Nuovi farmaci e nefroprotezione: Il punto di vista del Nefrologo

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Il dr. Roberto Boero dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche.

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Cronologia dello sviluppo dei farmaci efficaci nel diabete con danno renale

La modulazione del RAAS nel DM tipo 2

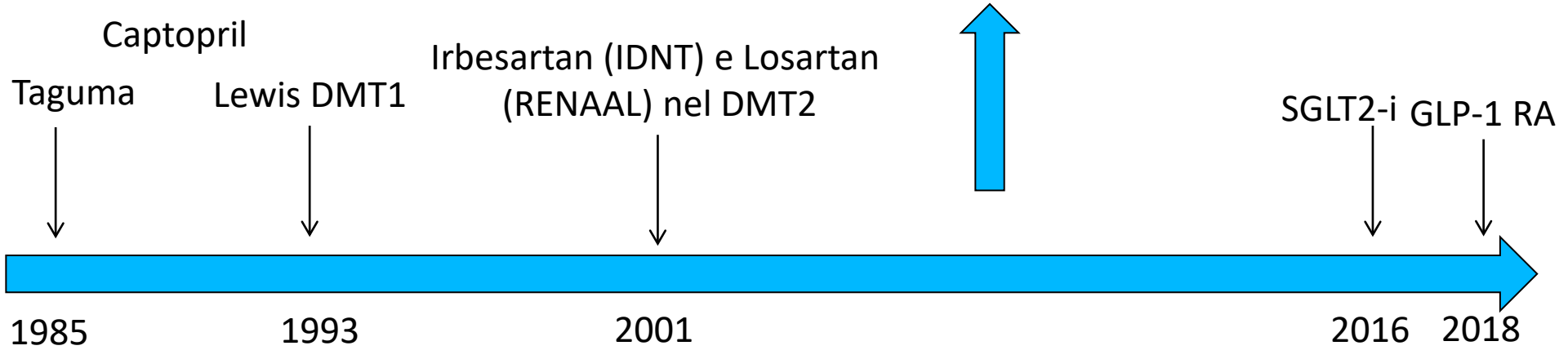
- Proteinuria residua ➔ rischio residuo
- Blocco più intensivo (doppio blocco RAAS) ➔ iperpotassiemia/insufficienza renale acuta

La (difficile) ricerca di trattamenti alternativi

- Inibitori recettori ETa endotelina (Atrasentan) ➔ ritenzione idro-sodica, scompenso cardiaco

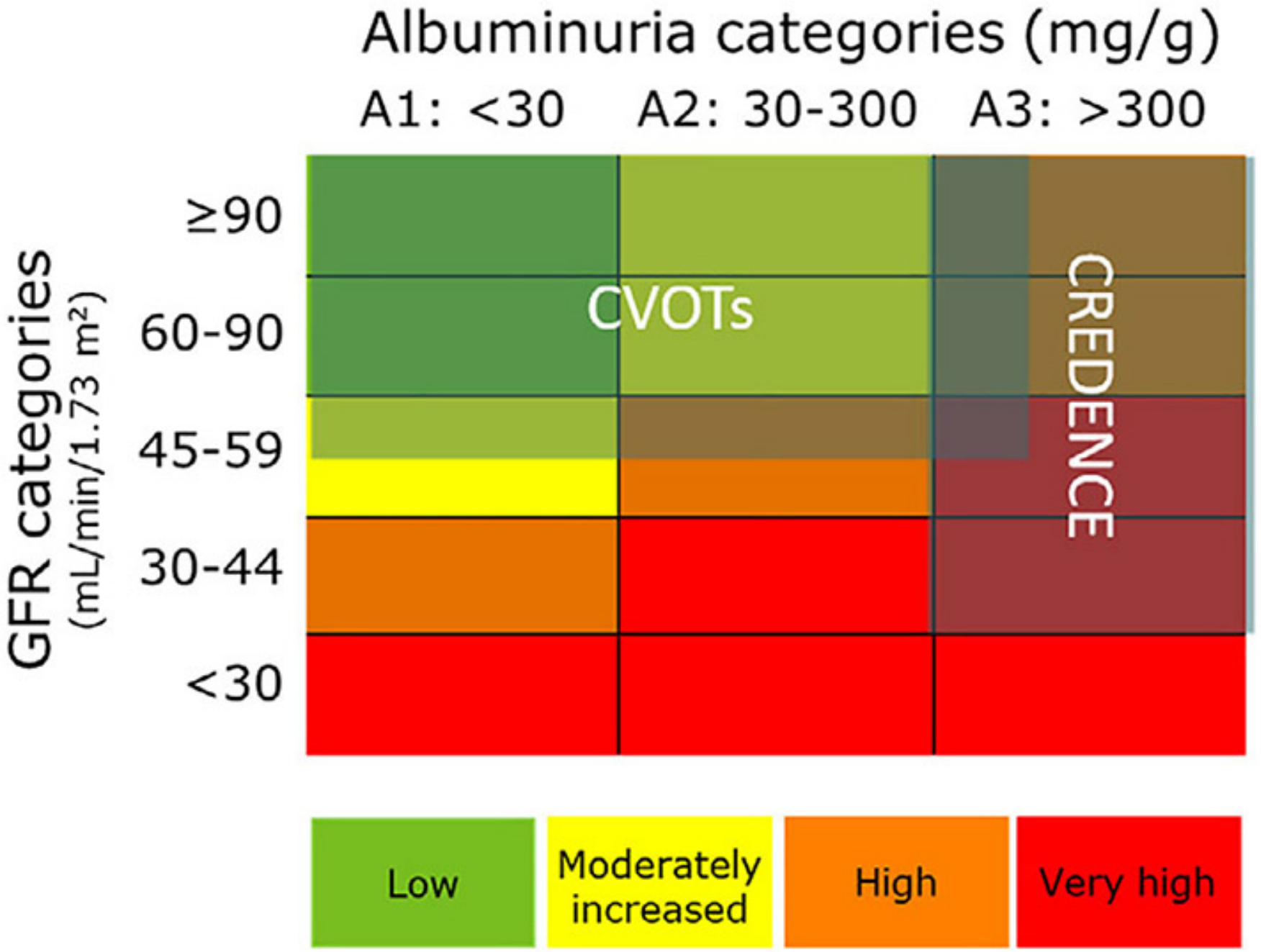
Il problema del danno renale non albuminurico nel DM tipo 2

- Circa il 50% dei pazienti con diabete tipo 2 e eGFR<60 ml/min hanno escrezione urinaria di albumina normale
- Blocco del RAAS non è efficace in questo fenotipo



Agenda

- Effetti degli SGLT2-i sugli esiti renali
- Meccanismo d’azione
  - Effetti glomerulari
  - Effetti tubulari e sui fluidi corporei
- Conclusioni

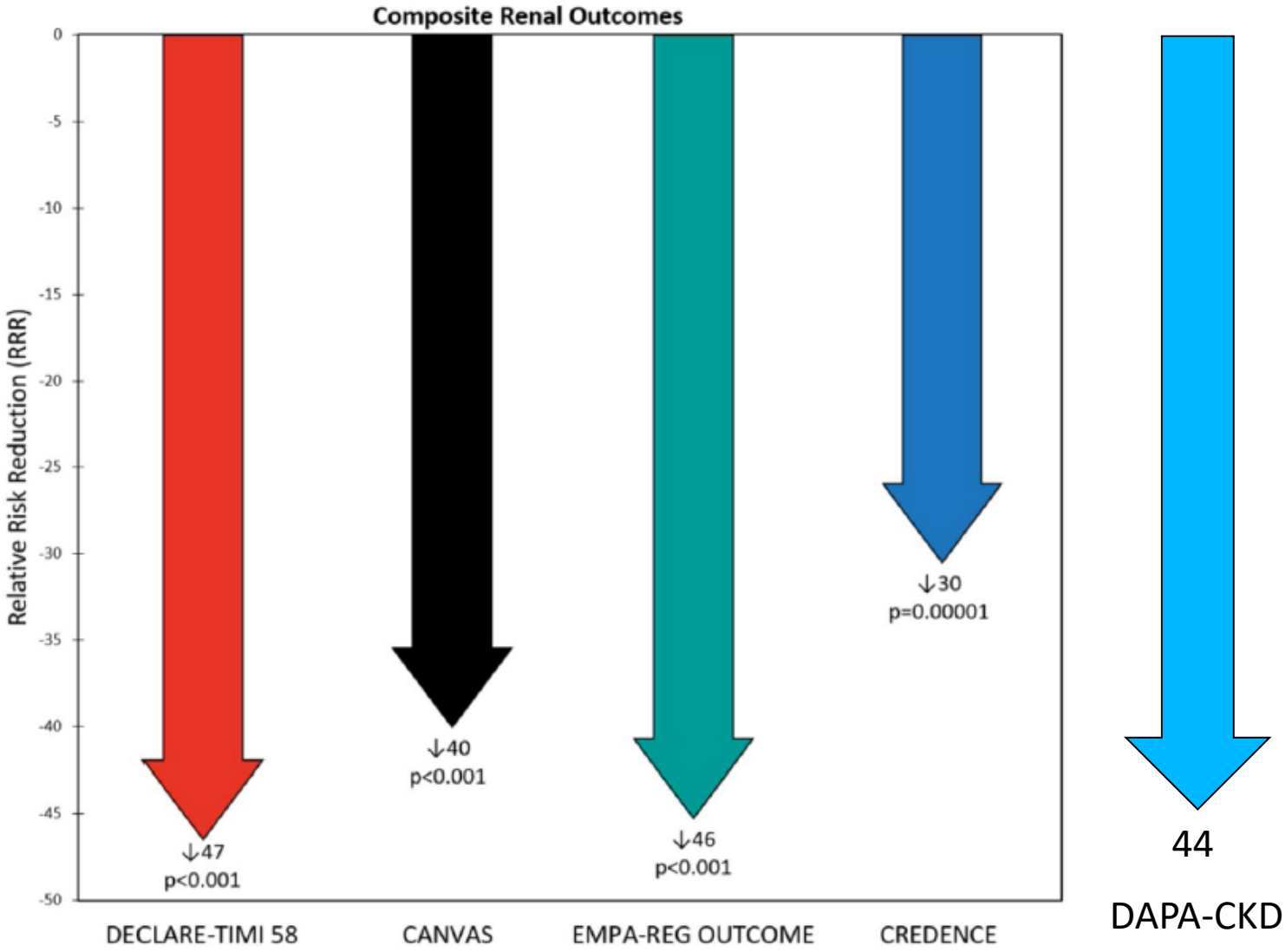

Albuminuria categories (mg/g)
A1: <30
A2: 30-300
A3: >300
GFR categories
(mL/min/1.73 m²)
≥90
60-90
45-59
30-44
<30
CVOTs
CREDENCE
Low
Moderately increased
High
Very high

SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis

	EMPA-REG OUTCOME	CANVAS Program	DECLARE-TIMI 58	CREDENCE	DAPA –CKD	EMPA-KIDNEY
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Dapaglifozin	Empaglifozin
Dose (mg)	10 and 25	100 and 300	10	100	10	10
Number of participants	7020	10142	17160	4401	4304 (67.5% T2DM)	5000 (T2DM and not)
Mean age (years)	63·1	63·3	63·9	63·0	61.8	
Sex						
Men	5016 (71·5%)	6509 (64·2%)	10738 (62·6%)	2907 (66·1%)	67	
Women	2004 (28·5%)	3633 (35·8%)	6422 (37·4%)	1494 (33·9%)	33	
Median follow-up (years)	3·1	2·4	4·2	2·6*	2.4	
eGFR inclusion criteria	≥30 (MDRD)	≥30 (MDRD)	CrCl ≥60 mL/min (Cockcroft-Gault)	30 to <90 (CKD-EPI)	25-75	eGFR ≥20-<45
Baseline eGFR subgroup (mL/min per 1·73 m²)†‡						
≥90	1538 (21·9%)	2476 (24·4%)	8162 (47·6%)	0		
60 to <90	3661 (52·2%)	5625 (55·5%)	7732 (45·1%)	1809 (41·1%)		
45 to <60	1249 (17·8%)	1485 (14·6%)	1265 (7·4%)§	1279 (29·1%)		
<45	570 (8·1%)	554 (5·5%)	NA	1313 (29·8%)		
Missing baseline eGFR	2 (<0·1%)	2 (<0·1%)	1 (<0·1%)	0		
UACR criteria (mg/g)	None	None	None	>300 to 5000	200-5000	eGFR: ≥45-<90 UACR: ≥200
Baseline UACR subgroup (mg/g)‡						
<30	4171 (59·4%)	7007 (69·1%)	11644 (67·9%)	0		
30–300	2013 (28·7%)	2266 (22·3%)	4030 (23·5%)	0		
>300	769 (11·0%)	760 (7·5%)	1169 (6·8%)	4401 (100·0%)		
Missing baseline UACR	67 (1·0%)	109 (1·1%)	317 (1·8%)	0		
Baseline use of RAS blockade	5666 (80·7%)	8116 (80·0%)	13950 (81·3%)	4395 (99·9%)	98%	

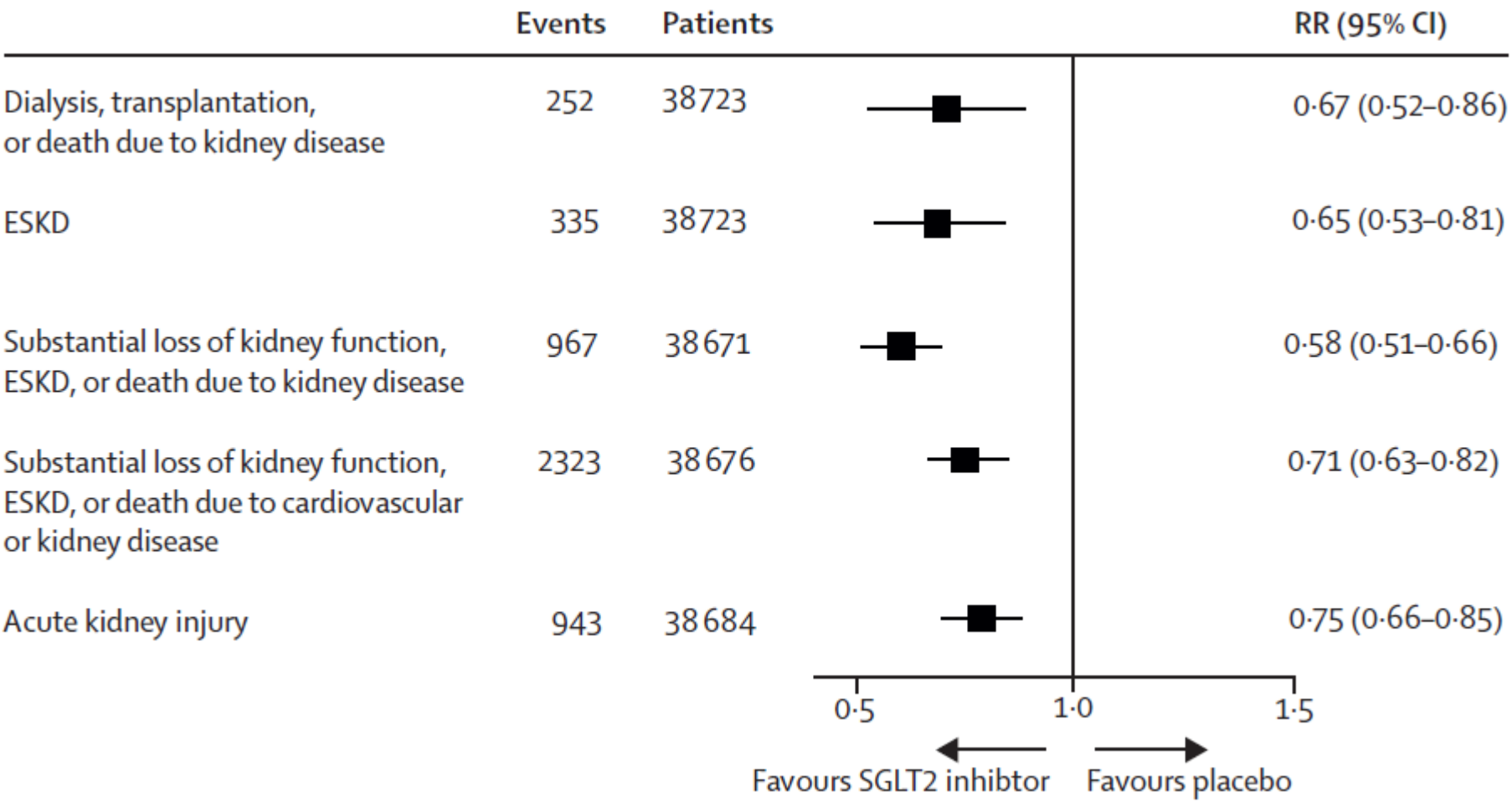
Lancet Diabetes Endocrinol 2019

Composite renal outcome relative risk reductions



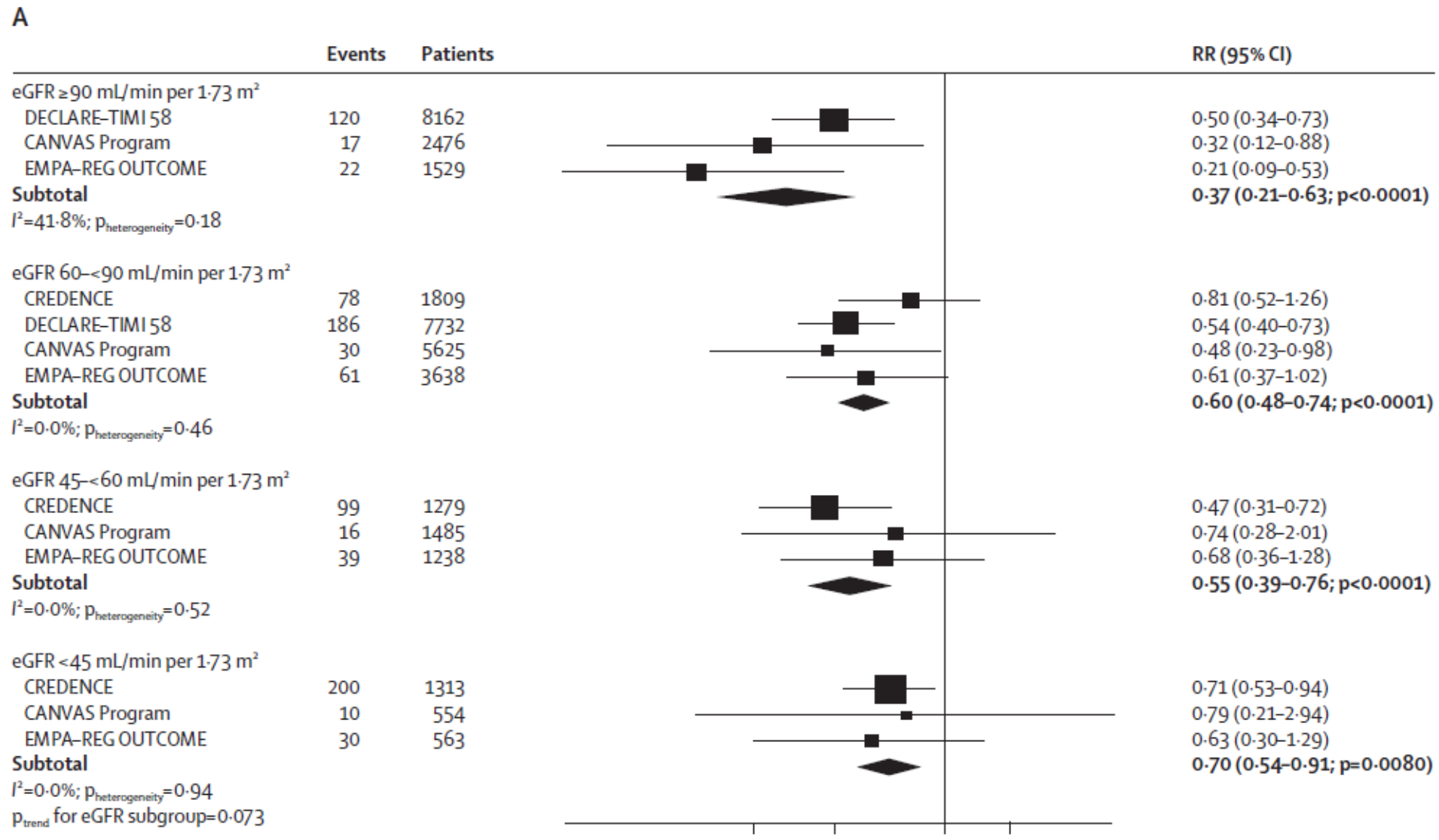
Kluger *et al. Cardiovasc Diabetol (2019) 18:99*

