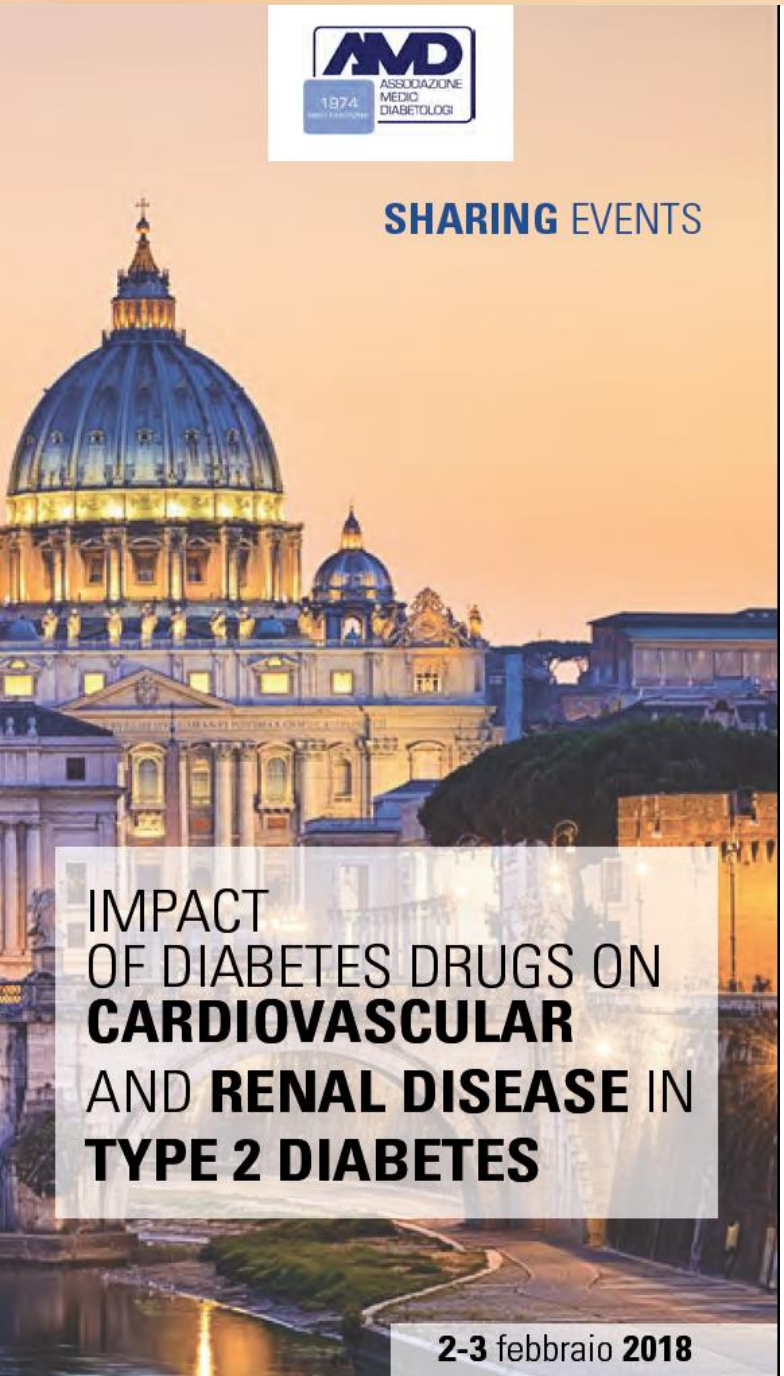


EFFETTO DEI NUOVI FARMACI SUL RENE

SGLT2 inibitori

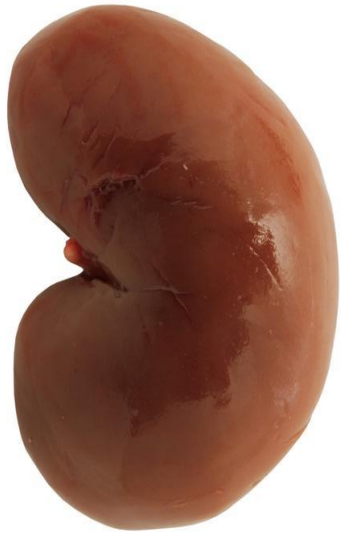
Roberto Trevisan,
Malattie Endocrine – Diabetologia,
ASST – Papa Giovanni XXIII, Bergamo

SGLT2 inhibition and potential renal protection

SGLT2i

Indirect benefits for the kidney

- Improved glycaemic control
- Reduced insulin levels
- Increased insulin sensitivity
- Reduced blood pressure
- Reduced body weight/fat
- Reduced plasma uric acid

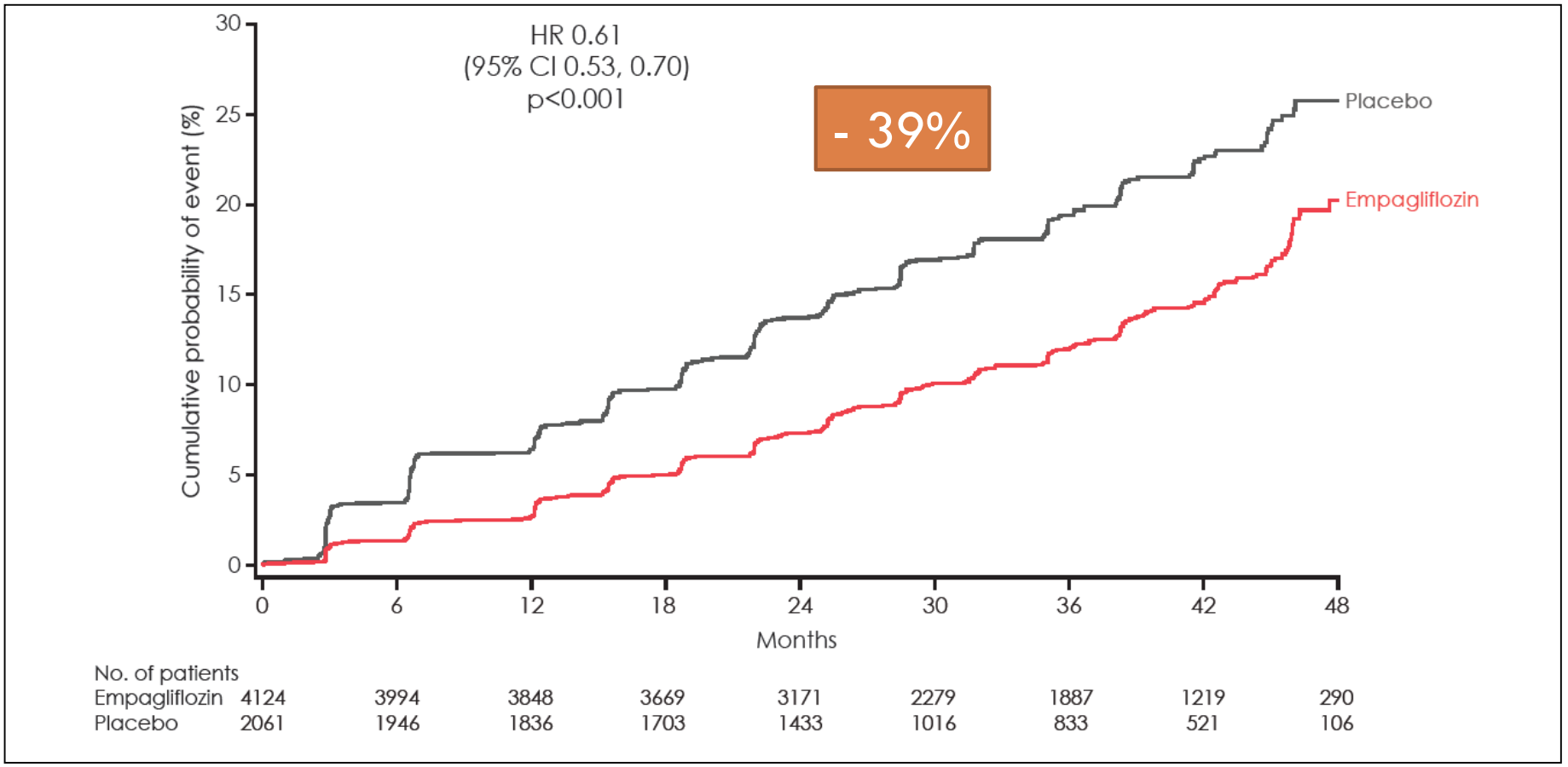


Potential direct benefits

- Reduction in hyperfiltration
- Inhibition of intra-renal RAS?
- Attenuation of renal hypertrophy
- Reduction in tubulotoxicity of glucose

