Il dr ROBERTO TREVISAN dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- NOVO
- SANOFY
- LILLY
- NOVARTIS
- ASTRA ZENECA
- MEDTRONIC
- MERCK
- TAKEDA

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.).

SID
Società Italiana di Diabetologia
fondata nel 1964

Impatto degli inibitori di SGLT2 nei pazienti con diabete tipo 2
Milano, 26 giugno 2018

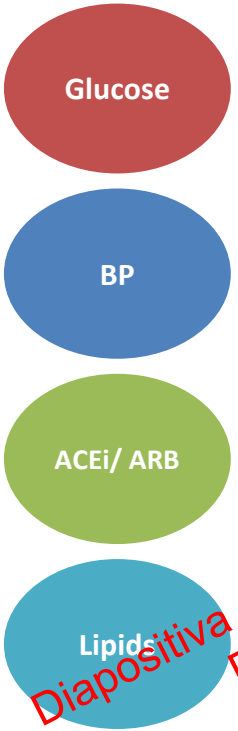
Cosa aggiungono gli inibitori di SGLT2 in termini di nefro-protezione?

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

OUTLINE

- Premessa
- Risultati renali degli STUDI CLINICI (CVOTs)
  - Effetti sull'albuminuria
  - Effetti sull'eGFR
- Meccanismi
- Eventi avversi

A multifactorial intervention strategy is recommended in DKD



HbA1c target individualised, but generally ~7%[1]

Target of <130/80 mmHg[2]

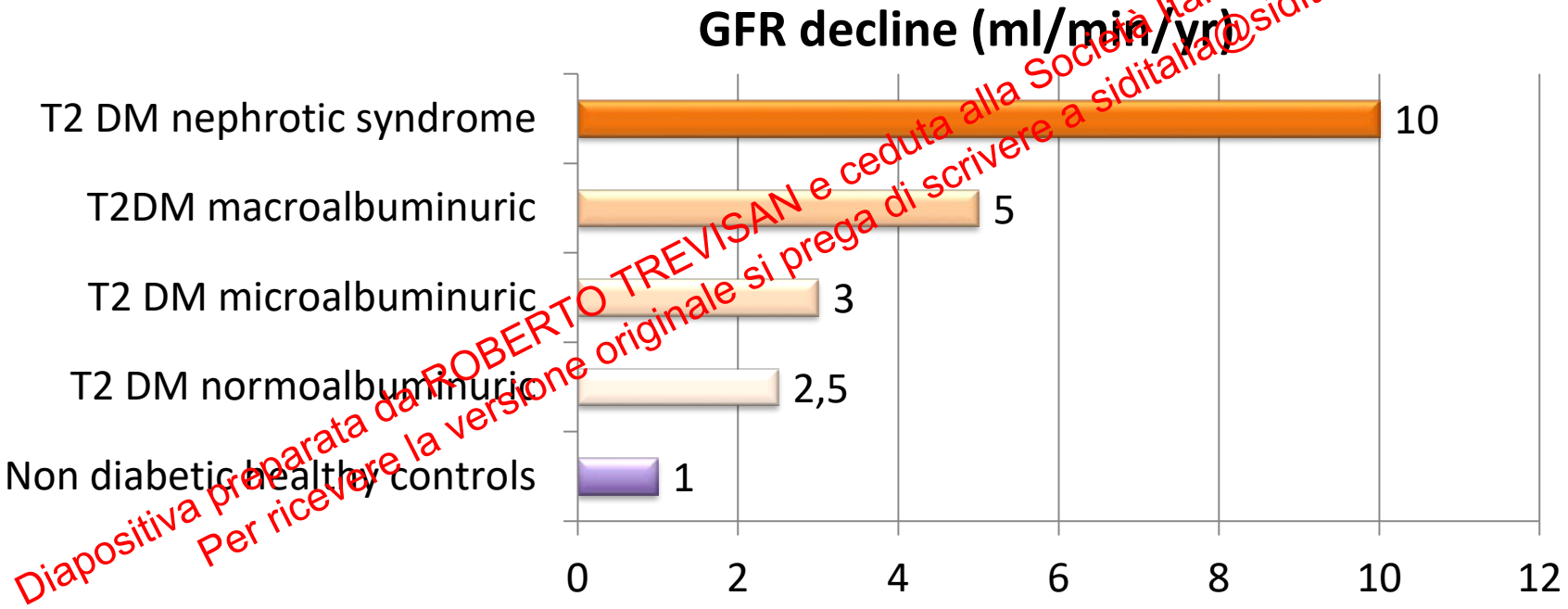
Use ACEi or ARBs when albumin excretion ≥30 mg/g[1]

Lipid-lowering recommended to reduce risk of atherosclerotic events; statins not recommended in patients on haemodialysis[1]

1. National Kidney Foundation. *Am J Kidney Dis* 2012;60:850; 2. NICE. Clinical guideline: Type 2 diabetes (CG87), May 2009

Lancet Diabetes Endocrinol 2015; 3: 382–91

Glomerular filtration rate (GFR) decline in healthy patients compared with patients with type 2 diabetes and normo-, micro-, macroalbuminuria, or severe proteinuria



Data from studies that did repeated measurements of GFR using gold standard procedures

SGLT2 I: RISULTATI RENALI DI EMPAREG E CANVAS

A New Chapter for Diabetic Kidney Disease

Ian H. de Boer, M.D.

Many clinical outcomes have improved over the past two decades for people living with diabetes.[1] However, relatively little progress has been made in the treatment of diabetic kidney disease. Among adults with diabetes in the United States, the prevalence of diabetic kidney disease

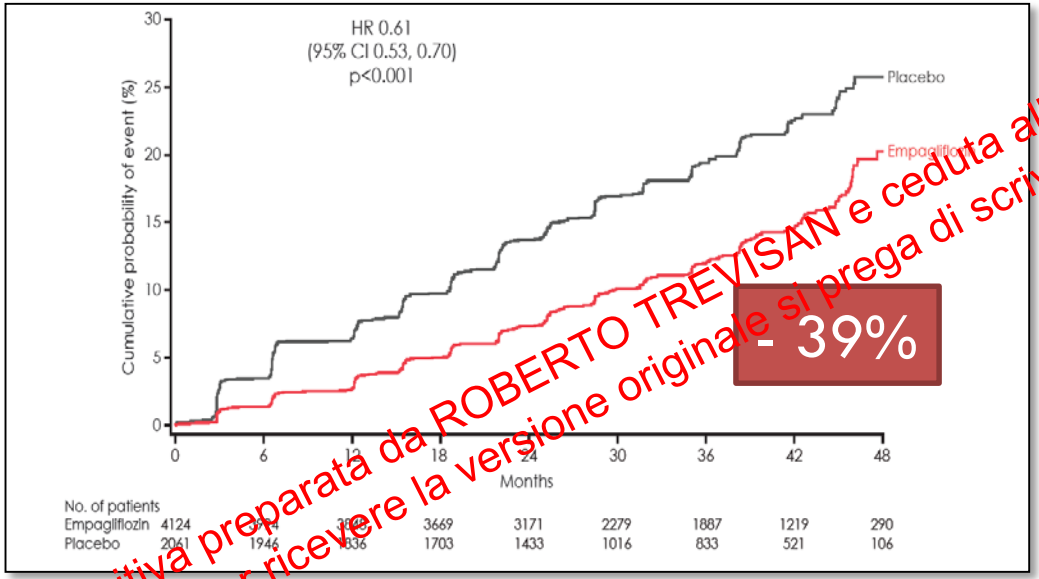
N ENGL J MED 377;9 NEJM.ORG AUGUST 31, 2017

The New England Journal of Medicine

Differenze tra EMPA-REG e CANVAS

Popolazione	EMPA-REG	CANVAS
eGFR < 60 ml/min/1.73m^2)	>30 ml/min/1.73 m^2 **26%**	>30 ml/min/1.73 m^2 **19%**
UACR Microalb Macroalb	 29% **11%**	 22% **7%**
HbA1c	Da 7 a 9%	Da 7 a 10,5%
Uso ACEi o ARB	80%	80%
Storia di malattia CV	Storia di CV **Prevenzione secondaria**	Età >30 aa con storia CV o età > 50 aa con almeno 2 fattori di rischio **Prevenzione primaria (in parte)**
Pazienti arruolati	7.020	10.142
Farmaco	Empa 10 o 25 mg o placebo	Cana 100 o 300 mg o placebo
Durata	3,1 anni	5,7 (Canvas) o 2,1 (Canvas-R)

EMPA-REG: Incident or worsening nephropathy



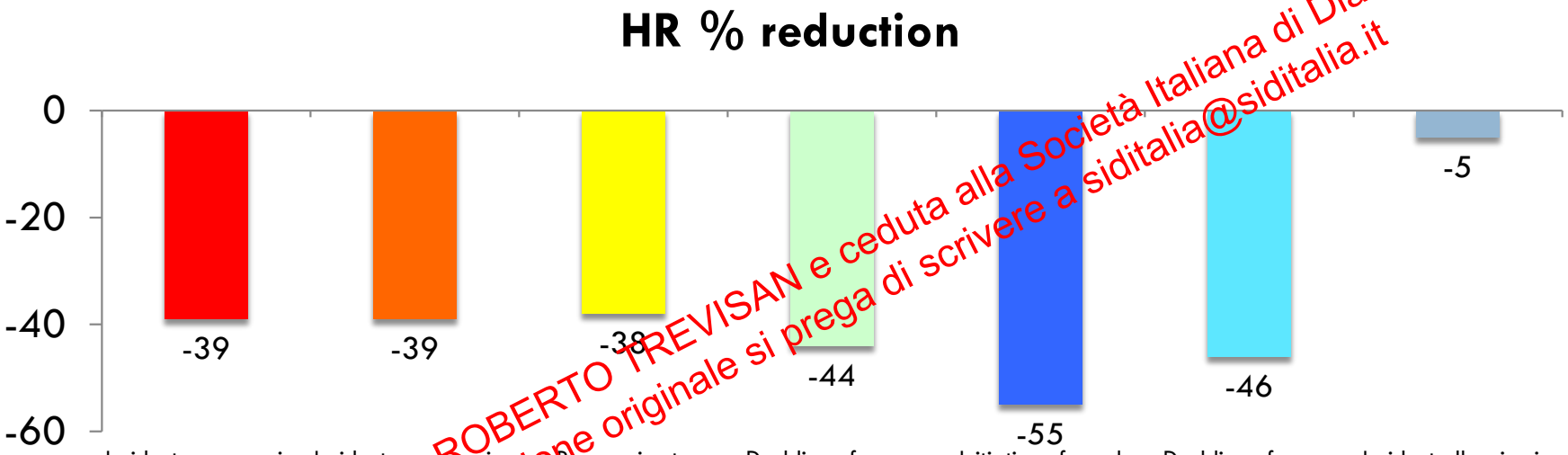
- 39%

Outcome Renale

- Macroalbuminuria
- Raddoppio Cr
- RRT
- Morte renale

N Engl J Med 2015;373:2117-28

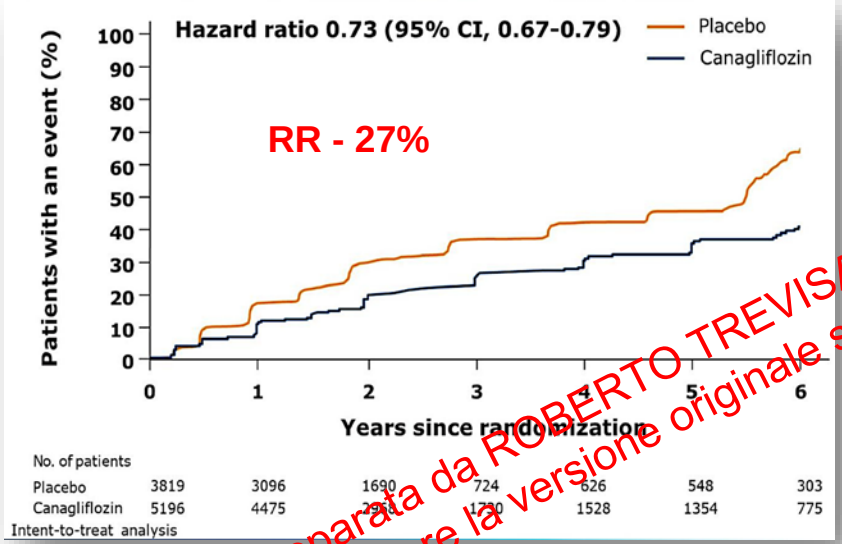
EMPAREG: Renal Outcomes



EMPA vs PLACEBO % of events	16.2 vs 23.6	12.7 vs 18.8	11.2 vs 16.2	1.5 vs 2.6	0.3 vs 0.6	1.7 vs 3.1	51.5 vs 51.2