Summary of the effects of SGLT2 inhibition on major kidney outcomes



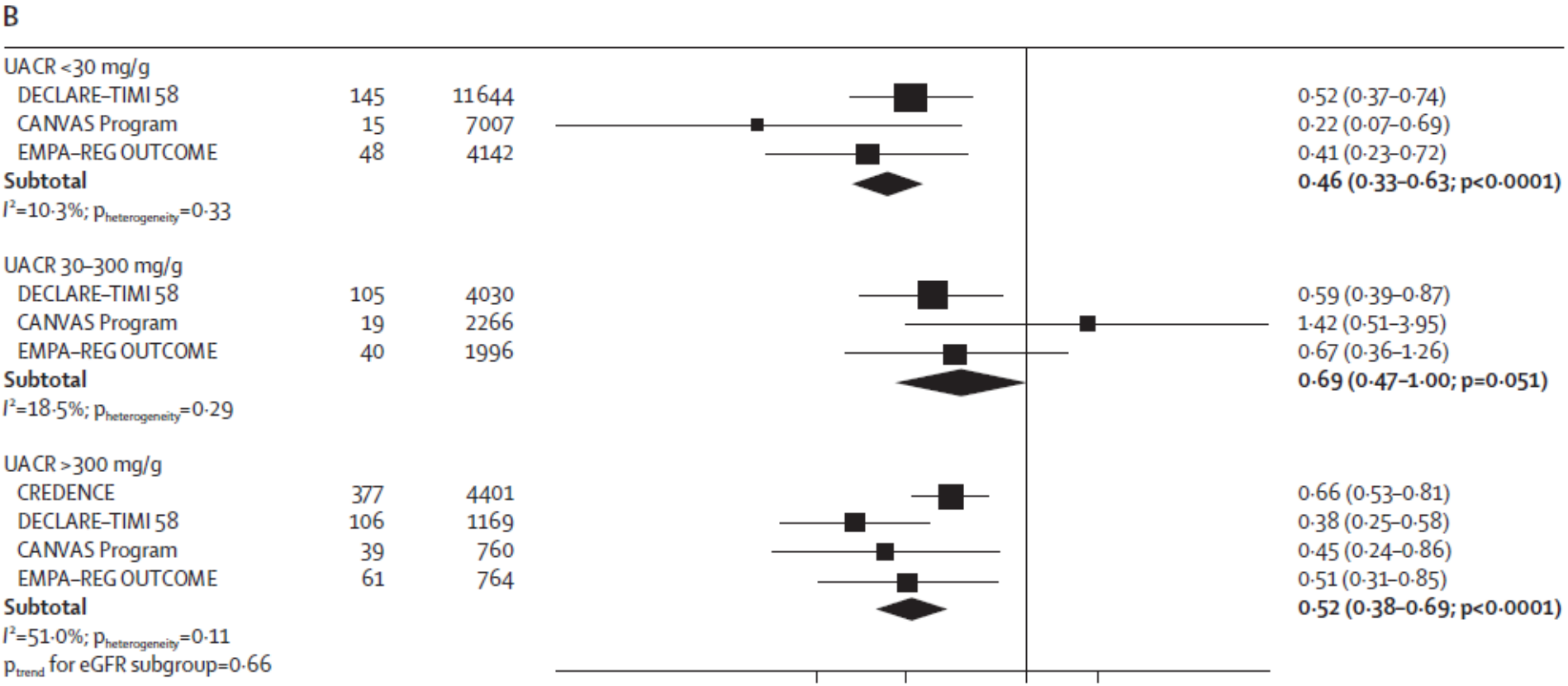
Lancet Diabetes Endocrinol 2019

Effect of SGLT2 inhibitors on substantial loss of kidney function, ESKD, or death due to kidney disease, stratified by baseline eGFR (A)



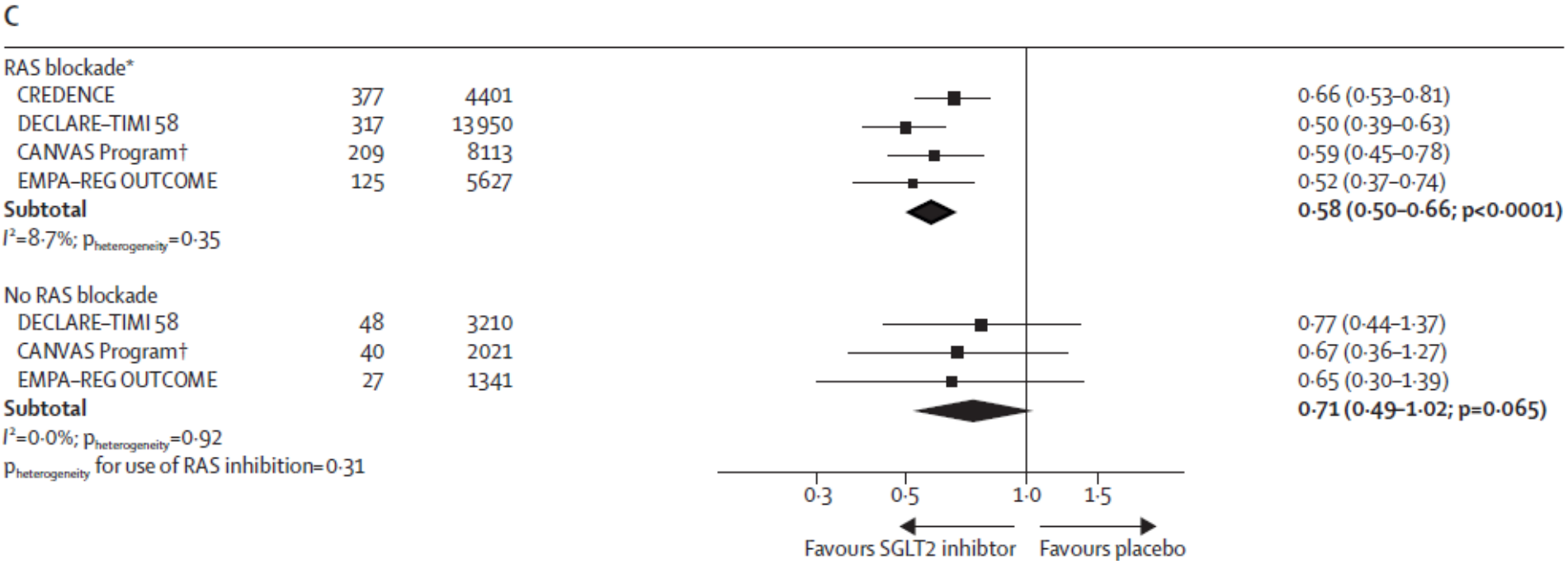
Lancet Diabetes Endocrinol 2019

Effect of SGLT2 inhibitors on substantial loss of kidney function, ESKD, or death due to kidney disease, stratified by baseline UACR (B)



Lancet Diabetes Endocrinol 2019

Effect of SGLT2 inhibitors on substantial loss of kidney function, ESKD, or death due to kidney disease, stratified by use of RAS blockade (C)



Lancet Diabetes Endocrinol 2019

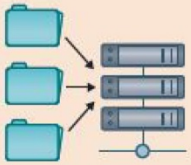
Meta-analysis

Is the combination of sodium–glucose transporter 2 inhibitors and renin–angiotensin system blockers in type 2 diabetes effective and safe?

Background

SGLT2 inhibitors and ACEI/ARBs are the future in diabetes management. Safety and tolerability of combination therapy is unknown

Methods



Electronic databases: PubMed, EMBASE, Web of Science and Cochrane

Up to May 2020

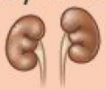
2 independent reviewers

7 RCTs, **1757** patients with type 2 diabetes

Results

SGLT-2 inhibitors and ACEI/ARB compared with ACEI/ARB alone

Primary outcomes

	Kidney function	24 h blood pressure		Proteinuria	HbA1C
					
	eGFR	SBP	DBP	UACR	
	−3.46 mL/min/1.73 m²	−4.59 mmHg	−2.08 mmHg	−29.70%	−0.48
(95% CI)	(−4.85 to −2.07)	(−6.54 to −2.63)	(−3.29 to −0.87)	(−42.48 to −16.92)	(−0.68 to −0.28)

Safety outcomes

	All adverse effects	Hypoglycaemia	Genital infection	Urinary infection
				
	RR 1.08	RR 1.37	RR 1.88	RR 2.04
(95% CI)	(0.96 to 1.22)	(1.03 to 1.82)	(0.90 to 3.95)	(0.92 to 4.50)

Conclusion

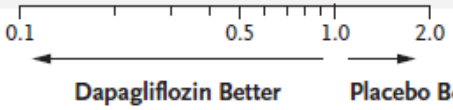
Combination therapy with SGLT2 inhibitors and ACEI/ARB was effective, well-tolerated, and could achieve additional clinical benefits. There was an increased risk of hypoglycaemia

ndt NEPHROLOGY DIALYSIS TRANSPLANTATION
era edta

Beichen Tian et al. NDT (2021)
@NDTSocial

Dapagliflozin in Patients with Chronic Kidney Disease

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)



N Engl J Med 2020;383:1436-46.