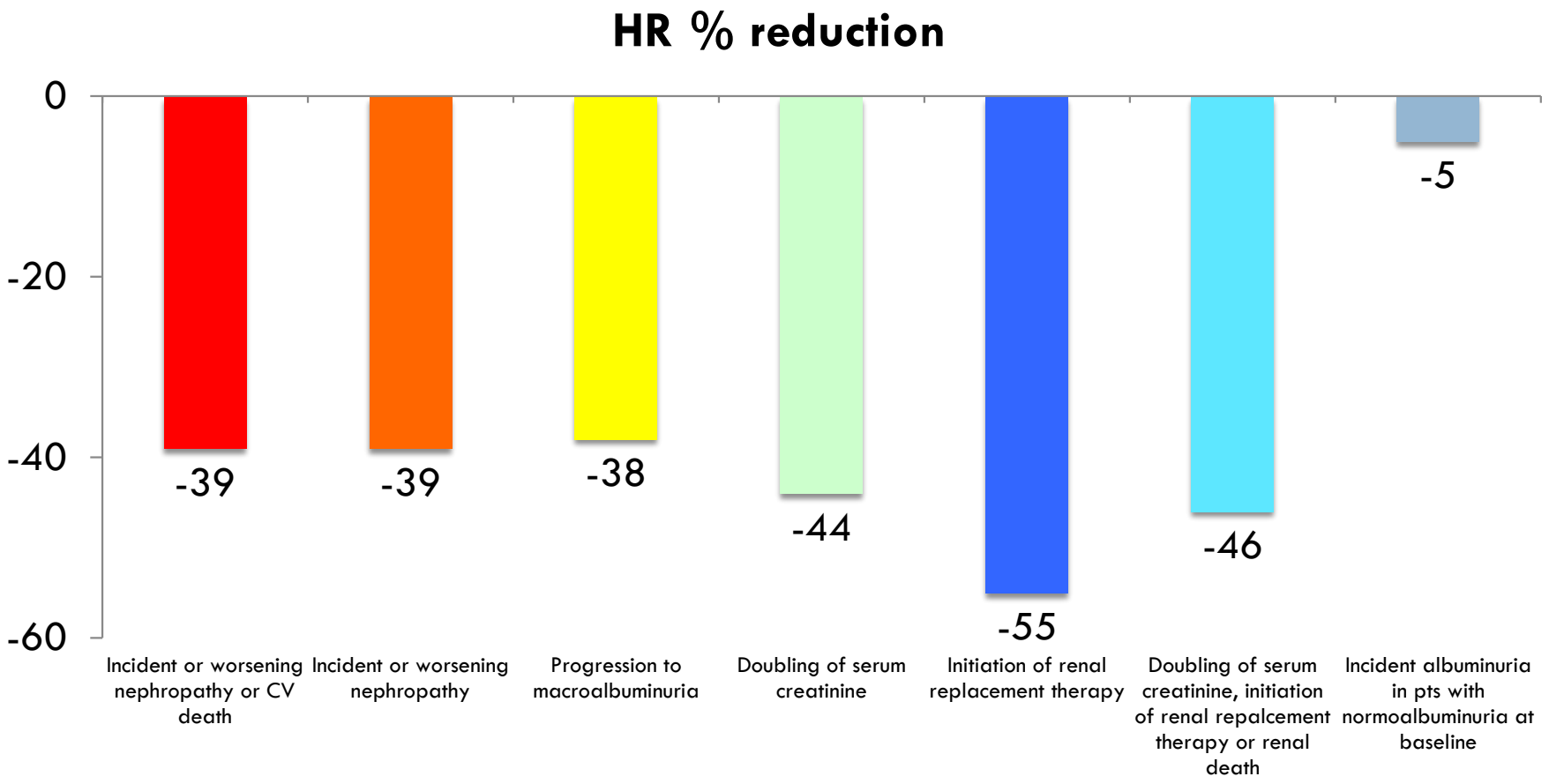
EMPA-REG: Incident or worsening nephropathy

N Engl J Med 2015;373:2117-28



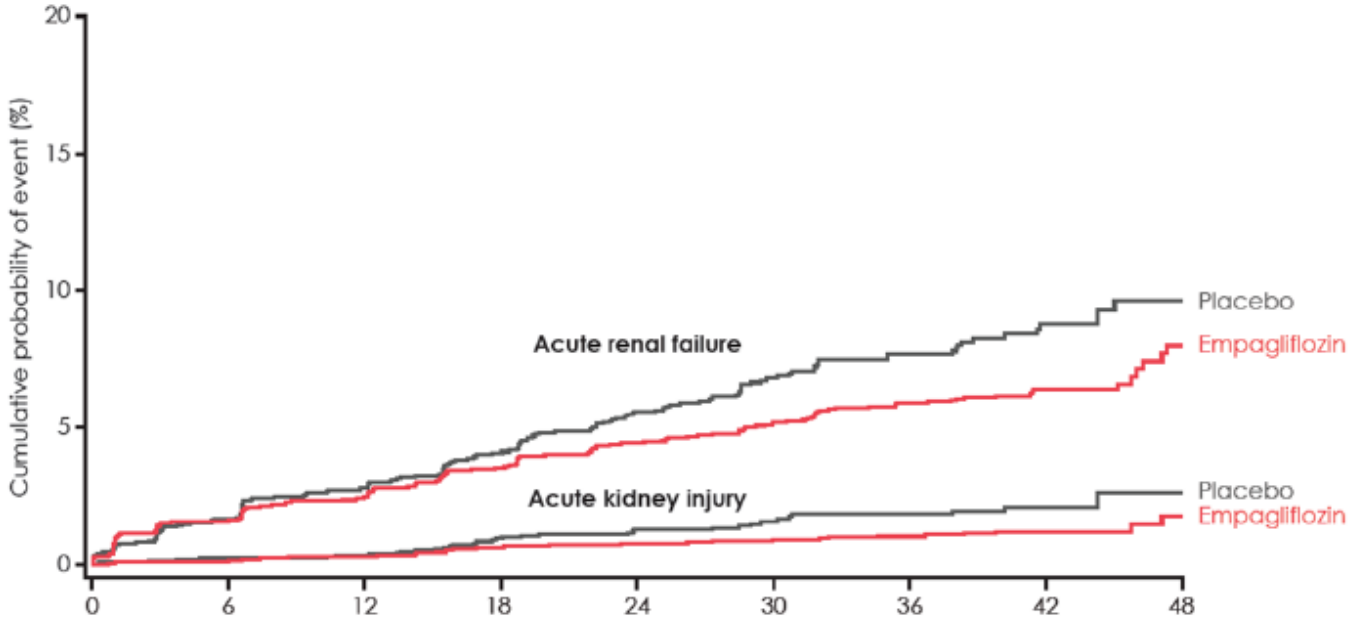
EMPAREG: Renal Outcomes

N Engl J Med 2015;373:2117-28



Acute renal failure and acute kidney injury

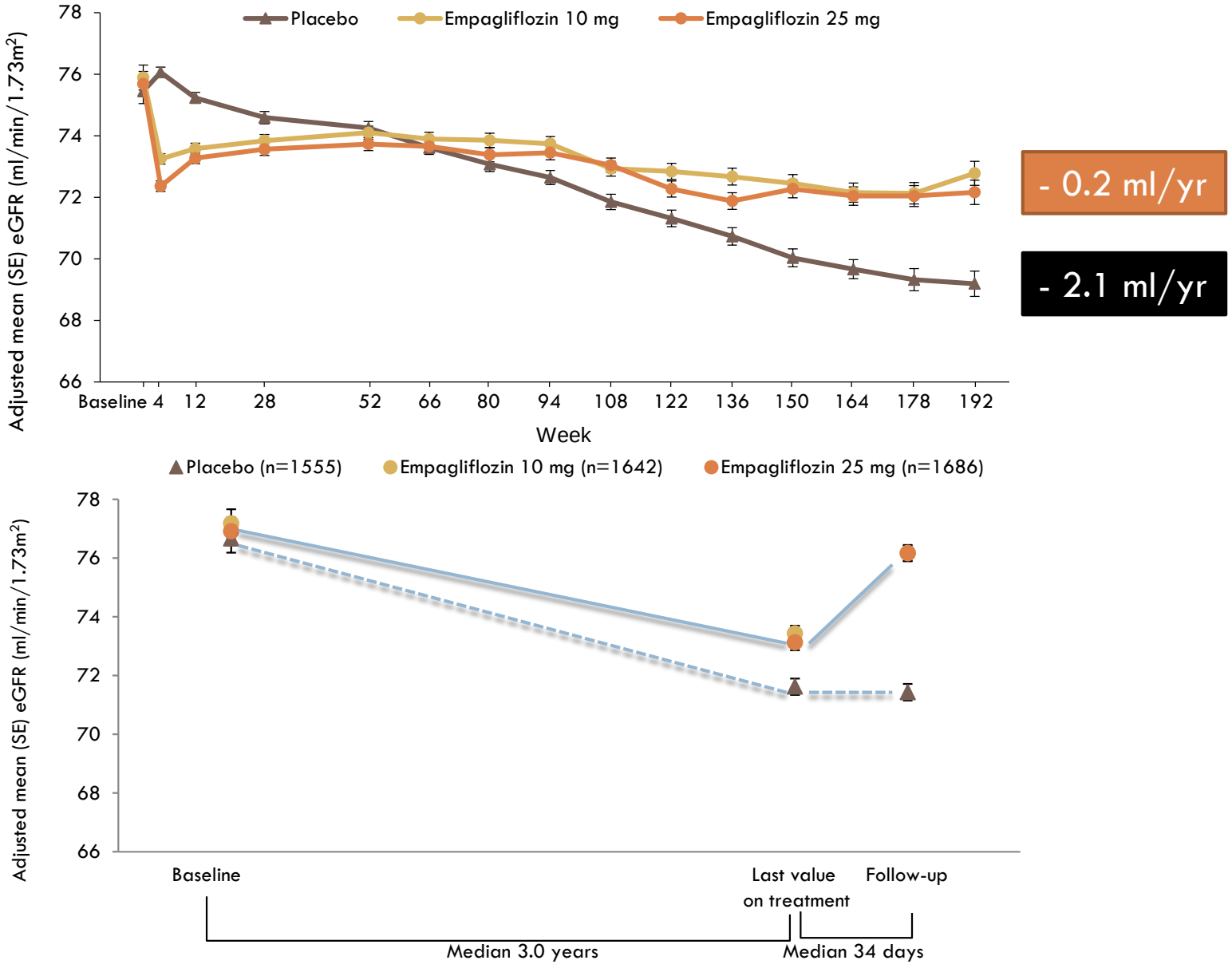
Wanner C, et al. *N Engl J Med* 2016;375:323–334