N Engl J Med 2015;373:2117-28

CANVAS: Progressione dell'Albuminuria



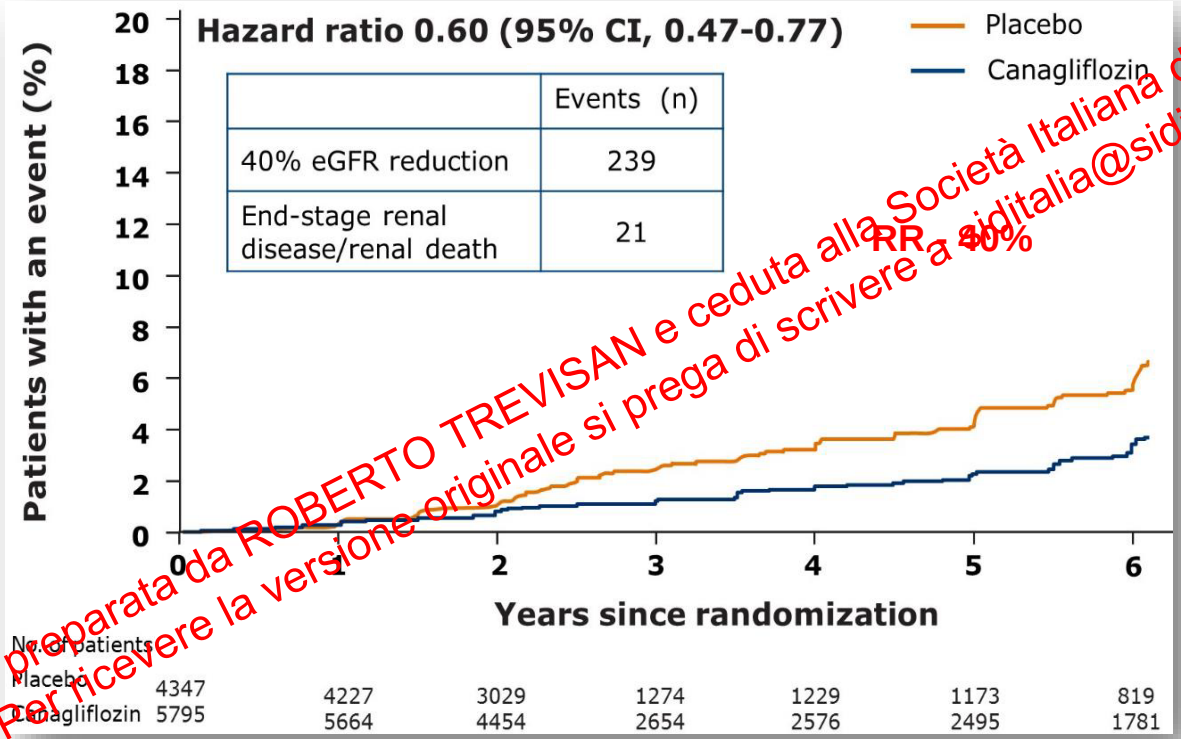
	Placebo	Cana	HR (95% CI)
Progression of albuminuria	**28.71 (1114/3819)**	**89.38 (1341/5196)**	**0.73 (0.67, 0.79)**
Normo at baseline	130.84 (860/2899)	100.44 (1130/3910)	**0.80** (0.73, 0.88)
Micro at baseline	121.97 (254/920)	56.22 (211/1286)	**0.47** (0.39, 0.57)

Progression was defined as more than a 30% increase in albuminuria and a change from either normo- to micro- or macroalbuminuria or from micro to macroalbuminuria.

Neal B et al NEJM 2017; 377:644-57

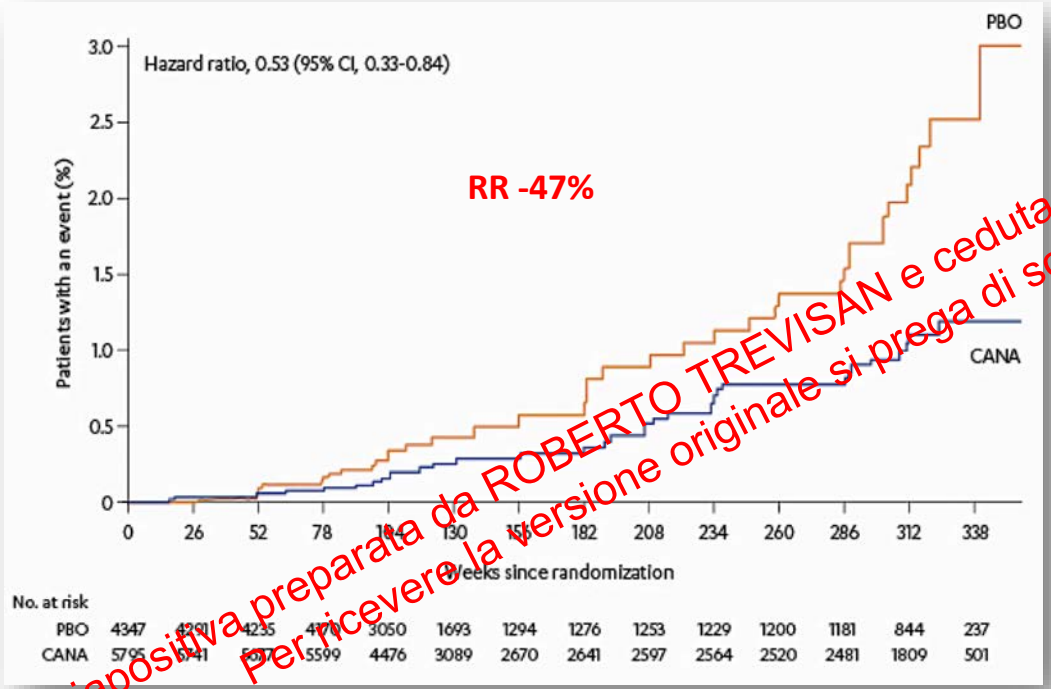
Perkovic V et al Poster ASN 2017

CANVAS: Outcome Renale Composito



Neal B et al NEJM 2017; 377:644-57

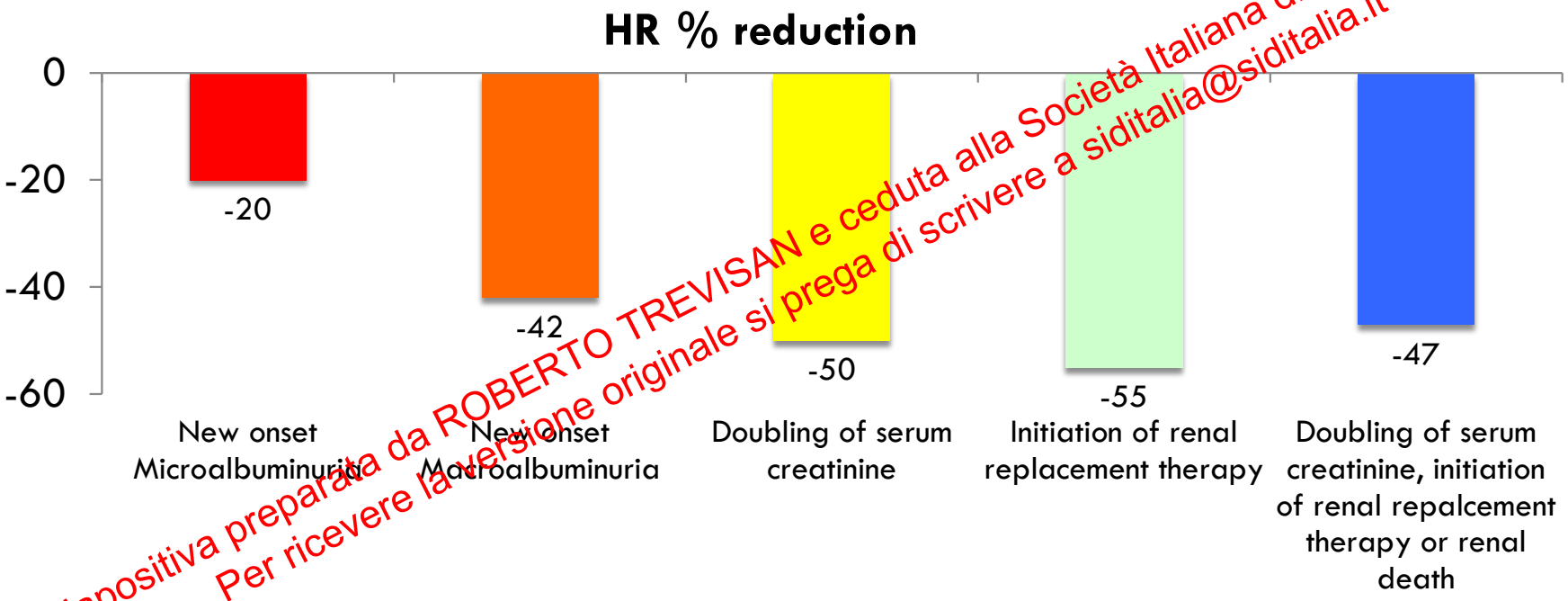
CANVAS: Outcome Composito Renale



- **Raddoppio Creatininemia**
- **ESRD**
- **Morte renale**

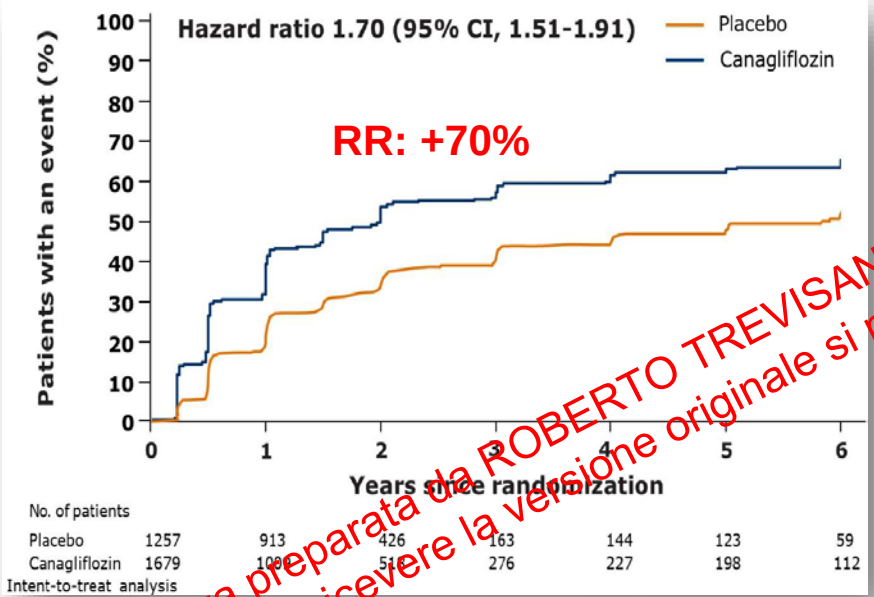
Neuen BL. Poster National Kidney Foundation Aprile 2018