Agenda

- Effetti degli SGLT2-i sugli esiti renali
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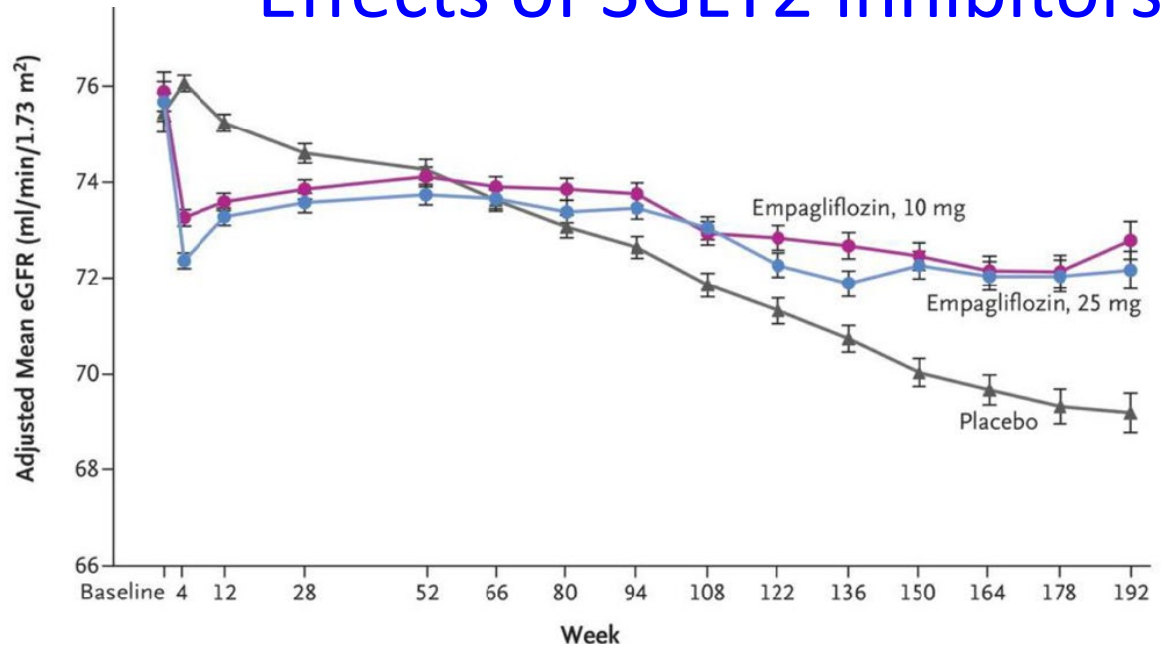
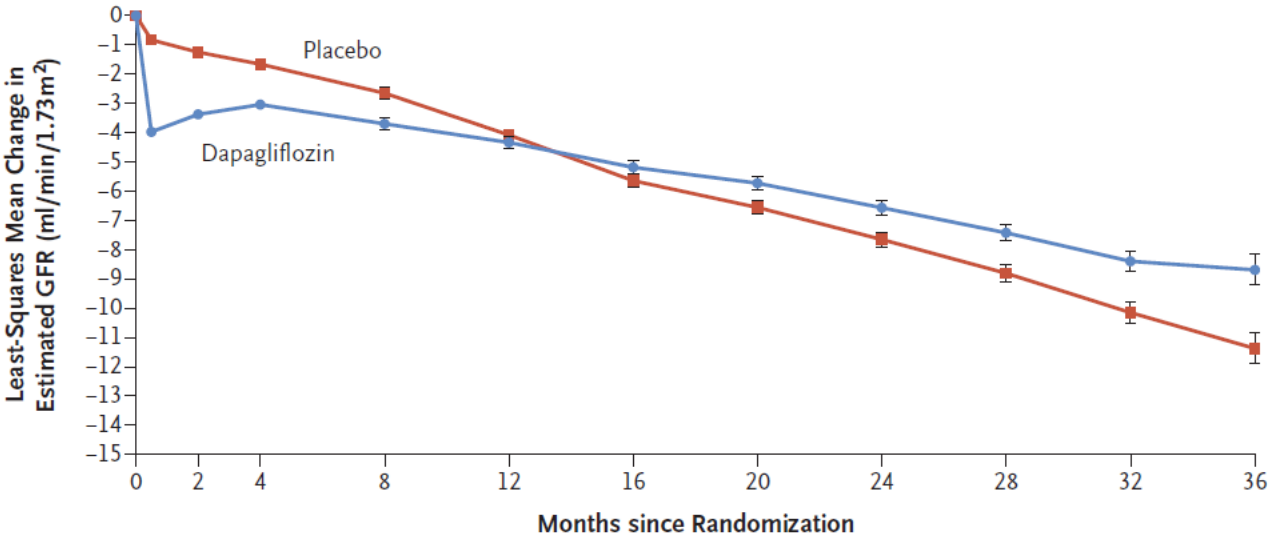
Effects of SGLT2 inhibitors on GFR



Circulation. 2016;134:752–772

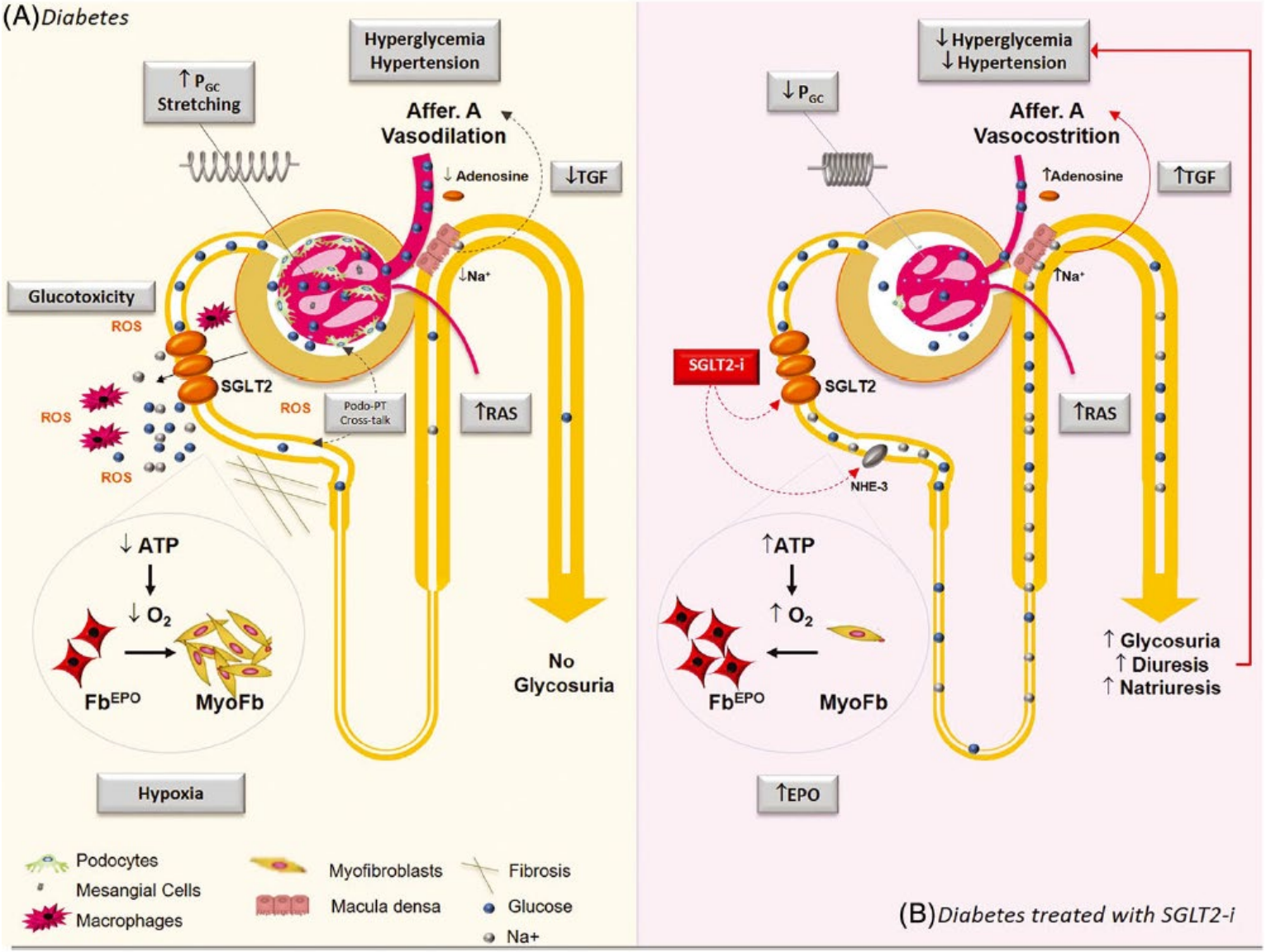


The mean estimated GFR at baseline was 43 ml/min

No. of Participants											
Placebo	2152	2029	1981	1866	1795	1753	1672	1443	935	447	157
Dapagliflozin	2152	2031	2001	1896	1832	1785	1705	1482	978	496	157

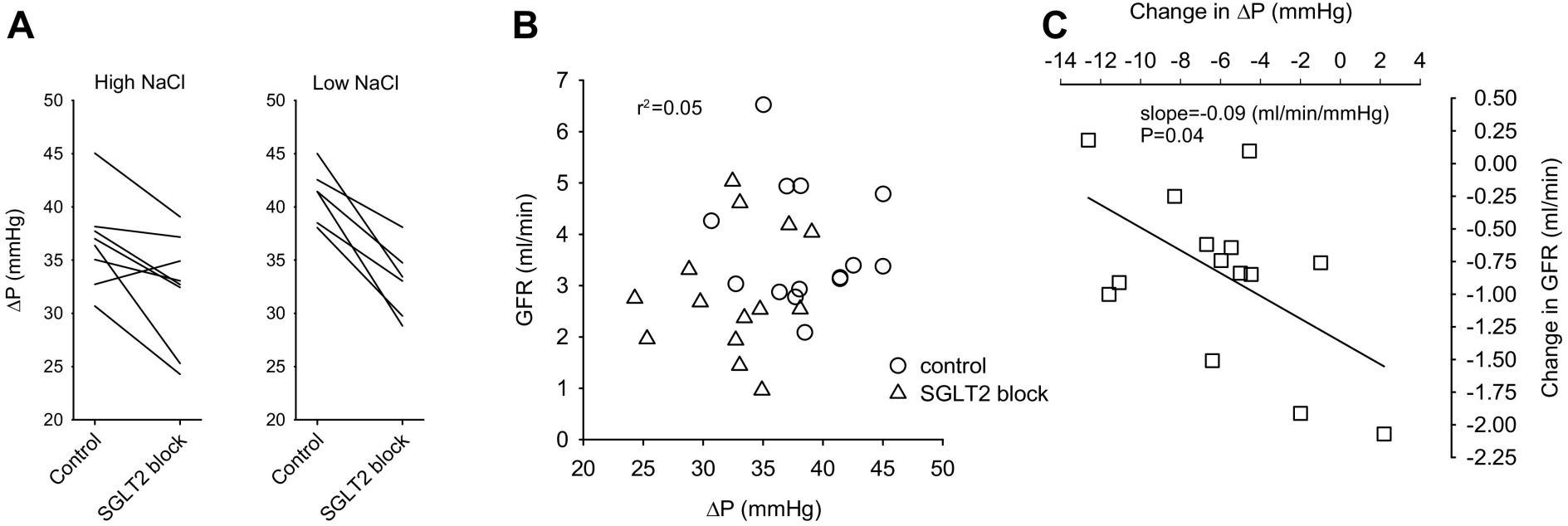
N Engl J Med 2020;383:1436-46

Mechanisms implicated in renal protective effect of sodium-glucose cotransporter 2 (SGLT2) inhibition