No. of patients									
Acute renal failure									
Empagliflozin	4687	4359	4159	3937	3398	2463	1897	975	268
Placebo	2333	2167	2031	1889	1588	1133	866	403	108
Acute kidney injury									
Empagliflozin	4687	4415	4238	4037	3505	2545	1965	1014	279
Placebo	2333	2194	2078	1944	1653	1178	902	427	111

- Kaplan-Meier estimates in patients treated with ≥1 dose of study drug based on events that occurred during treatment or ≤7 days after last intake of study drug. *Post-hoc* analyses.
  Acute renal failure: narrow standardized MedDRA query "acute renal failure".

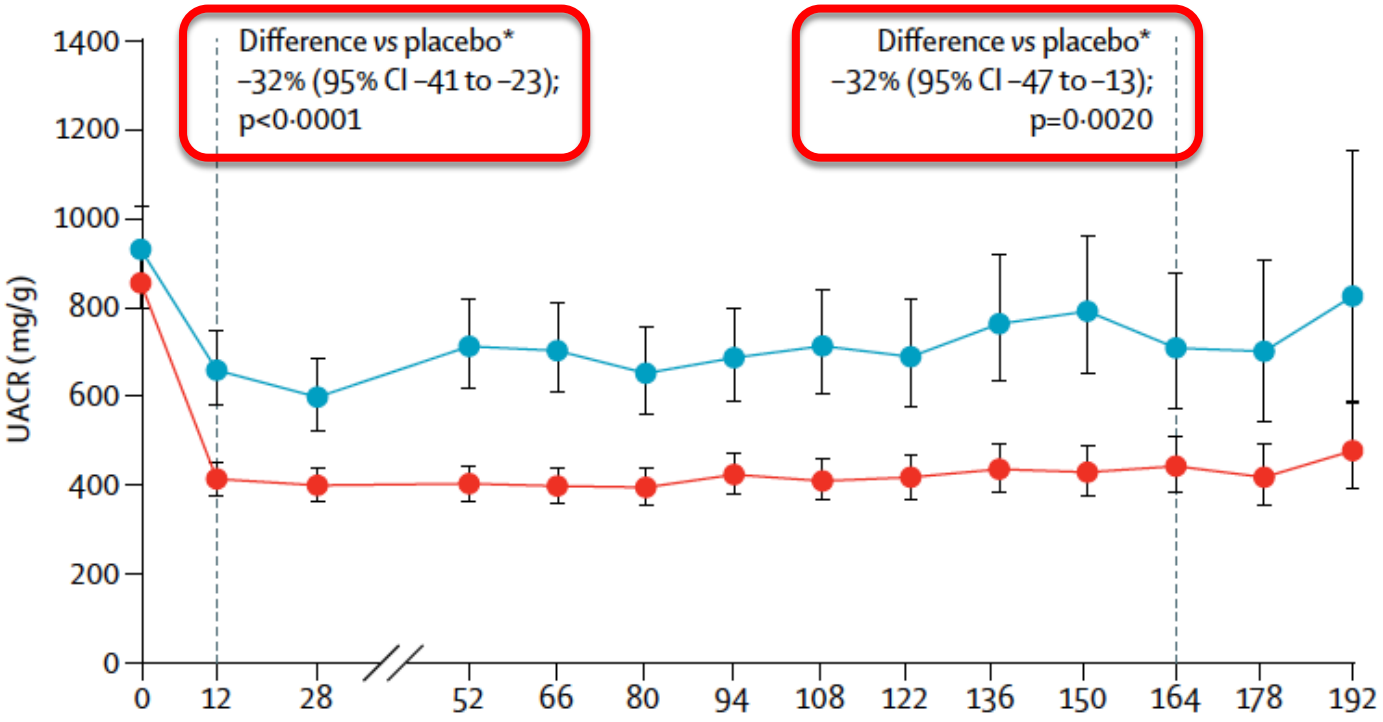
EMPAREG Study: eGFR decline during the study



Christoph Wanner et al. published online June 14, 2016, at NEJM.org

EMPAREG STUDY:Urinary albumin-to-creatinine ratio over 192 weeks in patients with MACROALBUMINURIA at baseline

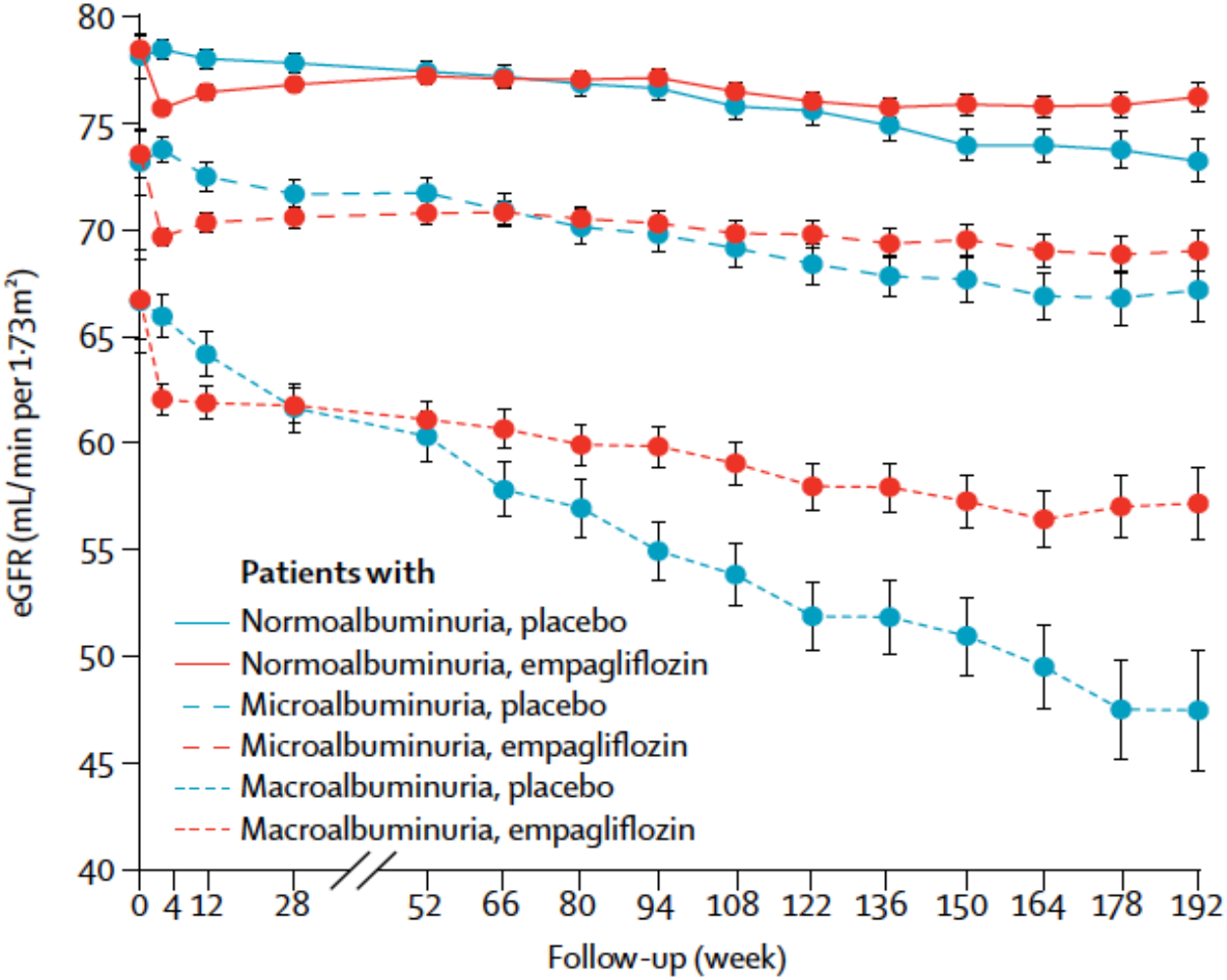
Lancet Diabetes Endocrinol 2017; 5: 610–21



