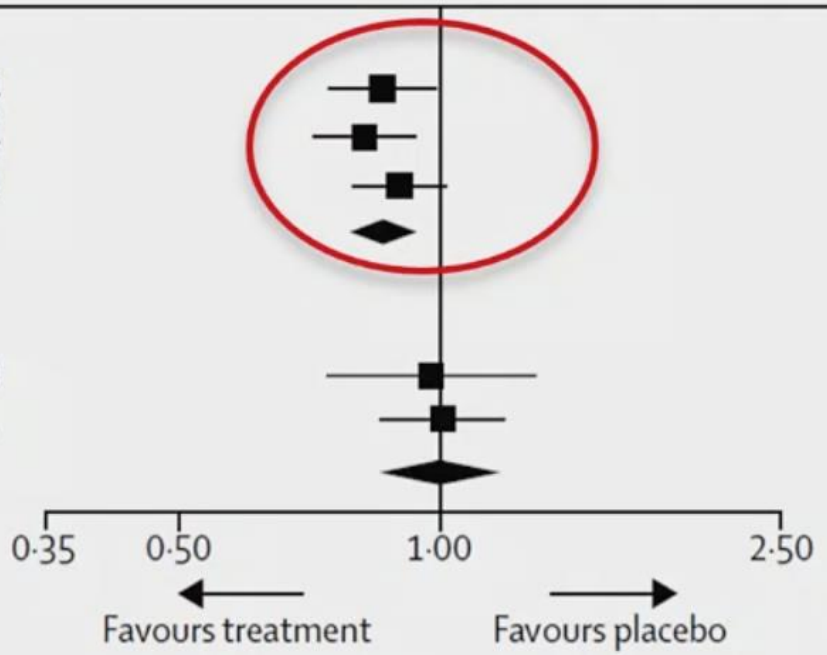
Wiviott, et al. N Engl J Med 2019

EMPAREG-OUTCOME, CANVAS & DECLARE-TIMI 58

Stratification by presence of CV disease

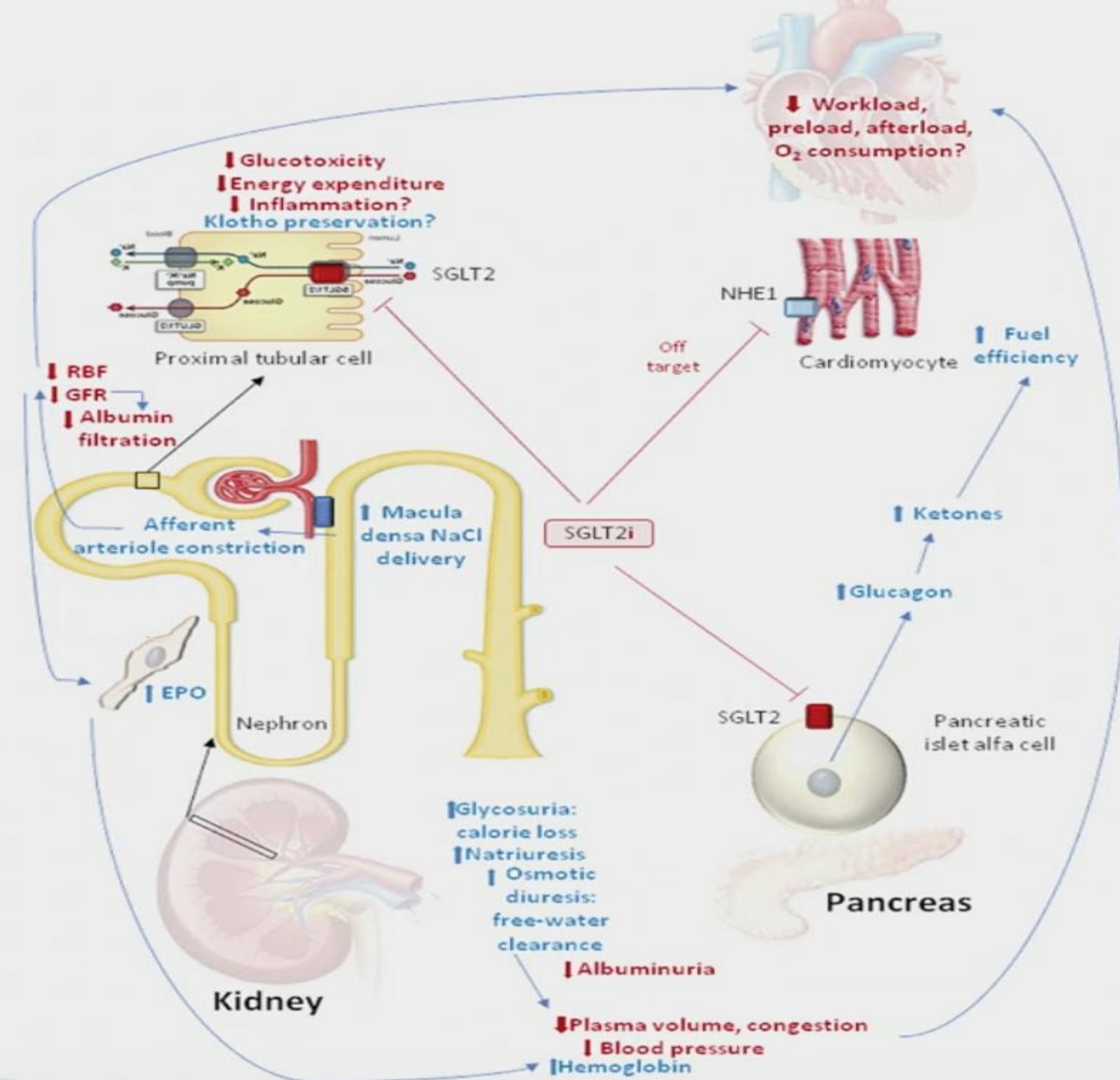
Composite of myocardial infarction, stroke, and cardiovascular death

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo		
Patients with atherosclerotic cardiovascular disease							
EMPA-REG OUTCOME	4687	2333	772	37·4	43·9	29·4	0·86 (0·74–0·99)
CANVAS Program	3756	2900	796	34·1	41·3	32·4	0·82 (0·72–0·95)
DECLARE-TIMI 58	3474	3500	1020	36·8	41·0	38·2	0·90 (0·79–1·02)
Fixed effects model for atherosclerotic cardiovascular disease (p=0·0002)							**0·86 (0·80–0·93)**
Patients with multiple risk factors							
CANVAS Program	2039	1447	215	15·8	15·5	25·9	0·98 (0·74–1·30)
DECLARE-TIMI 58	5108	5078	539	13·4	13·3	74·1	1·01 (0·86–1·20)
Fixed effects model for multiple risk factors (p=0·98)							**1·00 (0·87–1·16)**



Zelniker et al. *Lancet* 2018

What are the mechanisms for cardioprotection with SGLT2-i?



Sarafidis et al. *Nephrol Dial Transplant* 2019

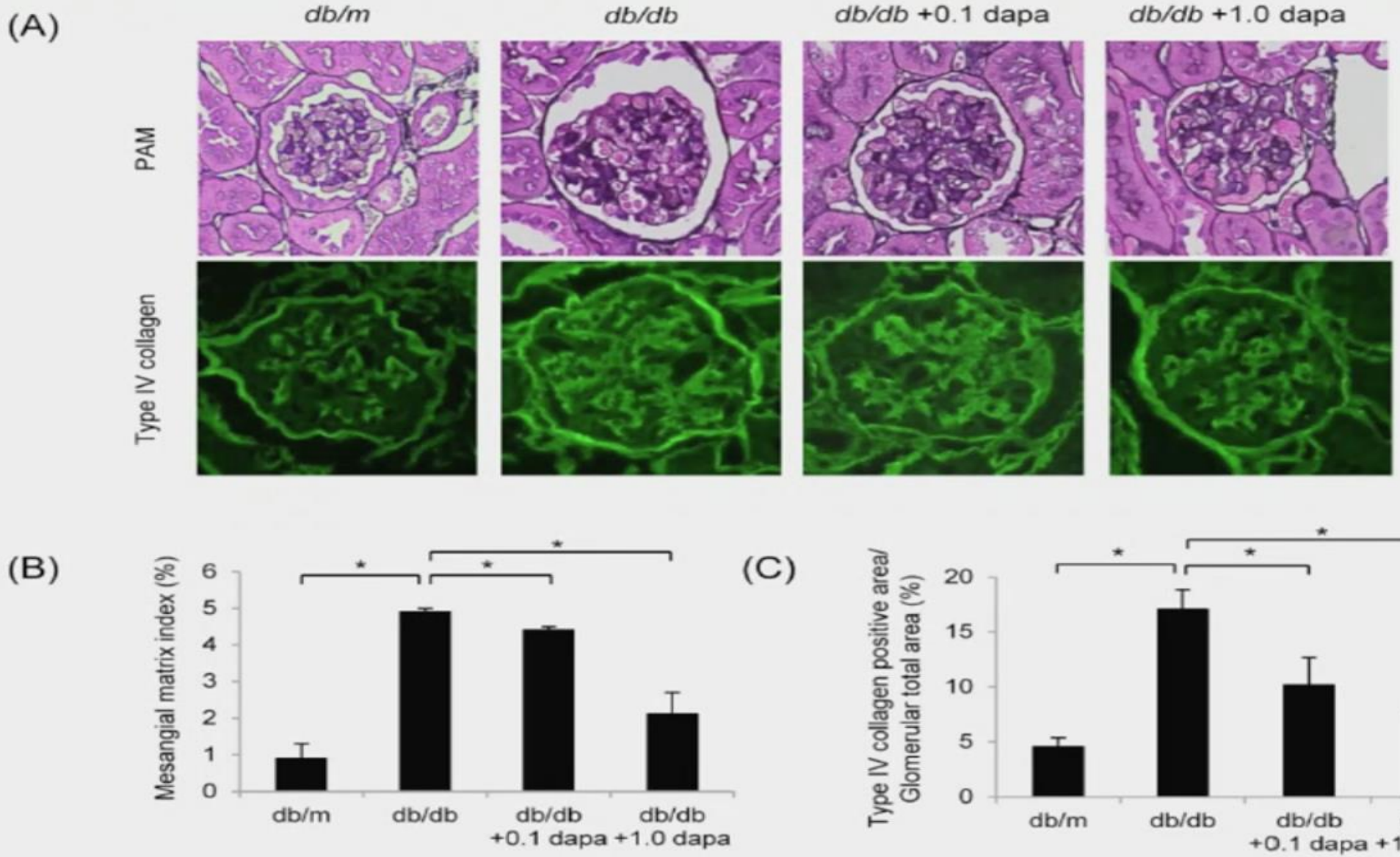
What are the mechanisms for cardioprotection with SGLT2-i?

- Is it BP & arterial stiffness reduction?
- Is it the diuretic action?
- Is it RAAS inhibition?
- Is it body fat reduction?
- Is it hemoglobin increase?
- Is it delay of CKD progression?

SGLT-2 inhibitors

Effects on renal outcomes

Dapagliflozin in diabetic nephropathy

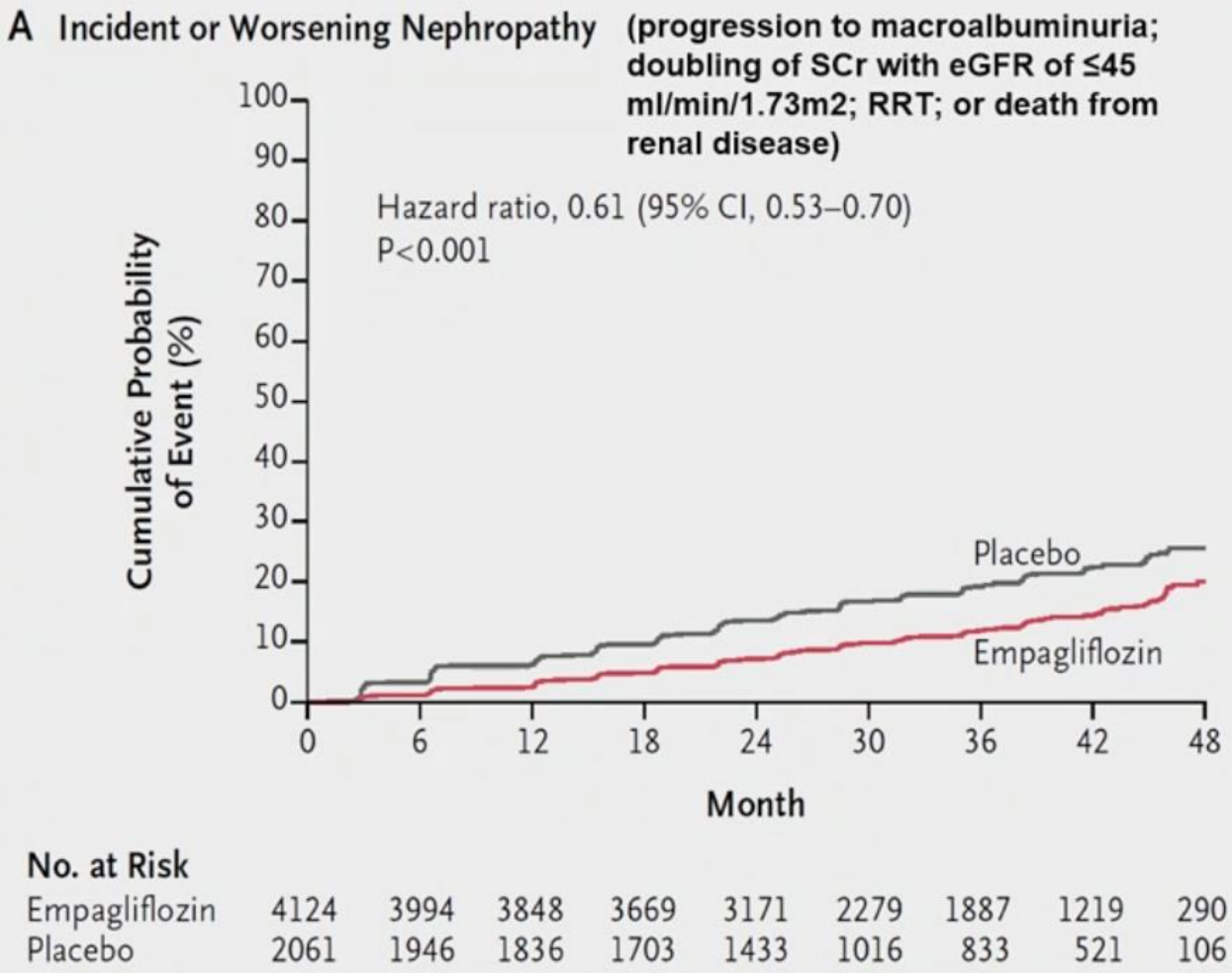


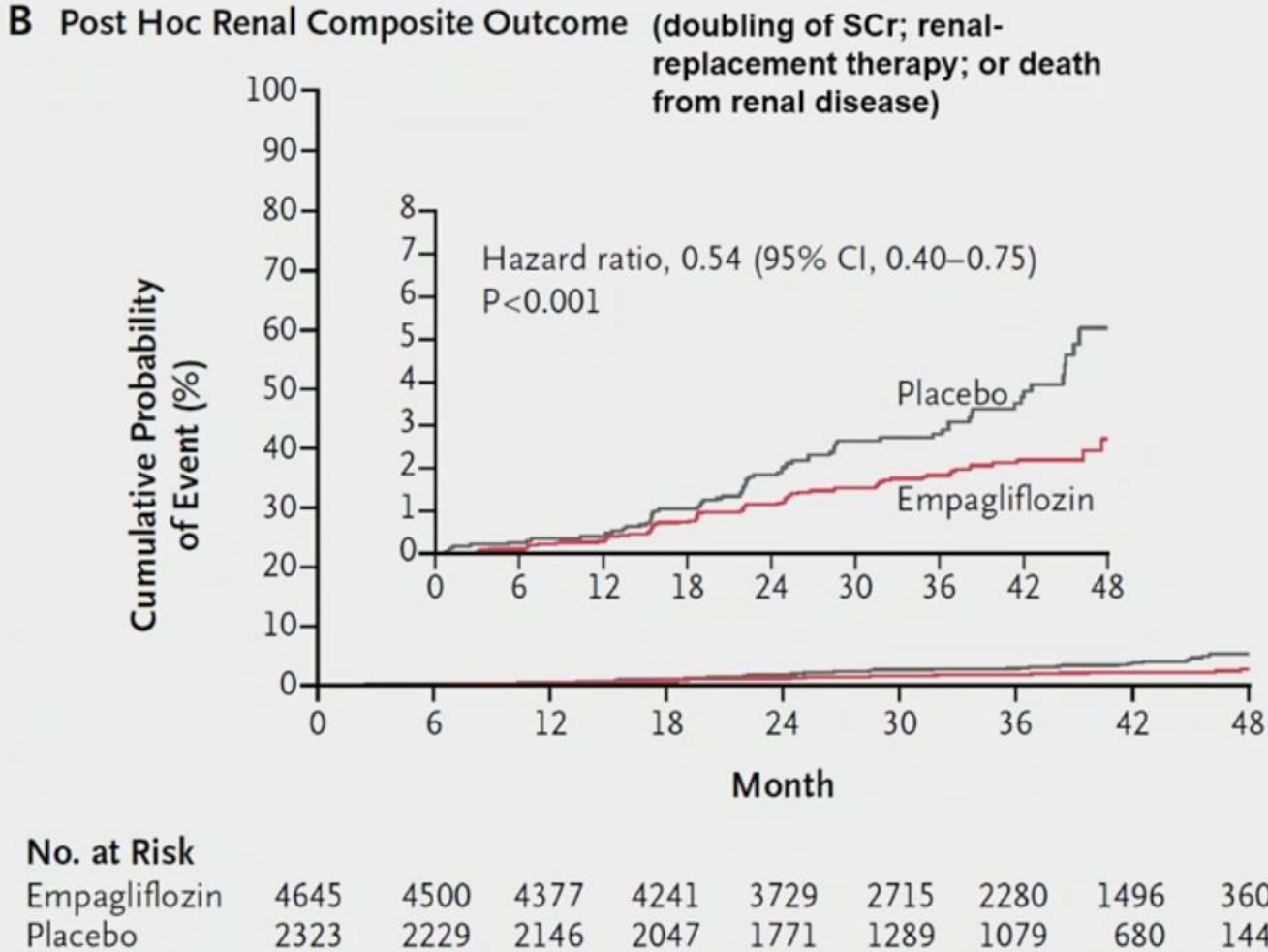
Terami et al. *PLOS One* 2014

SGLT-2 inhibitors and albuminuria

EMPA-REG OUTCOME: Renal Events

7020 patients, 1819 with GFR <60 ml/min, 2012 micro- & 769 macroalbuminuria, >80% on RAS blockers