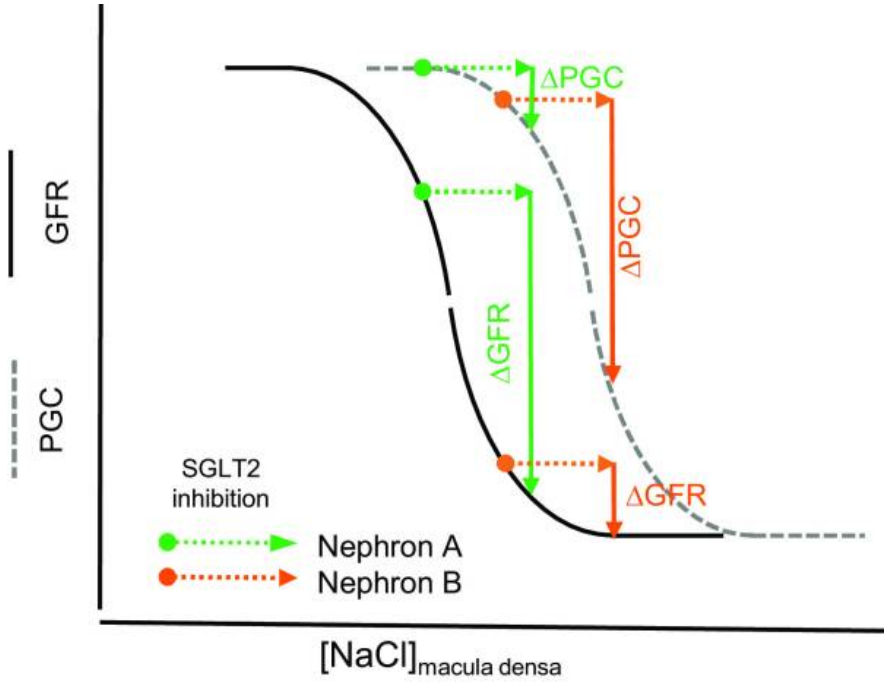
Diabetes Metab Res Rev. 2019;e3171.

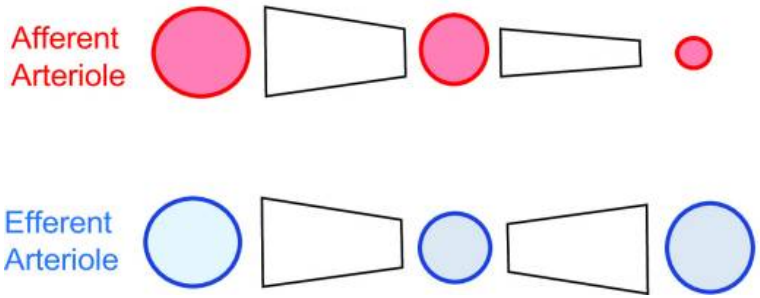
Effects of acute SGLT2 blockade on the glomerular filtration rate (GFR) and transcapillary pressure difference (ΔP)



Am J Physiol Renal Physiol. 2021 May 1; 320(5): F761–F771

Glomerular hemodynamic effects of SGLT2 inhibitor superimposed on a model of tubuloglomerular feedback (TGF), which incorporates effects on pre- and postglomerular resistances





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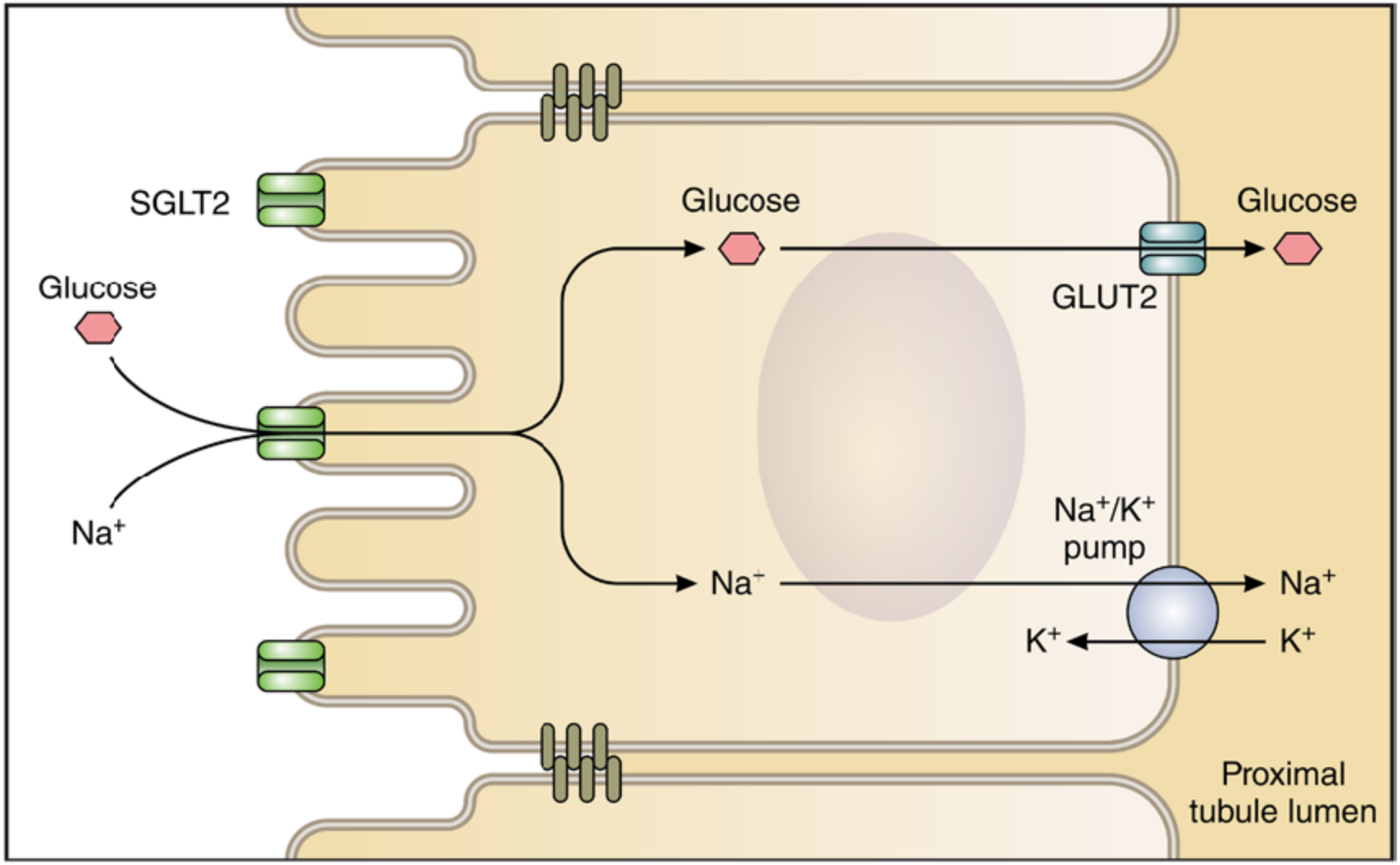
The sodium-glucose cotransporter-2 (SGLT2) mechanism in the proximal tubule