Number of patients														
Placebo	257	249	233	220	206	193	195	168	137	109	100	86	56	31
Empagliflozin	498	480	477	452	435	404	425	377	324	265	241	206	157	96

EMPA-REG STUDY: Estimated glomerular filtration rate over 192 weeks

Lancet Diabetes Endocrinol 2017; 5: 610–21



Normoalbuminuria

Microalbuminuria

- 0.8 ml/yr

Macroalbuminuria

- 5.4 ml/yr

EMPA-REG OUTCOME

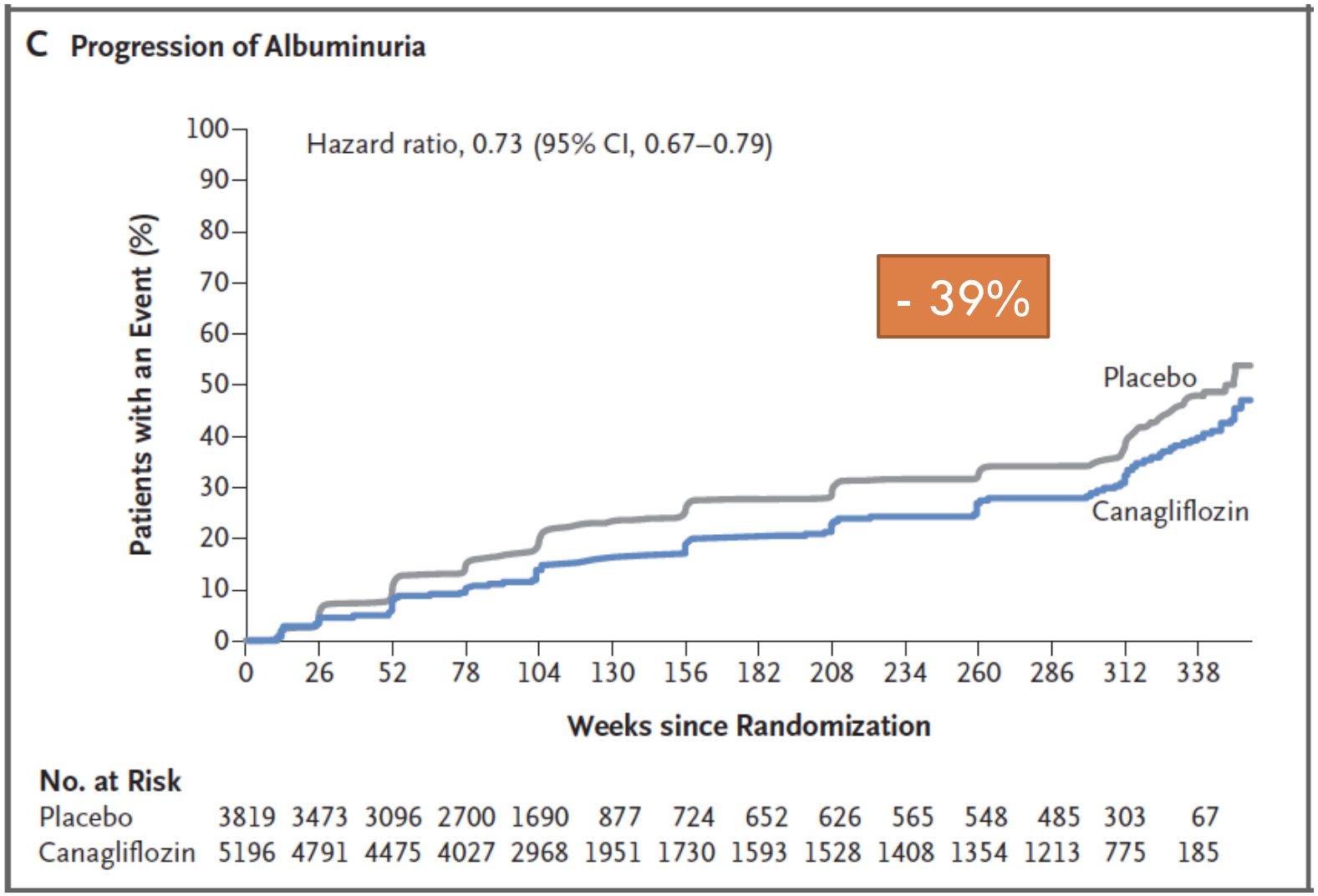
I dati clinici e metabolici nei pazienti trattati con emapglifozin rispetto al placebo

A1c (%)	-0.2 /-0.4
Weight (kg)	-1 Kg
SBP (mmHg)	-3 mmHg
LDL (mg/dl)	n.s. increase
HDL (mg/dl)	+ 2 mg
Uric acid (mg/dl)	-0.4 mg/dl

I dati clinici e metabolici non spiegano "da soli" I risultati di Empa-Reg

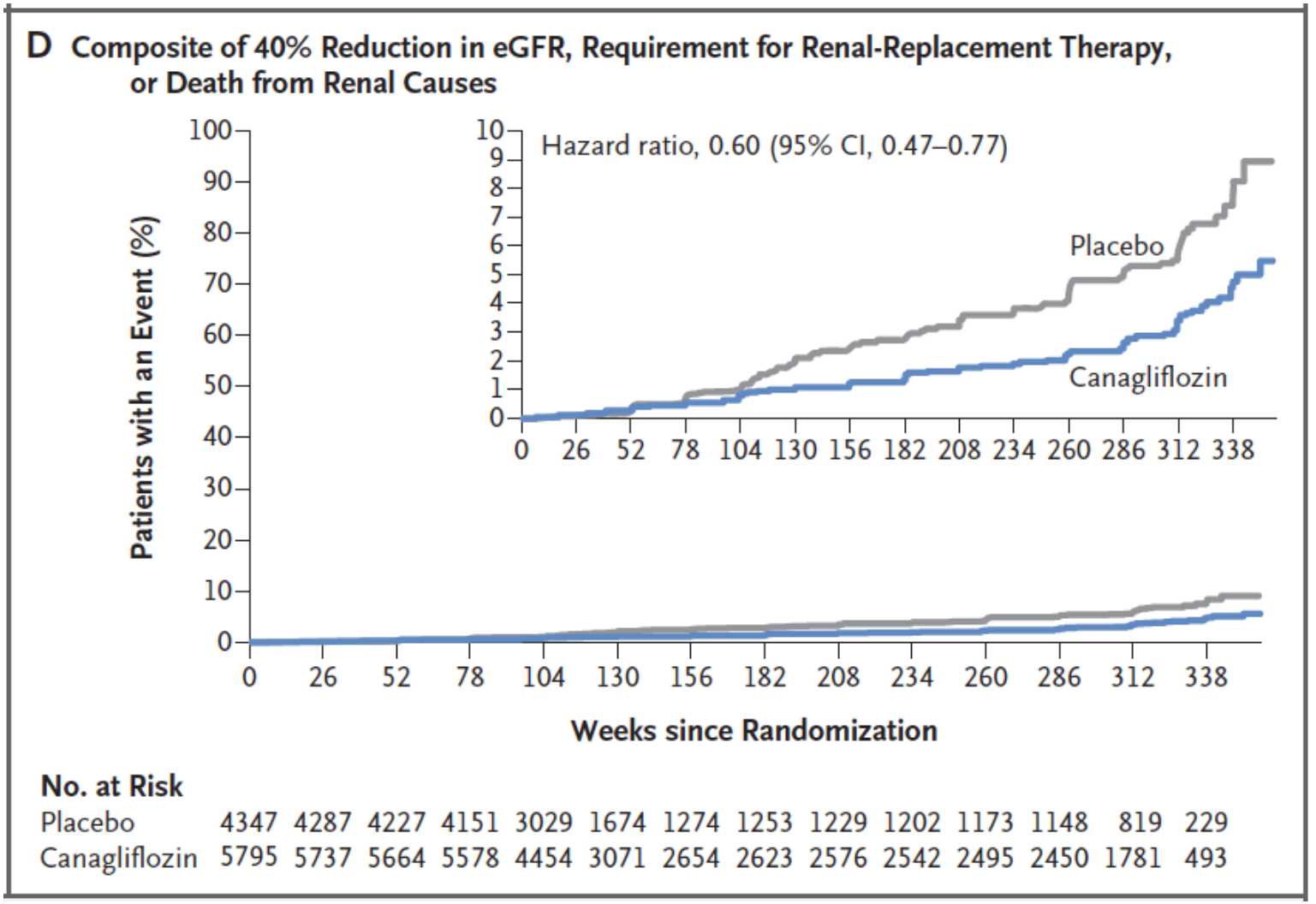
CANVAS: Progression of albuminuria was defined as more han a 30% increase in albuminuria and a change from either normoalbuminuria to microalbuminuria or macroalbuminuria or from microalbuminuria to macroalbuminuria.