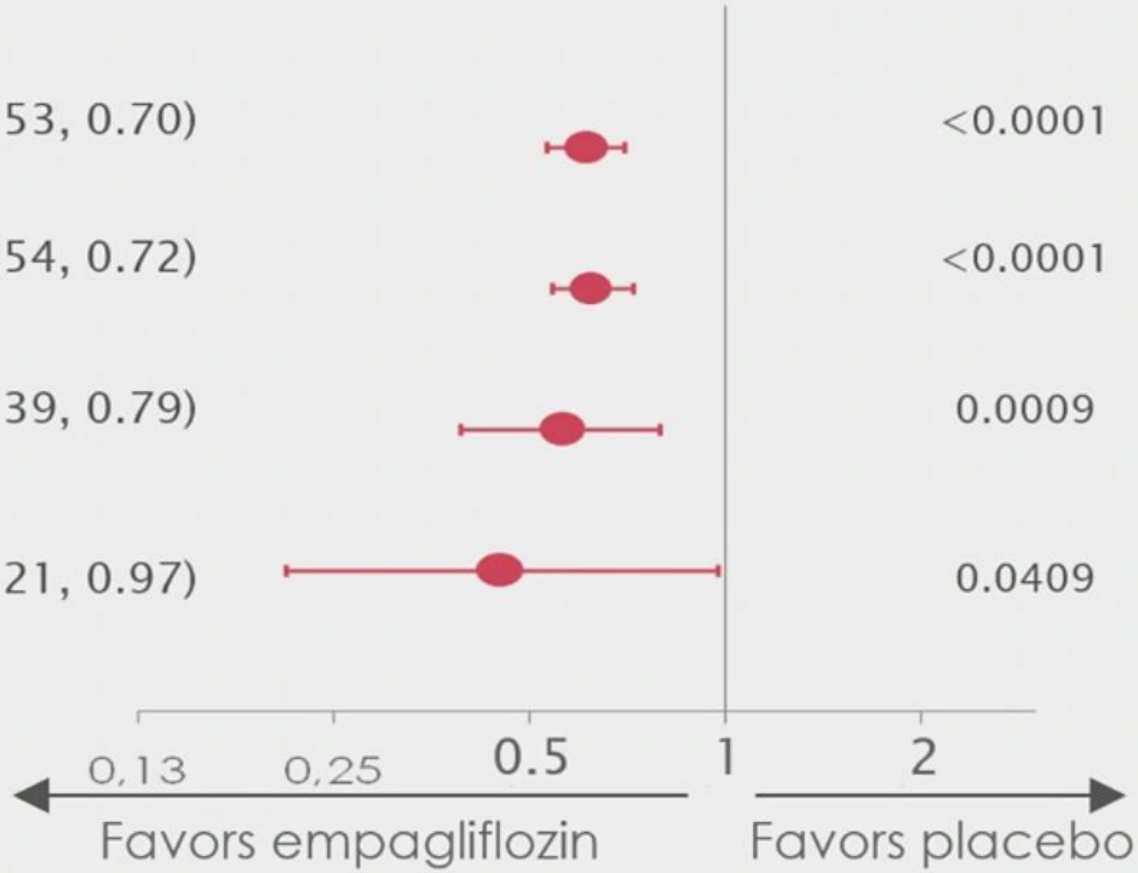


Wanner et al. *N Engl J Med* 2016

EMPA-REG Renal: Individual components

	Empagliflozin	Placebo	Hazard ratio (95% CI)	p-value
	n with event/ N analyzed			
Incident or worsening nephropathy	525/4124	388/2061	0.61 (0.53, 0.70)	<0.0001
New onset macroalbuminuria	459/4091	330/2033	0.62 (0.54, 0.72)	<0.0001
Doubling of serum-creatinine*	70/4645	60/2323	0.56 (0.39, 0.79)	0.0009
Initiation of renal replacement therapy	13/4687	14/2333	0.45 (0.21, 0.97)	0.0409

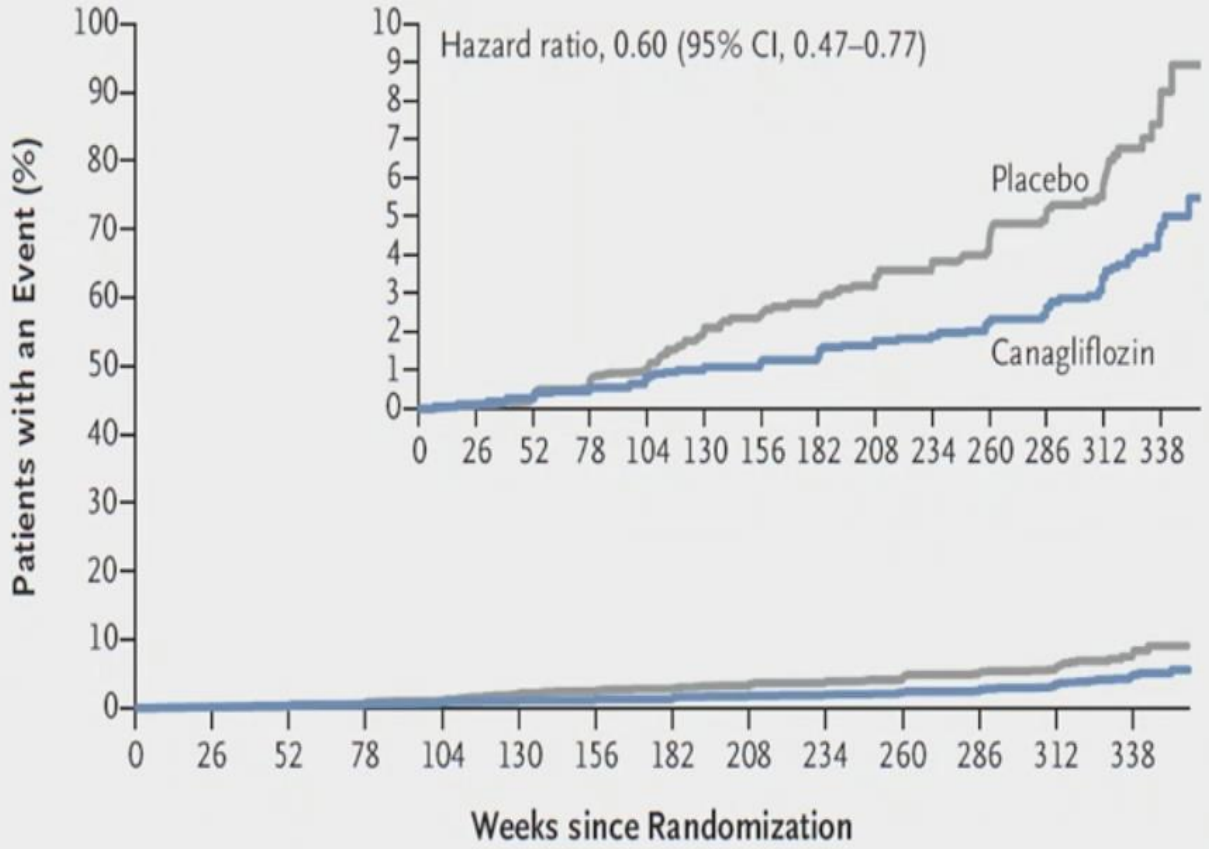
*Accompanied by eGFR (MDRD) ≤45 mL/min/1.73m^2.
Cox regression analyses.



Wanner et al. N Engl J Med 2016

Canagliflozin and renoprotection: the CANVAS program

≥40% decrease eGFR, requirement of RRT, or death from renal causes

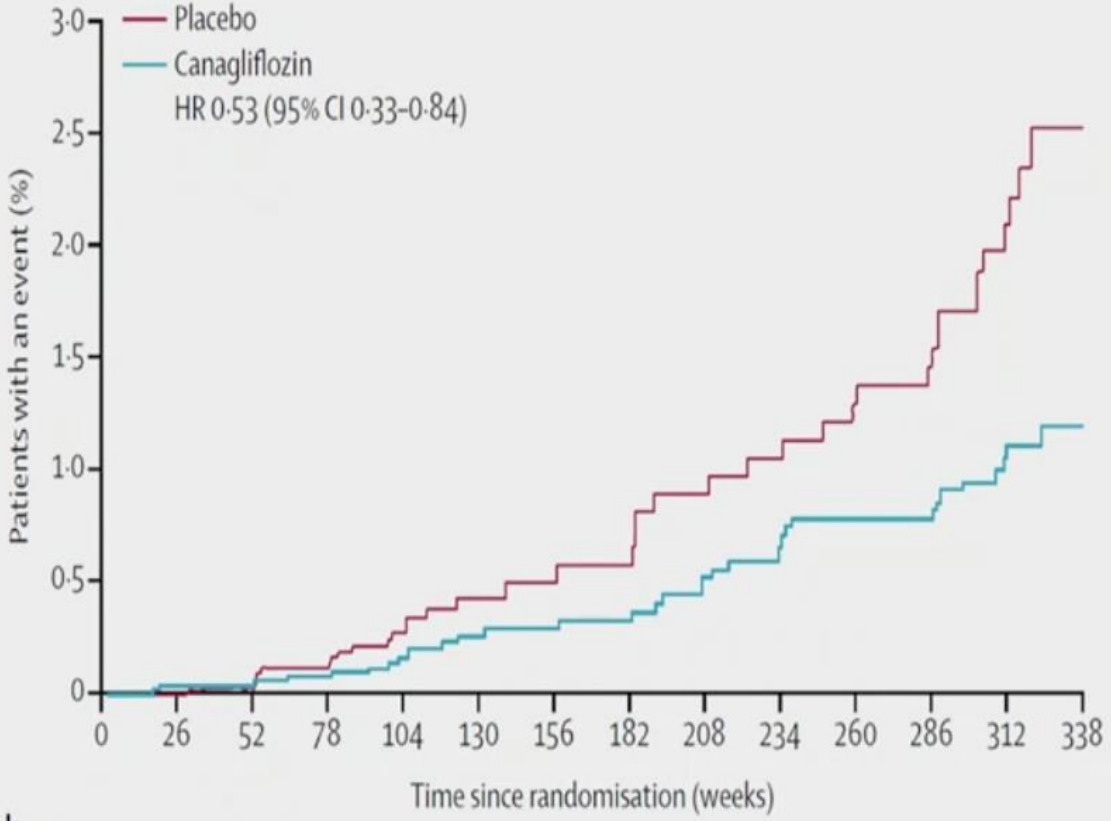


o. at Risk

acebo	4347	4287	4227	4151	3029	1674	1274	1253	1229	1202	1173	1148	819	229
anagliflozin	5795	5737	5664	5578	4454	3071	2654	2623	2576	2542	2495	2450	1781	493

Neal B, et al. *N Engl J Med* 2016

Doubling of SCr, ESKD, or death from renal causes



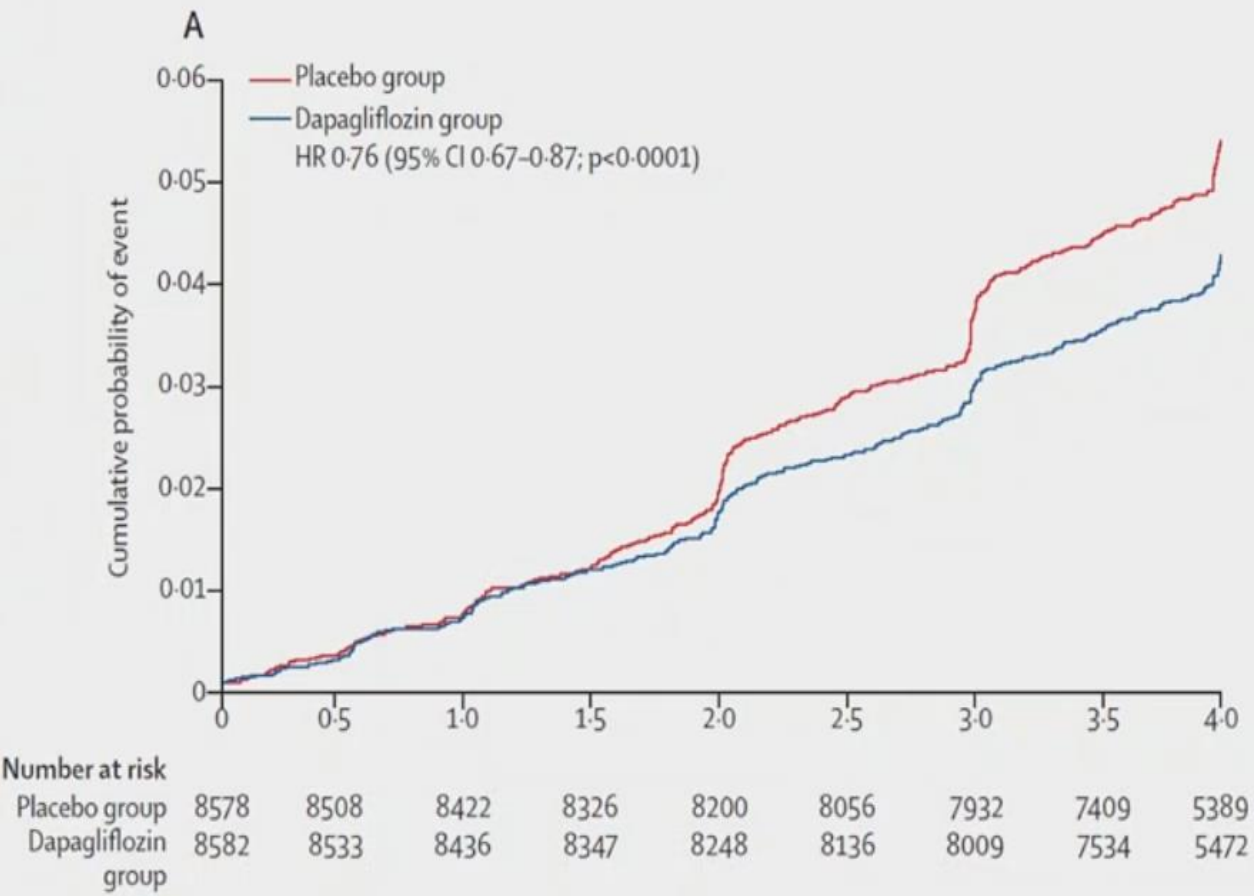
Number at risk

Placebo	4347	4291	4235	4170	3050	1693	1294	1276	1253	1229	1200	1181	844	237
Canagliflozin	5795	5741	5677	5599	4476	3089	2670	2641	2597	2564	2520	2481	1809	501