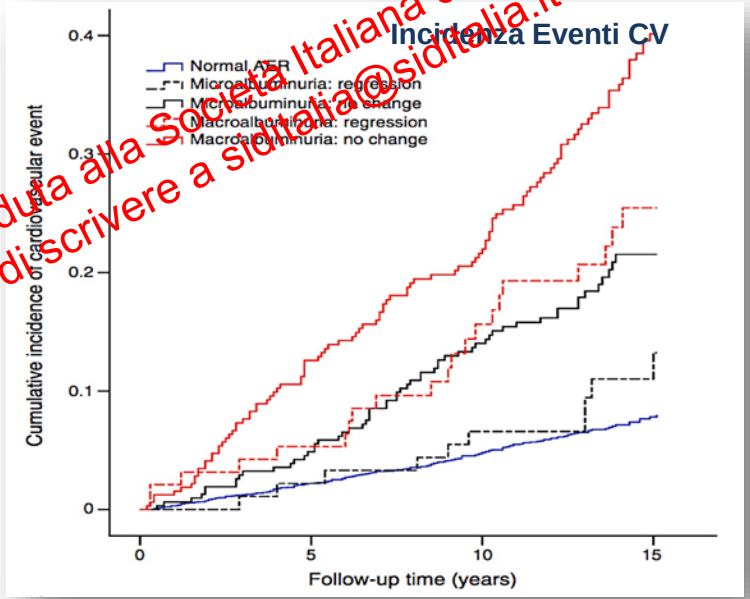
CANVAS: Renal Outcomes



Perkovic V et al Poster ASN 2017

CANVAS: Regressione dell'Albuminuria



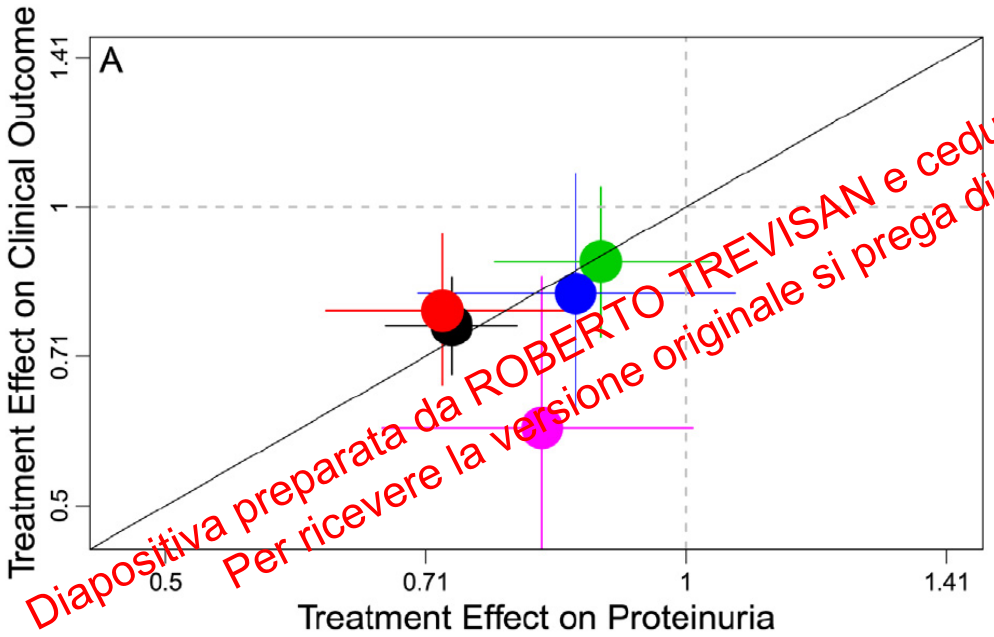


Neal B et al NEJM 2017; 377:644-57

Jansson FJ, Diabetologia. 2018;61:1203-1211

Early Change in Proteinuria as a Surrogate End Point for Kidney Disease Progression: An Individual Patient Meta-analysis

Clinical Outcome (time to doubling of serum creatinine level, end-stage renal disease, or death)



Black: RAS blockade versus placebo

Red: RAS blockade versus Ca channel blocker

Green: intensive blood pressure

Magenta: immunosuppressive therapies

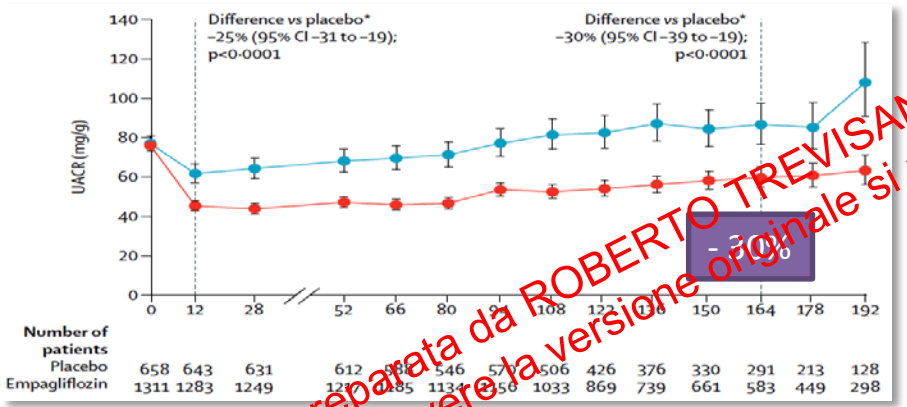
Am J Kidney Dis. 2014;64(1):74-85

SGLT2 I: EFFETTO SULL'ALBUMINURIA

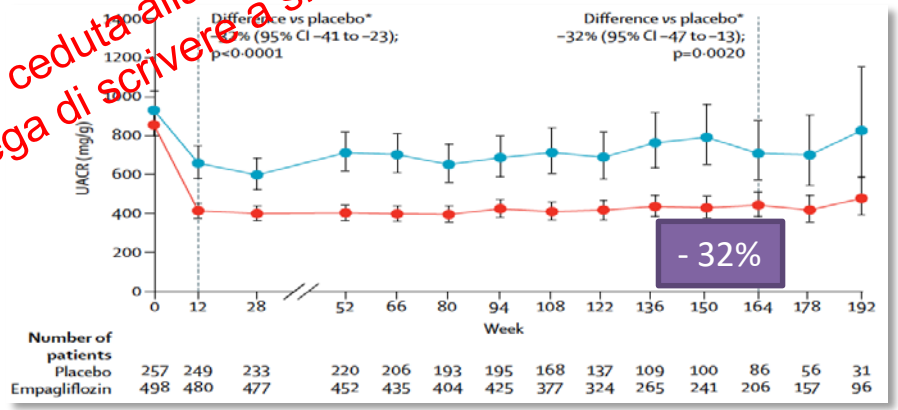
Soprattutto nei diabetici con albuminuria