N Engl J Med. 2017;377:644-657



CANVAS: 40% Reduction in eGFR, initiation of renal replacement therapy, or death from renal disease

N Engl J Med. 2017;377:644-657



Effects of canagliflozin versus placebo on renal outcomes in CANVAS, CANVAS-R, and the CANVAS Program

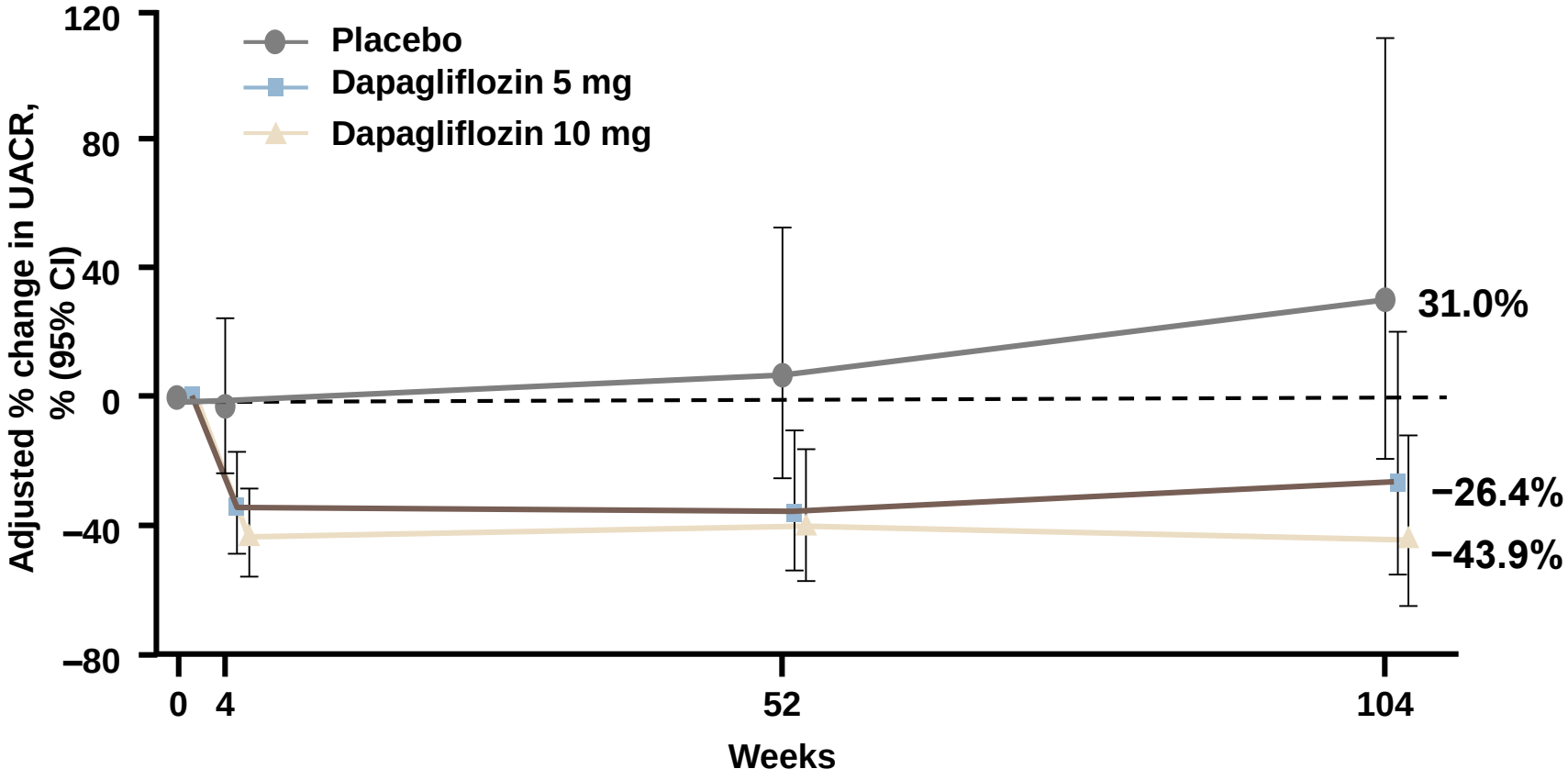
N Engl J Med. 2017;377:644-657

	Canagliflozin n/N	Placebo n/N	Hazard ratio (95% confidence interval)
Progression of albuminuria			
CANVAS	895/2655	479/1301	0.80 (0.72–0.90)
CANVAS-R	446/2541	635/2518	0.64 (0.57–0.73)
CANVAS Program	1341/5196	1114/3819	0.73 (0.67–0.79)
Regression of albuminuria			
CANVAS	434/786	162/400	1.56 (1.30–1.87)
CANVAS-R	451/893	283/857	1.80 (1.55–2.09)
CANVAS Program	885/1679	445/1257	1.70 (1.51–1.91)
40% reduction in eGFR,[‡] RRT, or renal death[§]			
CANVAS	91/2888	78/1442	0.56 (0.41–0.75)
CANVAS-R	33/2907	47/2905	0.71 (0.45–1.11)
CANVAS Program	124/5795	125/4347	0.60 (0.47–0.77)