Circulation. 2016;134:752–772

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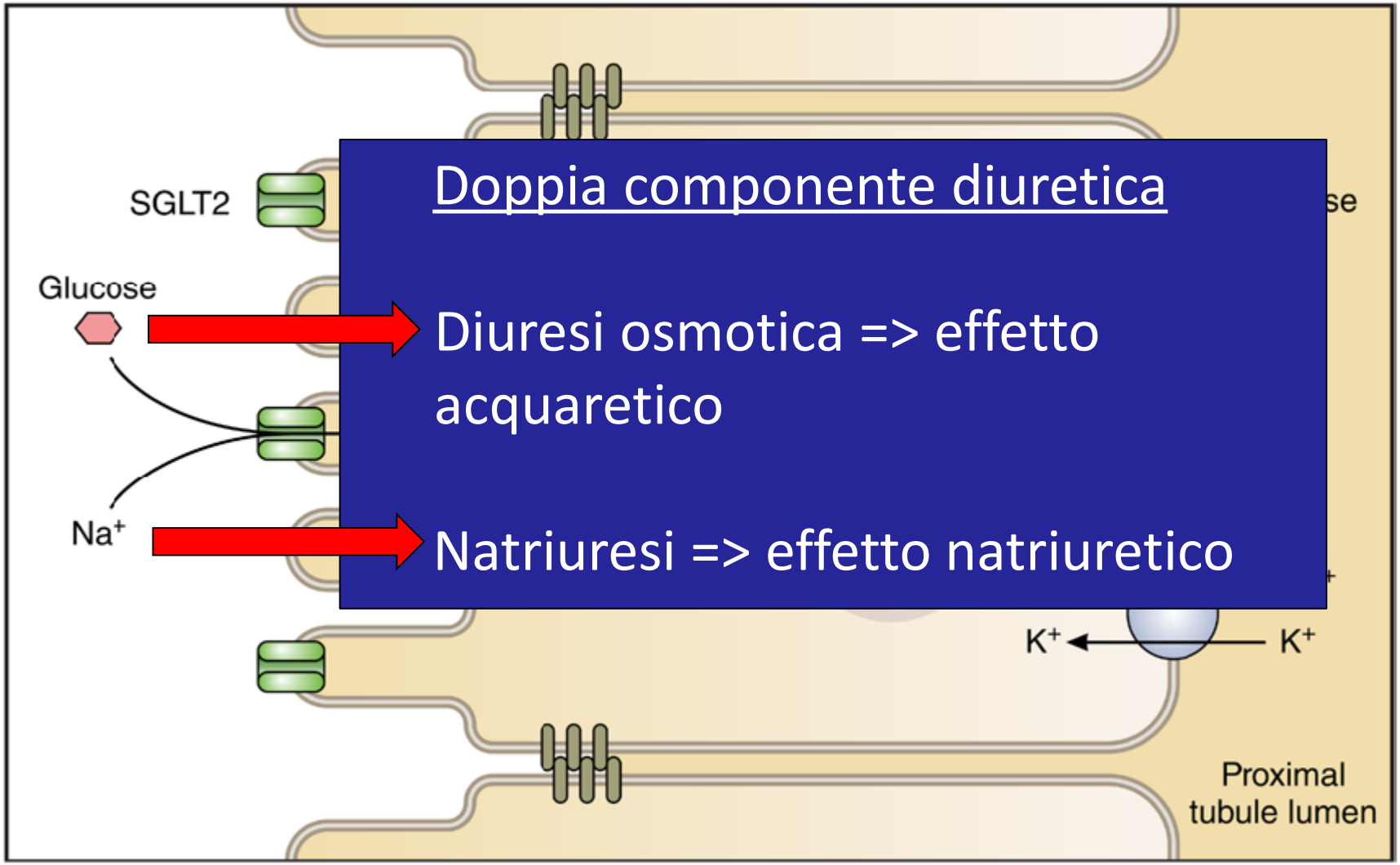
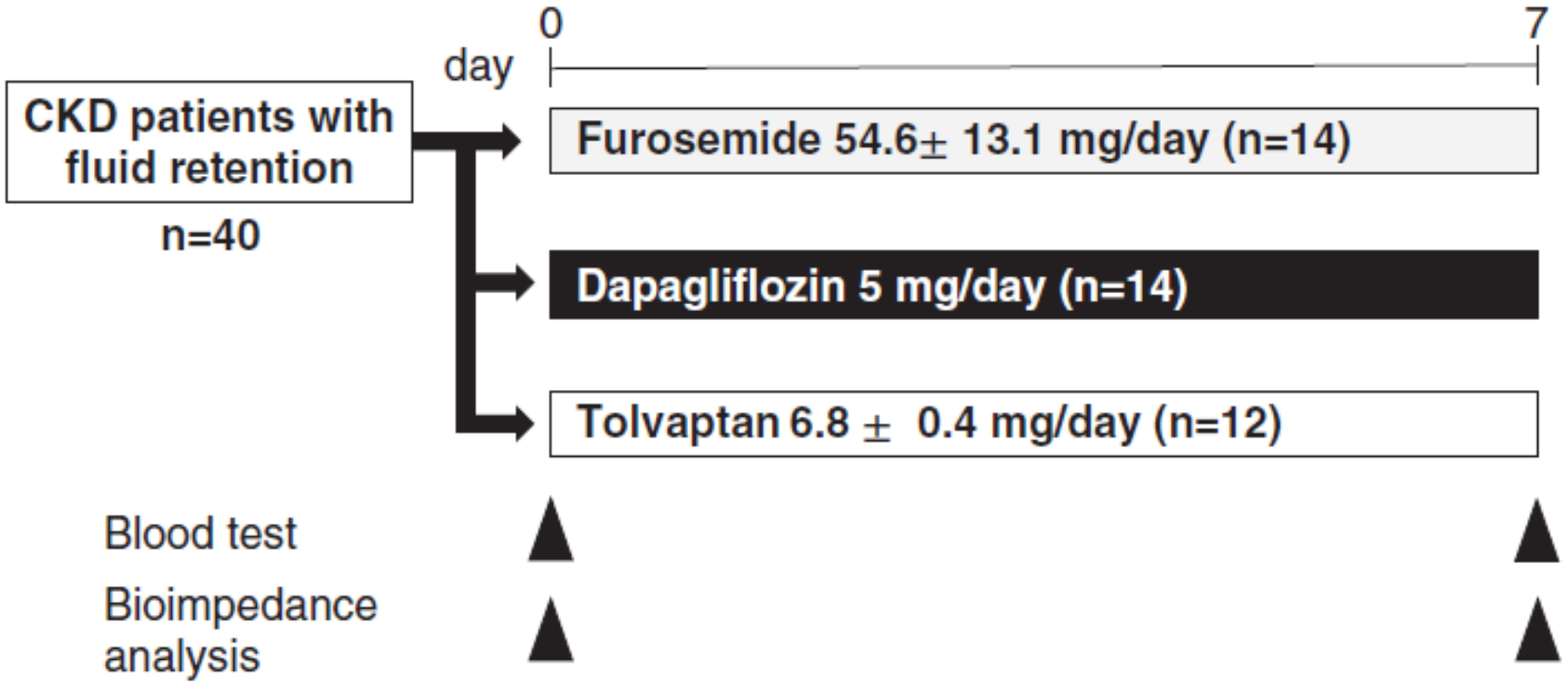


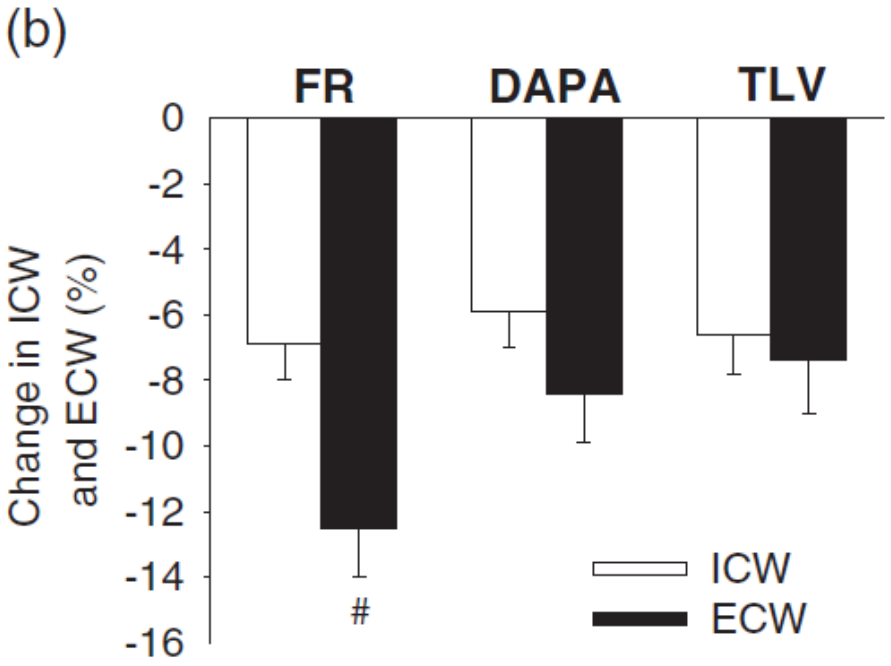
Circulation. 2016;134:752–772

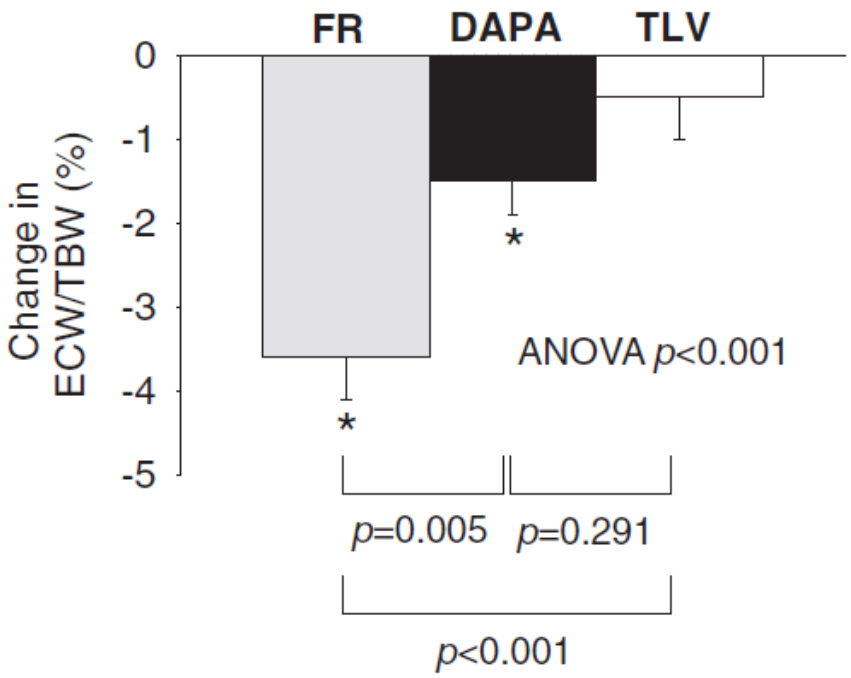
Effects of the sodium-glucose cotransporter 2 inhibitor dapagliflozin on fluid distribution: A comparison study with furosemide and tolvaptan



Ohara K et al Nephrology 24 (2019) 904–911

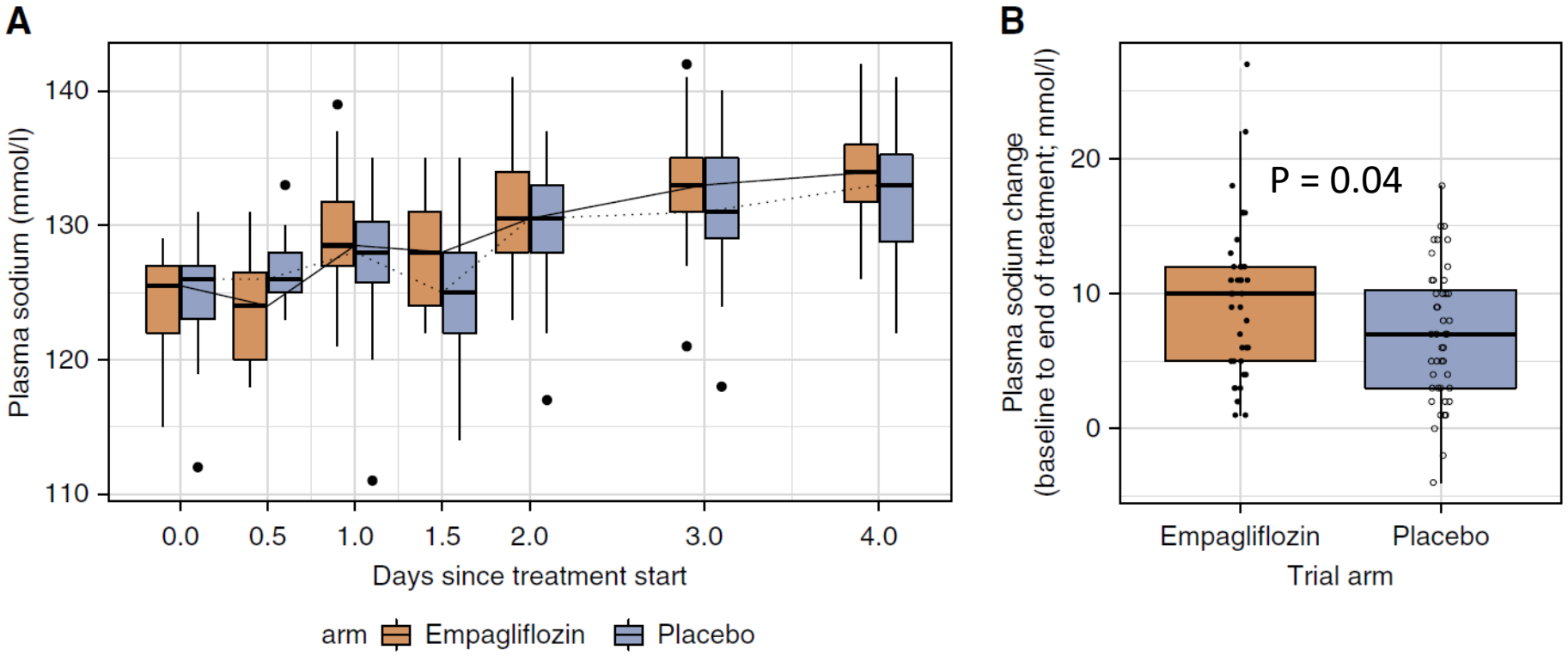
Effects of the sodium-glucose cotransporter 2 inhibitor dapagliflozin on fluid distribution: A comparison study with furosemide and tolvaptan