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

With **Microalbuminuria**



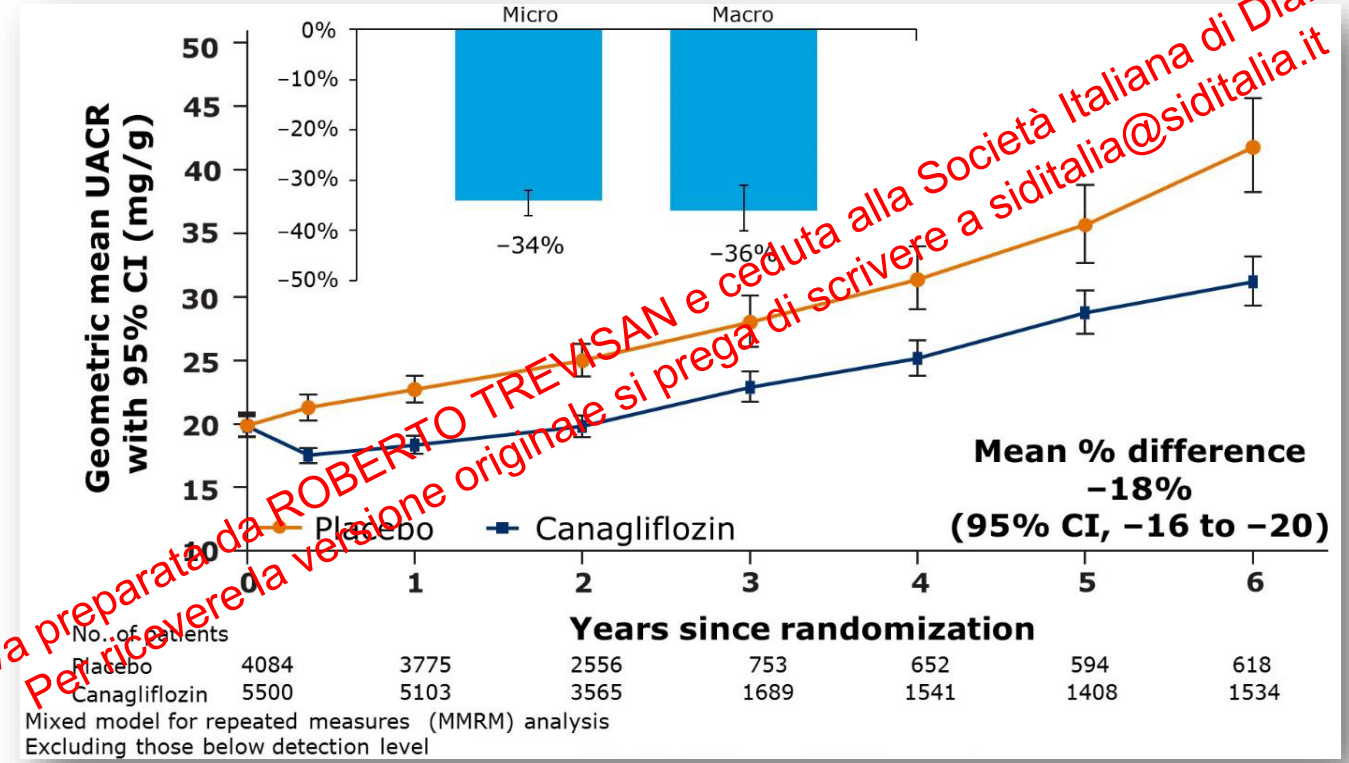
With **Macroalbuminuria**



On top of intensive glucose, lipid e blood pressure treatments

Lancet Diabetes Endocrinol 2017; 5: 610–21

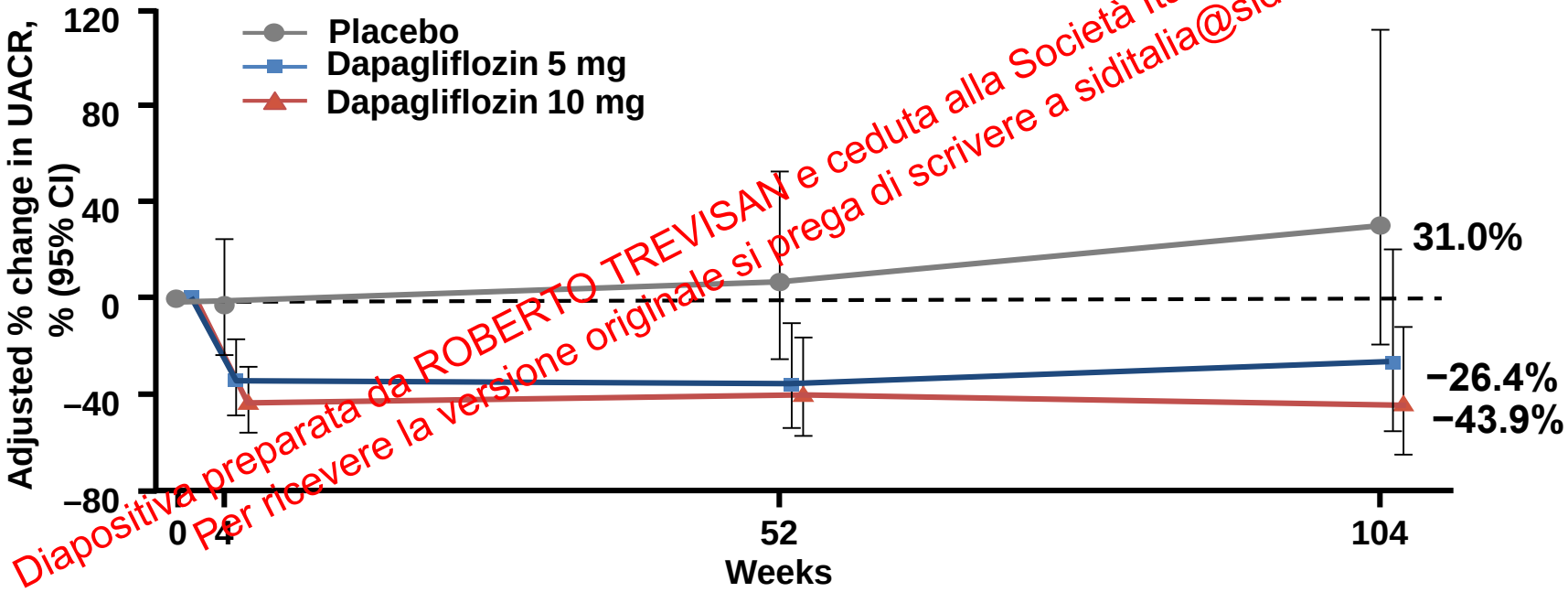
CANVAS: Escrezione Renale di Albumina (UACR)



Neal B et al NEJM 2017; 377:644-57

Effects of Dapagliflozin on albuminuria

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



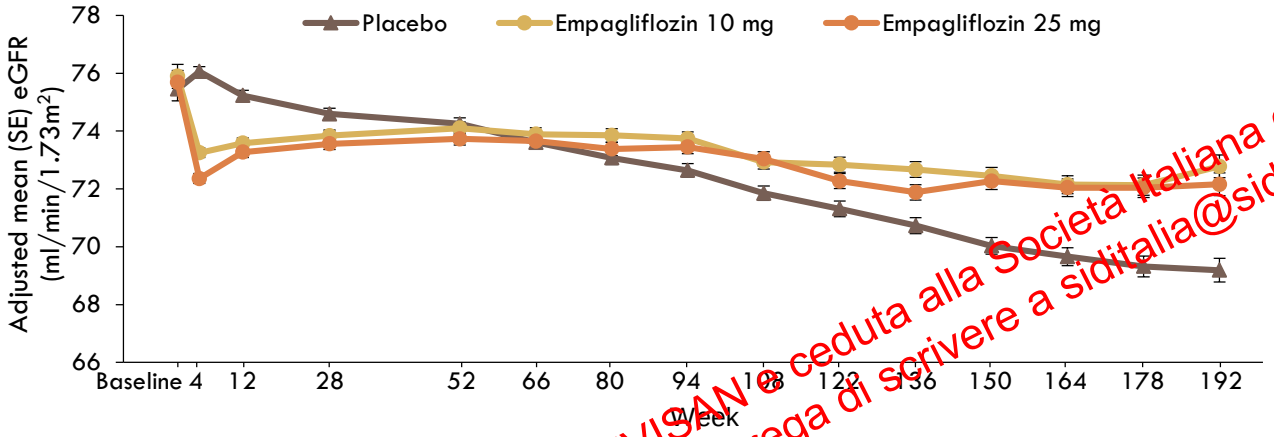
Fioretto P, et al. Diabetologia 2016

SGLT2 I: EFFETTO SULL'EGFR

Soprattutto nei diabetici con CKD

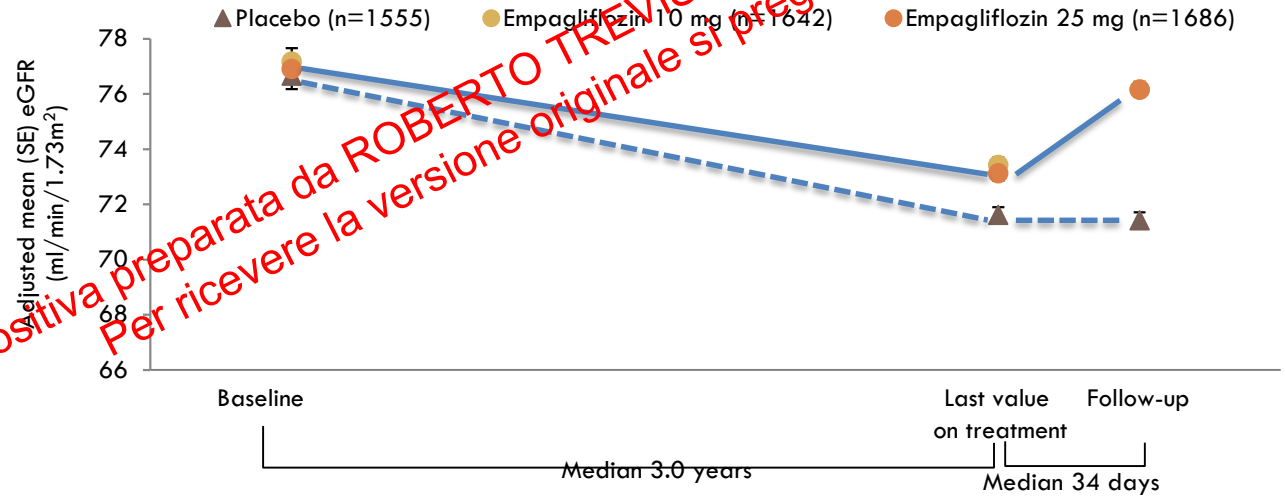
EMPAREG Study: eGFR decline during the study