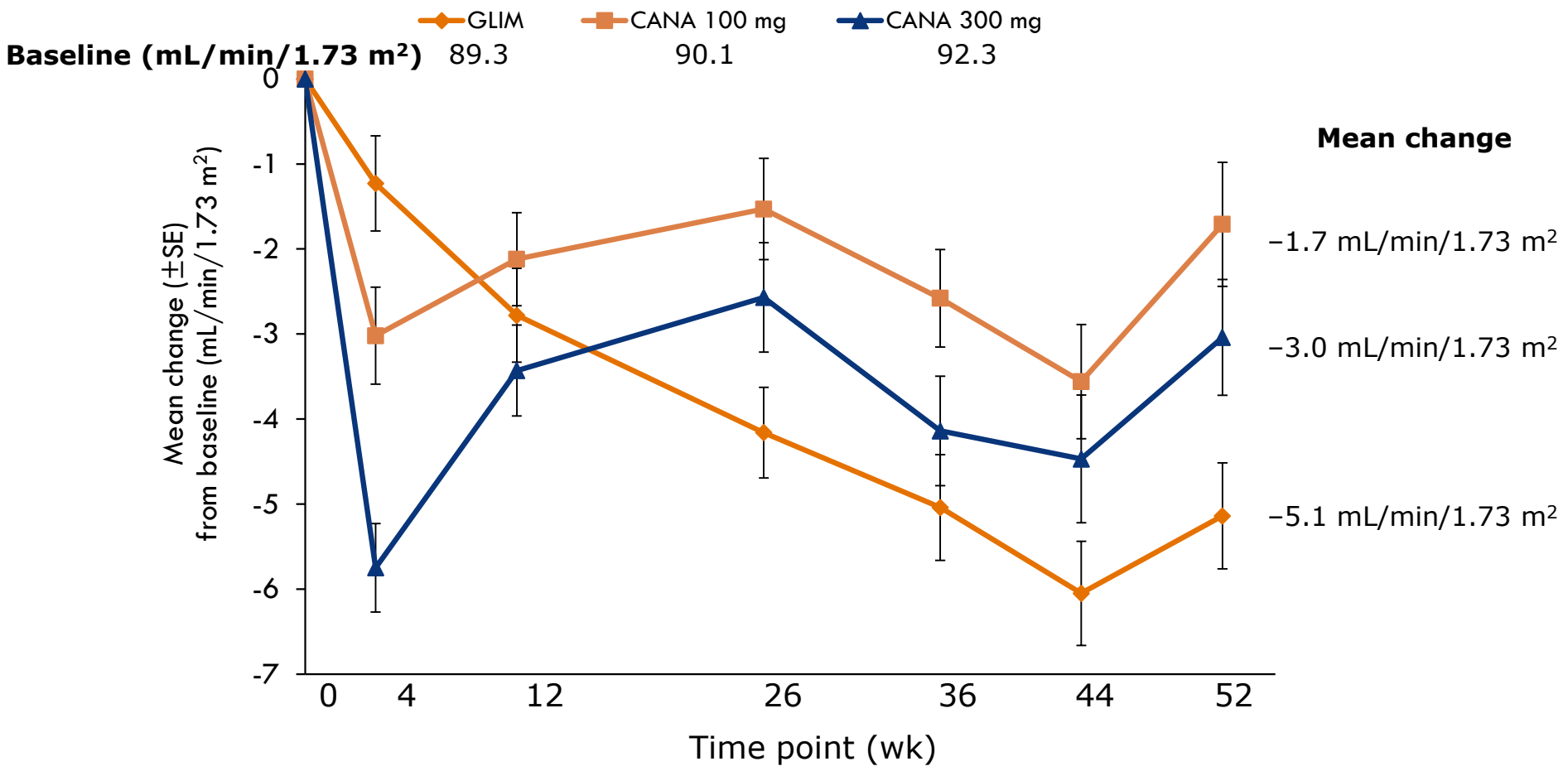
Effects of Dapagliflozin on albuminuria

A post-hoc analysis of166 patients with CKD stage 3 and increased albuminuria

Fioretto P, et al. Diabetologia 2016

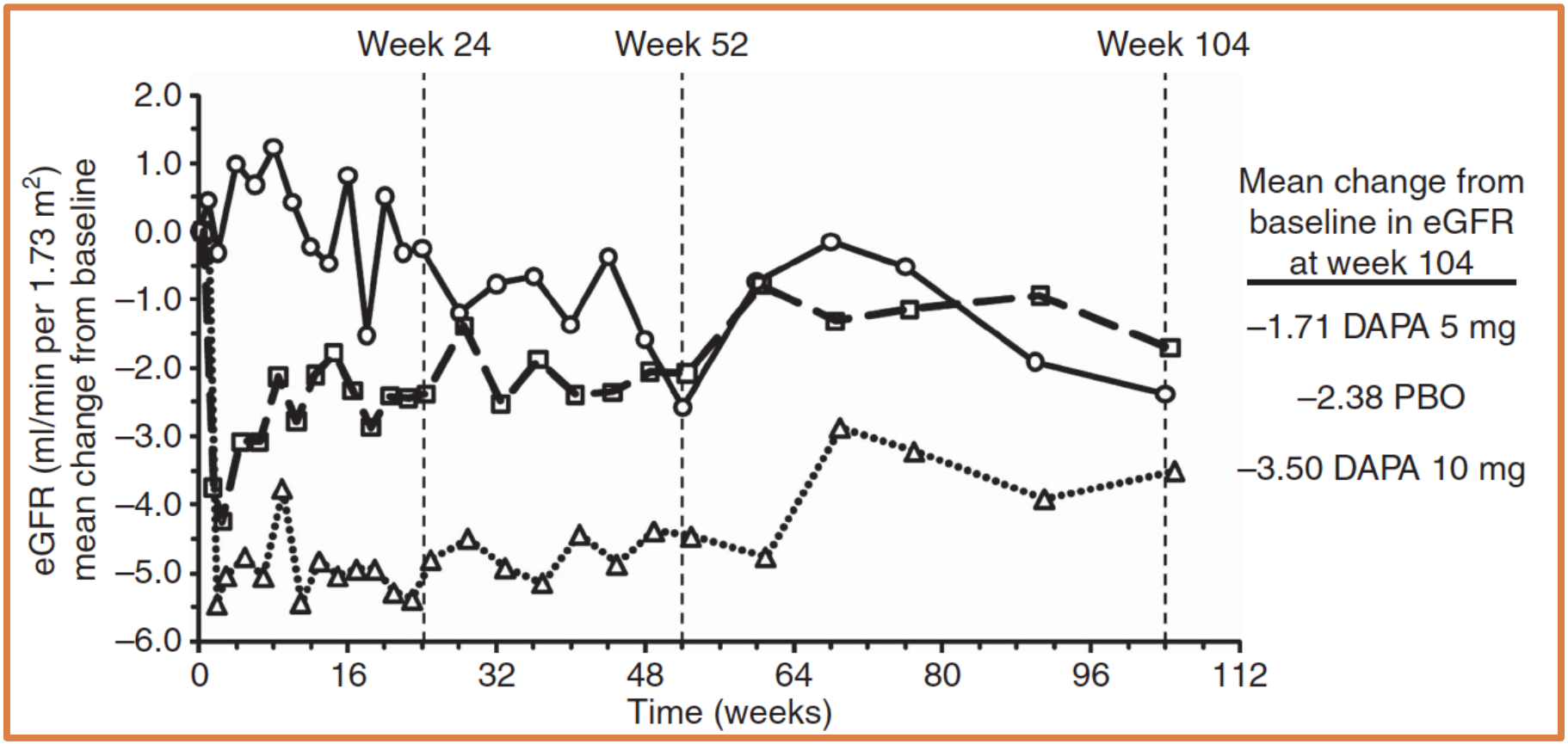


Change in eGFR Over Time



Cefalu WT et al. Lancet. 2013; 382(9896):941-50.

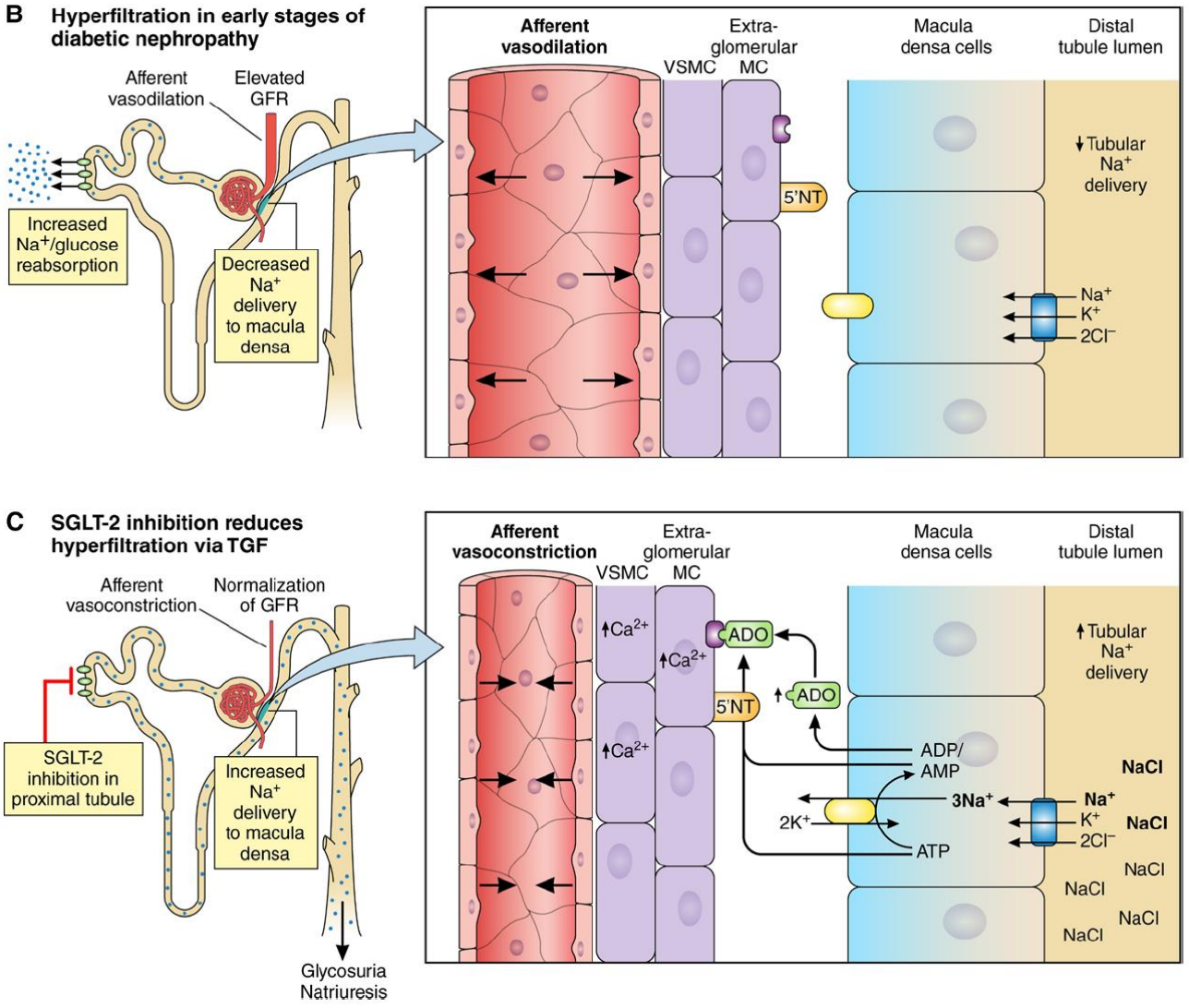
Mean change from baseline in **eGFR** for placebo (circles), **dapagliflozin** 5-mg (squares), and **dapagliflozin** 10-mg (triangles) groups, all plus original pre-enrollment antidiabetic regimen up to 104 weeks including data after rescue.