Perkovic, et al. *Lancet Diab Endocrinol* 2018

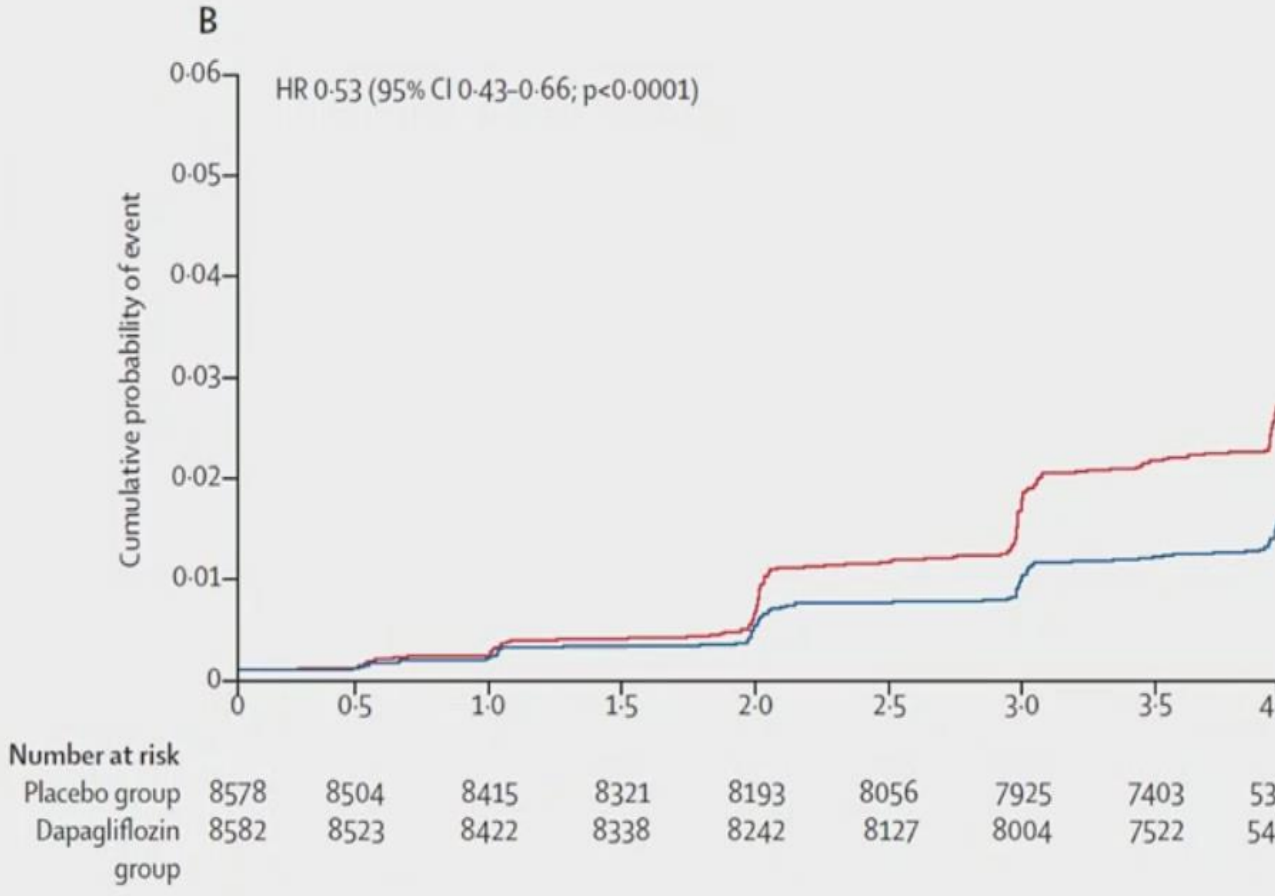
Dapagliflozin and renoprotection: DECLARE-TIMI 58

≥40% decrease of eGFR to <60 ml/minute/1.73 m^2, ESRD, or death from renal or cardiovascular causes



Wiviott, et al. *N Engl J Med* 2019

≥40% decrease of eGFR to <60 ml/minute/1.73 m^2, ESRD, or death from renal causes



Mozenzon, et al. *Lancet Diab Endocrinol* 2019

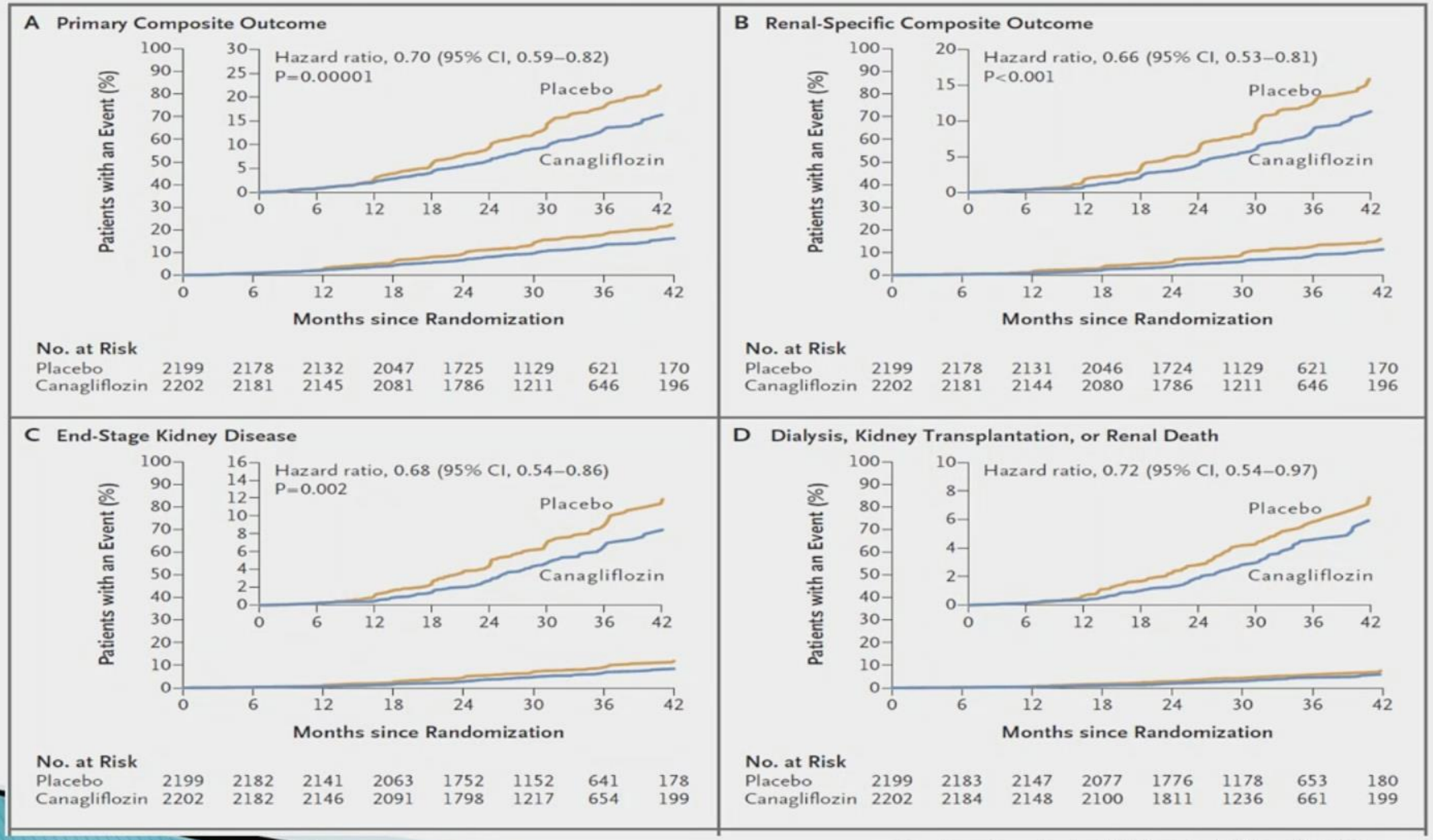
ORIGINAL ARTICLE

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

- 4401 patients with DM type 2 on RAS blockade
- eGFR 30-90 ml/min/1.73 m2
- ACR 300 – 5000 mg/g
- canagliflozin vs placebo
- early stop for benefit; median follow-up of 2.62 years

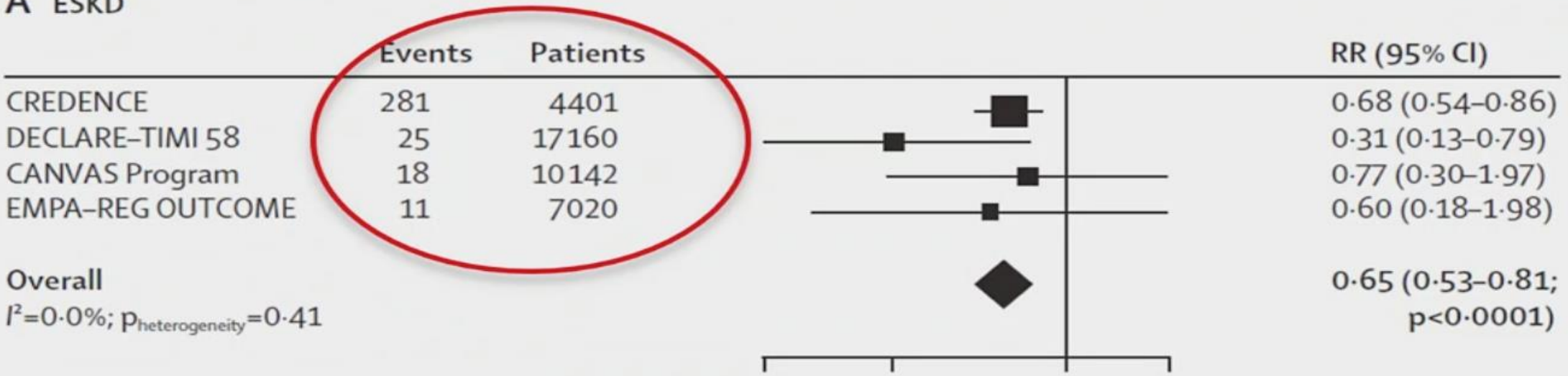
Canagliflozin and renoprotection: CREDENCE study



Perkovic et al. *N Engl J Med* 2019

SGLT-2 inhibitors and renoprotection

A ESKD



	Events	Patients	RR (95% CI)
CREDENCE	281	4401	0·68 (0·54–0·86)
DECLARE–TIMI 58	25	17160	0·31 (0·13–0·79)
CANVAS Program	18	10142	0·77 (0·30–1·97)
EMPA–REG OUTCOME	11	7020	0·60 (0·18–1·98)
Overall			0·65 (0·53–0·81; p<0·0001)
I^2=0·0%; $p_{heterogeneity}$=0·41			

B Substantial loss of kidney function, ESKD, or death due to kidney disease

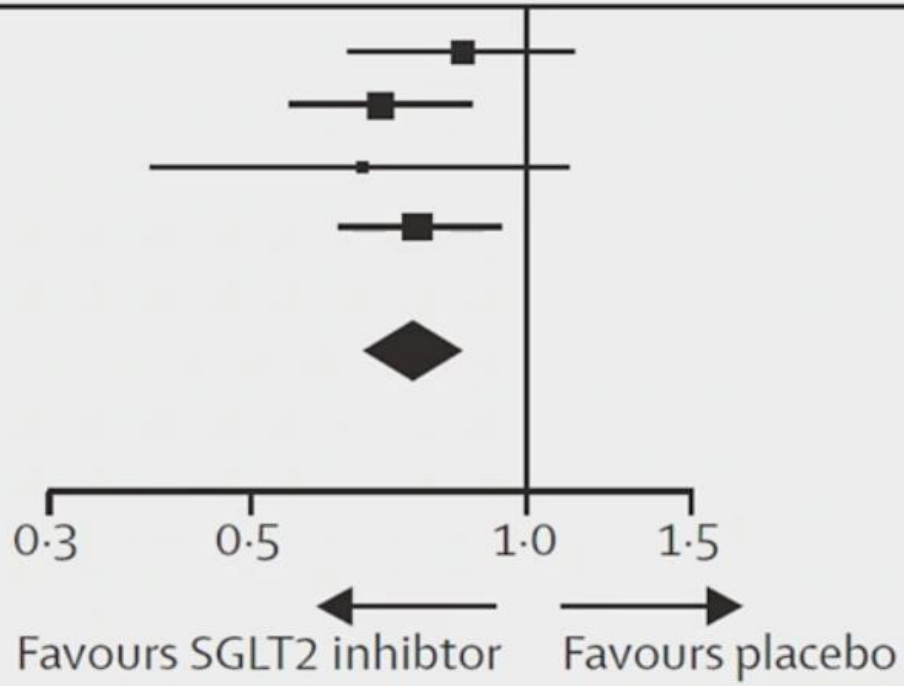
CREDENCE	377	4401	0·66 (0·53–0·81)
DECLARE–TIMI 58	365	17160	0·53 (0·43–0·66)
CANVAS Program	73	10142	0·53 (0·33–0·84)
EMPA–REG OUTCOME	152	6968	0·54 (0·40–0·75)
Overall			0·58 (0·51–0·66; p<0·0001)
I^2=0·0%; $p_{heterogeneity}$=0·49			

Neuen et al. *Lancet Diabetes Endocrinol* 2019

SGLT-2 inhibitors and AKI risk

	Events	Patients	RR (95% CI)
CREDENCE	184	4397	0·85 (0·64–1·13)
DECLARE–TIMI 58	300	17143	0·69 (0·55–0·87)
CANVAS Program	58	10134	0·66 (0·39–1·11)
EMPA–REG OUTCOME	401	7010	0·76 (0·62–0·93)
Overall			**0·75 (0·66–0·85; p<0·0001)**

I^2=0·0%; $p_{heterogeneity}$=0·68



Neuen et al. *Lancet Diabetes Endocrinol* 2019

SGLT-2 inhibitors and nephroprotection

Potential mechanisms

Renal Hemodynamic Effect of Sodium-Glucose Cotransporter 2 Inhibition in Patients With Type 1 Diabetes Mellitus

David Z.I. Cherney, MD, PhD*; Bruce A. Perkins, MD, MPH*; Nima Soleymanlou, PhD*; Maria Maione, RN; Vesta Lai, RN; Alana Lee, RN; Nora M. Fagan, MS; Hans J. Woerle, MD; Odd Erik Johansen, MD, PhD; Uli C. Broedl, MD†; Maximilian von Eynatten, MD†

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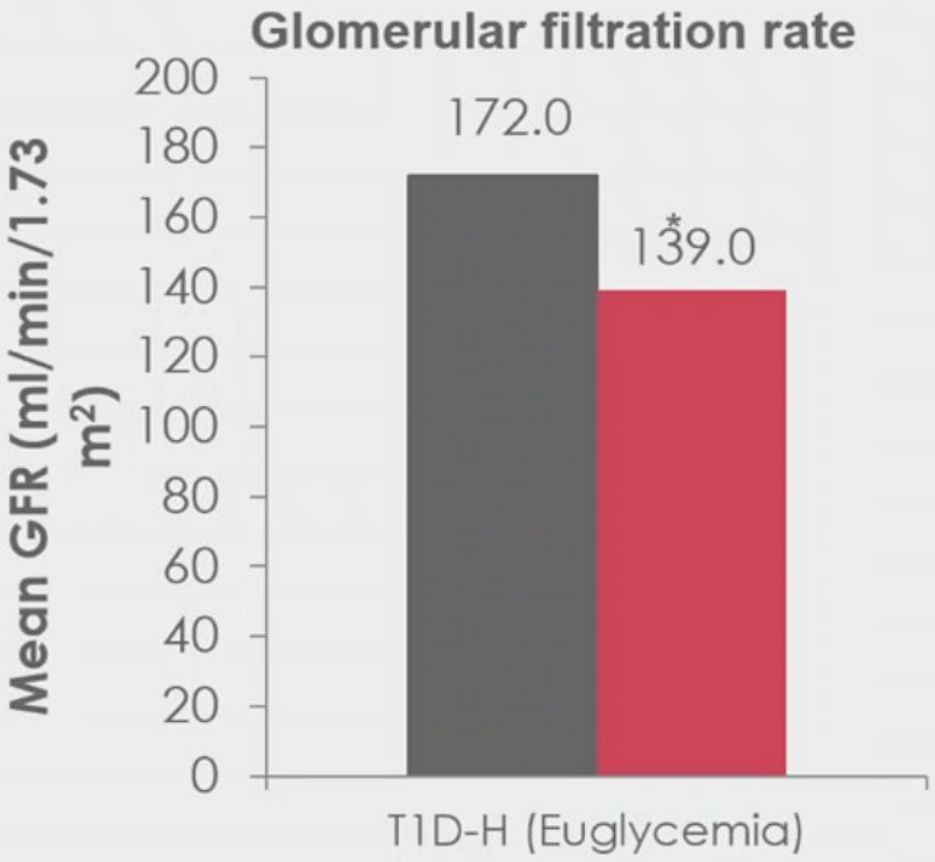

GFR reduced by
-33 ml/min/1.73

■ Baseline
■ Empagliflozin
*$p<0.01$

Type 1 Diabetes:

27 Type 1 diabetes patients with hyperfiltration. Mean GFR recorded at baseline and after 8 weeks treatment with empagliflozin 25 mg QD

Cherney D *et al. Circulation* 2014;129:587

Renal Hemodynamic Effect of Sodium-Glucose Cotransporter 2 Inhibition in Patients With Type 1 Diabetes Mellitus

David Z.I. Cherney, MD, PhD*; Bruce A. Perkins, MD, MPH*; Nima Soleymanlou, PhD*; Maria Maione, RN; Vesta Lai, RN; Alana Lee, RN; Nora M. Fagan, MS; Hans J. Woerle, MD; Odd Erik Johansen, MD, PhD; Uli C. Broedl, MD†; Maximilian von Eynatten, MD†