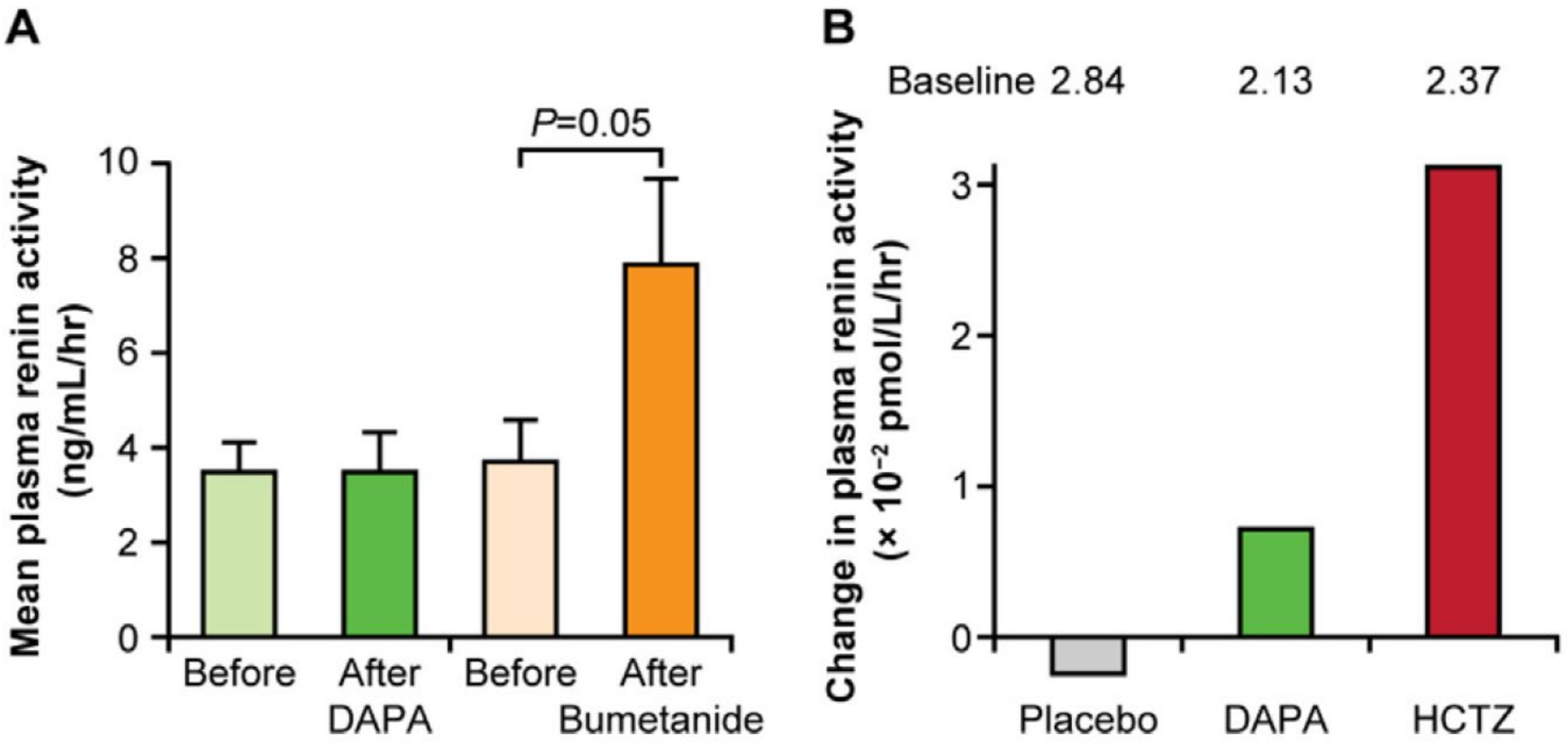
Ohara K et al Nephrology 24 (2019) 904–911

A Randomized Trial of Empagliflozin to Increase Plasma Sodium Levels in Patients with the Syndrome of Inappropriate Antidiuresis



JASN 31: 615–624, 2020

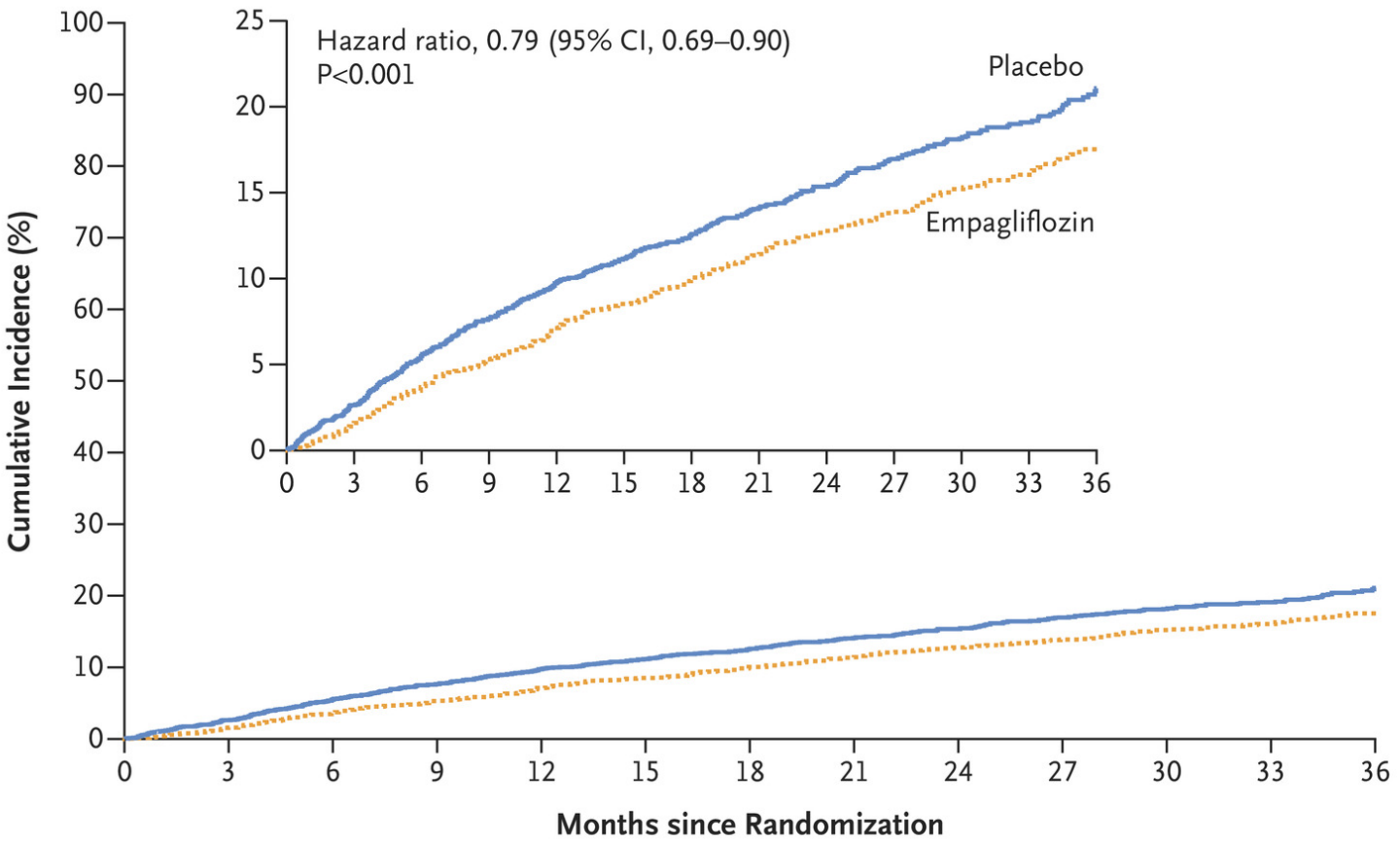
Plasma renin activity with SGLT2 inhibition