Kidney International (2014) 85, 962–971

Putative mechanism for sodium-mediated changes in adenosine bioactivity at the afferent arteriole

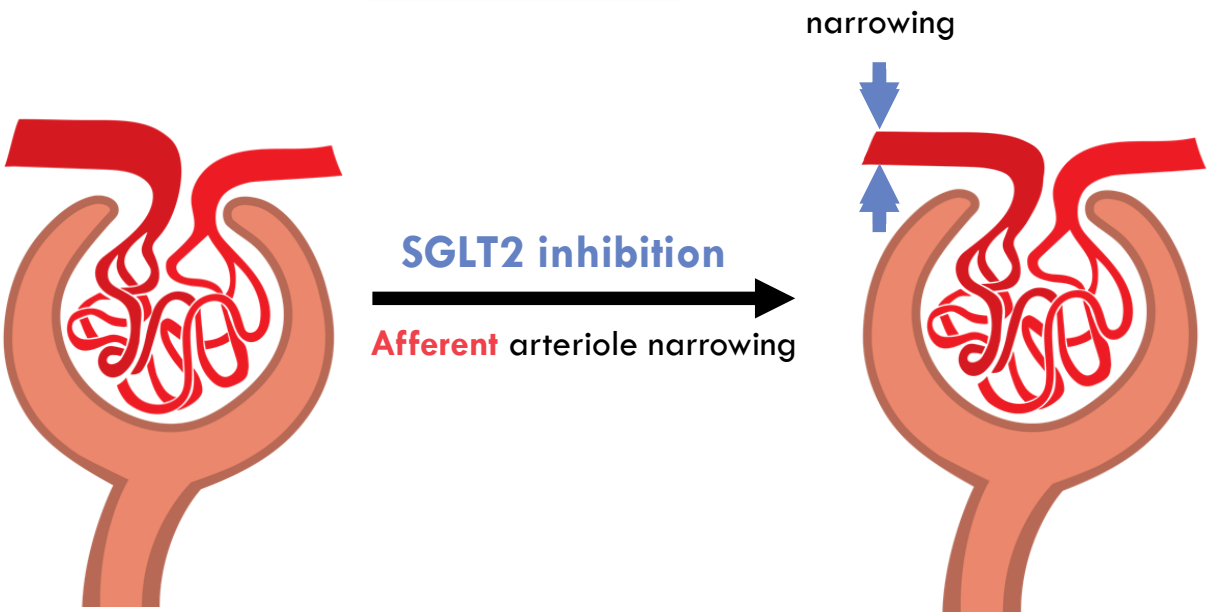
Circulation. 2016;134:752–772



SGLT2i exerts a hemodynamic effect within the kidney

By restoring the Tubulo-Glomerular Feedback (TGF), SGLT2i increase the afferent arteriole tone, thereby lowering glomerular hypertension

Action:

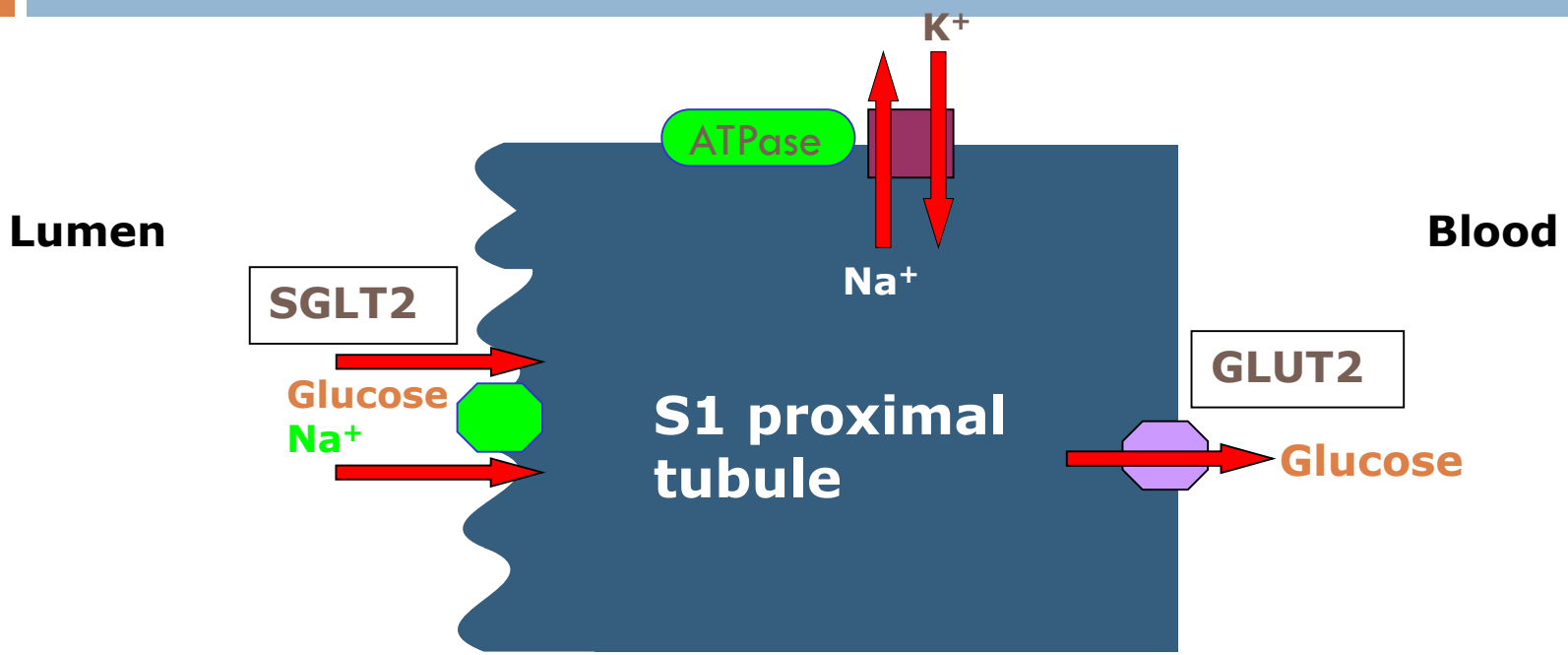


Clinical implications:

- Glomerular pressure decreases
- Early clinical marker:
  - Initial dip in GFR
  - Reduction of albuminuria

Adapted from: Cherney D *et al. Circulation* 2014;129:587
Skrtic M *et al. Diabetologia* 2014;57:2599

SGLT2 Mediates Glucose Reabsorption in the Kidney



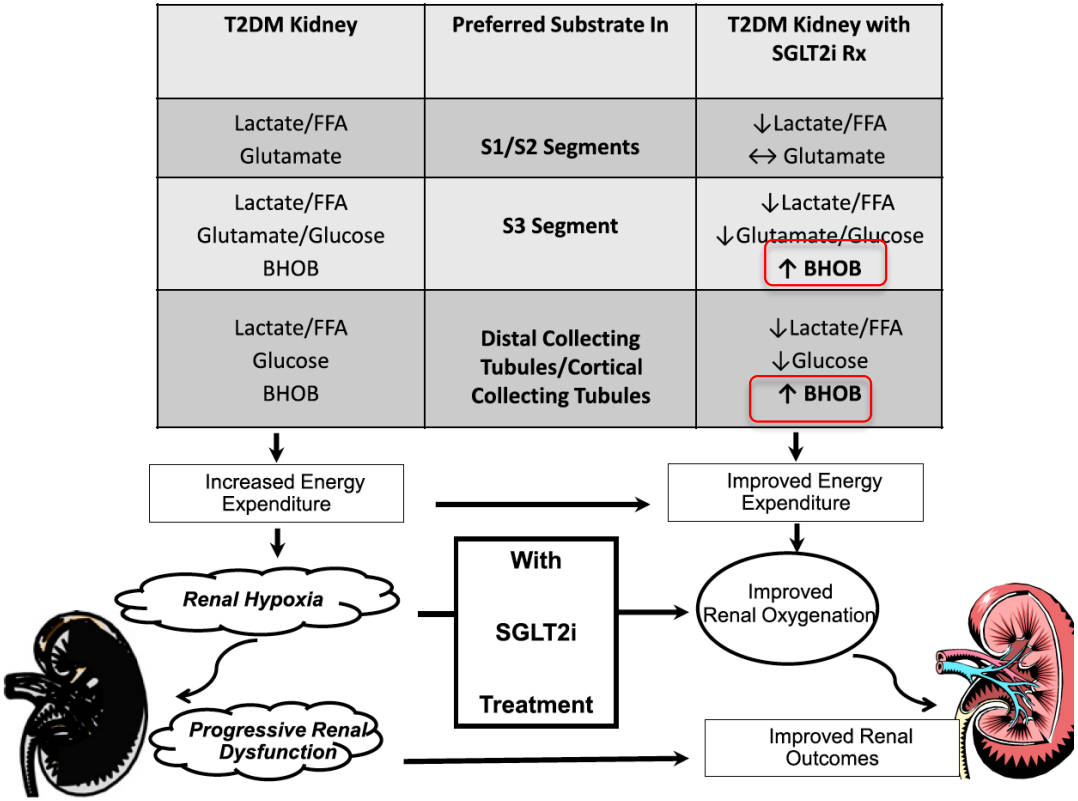
SGLT2: Major transporter of glucose in the kidney[1-3]

- Low affinity, high capacity for glucose
- Co-transports Na+ and glucose at 1:1 stoichiometry
- Nearly exclusively expressed in the S1 portion of the proximal tubule
- Responsible for majority of renal glucose reabsorption in the proximal tubule

[1]Hediger MA, Rhoads DB. *Physiol Rev* 1994;74:993-1026; [2]Magen D, et al. *Kidney Int*. 2005;67:34-41;
[3]Kanai Y, et al. *J Clin Invest* 1994;93:397-404

Postulated changes in renal fuel metabolism before and after SGLT2 inhibitor therapy