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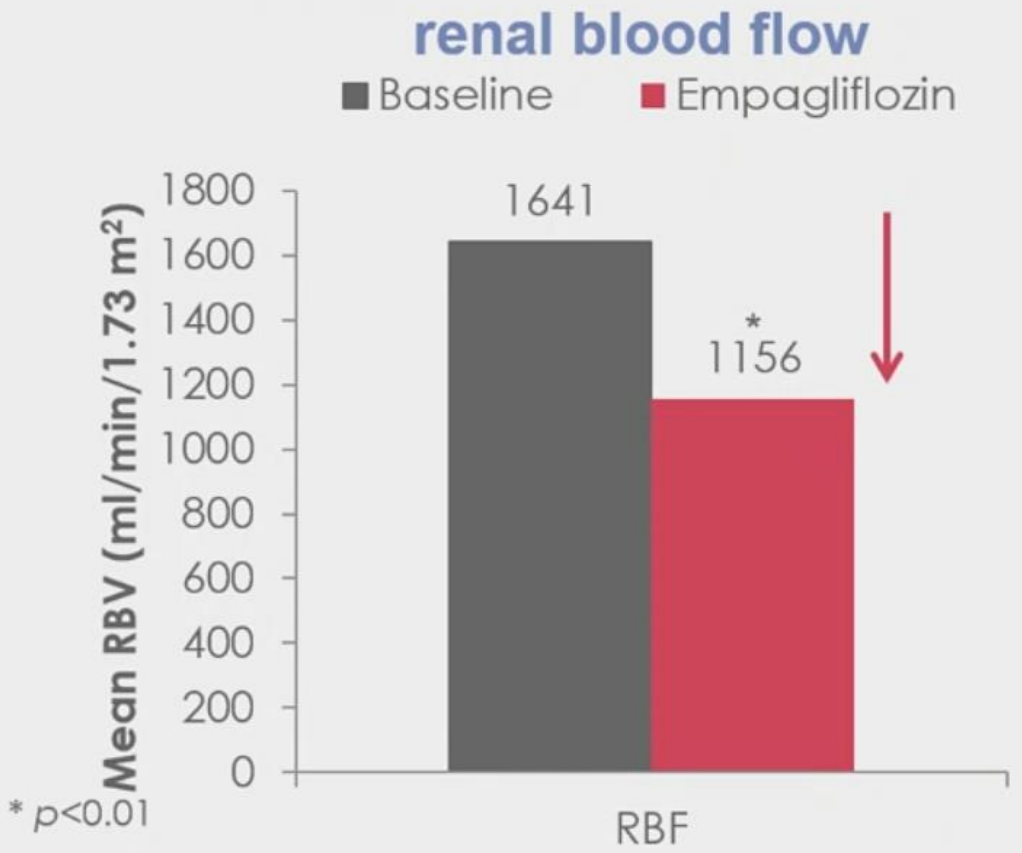
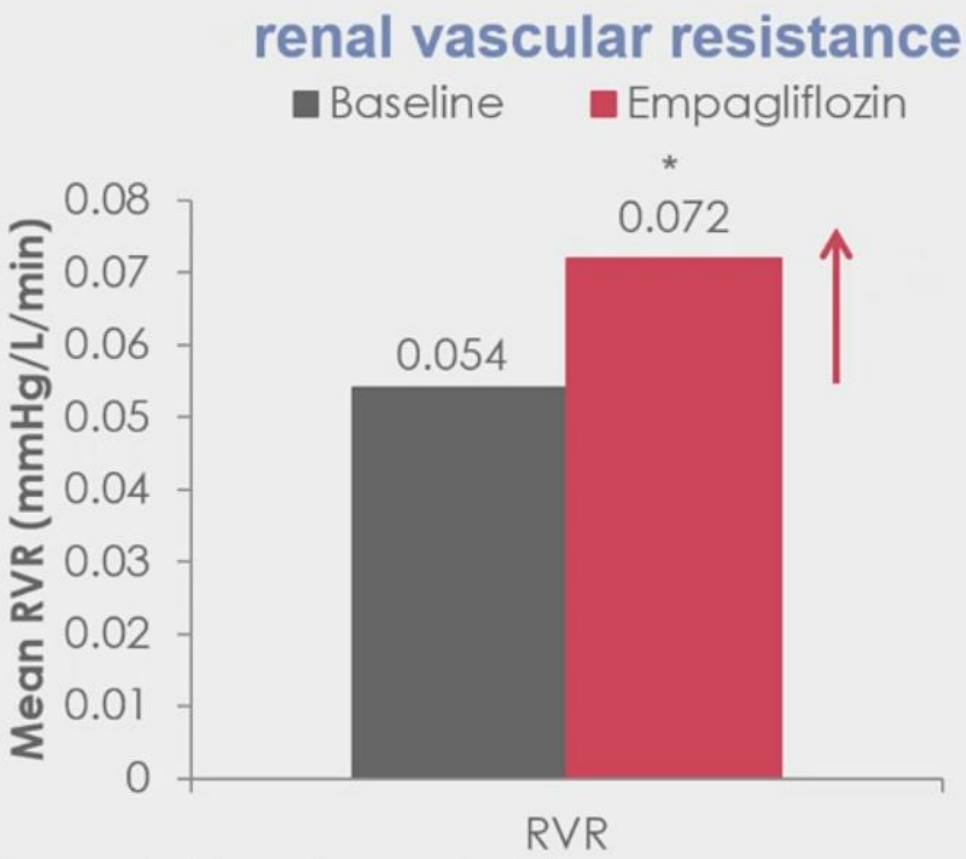
reduced **renal blood flow** + increased **renal vascular resistance** = **afferent vasoconstriction**

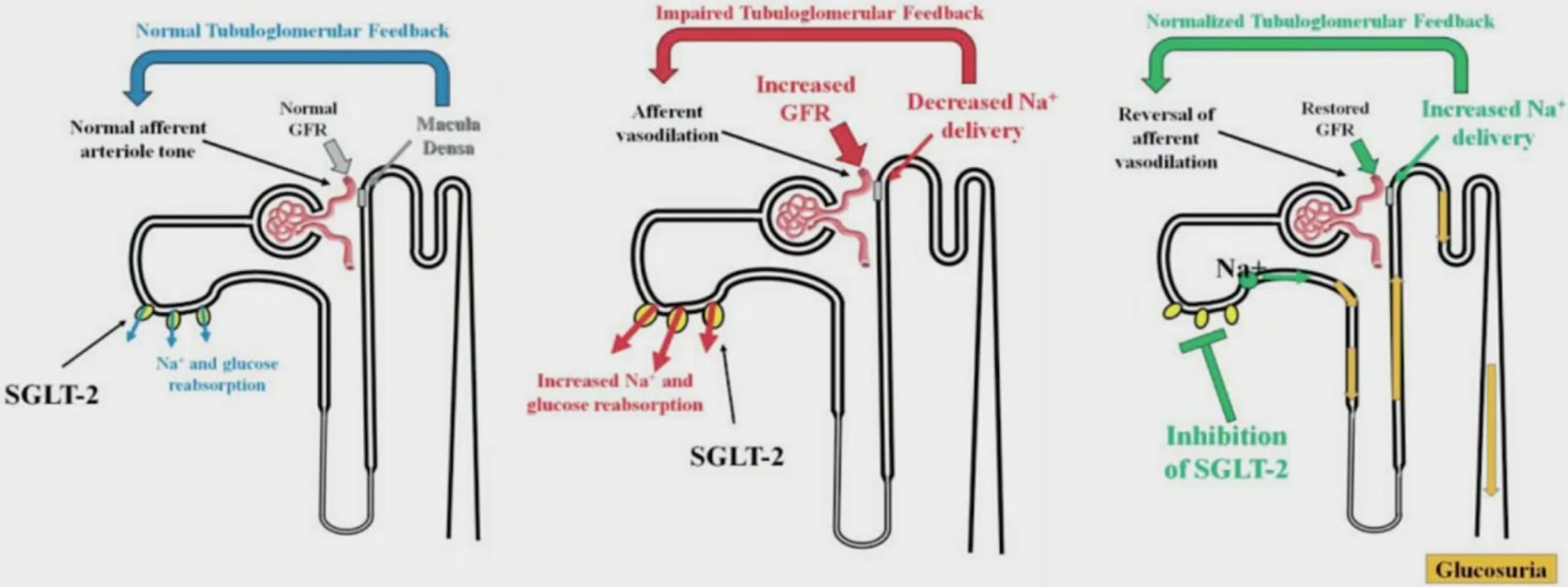




Patients with type 1 diabetes and hyperfiltration at baseline. RBV and RVR recorded in euglycaemic state.
RBF, renal blood flow; RVR, renal vascular resistance

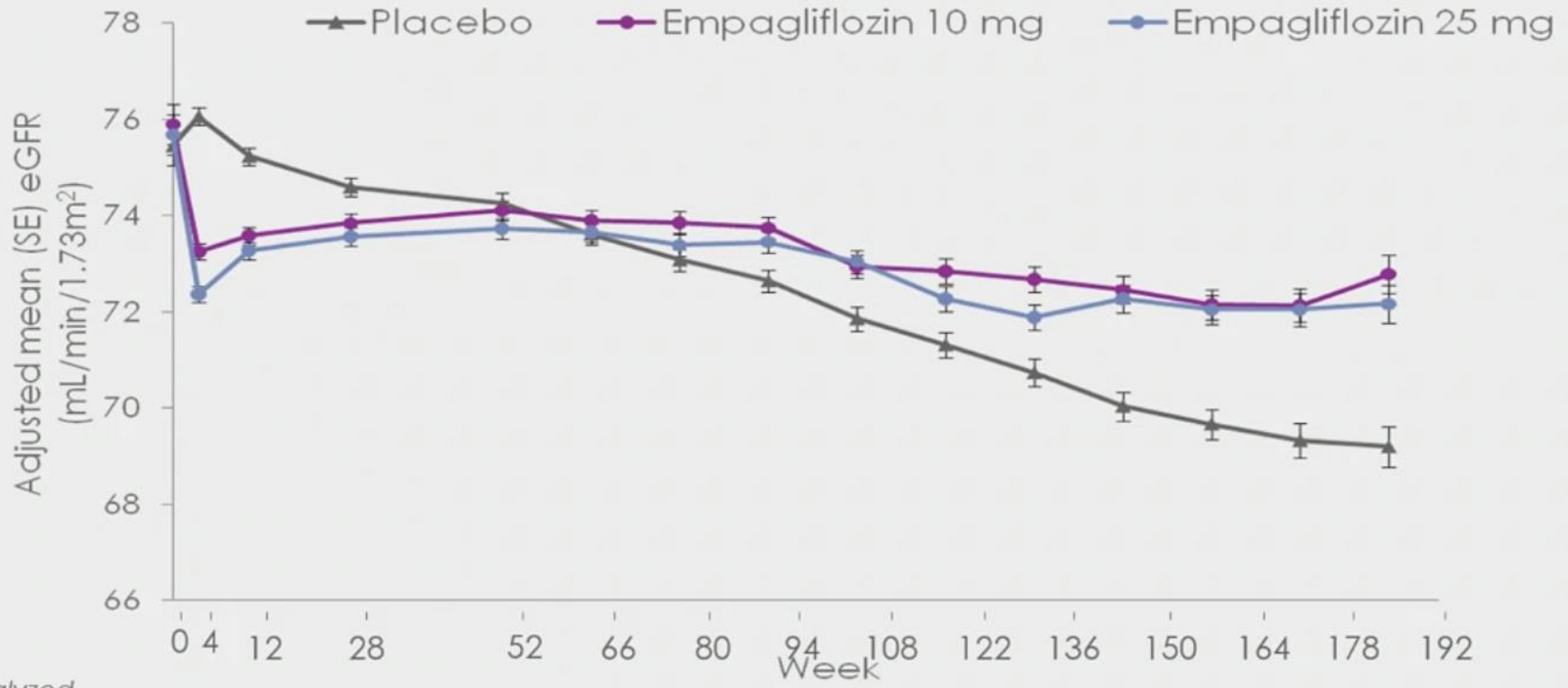
Cherney D *et al. Circulation* 2014;129:587

SGLT-2 inhibitors reverse afferent vasodilation



Sarafidis et al. *Nephrol Dial Transplant* 2019

EMPAREG-RENAL: eGFR over 192 weeks



No. analyzed														
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in follow-up for adverse/outcome events															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3492	2707	1703

Mixed model repeated measures analysis. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

SGLT-2 inhibitor effects in T1DM vs T2DM

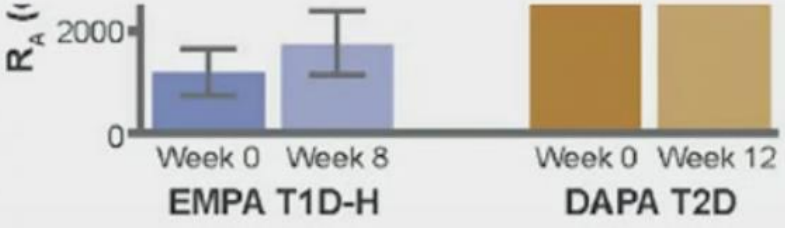
www.kidney-international.org editorial

Renal hemodynamic effects of sodium-glucose cotransporter 2 inhibitors in hyperfiltering people with type 1 diabetes and people with type 2 diabetes and normal kidney function

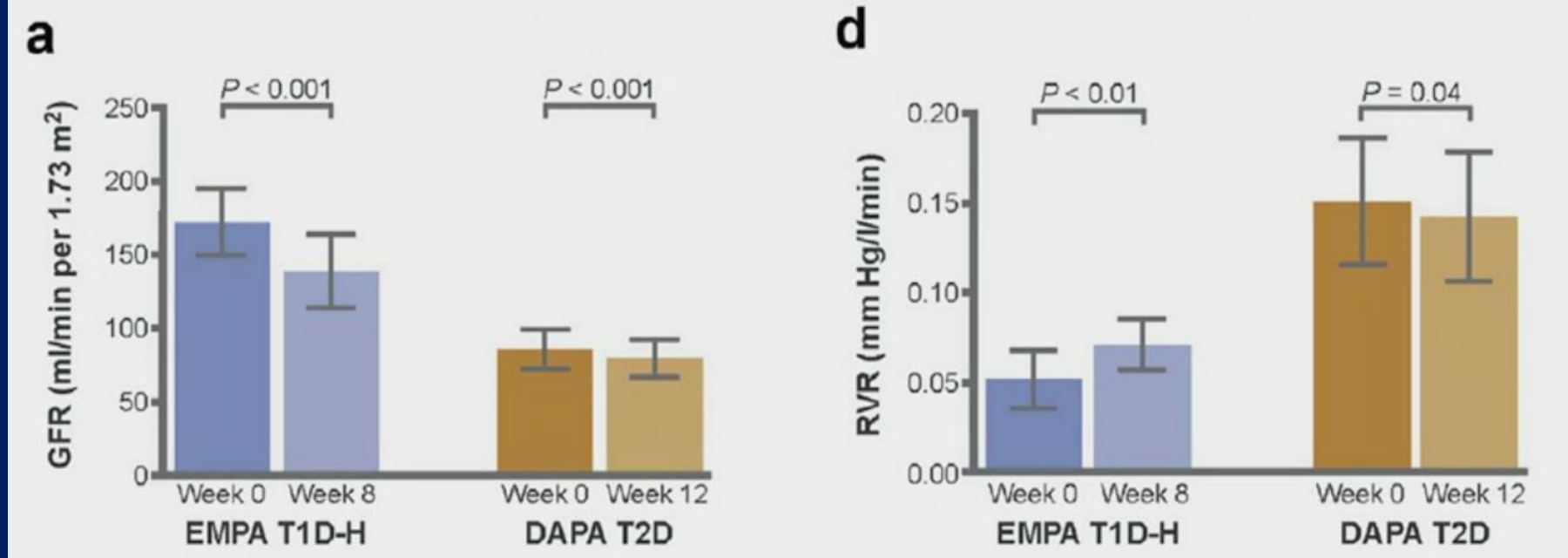
Erik J.M. van Bommel[1,11], Yuliya Lytvyn[2,11], Bruce A. Perkins[3,4], Nima Soleymanlou[5], Nora M. Fagan[6], Audrey Koitka-Weber[7,8,9], Jaap A. Joles[10], David Z.I. Cherney[2,11] and Daniël H. van Raalte[1,11]

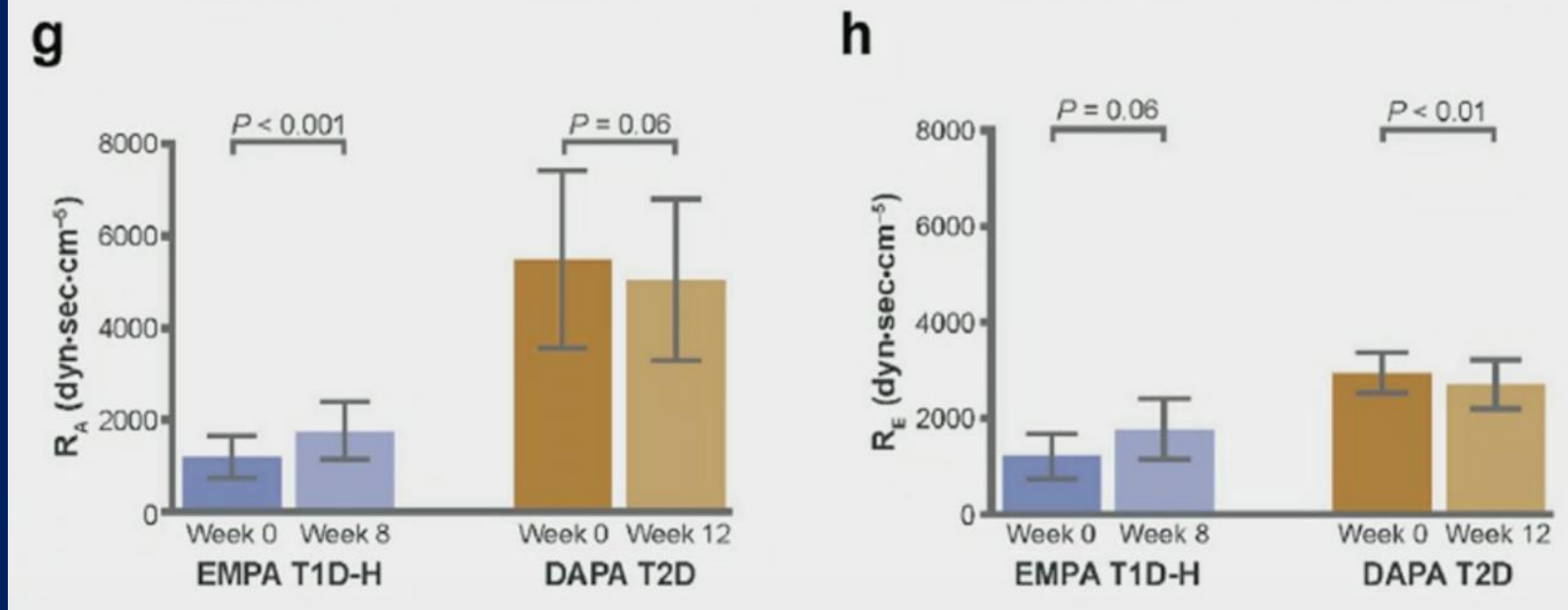
Kidney International (2020) **97,** 631–635; https://doi.org/10.1016/j.kint.2019.12.021