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



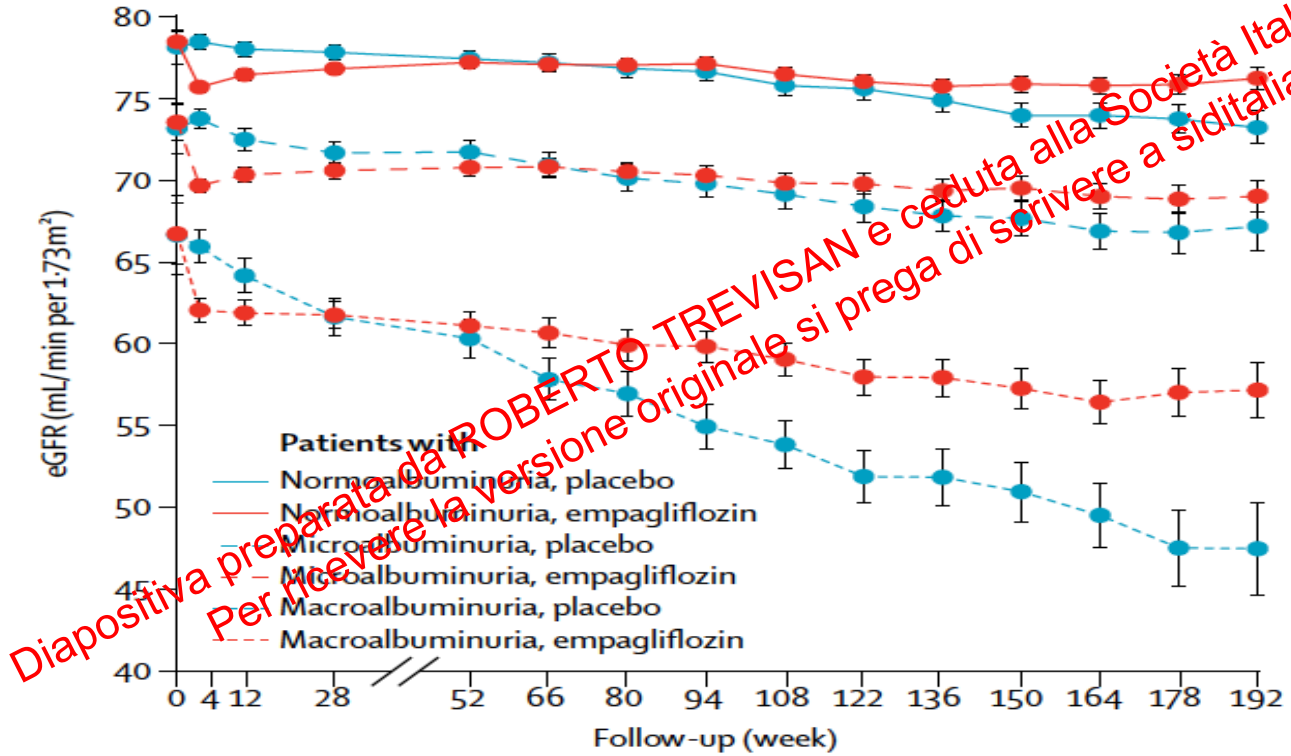
- 0.2 ml/yr

- 2.1 ml/yr



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

Lancet Diabetes Endocrinol 2017; 5: 610–21



Normoalbuminuria

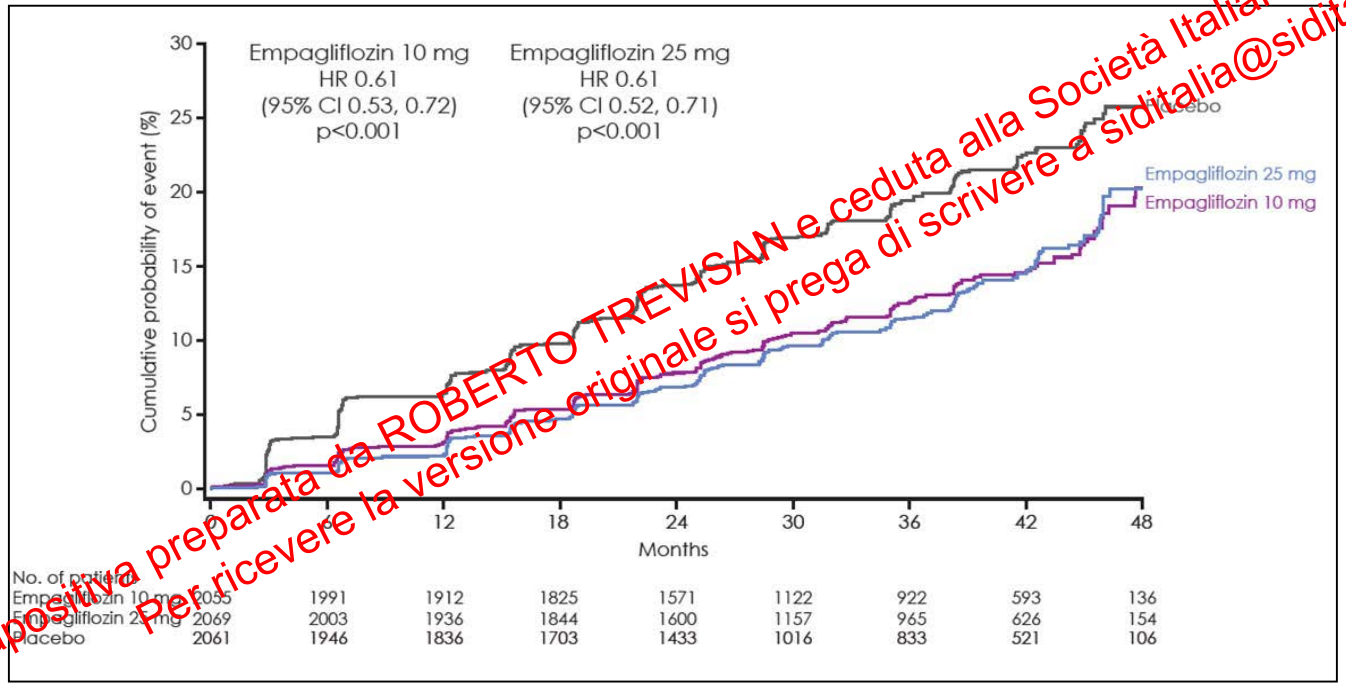
Microalbuminuria

- 0.8 ml/min/yr

Macroalbuminuria

- 5.4 ml/min/yr

Incident or worsening nephropathy in patients with prevalent kidney disease*

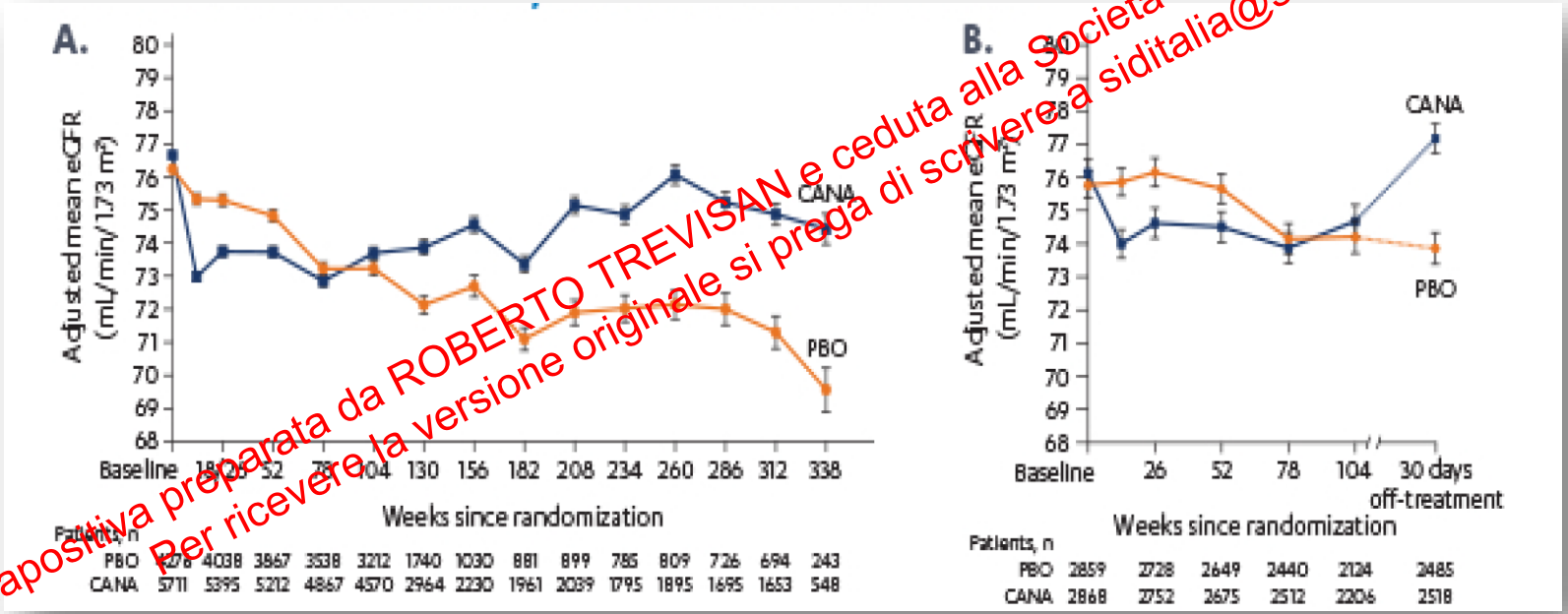


Christoph Wanner et al. published online June 14, 2016 (supplement), at NEJM.org

CANVAS: eGFR Over Time

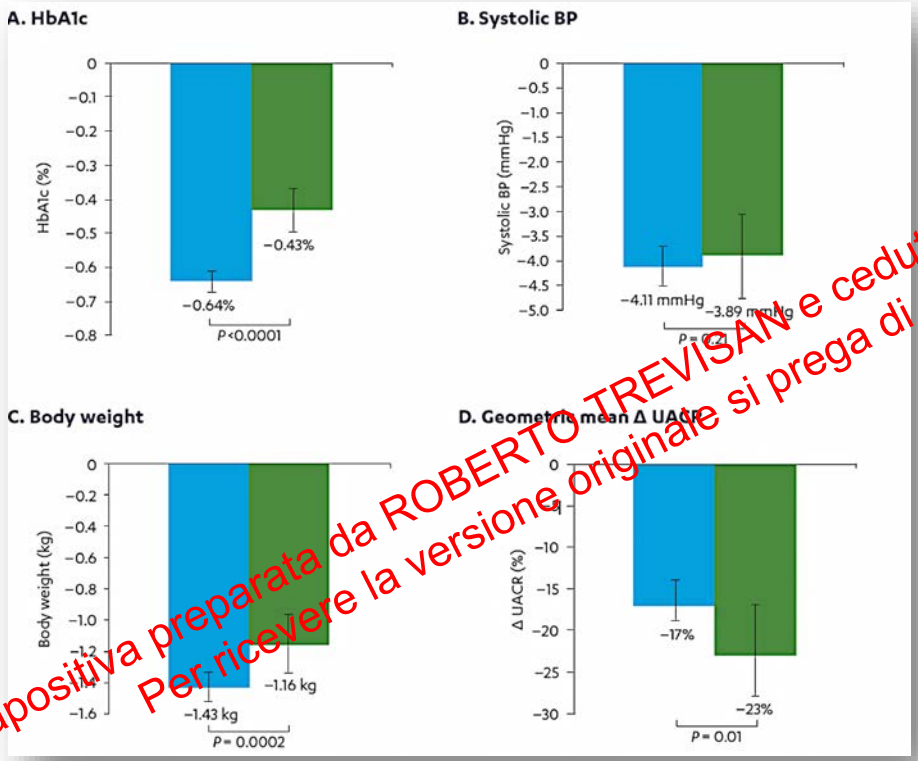
CANVAS Program

CANVAS-R



Neuen BL. Poster National Kidney Foundation Aprile 2018

CANVAS: Endpoints intermedi



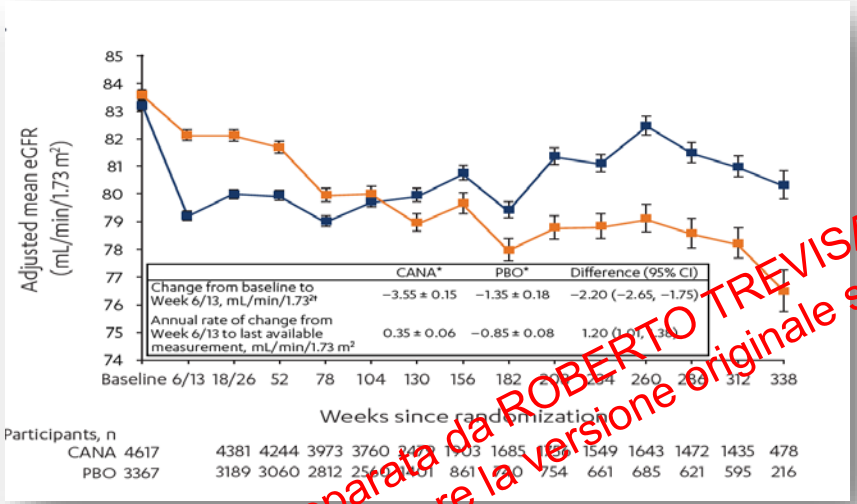
eGFR<60 ml/min/1.73 m^2

eGFR□60 ml/min/1.73 m^2

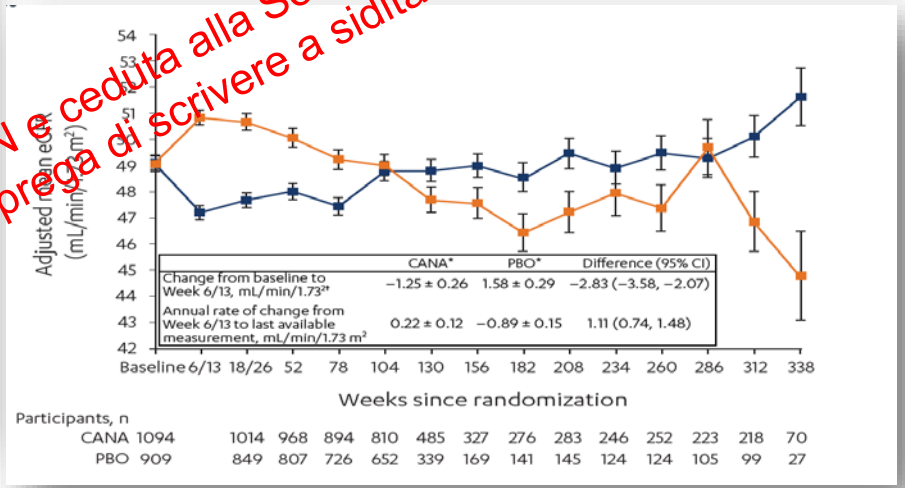
Neuen BL. Poster National Kidney Foundation Aprile 2018

CANVAS: eGFR over time

eGFR□60 ml/min/1.73 m²



eGFR<60 ml/min/1.73 m²



Neuen BL. Poster National Kidney Foundation Aprile 2018

CANVAS: Outcome composito:↓40% eGFR, ESRF, morte renale

eGFR□60 ml/min/1.73 m²

eGFR<60 ml/min/1.73 m²

Outcome	eGFR	Events	Events/1000 PY CANA	PBO	HR (95% CI)	Interaction *P* value
Renal composite outcomes						
40% reduction in eGFR, ESKD, or renal death	All	249	5.5	9.0	0.60 (0.47-0.77)	0.28
	≥60	166	4.4	7.6	0.53 (0.39-0.73)	
	<60	83	11.4	15.0	0.76 (0.49-1.17)	
dSCr, ESKD, or renal death	All	73	1.5	2.8	0.53 (0.33-0.84)	0.21
	≥60	47	1.1	2.4	0.42 (0.23-0.75)	
	<60	26	2.2	4.4	0.81 (0.37-1.77)	