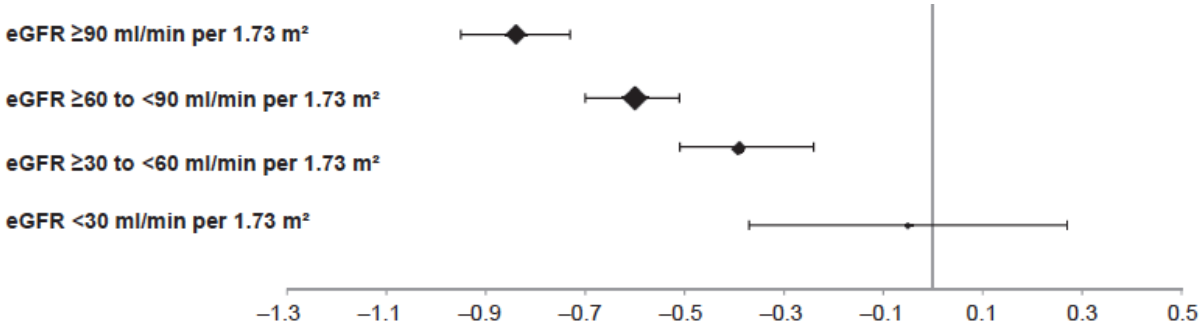
Mudaliar S et al., Diabetes Care 2016



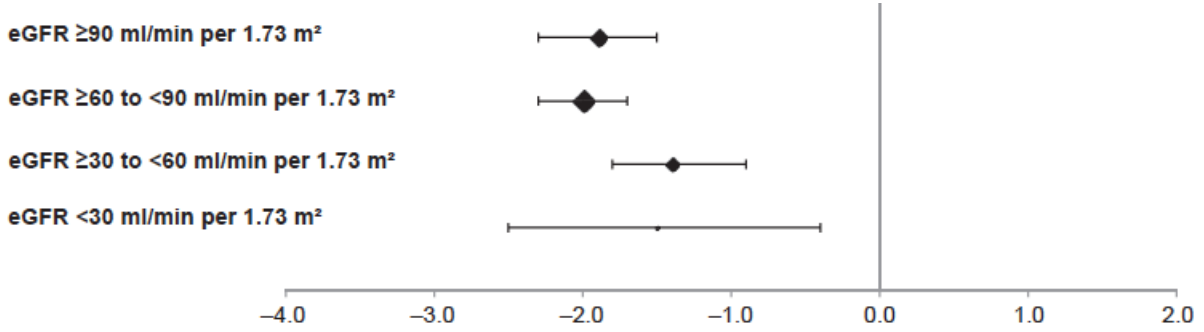
- The kidney is highly metabolically active with O_2 consumption (QO_2) per gram of tissue being second only to the heart
- Oxidative metabolism is the principal source of energy in the kidney. The renal cortex uses many metabolic substrates, including lactate, FFAs, glutamine, citrate, ketone bodies, and, to a very small extent, glucose
- SGLT2 inhibitors could improve fuel efficiency, lowering QO_2, relieving hypoxic stress, improving renal function, and preventing progression to CKD

Contrasting influences of renal function on blood pressure, body weight, and HbA1c reductions with empagliflozin

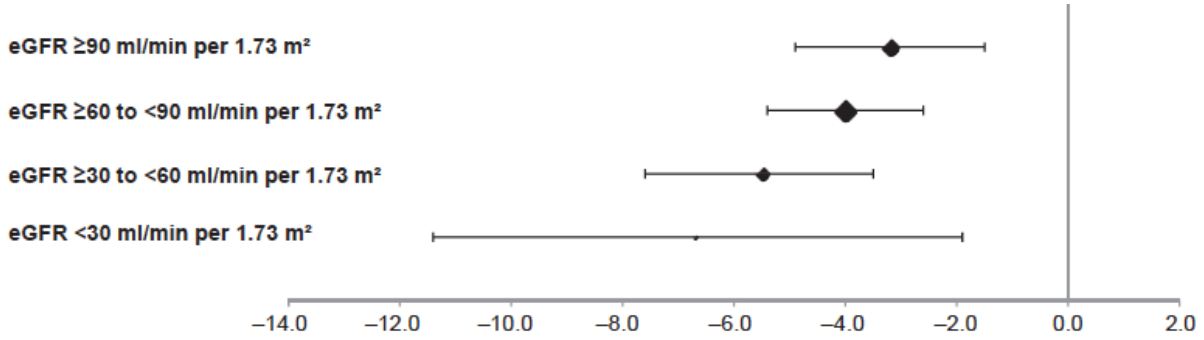
HbA1c



Weight

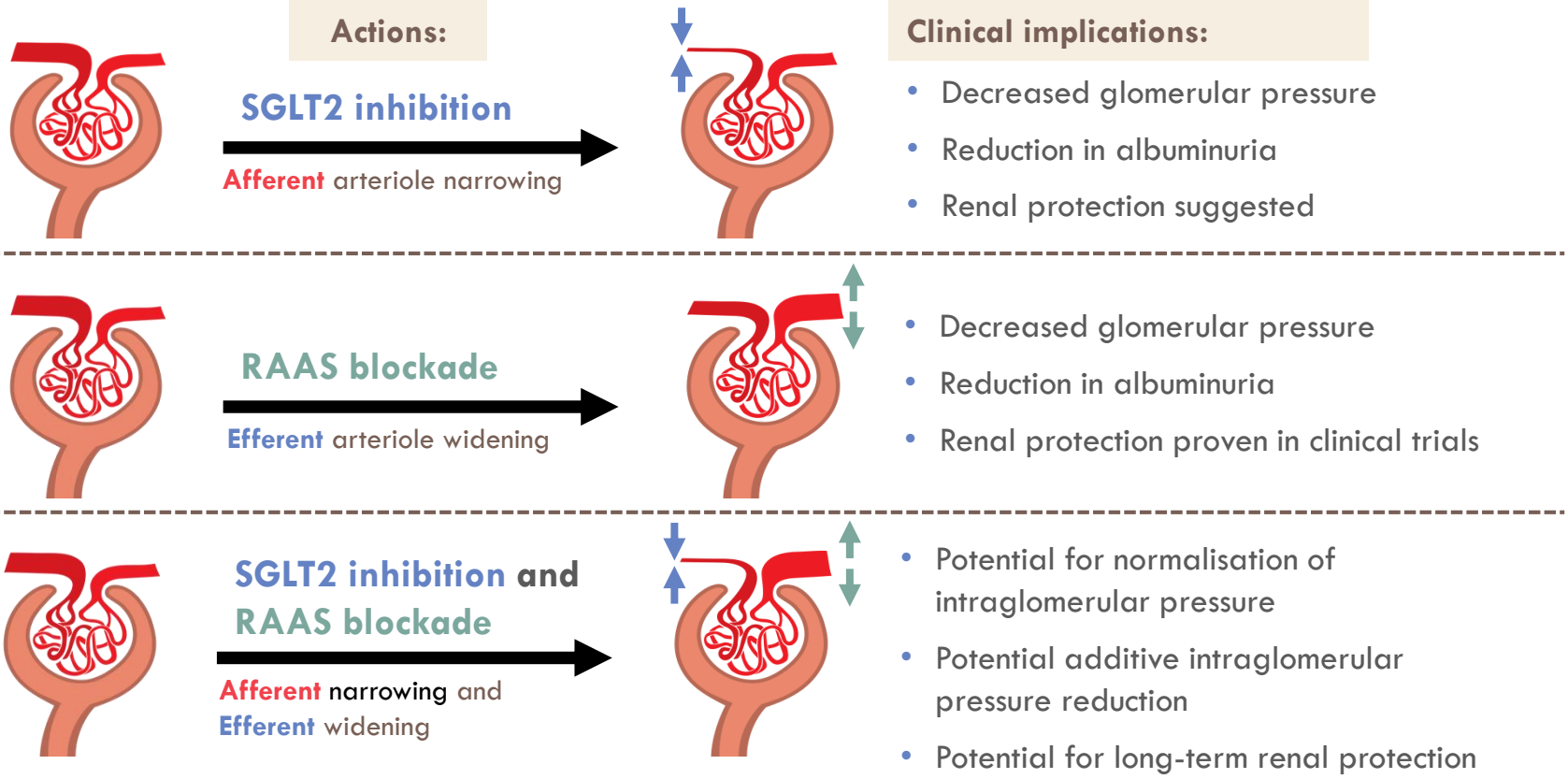


SBP



Kidney International (2018) 93, 231–244

Future outlook – Dual SGLT2 and RAAS inhibition



Adapted from: Cherney D *et al. Circulation* 2014;129:587-597; Lewis *et al. N Engl J Med* 2001;345:851; Kon V *et al. Kidney Int* 1993;44:545

CONCLUSIONI

- I SGLT2i (in particolare empaglifozin) riducono non solo l'albuminuria, ma anche riducono la progressione della malattia renale nel paziente diabetico ad alto rischio, anche con ridotta funzione renale.
- Gli effetti sulla funzione renale (GFR e albuminuria) sono rapidi e indipendenti dall'effetto sulla glicemia.
- Meccanismi EMODINAMICI e METABOLICI sono coinvolti nella nefroprotezione indotta dagli SGLT2i.
- Sono sicuramente indicati nel paziente diabetico con albuminuria e, per il momento, con eGFR > 60 ml/min in aggiunta al trattamento con ACEi/ARBs.