KEYWORDS: diabetes; diabetic nephropathy; glomerular hyperfiltration; SGLT2 inhibition



SGLT-2 inhibitor effects in T1DM vs T2DM

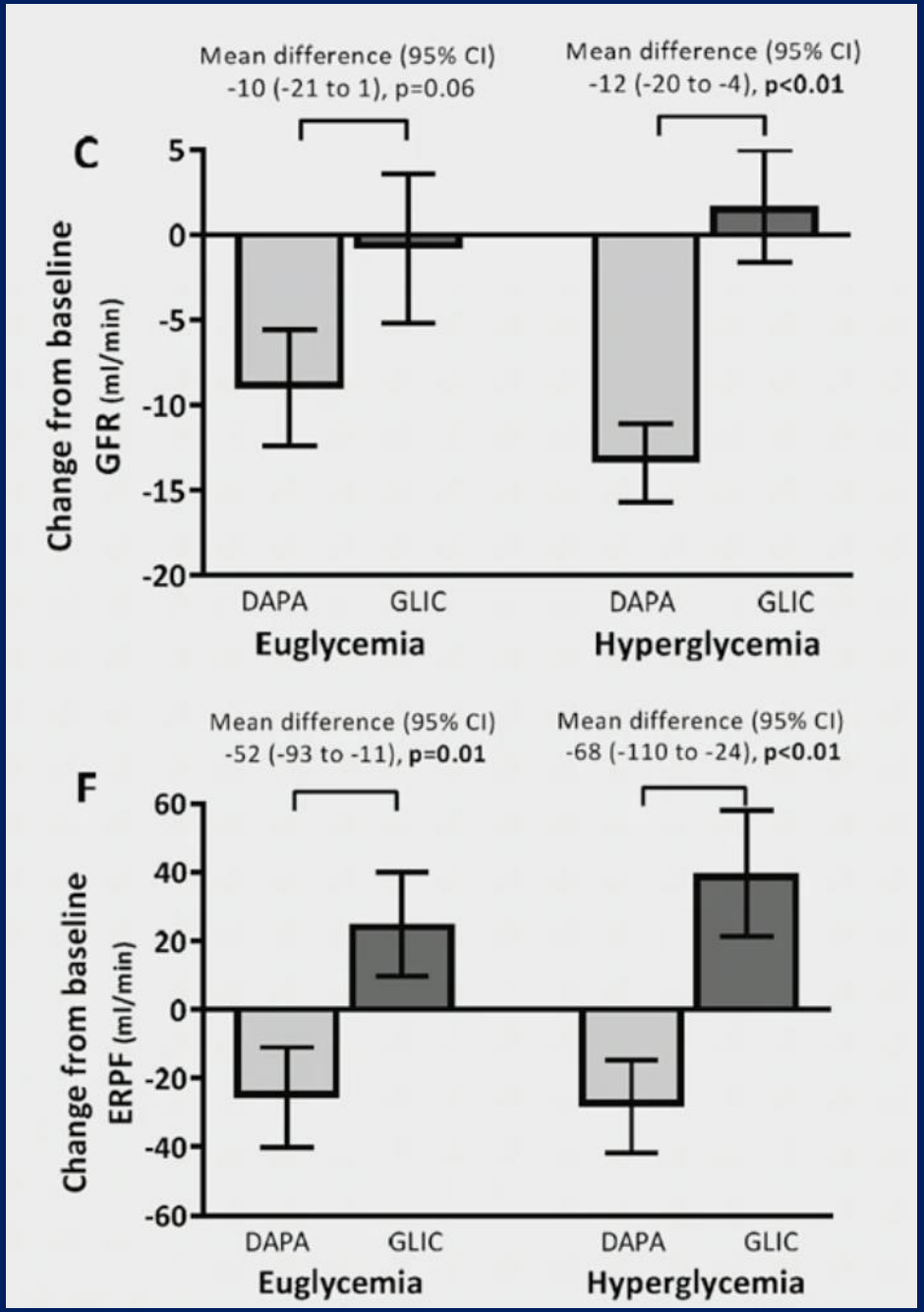




SGLT-2 inhibitor effects on T2DM

- 44 patients, Type 2 DM, on metformin
- 70% on RAS-blockers
- eGFR 85-90 ml/min/1.73m2; UACR 11 mg/mmol
- 24 Dapagliflozin vs 20 Gliclazide for 12 weeks
- clamped euglycemia & hyperglycemia

Van Bommel et al. *Kidney Int* 2020



The renal hemodynamic effects of the SGLT2 inhibitor dapagliflozin are caused by post-glomerular vasodilatation rather than pre-glomerular vasoconstriction in metformin-treated patients with type 2 diabetes in the randomized, double-blind RED trial.

44 participants

-Type 2 diabetes

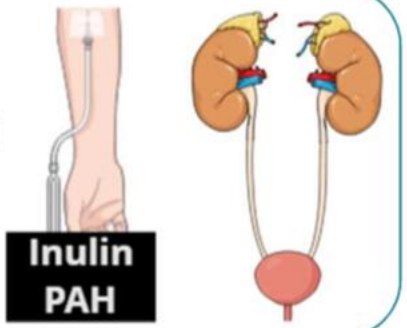
-Metformin treated

-Preserved renal function

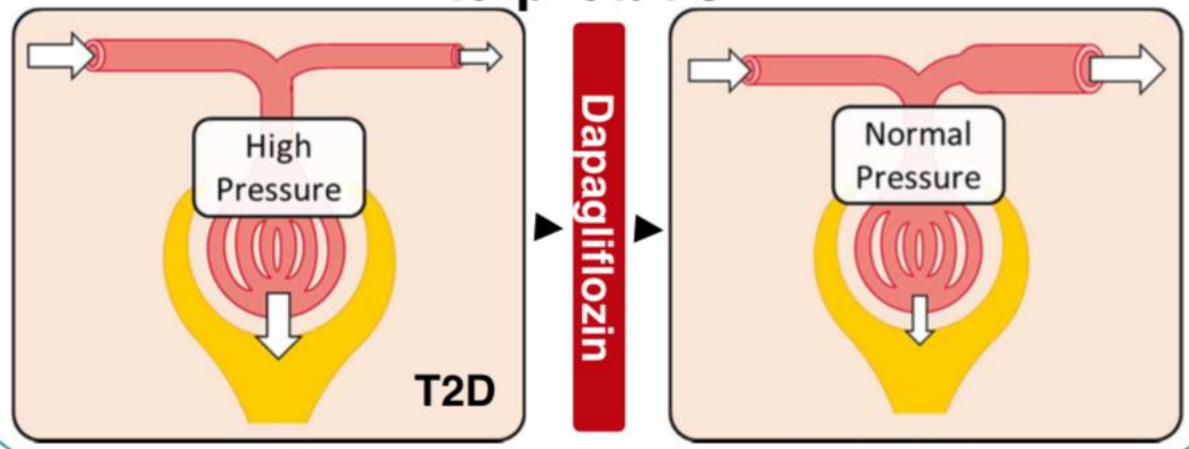
Dapagliflozin

Gliclazide

Clearances in controlled glycemic conditions



Interpretation



Results

	GFR	FF	RBF	RVR
Dapagliflozin	↓	↓	↔	↔
Gliclazide	↔	↔	↔	↔

CONCLUSION:

SGLT2 inhibition reduces measured GFR and FF in T2D, seemingly by lowering postglomerular arteriolar resistance

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Van Bommel *et al*, 2019

SGLT-2 inhibitors and BP

Study or Subgroup	SGLT-2 inhibitors Mean [mmHg]	SD [mmHg]	Total	Placebo/ Active control Mean [mmHg]	SD [mmHg]	Total	Weight	Mean Difference IV, Fixed, 95% CI [mmHg]
Bolinder, J Clin Endocrinol Metab. 2012	-2.7	10.6095	89	0.1	10.6095	91	3.1%	-2.80 [-5.90, 0.30]
Cherney, Diabetologia 2016 macro	-7	14.3206	128	-0.7	14.3206	87	1.9%	-6.30 [-10.20, -2.40]
Cherney, Diabetologia 2016 micro	-5.5	13.1791	388	-1	13.1791	248	6.6%	-4.50 [-6.60, -2.40]
Haneda, Clin Ther. 2016	-0.5	15.7692	95	2.1	15.7692	50	1.0%	-2.60 [-8.00, 2.80]
Heerspink, Diabetes Obes Metab. 2016	-9.8	11.3439	155	-6.3	10.991	163	4.9%	-3.50 [-5.96, -1.04]
Kashiwagi (EMIT), Diabetol Int 2014	-5.5	13.21	165	-1.3	13.23	75	2.3%	-4.20 [-7.81, -0.59]
Kashiwagi (LANTERN), Diabetes Obes Metab. 2015	-4.6	16.16	119	-2.7	10.08	46	1.7%	-1.90 [-6.01, 2.21]
Kashiwagi (SPOTLIGHT), Diabetol Int 2014	-5.9	13.79	97	-2.5	14.46	54	1.3%	-3.40 [-8.13, 1.33]
Kohan, J Nephrol. 2016	-3.9698	13.8006	3152	-0.9	13.1	1393	41.6%	-3.07 [-3.91, -2.23]
Kohan, Kidney Int. 2014	-1.3935	17.3163	168	4.14	14.07	84	1.8%	-5.53 [-9.52, -1.54]
Nauck, Diabetes Care. 2011	-4.3	12.274	400	0.8	12.274	401	10.1%	-5.10 [-6.80, -3.40]
Nomoto,Diabetology & Metabolic Syndrome 2017	-2.85	13.6141	12	4.45	18.3285	15	0.2%	-7.30 [-19.36, 4.76]
Petrykiv, Diabetes Obes Metab. 2017	-4.8	9.948	33	0.5	9.948	33	1.3%	-5.30 [-10.10, -0.50]
Ridderstraele, Lancet Diabetes Endocrin 2014	-3.1	12.6805	765	2.5	12.8046	780	18.2%	-5.60 [-6.87, -4.33]
Yale, Diabetes Obes Metab. 2014	-6.1	10.6213	179	-0.1	10.6213	90	4.1%	-6.00 [-8.69, -3.31]
Total (95% CI)								

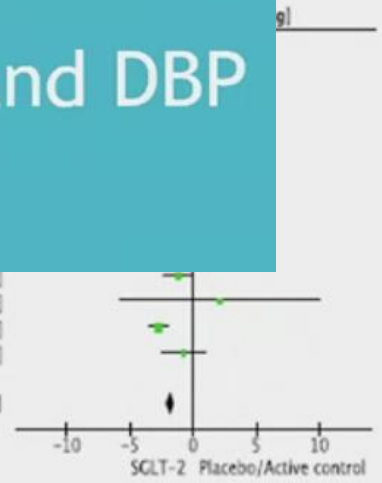
Heterogeneity: Chi² = 19.
Test for overall effect: Z =

Mean Difference
IV, Fixed, 95% CI [mmHg]

> "…All of the approved SGLT-2 inhibitors provide a mild but meaningful reduction up to 5/3 mmHg in office SBP and DBP as monotherapy or add-on therapy."

Nauck, Diabetes Care. 2011	-1.6	7.942	400	-0.4	7.942	401	9.4%	-1.20 [-2.30, -0.10]
Nomoto,Diabetology & Metabolic Syndrome 2017	4.1	11.4894	12	2	8.8483	15	0.2%	2.10 [-5.79, 9.99]
Ridderstraele, Lancet Diabetes Endocrin 2014	-1.8	8.4537	765	0.9	7.1137	780	18.7%	-2.70 [-3.48, -1.92]
Yale, Diabetes Obes Metab. 2014	-2.19	6.8308	179	-1.4	6.8308	90	3.8%	-0.79 [-2.52, 0.94]
Total (95% CI)			5757			3414	100.0%	-1.79 [-2.13, -1.45]

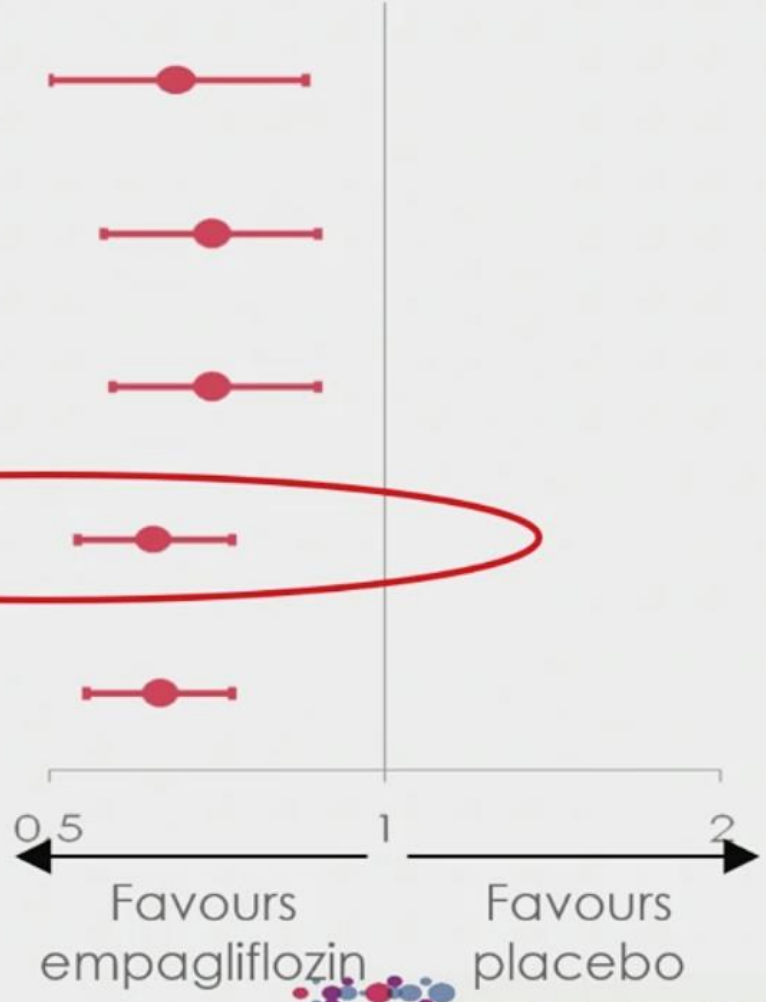
Heterogeneity: Chi² = 20.36, df = 12 (P = 0.06); I² = 41%
Test for overall effect: Z = 10.40 (P < 0.00001)



Imprialos, Sarafidis, Karagiannis. *J Hypertens 2015*
Piperidou et al, *J Hypertens 2019*

EMPA-REG: outcomes reflecting HF burden

	Patients with event/analysed (%)		
	Empagliflozin	Placebo	HR (95% CI)
Adjudicated HHF	126/4687 (2.7)	95/2333 (4.1)	0.65 (0.50, 0.85)
Investigator-reported heart failure*	204/4687 (4.4)	143/2333 (6.1)	0.70 (0.56, 0.87)
Adjudicated HHF or investigator-reported heart failure*	217/4687 (4.6)	151/2333 (6.5)	0.70 (0.57, 0.87)
Introduction of loop diuretics	340/3962 (8.6)	262/1969 (13.3)	0.62 (0.53, 0.73)
Introduction of loop diuretics or adjudicated HHF	411/4027 (10.2)	313/2013 (15.5)	0.63 (0.54, 0.73)