Participants, n

CANA 4684 4644 4593 4539 3662 2255 2188 2166 2133 2100 1541

PBO 3417 3375 3331 3280 1363 1050 1034 1010 989 969 699

Participants, n

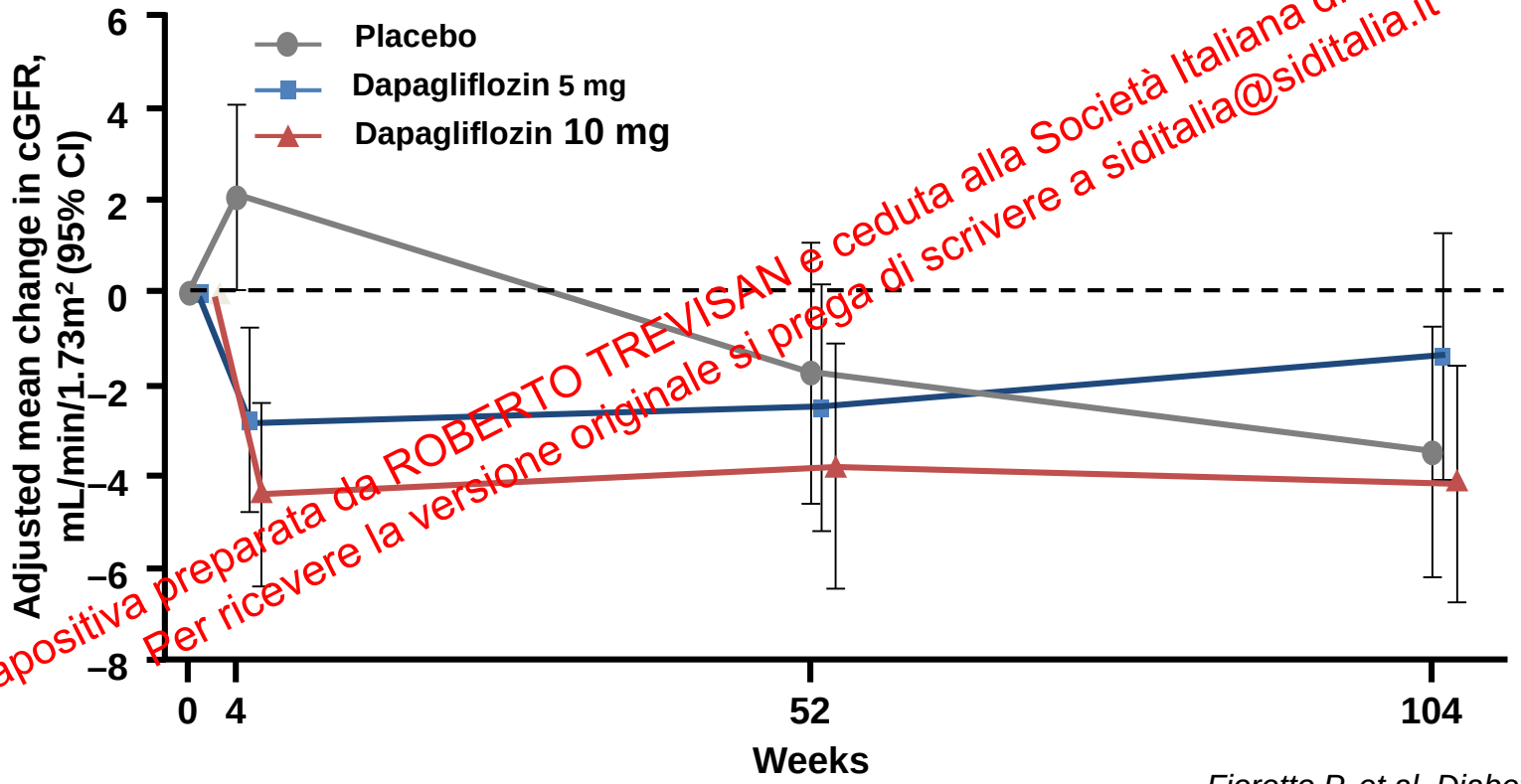
CANA 1110 1092 1070 1038 791 493 398 394 387 375 361 349 239

PBO 929 911 895 870 624 310 208 202 194 191 183 178 119

Neuen BL. Poster National Kidney Foundation Aprile 2018

Effects of Dapagliflozin on eGFR in CKD 3

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



Fioretto P, et al. Diabetologia 2016

Meccanismi

EMPA-REG OUTCOME

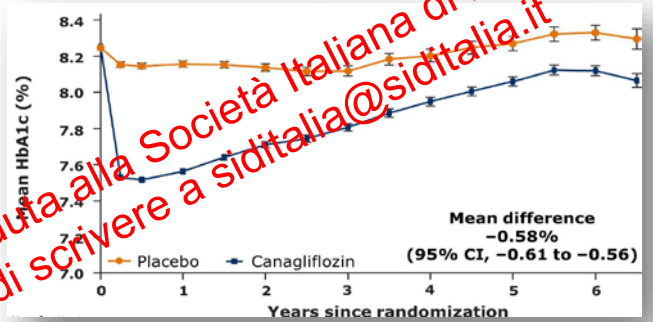
I dati clinici e metabolici nei pazienti trattati con emapglifozin rispetto al placebo

- 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

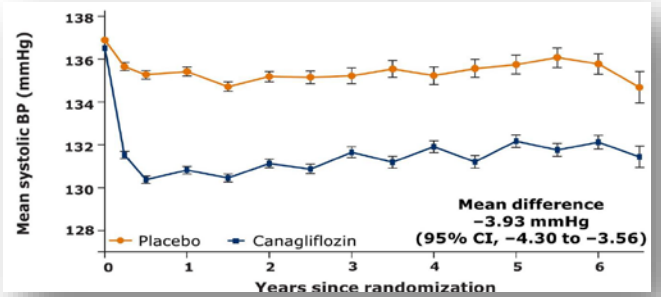
I dati clinici e metabolici non spiegano "da soli" I risultati renali di Empa-Reg

CANVAS

HbA1c



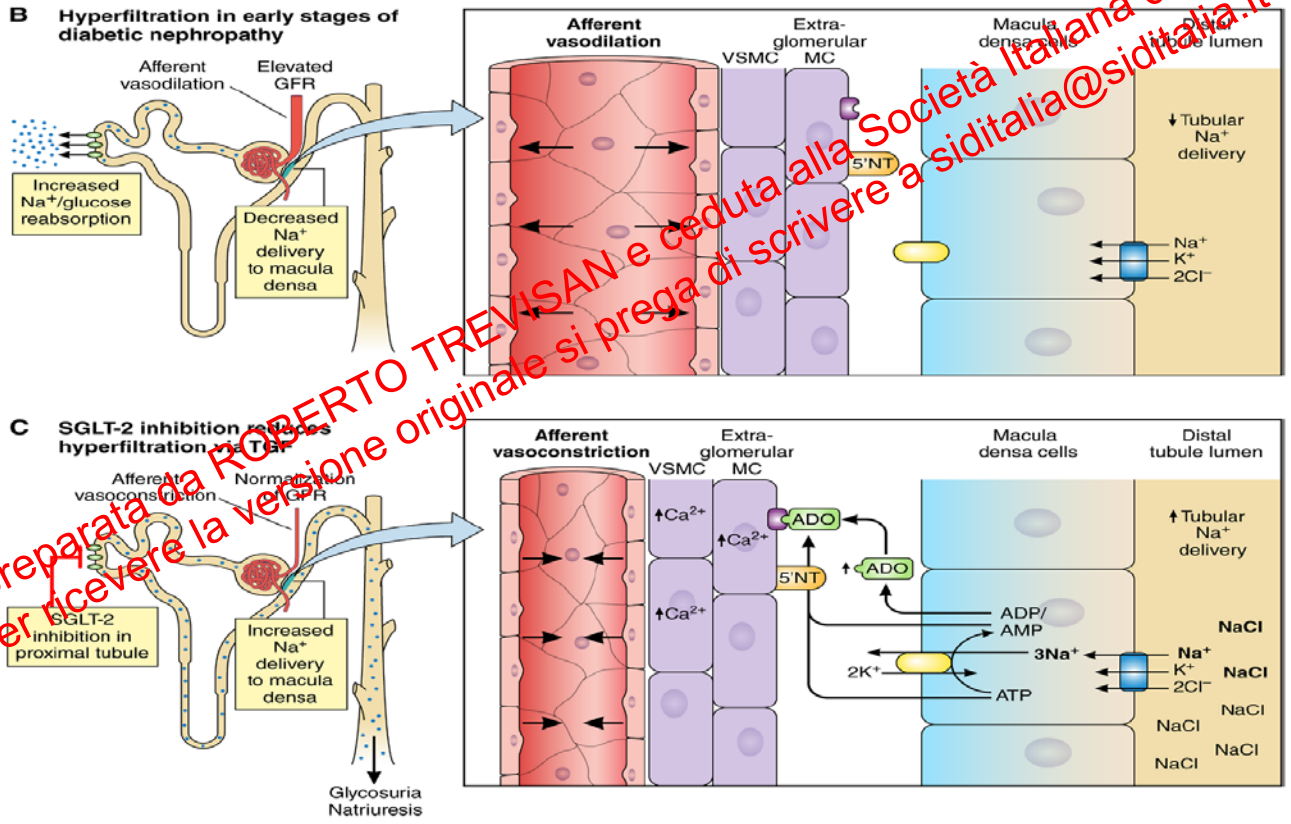
Pressione Sistolica



Neal B et al NEJM 2017; 377:644-57

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

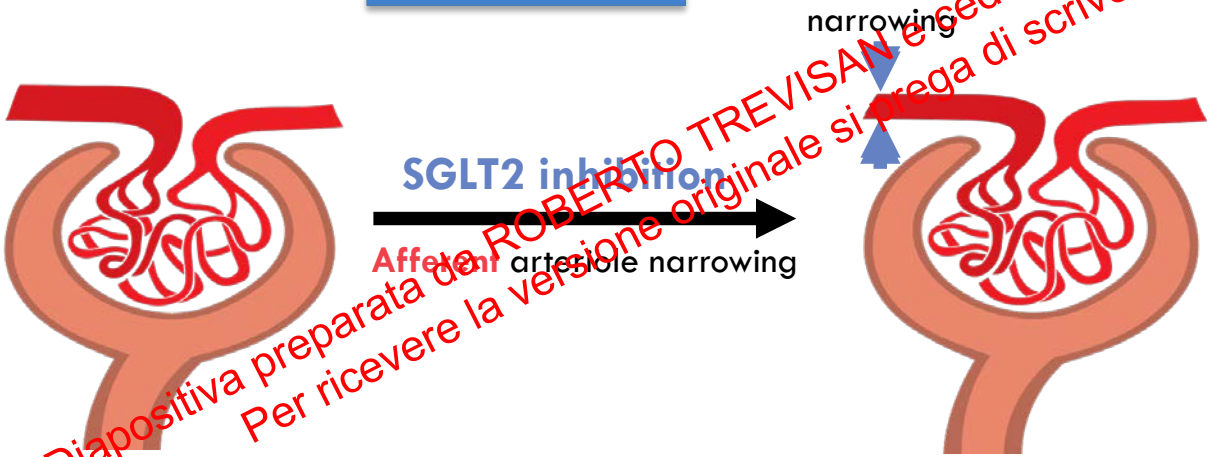
Circulation. 2016;134:752–772



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:

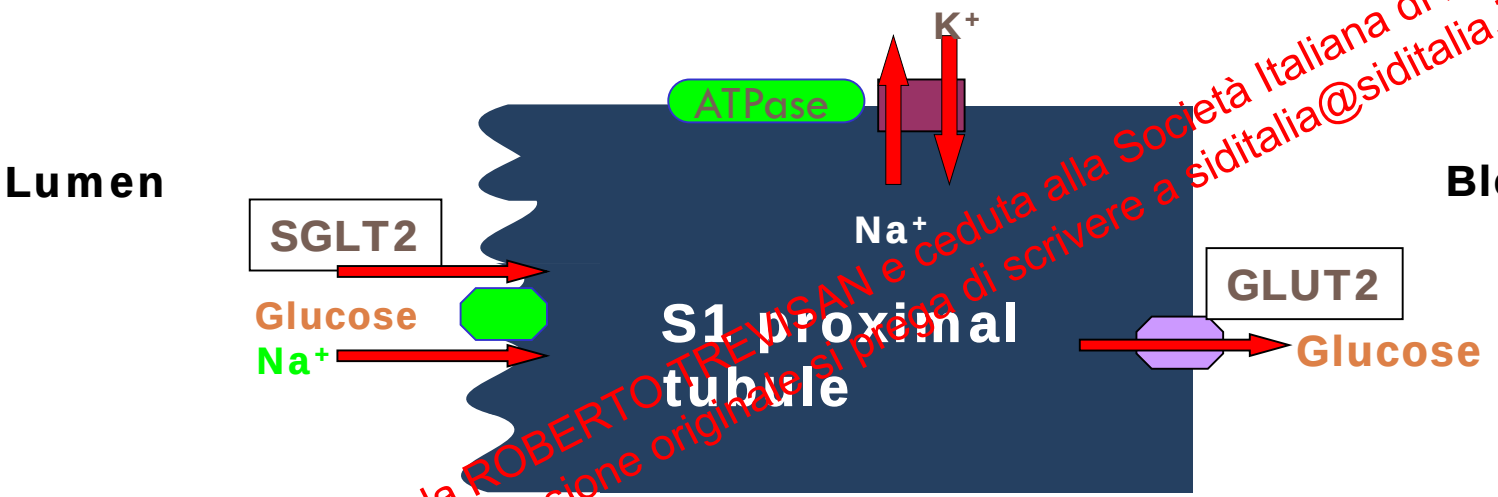


Clinical implications:

- 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

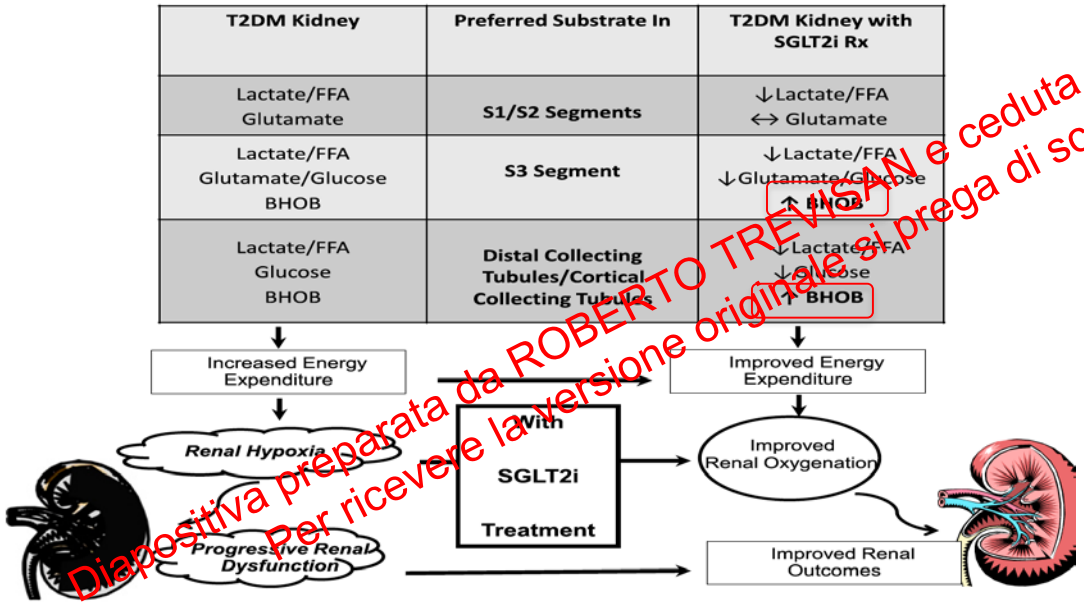


SGLT2: Major transporter of glucose in the kidney[1-3]

- 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

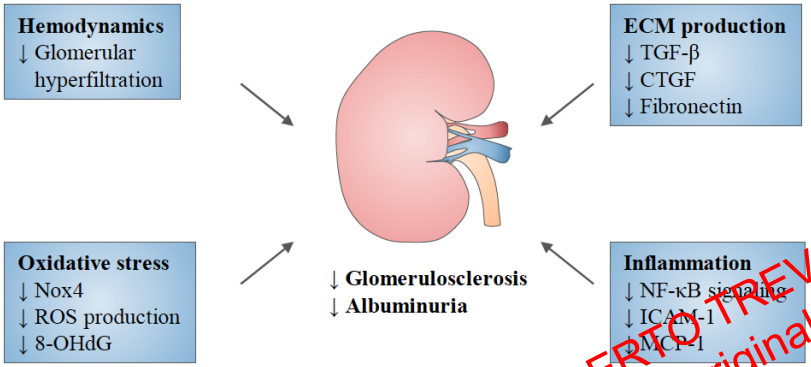
Postulated changes in renal fuel metabolism before and after SGLT2 inhibitor therapy

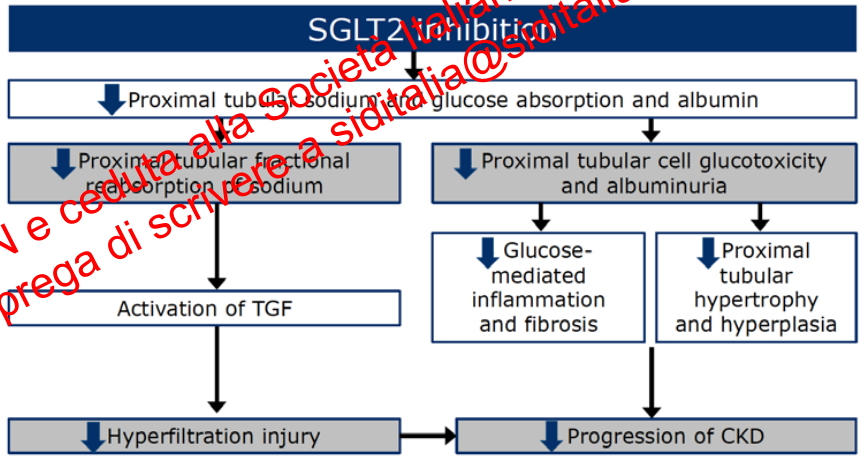


- The kidney is highly metabolically active with O_2 consumption (QO_2) per gram of tissue being second only to the heart
- Oxidative metabolism is the principal source of energy in the kidney. The renal cortex uses many metabolic substrates, including lactate, FFAs, glutamine, citrate, ketone bodies, 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

Mudaliar S et al., Diabetes Care 2016

SGLT2i: Meccanismi di beneficio renale



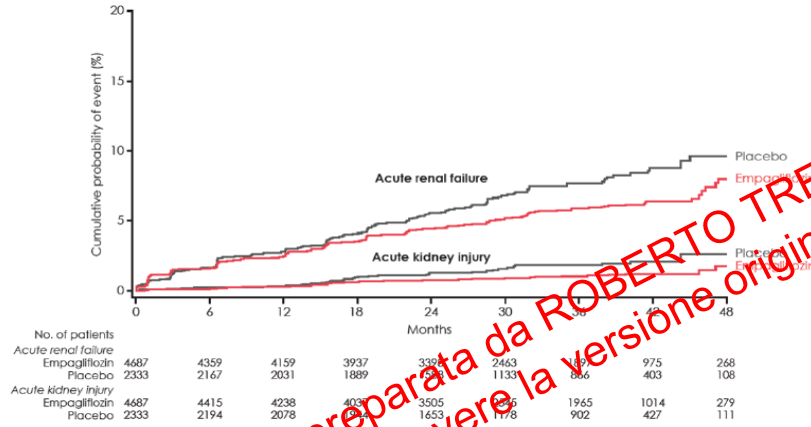


RIDUZIONE:
- Fibrosi
- Stress Ossidativo
- Infiammazione

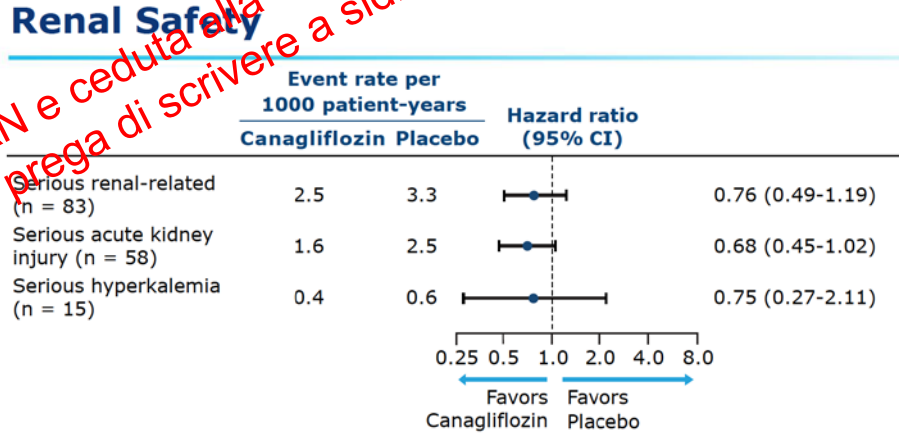
TUBULO RENALE:
- ↓ Glucotossicità
- ↓ Albuminuria

Acute renal failure and acute kidney injury

EMPAREG



CANVAS



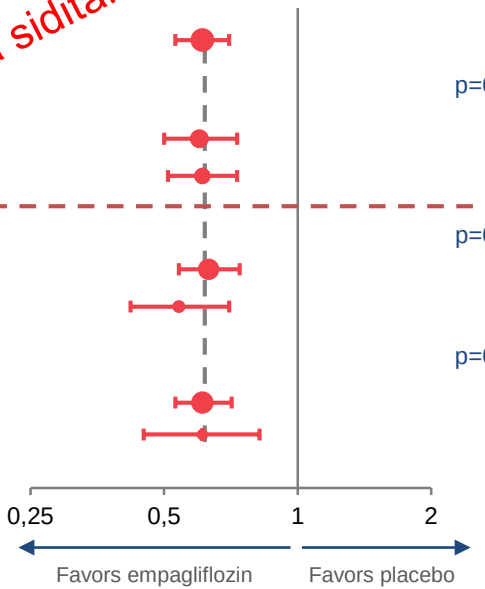
Efficacy and Safety of Dapagliflozin in Patients with Type 2 Diabetes and Moderate Renal Impairment (Chronic Kidney Disease Stage 3A): The DERIVE Study

Any serious AE	9 (5.6)	14 (8.7)
Any related serious AE	1 (0.6)	0
Any serious AE leading to discontinuation	2 (1.9)	2 (1.2)
AEs of interest		
Genital Infection	3 (1.9)	2 (1.2)
Urinary tract infection	4 (2.5)	6 (3.7)
Hypotension/dehydration/hypovolaemia	3 (1.9)	0
Renal impairment/failure	1 (0.6)	2 (1.2)
Bone fractures	0	0
DKA	0	0

Diabetes Obes Metab 2018

INCIDENT OR WORSENING NEPHROPATHY BY BACKGROUND DIURETIC THERAPY

	Empagliflozin	Placebo	Hazard ratio (95% CI)	Hazard ratio (95% CI)	Interaction p-value
	n with event/N analyzed (%)				
All patients	525/4124 (12.7)	388/2061 (18.8)	0.61 (0.53, 0.70)		
Use of any diuretic					p=0.9457
No	256/2350 (10.9)	197/1197 (16.5)	0.60 (0.50, 0.73)		
Yes	269/1774 (15.2)	191/ 864 (22.1)	0.61 (0.51, 0.73)		
Use of thiazides					p=0.3060
No	386/3245 (11.9)	283/1633 (17.3)	0.63 (0.54, 0.74)		
Yes	139/879 (15.8)	105/428 (24.5)	0.54 (0.42, 0.70)		
Use of loop diuretics					p=0.9927
No	426/3535 (12.1)	310/1751 (17.7)	0.61 (0.53, 0.71)		
Yes	99/599 (16.5)	78/310 (25.2)	0.61 (0.45, 0.82)		



Cox regression analysis in patients treated with ≥1 dose of study drug.