Bjornstad P et al J Cardiac Fail 2021;00:19

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure



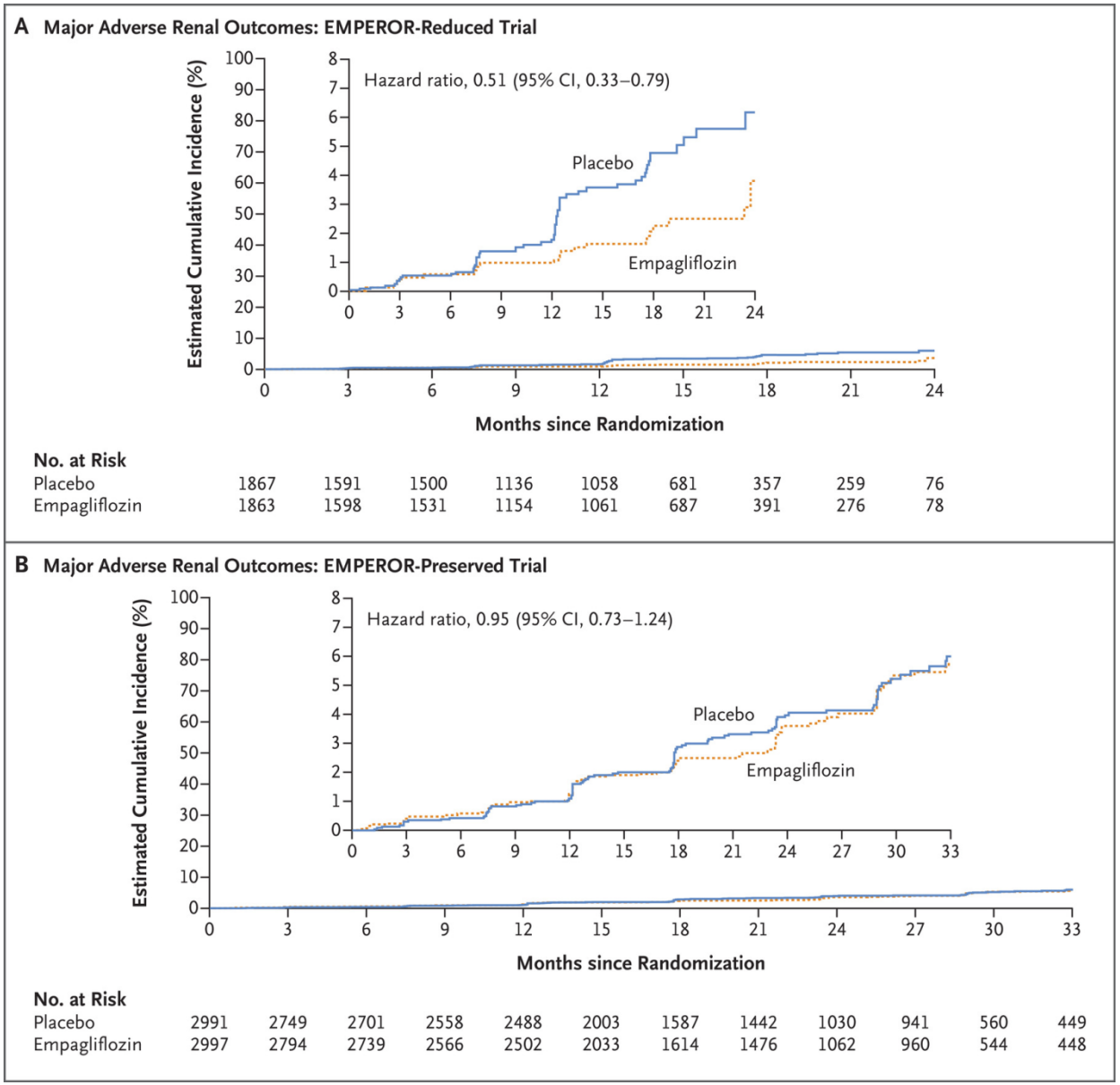
No. at Risk

Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

N Engl J Med 2021; 385:1451-1461

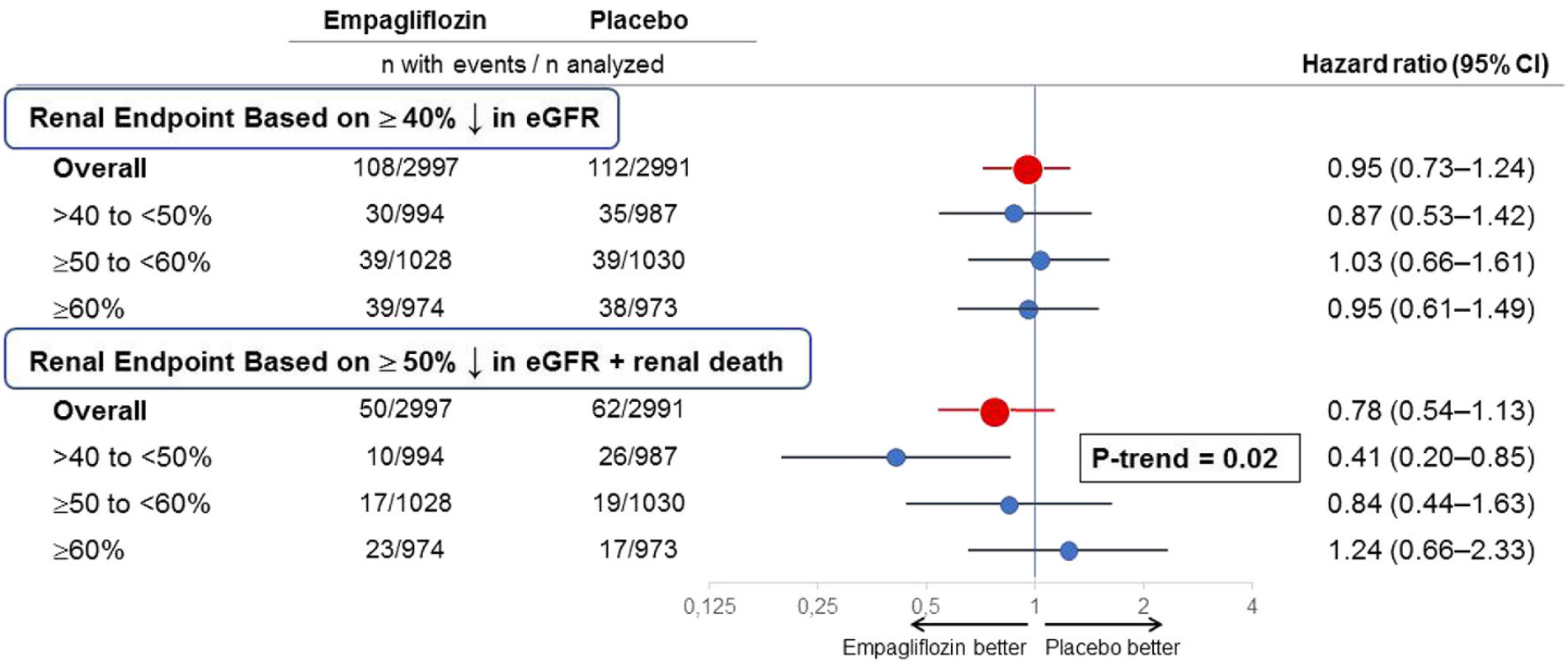
Incidence of Major Adverse Renal Outcomes in the EMPEROR-Reduced and EMPEROR-Preserved Trials

Profound and sustained decreases in the eGFR or renal-replacement therapy



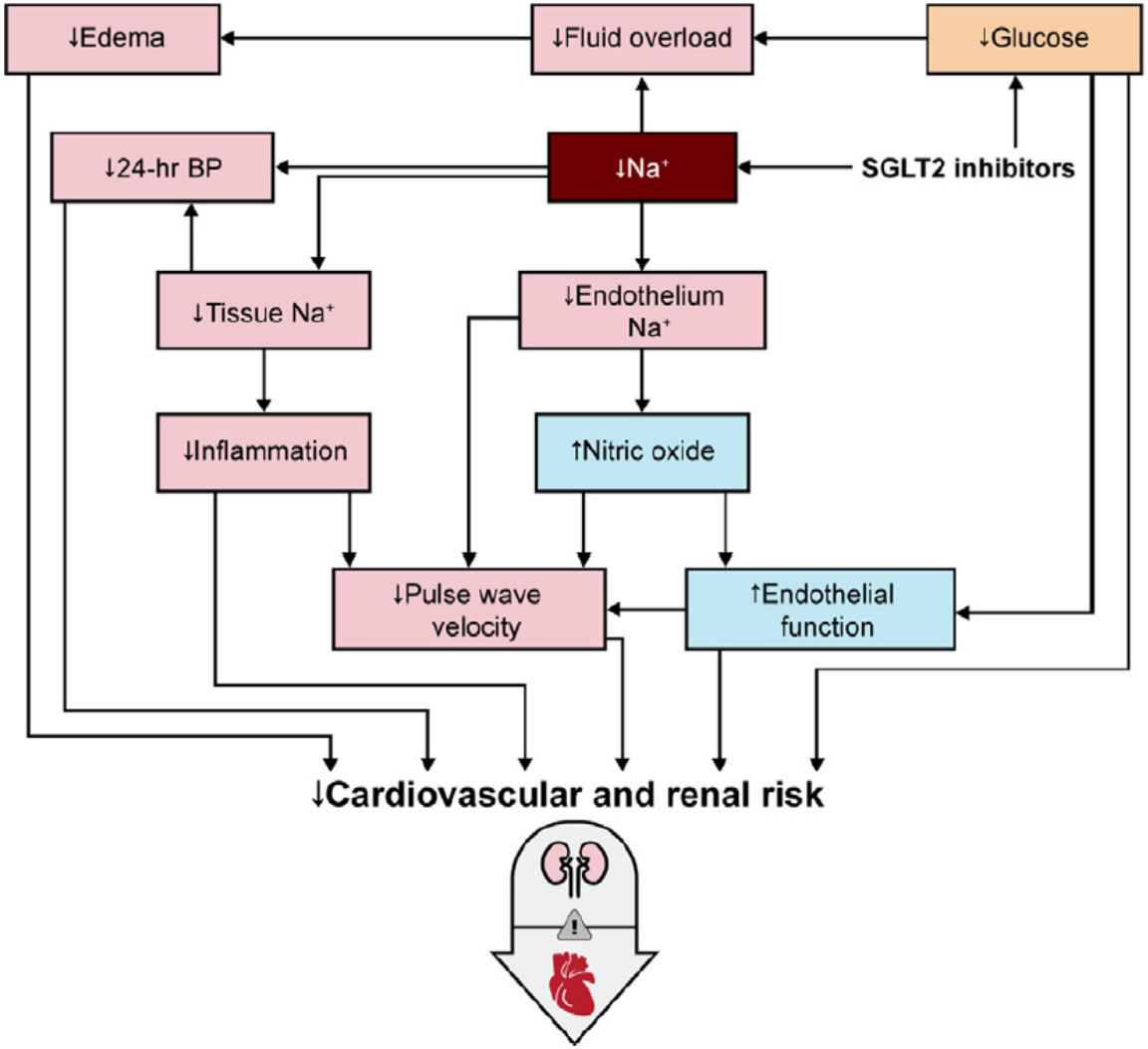
N Engl J Med 2021; 385:1531-1533

Effect of empagliflozin on major renal outcomes in EMPEROR-Preserved



European Journal of Heart Failure doi:10.1002/ejhf.2334

Putative sodium-centric mechanisms of benefit of SGLT2 inhibitors in people with type 2 diabetes and cardiorenal disease.



Bjornstad P et al J Cardiac Fail 2021;00:19

Riassunto

Effetti dell'inibizione di SGLT2

- Rallentamento evoluzione della CKD nei pazienti diabetici e non diabetici
- Riduzione incidenza di danno renale acuto
- Effetti natriuretico e acquaretico bilanciati
- Possibile effetto sull'accumulo tissutale di Na non osmotico


ROFLBOT