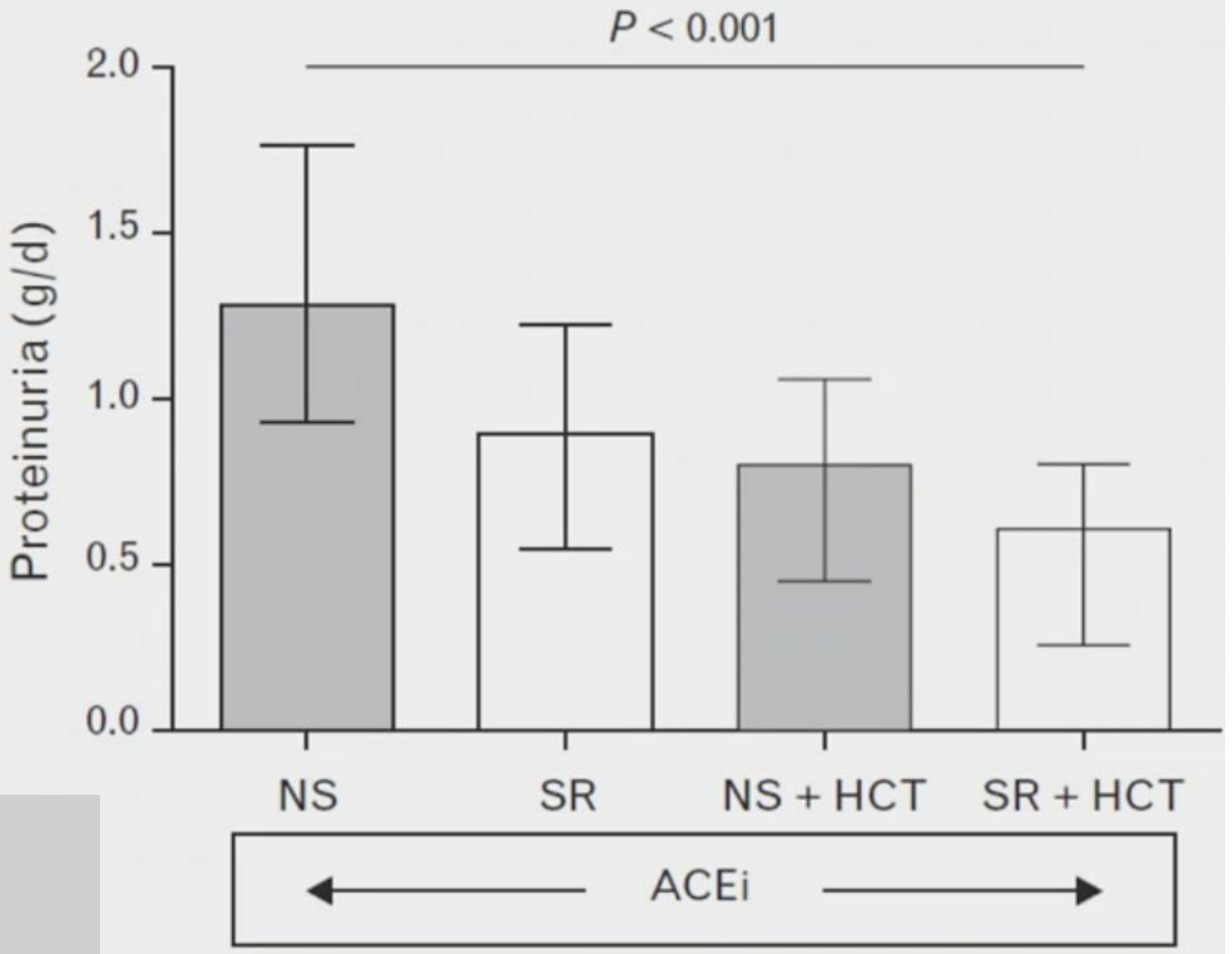
Cox regression analysis in patients treated with ≥1 dose of study drug.
*Investigator-reported heart failure was based on the narrow standardised MedDRA query 'cardiac failure'.
HHF, hospitalisation for heart failure.

Fitchett D et al. ESC 2016 Clinical Trial Update (2237)

EMPA-REG OUTCOME®

Effects of sodium restriction on proteinuria

- Crossover RCT
- 45 patients, Type 2 DM,
- micro- or macroalbuminuria on lisinopril 40 mg
- regular sodium or sodium restriction (50 mmol/day)
- hydrochlorothiazide 50 mg vs placebo



sodium restriction is an eff ective non-pharmacological intervention to increase RAAS blockade effi cacy in type 2 diabetic nephropathy.

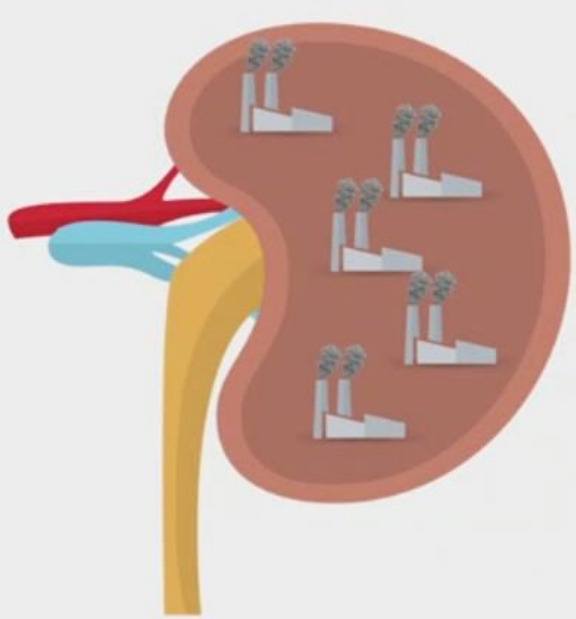
Kwakernaak et al. Lancet Diabetes Endocrinol 2014

SGLT-2 inhibitors and nephroprotection

Effects according to GFR

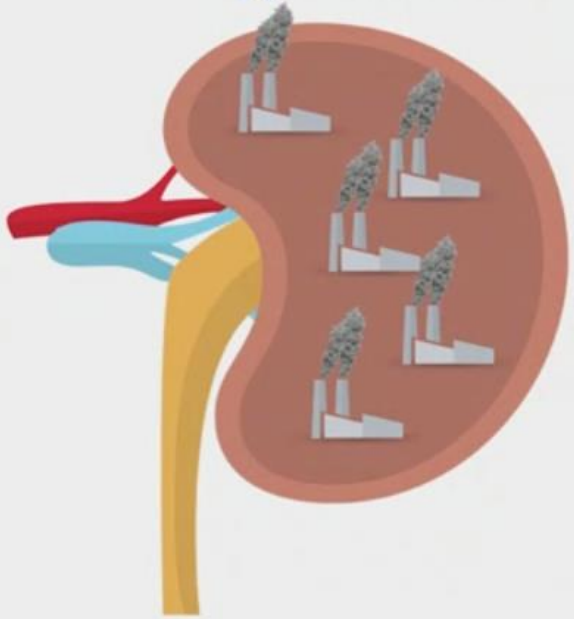
Single nephron hyperfiltration

Normal



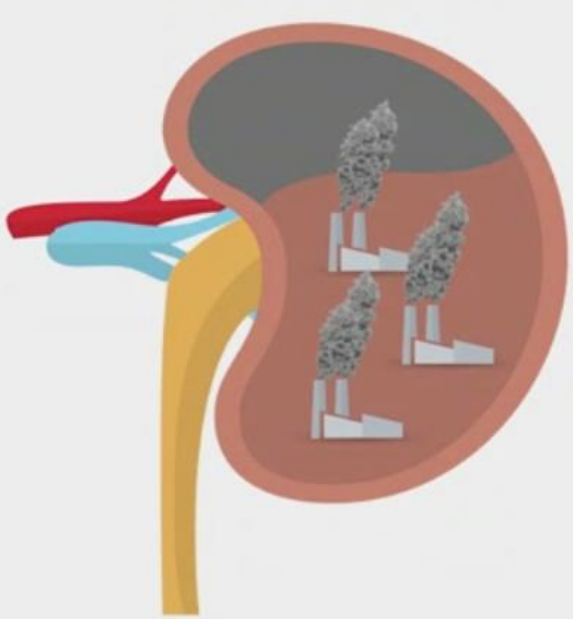
GFR >90 ml/min

Glomerular hypertension



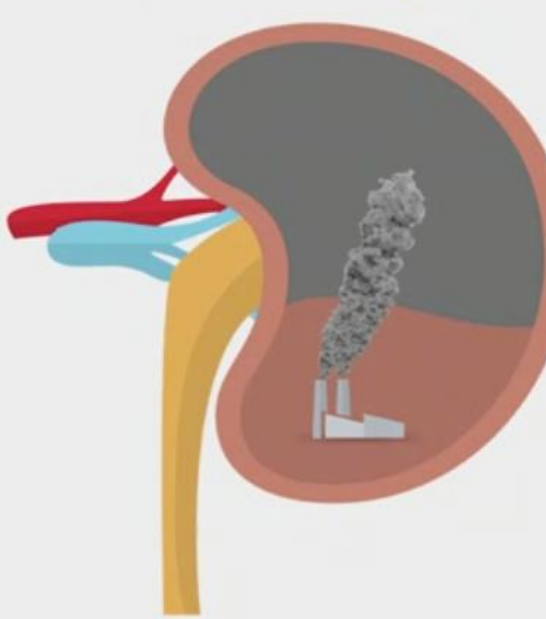
GFR >135ml/min
Hyperfiltration

CKD stage 3



GFR <60ml/min

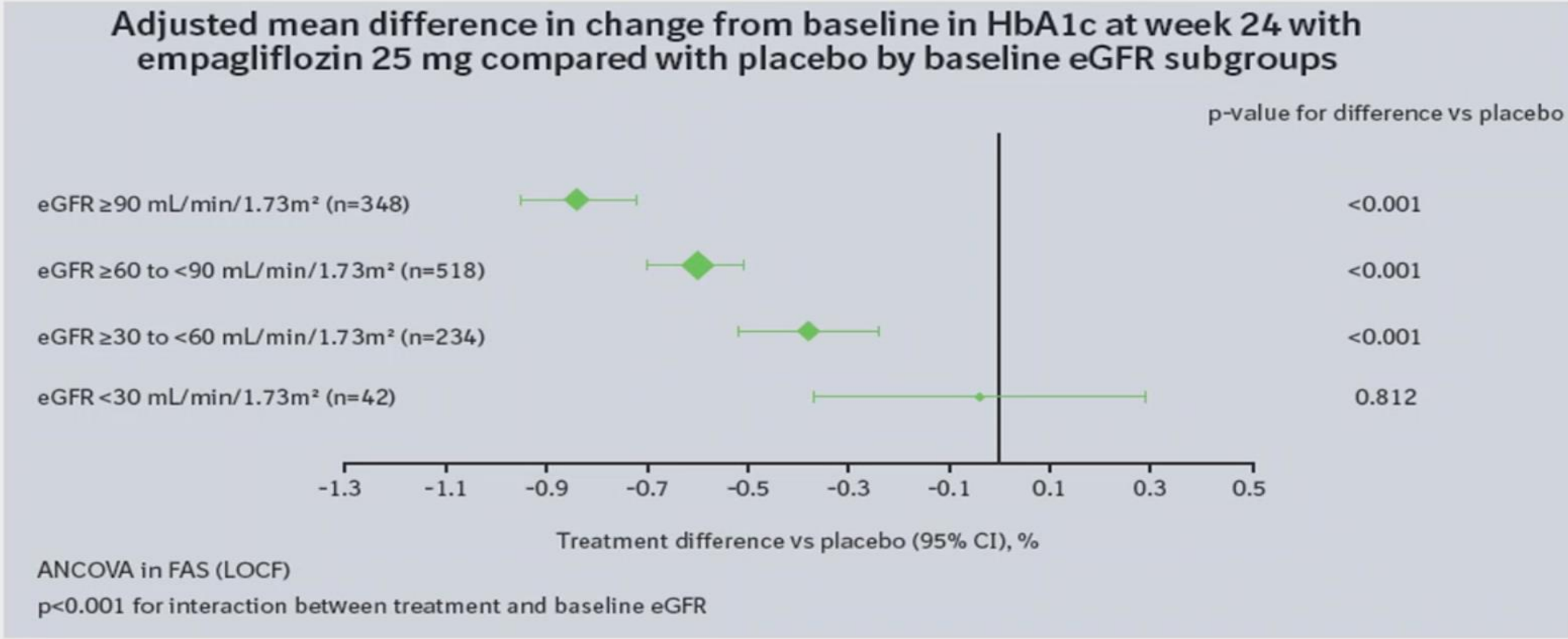
CKD stage 4



GFR <30ml/min

Brenner *et al*. *Kidney Int* 1996;49:1774
Kanzaki *et al*. *Hypertension Res* 2015;38:633

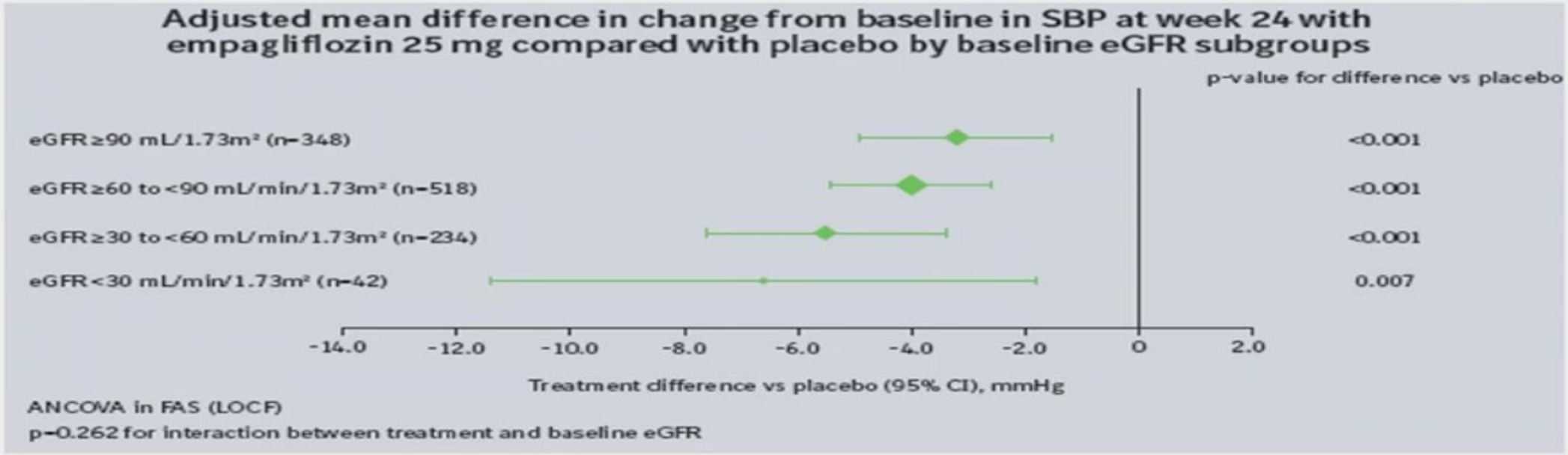
SGLT2-i effects on HbA1c according to eGFR

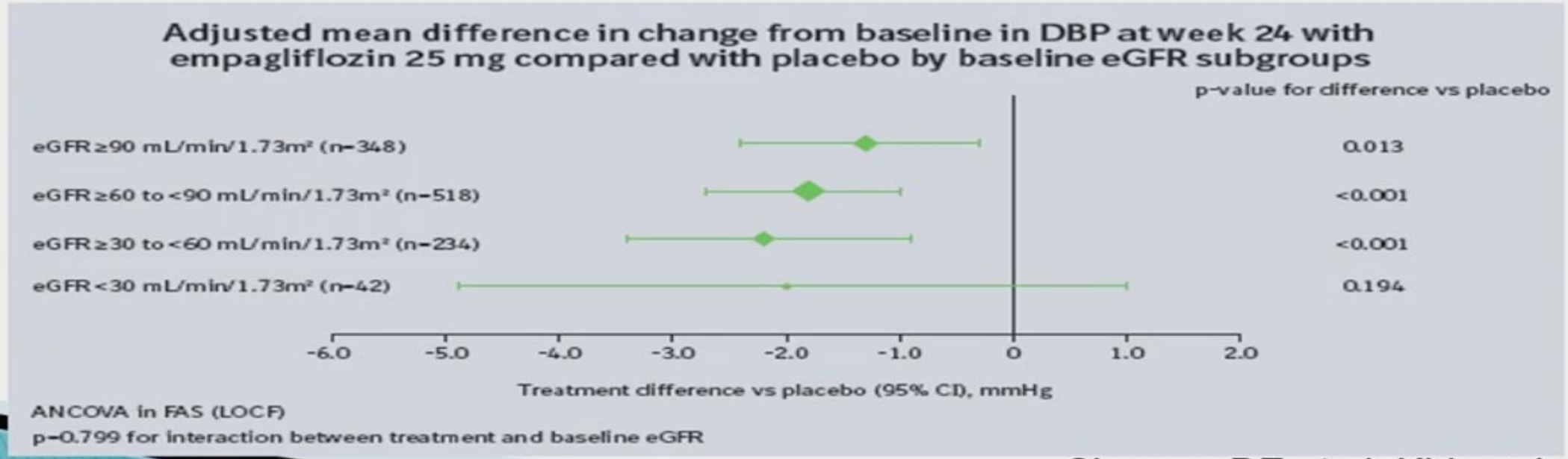


- Pooled data from 4 phase III clinical trials

Cherney DZ et al; Kidney Int 2018

SGLT2-i effects on BP according to eGFR

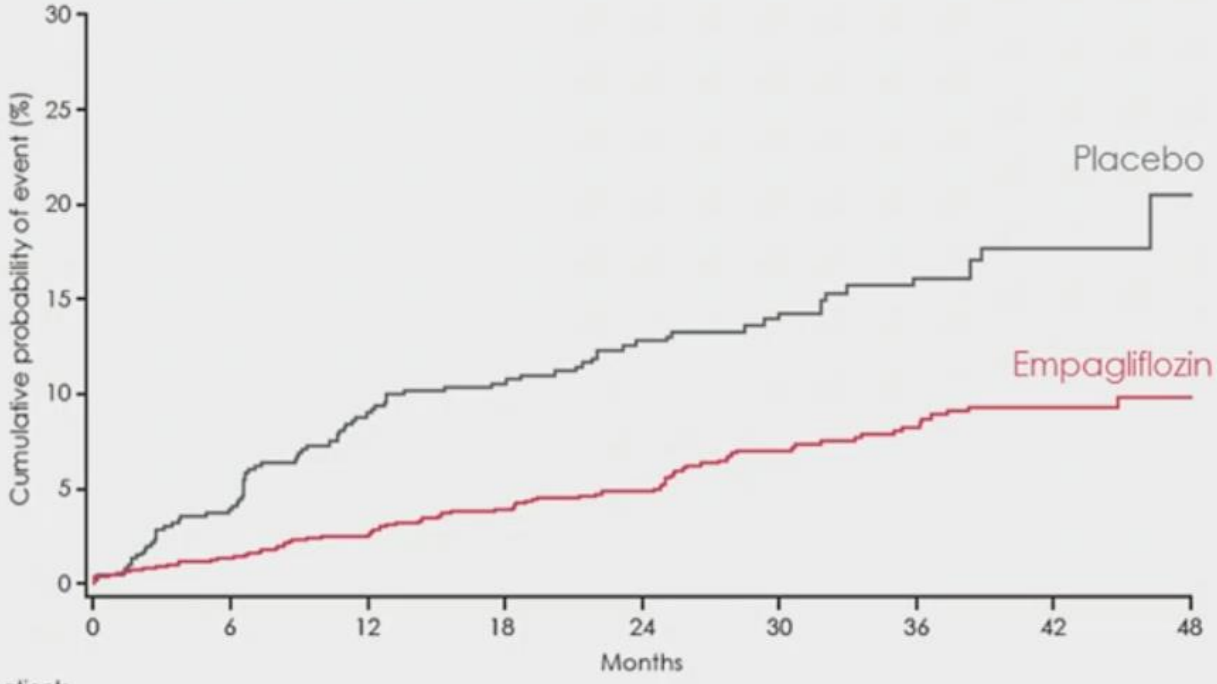




Cherney DZ et al; Kidney Int 2018

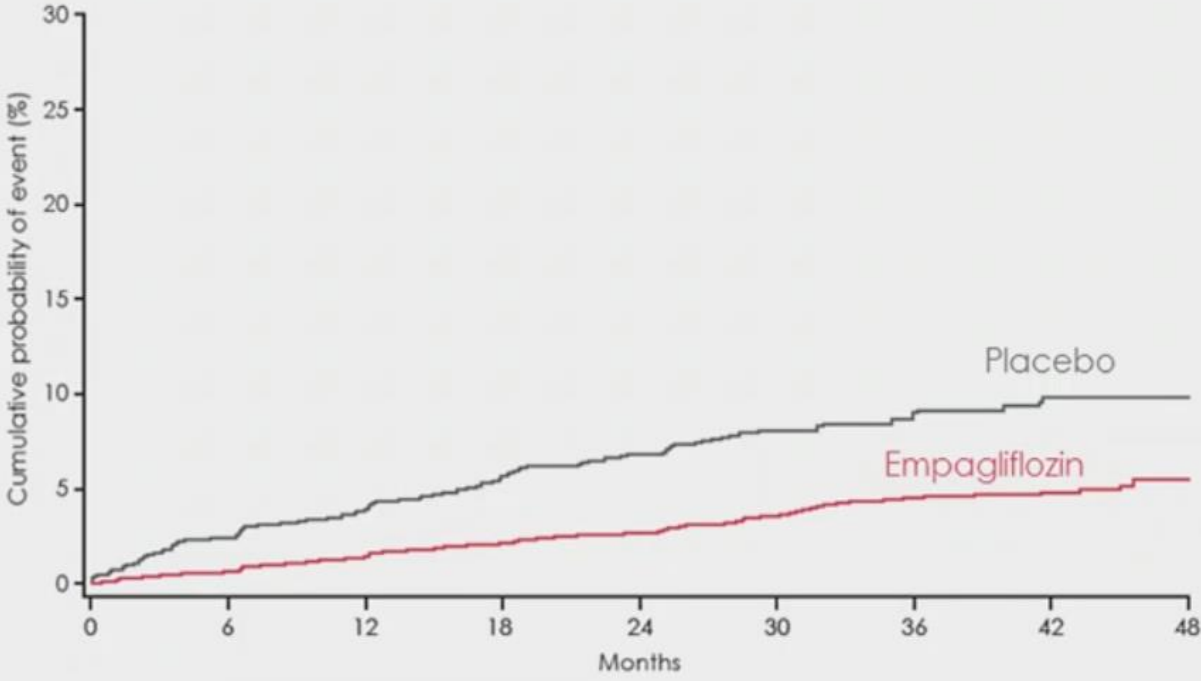
EMPA-REG: Oedema according to eGFR

Patients with eGFR <60 mL/min/1.73m^2 at baseline



No. of patients									
Empagliflozin	1212	1089	1024	951	810	587	439	218	74
Placebo	607	540	480	429	355	258	200	89	23

Patients with eGFR ≥60 mL/min/1.73m^2 at baseline



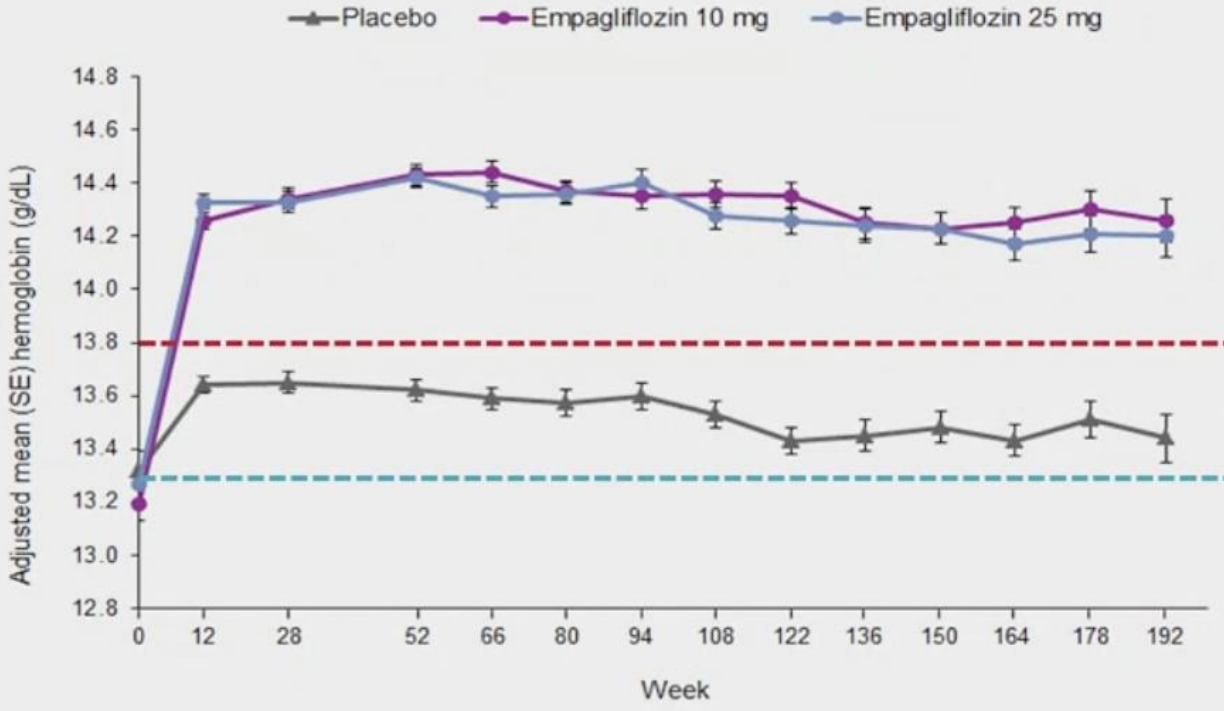
	3473	3293	3152	3004	2606	1864	1439	741	187
	1726	1604	1509	1406	1191	835	626	283	77

Kaplan-Meier estimates in patients treated with ≥1 dose of study drug based on events that occurred during treatment or ≤7 days after the last intake of study drug. *Post-hoc* analyses.

Levin A et al.; presented atAmerican Diabetes Association
77th Annual Scientific Sessions June 9 – 13, 2017, San Diego, CA

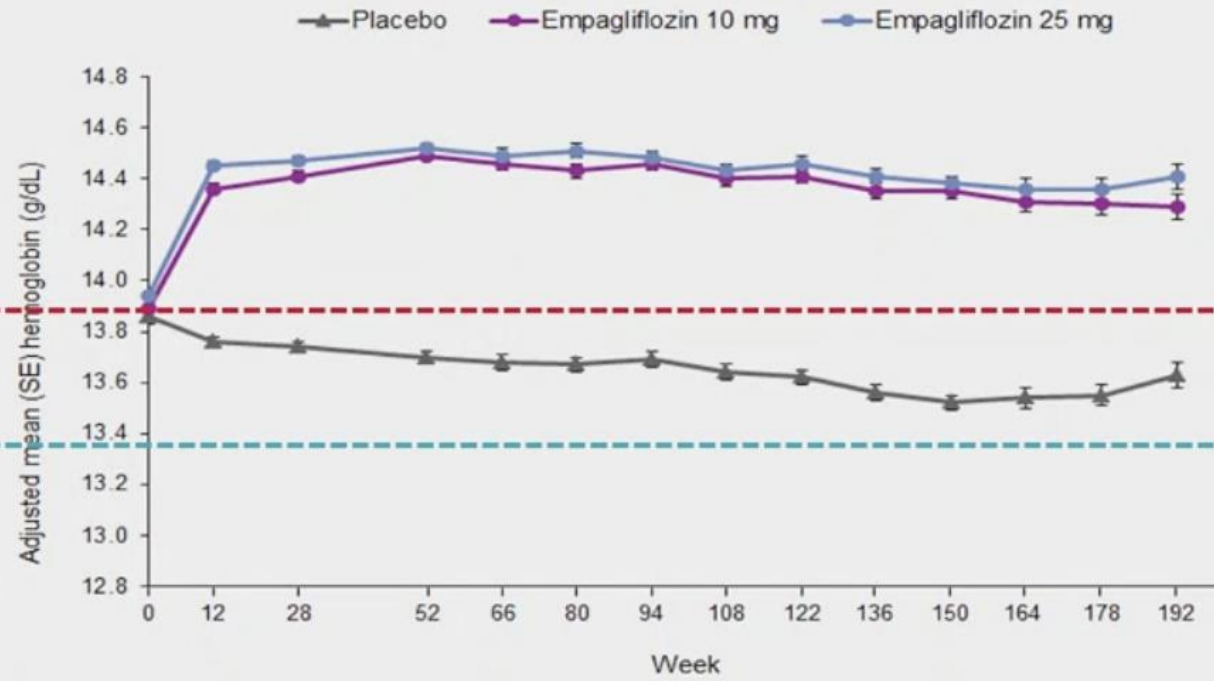
EMPA-REG: Hemoglobin change according to eGFR

Patients with eGFR <60 mL/min/1.73m² at baseline



Placebo	596	591	559	526	519	483	477	434	363	312	285	252	182	114
Empagliflozin 10 mg	589	583	562	537	520	502	499	437	390	326	292	248	196	123
Empagliflozin 25 mg	594	582	564	544	526	519	512	453	390	330	304	264	206	134

Patients with eGFR ≥60 mL/min/1.73m² at baseline



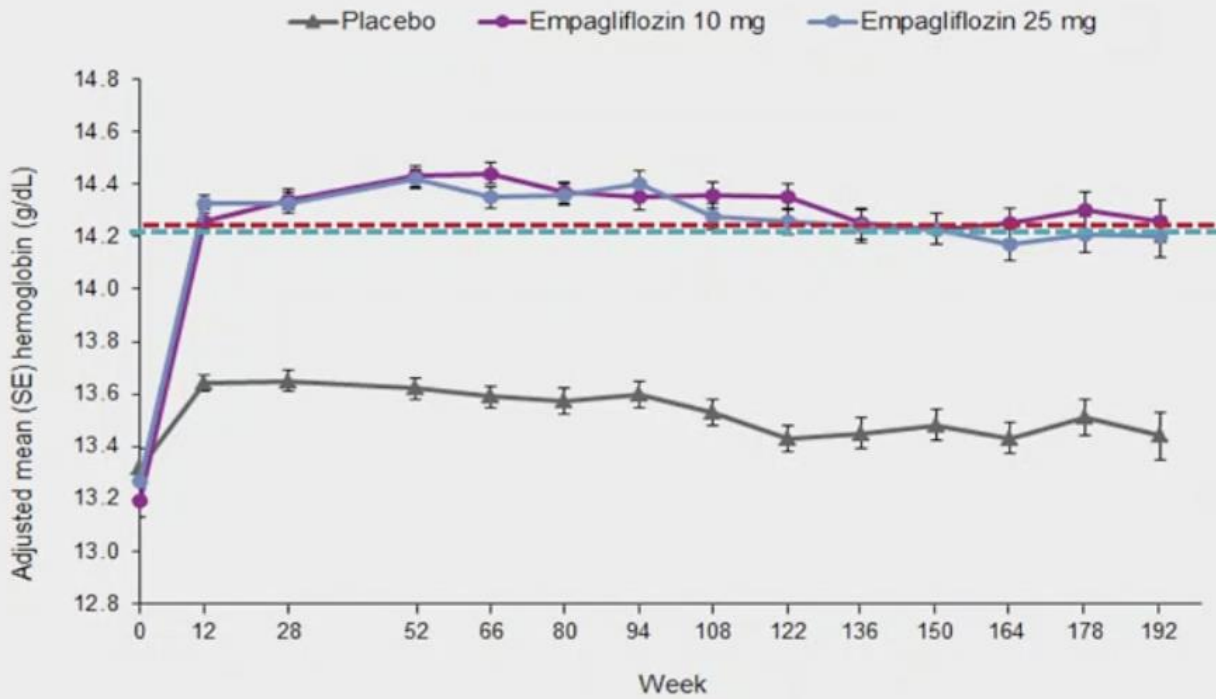
	1697	1671	1637	1579	1536	1509	1481	1324	1101	941	832	717	546	332
	1707	1680	1655	1605	1581	1560	1548	1388	1143	987	875	766	586	388
	1701	1687	1648	1606	1577	1546	1522	1406	1154	1000	895	784	618	386

Mixed model repeated measures analysis in treated set using all data up to individual trial completion.

Wanner C et al; Circulation 2018

EMPA-REG: Hemoglobin change according to eGFR

Patients with eGFR <60 mL/min/1.73m² at baseline



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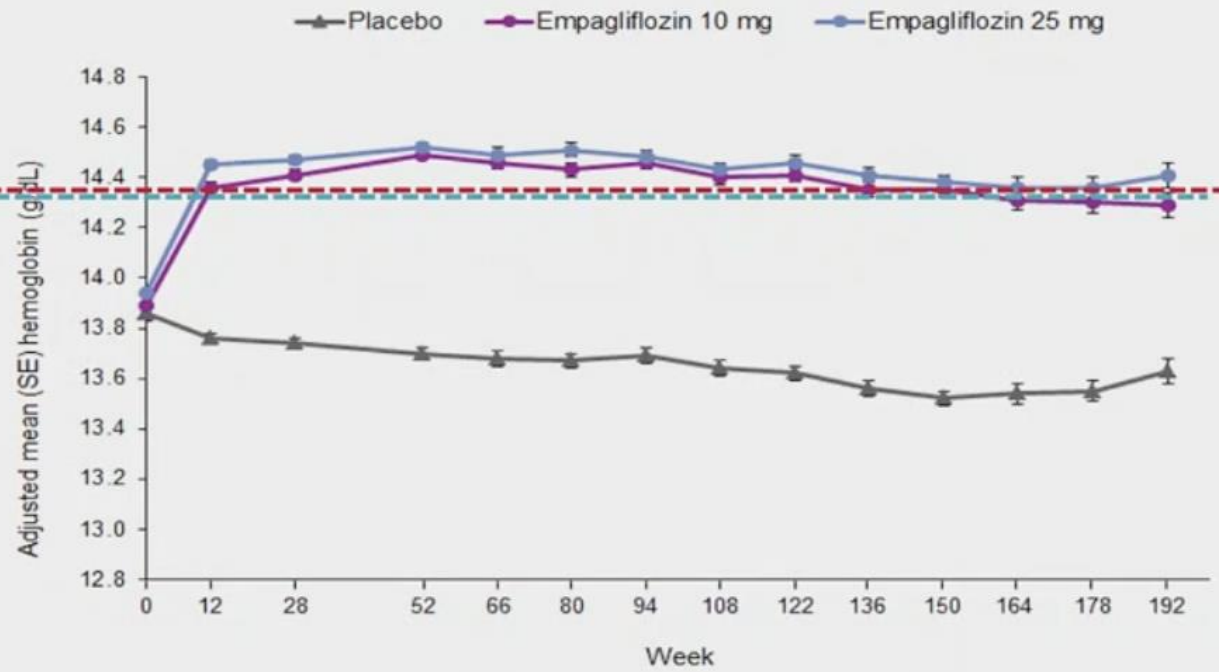
Patients with eGFR ≥60 mL/min/1.73m² at baseline



	1697	1671	1637	1579	1536	1509	1481	1324	1101	941	832	717	546	332
	1707	1680	1655	1605	1581	1560	1548	1388	1143	987	875	766	586	388
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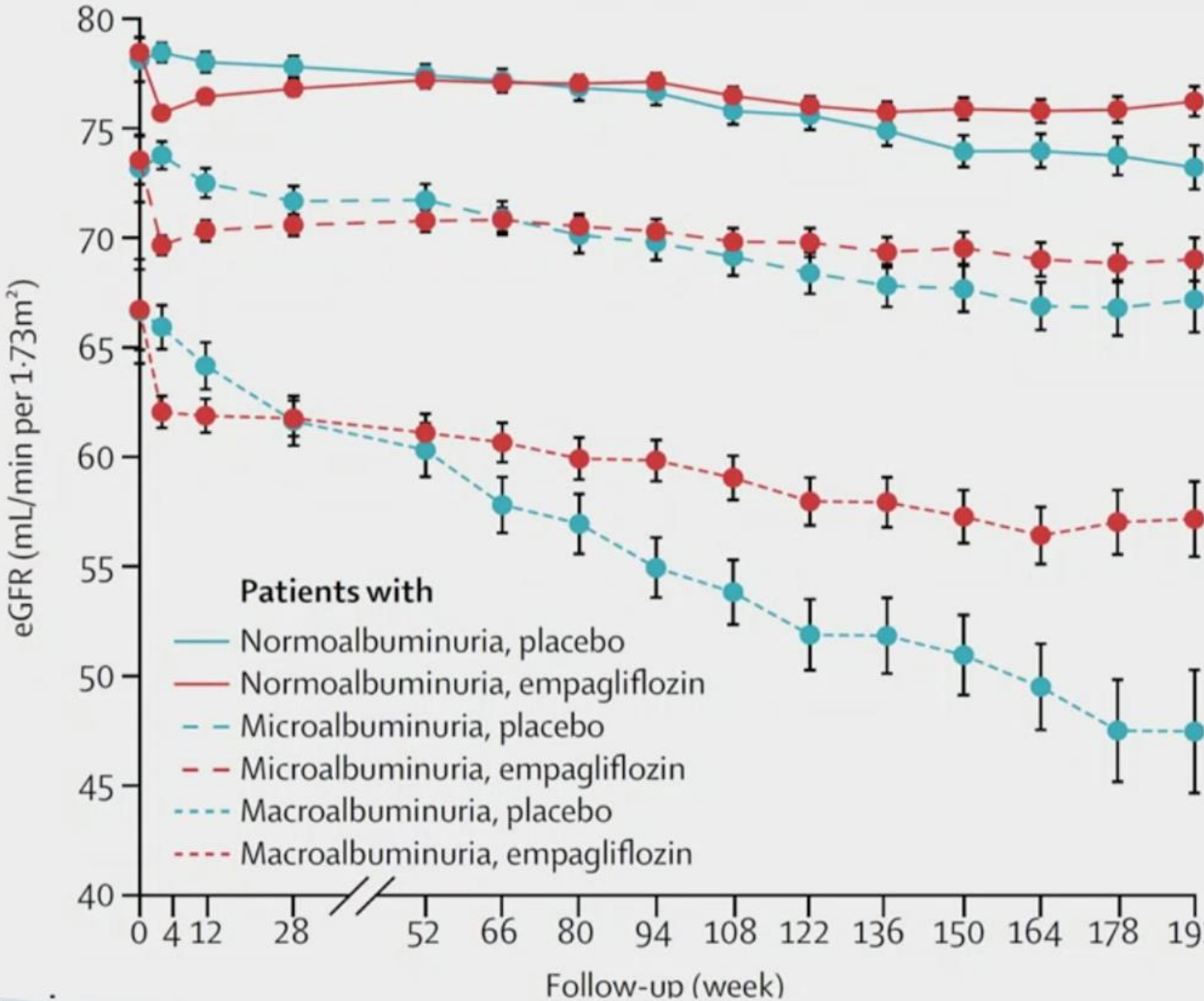
Mixed model repeated measures analysis in treated set using all data up to individual trial completion.

Wanner C et al; Circulation 2018

EMPA-REG: effects on GFR according to ACR status



Cherney DZ et al; Kidney Int 2018

Nephrol Dial Transplant (2019) 34: 208–230
doi: 10.1093/ndt/gfy407

ndt
Nephrology Dialysis Transplantation

SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA

Pantelis Sarafidis[1], Charles J. Ferro[2], Enrique Morales[3], Alberto Ortiz[4], Jolanta Malyszko[5], Radovan Hojs[6], Khaled Khazim[7], Robert Ekart[6], Jose Valdivielso[8], Denis Fouque[9], Gérard M. London[10], Ziad Massy[11], Petro Ruggenenti[12], Esteban Porrini[13], Andrej Wiecek[14], Carmine Zoccali[15], Francesca Mallamaci[15] and Mads Hornum[16]

doi: 10.1093/ndt/gfy407

ndt
Nephrology Dialysis Transplantation

SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA

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Francesca Mallamaci[15] and Mads Hornum[16]

Patients with type 2 DM and CKD (eGFR <60 ml/min/1.73m^2 or with eGFR >60 ml/min/1.73m^2 and micro- or macroalbuminuria) *not* on HbA1c target (HbA1c >7) on recommended metformin dose
or
not on HbA1c target (HbA1c >7) and metformin is *not tolerated or* contraindicated

↓

Use SGLT-2 inhibitor with evidence for cardio- and nephroprotection[1]

↓

If HbA1c remains above target or SGLT-2 inhibitor is not tolerated or contraindicated

↓

Use GLP-1 receptor agonist with evidence for cardio- and nephroprotection[2]

↓

If HbA1c above target GLP-1 receptor agonist is not tolerated or contraindicated

↓

Use another antidiabetic agent (DDP-4 i, TZD, SU, or basal insulin) according to current recommendations for Type 2 DM[3]

1. SGLT-2 inhibitors have been used in EMPA-REG OUTCOME and CANVAS studies up to 30 ml/min/1.73m^2 but their current indication for use is >45 ml/min/1.73m^2
2. Consult licensing indications for GLP-1 receptor agonists regarding combination treatment and use according to renal function
3. Follow recent ADA/EASD recommendations and current licensing data for combining antidiabetic agents and use according to renal function

What about non-diabetic CKD?

- AstraZeneca Websites
- Global site

Farxiga Phase III DAPA-CKD trial will be stopped early after overwhelming efficacy in patients with chronic kidney disease

PUBLISHED 30 March 2020

30 March 2020 07:00 BST

Farxiga is the first SGLT2 inhibitor to show meaningful
including both type-2 dia

The Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidn
patients with chronic kidney disease (CKD) will be stopped early followi
Committee (DMC) based on its determination of overwhelming efficacy.

The decision to stop the trial early was made following a routine assess
than originally anticipated and AstraZeneca will now initiate closure of th

Mene Pangalos, Executive Vice President, BioPharmaceuticals R&D, sa
particularly those without type-2 diabetes. We are very pleased the Data
overwhelming benefit. *Farxiga* has the potential to change the management of chronic kidney disease for patients around the world."

AstraZeneca

DAPACKD

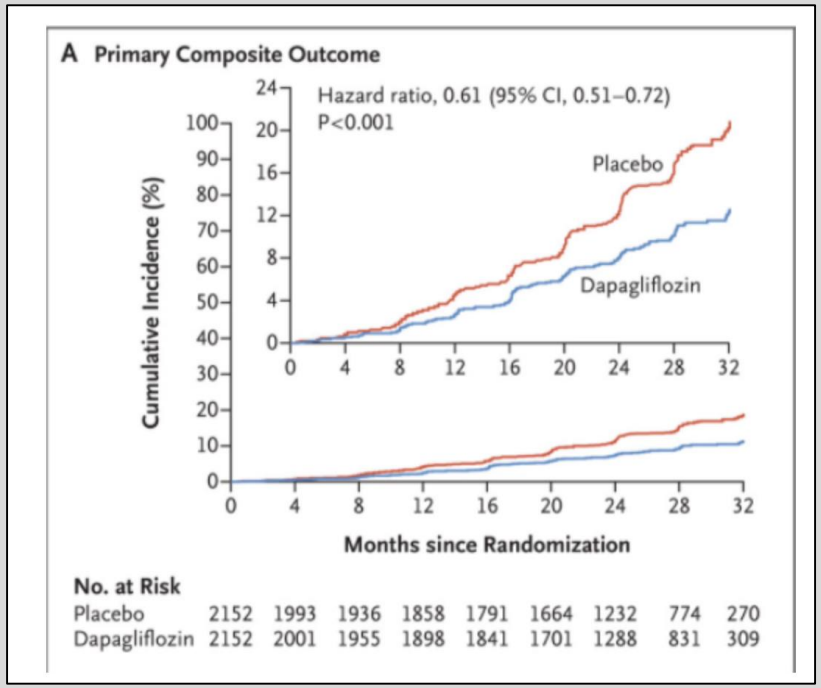
The DAPA-CKD Trial

The DAPA-CKD trial is a Phase III study designed to evaluate the efficacy of *Farxiga* (dapagliflozin), compared with placebo, in patients with chronic kidney disease (CKD) stages 2–4 and elevated urinary albumin excretion, with and without type-2 diabetes (T2D).

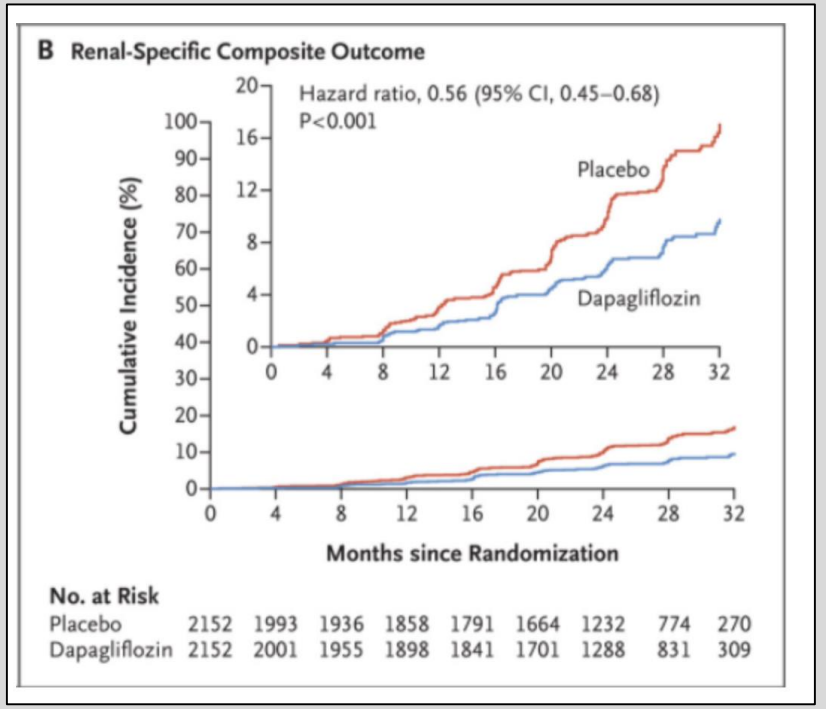
The study is a randomised, double-blind, placebo-controlled trial with 4,304 patients recruited across 21 countries.[1]

DAPA-CKD stands for **D**apagliflozin **A**nd **P**revention of **A**dverse outcomes in **C**hronic **K**idney **D**isease

First dedicated trial to evaluate an SGLT2 in CKD patients with and without T2D



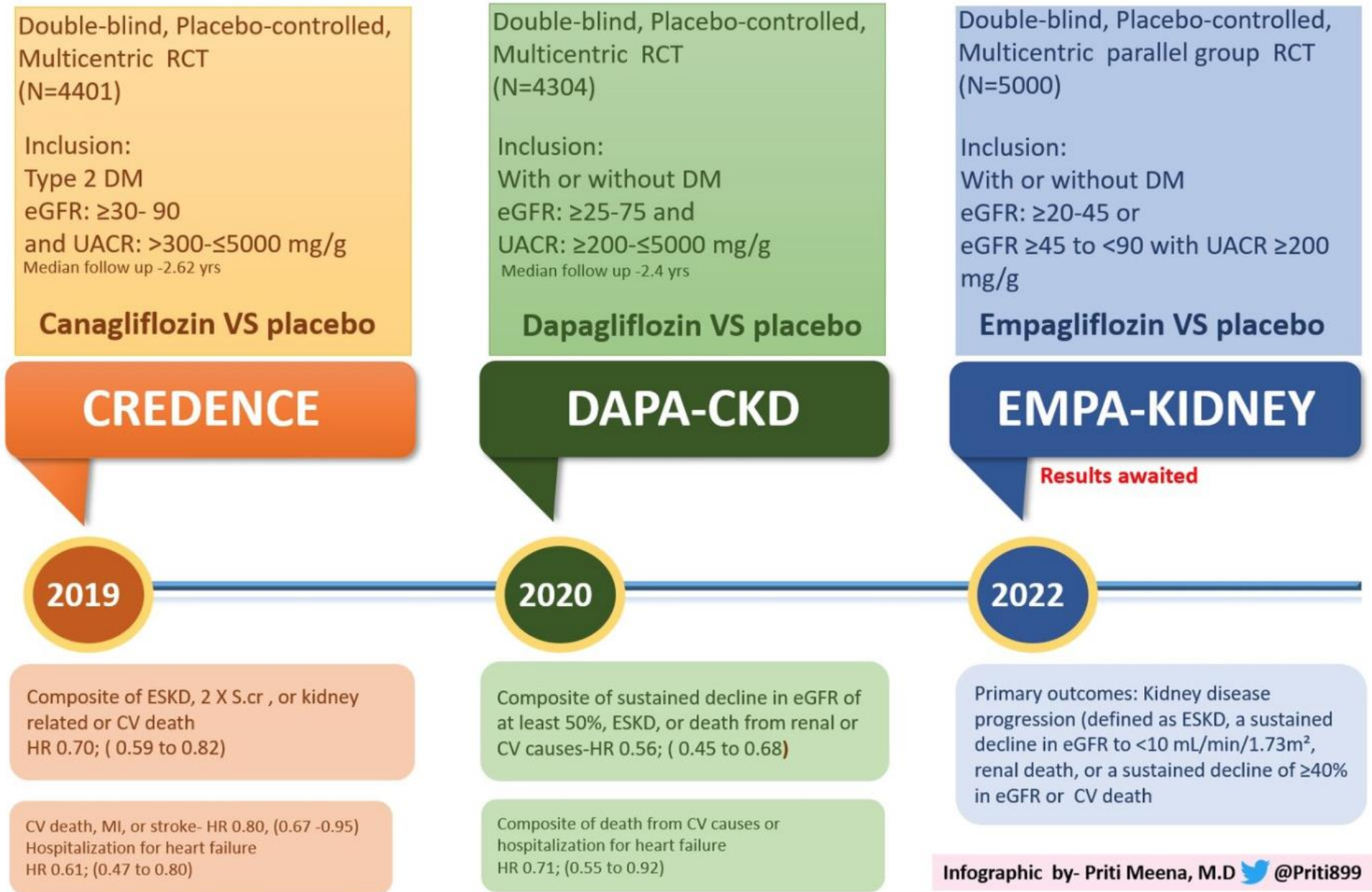
DAPA-CKD, NEJM 2020



Conclusion

Regardless of the presence or absence of diabetes, dapagliflozin significantly lowered the renal or cardiovascular events and deaths when compared to placebo.

DAPA-CKD is the first SGLT2 inhibitor trial to declare a favorable clinical outcome in non-diabetic CKD patients


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

Boehringer Ingelheim

Source URL: https://www.boehringer-ingelheim.com/EMPA-KIDNEY

Boehringer Ingelheim and Lilly announce an academic collaboration with University of Oxford to investigate the effects of empagliflozin in people with chronic kidney disease

- *University of Oxford to assess effect of empagliflozin on heart and kidney disease in people with chronic kidney disease*
- *EMPA-KIDNEY will be part of the empagliflozin clinical development programme which explores the efficacy and safety of empagliflozin across a broad spectrum of patients and clinical conditions*

EMPA-KIDNEY is a clinical trial testing whether taking a single pill of empagliflozin every day prevents worsening of kidney disease or deaths from heart disease in people who have chronic kidney disease.

Lilly and Company will provide

Conclusions

- SGLT-2 inhibitors are currently recommended as 2nd step treatment in T2DM
- Two large outcome trials with SGLT-2 inhibitors have shown reductions in CV events, CV mortality, and all-cause mortality
- Sub-analyses of three cardiovascular trials and one renal outcome trial have shown substantial reductions in the combined and the individual renal outcomes and eGFR “stabilization”
- Reduction in hyperfiltration +/- BP reduction and natriuresis are involved
- Ongoing trials in diabetic and non-diabetic CKD are awaited to shed further light in the field


Thank you