Mayer. Renal effects of empagliflozin in patients already using medications that alter intrarenal hemodynamics: An exploratory analysis from EMPA-REG OUTCOME® . Poster. ASN 2017

SGLT2-I e ridotta funzione renale

Attuale prescrivibilità

- **Empaglifozin**:
  - eGFR < 45 ml/min/1.73 m^2 CONTROINDICATO
  - eGFR ≥ 45 ml/min/1.73 m^2 PUO' ESSERE PROSEGUITO
- **Dapaglifozin:**
  - eGFR < 60 ml/min/1.73 m^2 NON INIZIARE
  - NON PROSEGUIRE SE eGFR PERSISTENTEMENTE < 60 ml/min/1.73 m^2
  - eGFR < 30 ml/min/1.73 m^2 CONTROINDICATO
- **Canaglifozin:**
  - eGFR tra 60 e 45 ml/min/1.73 m^2 NON SUPERARE I 100MG/DIE
  - eGFR < 45 ml/min/1.73 m^2 NON INIZIARE
  - eGFR < 30 ml/min/1.73 m^2 CONTROINDICATO

SID
Società Italiana di Diabetologia

POSITION STATEMENT

Farmaci ipoglicemizzanti, malattie cardiovascolari e renali

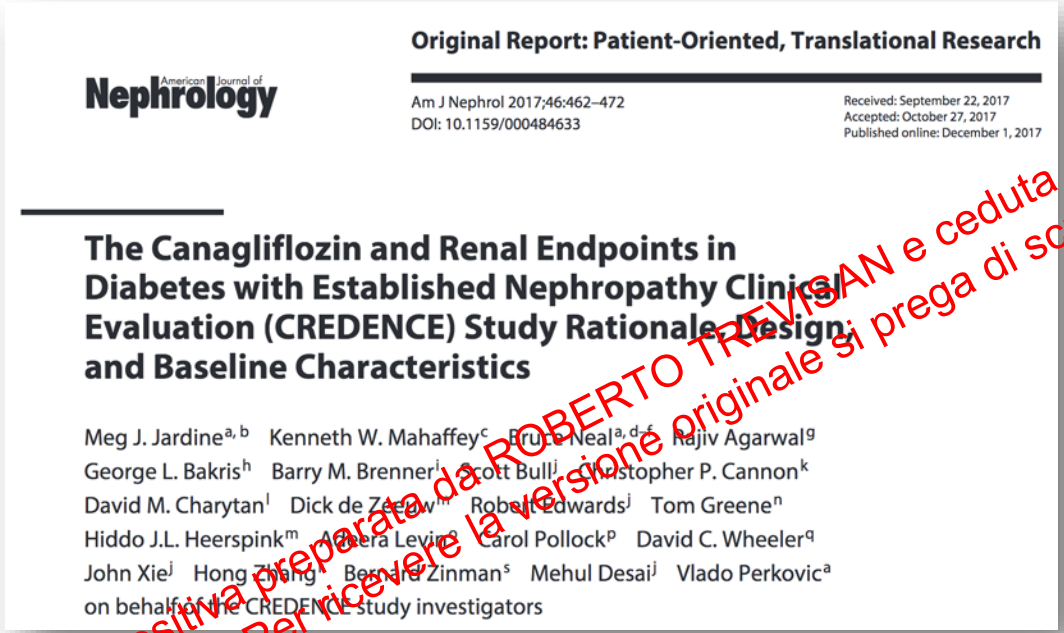
Enzo Bonora, Antonio Bossi, Daniela Bruttomesso, Angelo De Pascale, Gabriella Gruden, Davide Lauro, Frida Leonetti, Edoardo Mannucci, Roberto Miccoli, Annalisa Natalicchio, Gianluca Perseghin, Francesco Purrello, Ferdinando Sasso, Giorgio Sesti

Box 5 *- Empagliflozin, canagliflozin e liraglutide oltre a benefici cardiovascolari, hanno determinato, indipendentemente dagli effetti sulla glicemia, importanti benefici renali. In virtù di ciò, quanto meno in soggetti con pregressa malattia cardiovascolare, empagliflozin canagliflozin o liraglutide dovrebbero essere considerate utili nella nefroprotezione. È verosimile che l'effetto nefroprotettivo sia comune a tulle le molecole della classe degli inibitori di SGLT-2 e che i benefici di liraglutide siano condivisi anche da altri agonisti del recettore di GLP-1 ma ciò deve essere ancora verificato con studi clinici di outcome renale attualmente in corso.*

Box 7 *– L'EMA ha recepito in RCP i benefici cardiovascolari di empagliflozin e liraglutide nei soggetti con pregressa malattia cardiovascolare. Per empagliflozin e per gli altri inibitori di SGLT-2 è auspicabile che venga rimossa la raccomandazione che non permette il loro impiego in caso di insufficienza renale moderata, situanto meno nei soggetti con eGFR compreso fra 30 e 60 ml/min x 1.73m^2.*

Box 8 *- Alcune delle indicazioni d'uso degli inibitori di SGLT-2 e di liraglutide dovrebbero essere aggiornate secondo quanto emerso dagli studi EMPA-REG e LEADER.*

Lo studio CREDENCE



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The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) Study Rationale, Design, and Baseline Characteristics

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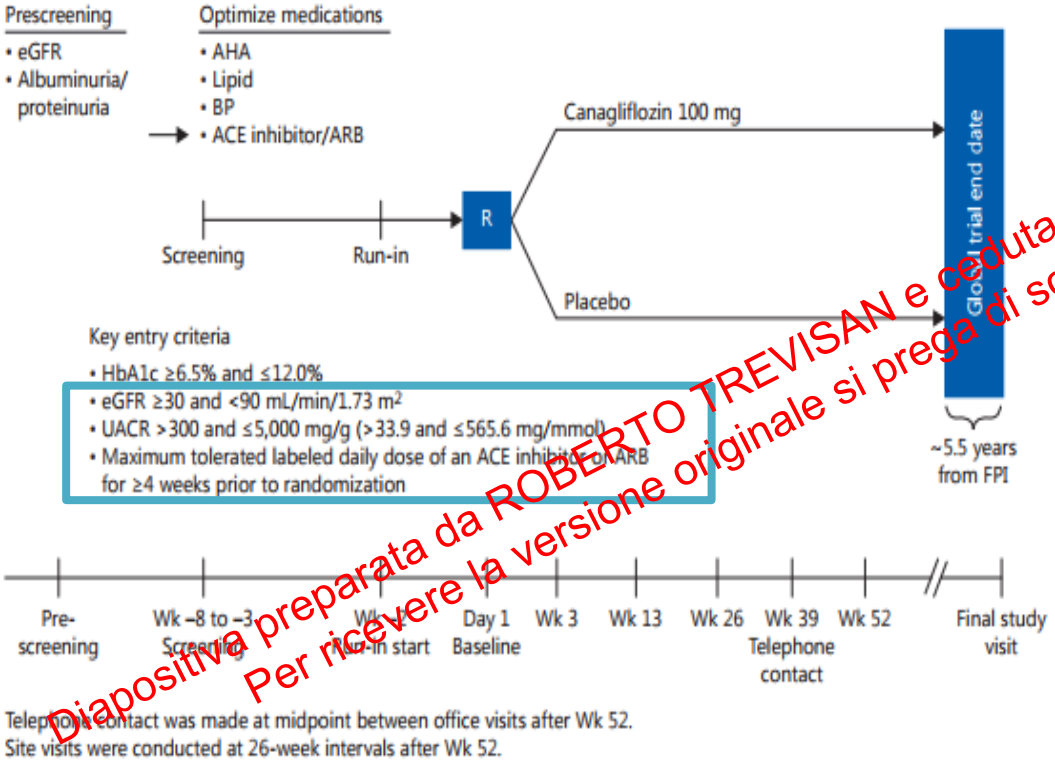
on behalf of the CREDENCE study investigators

OUTCOME RENALE PRIMARIO

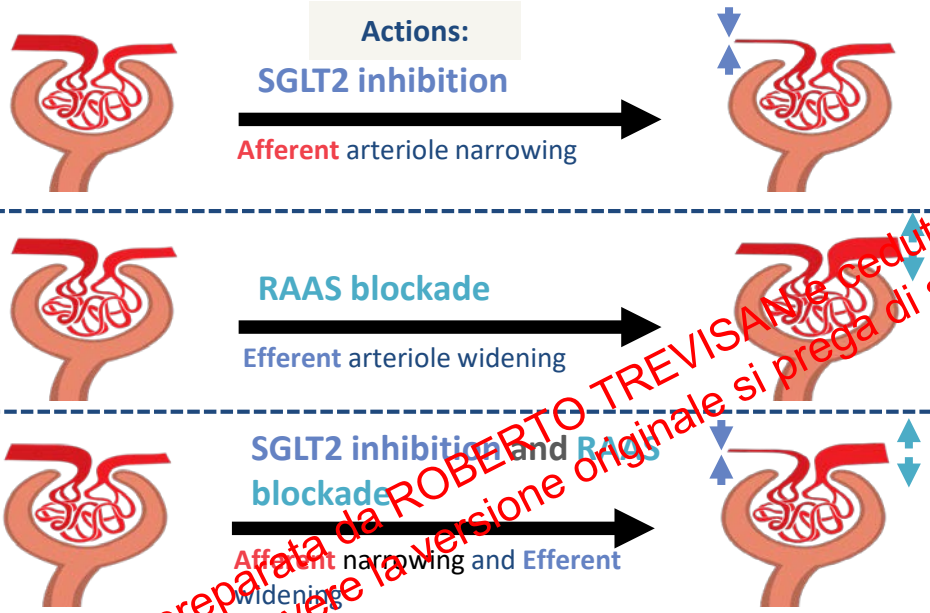
Jardine MJ Am J Nephrol 2017, 46:462-472

CREDENCE: Disegno dello Studio



- Studio randomizzato, doppio cieco, event-driven, placebo-controlled
- 695 centri diabetologici in 34 Paesi
- **4.401 T2DM**
- **Esclusi:** NON diabetici con accertata malattia renale, precedentemente trattati con immunosoppressori, dializzati o con precedente trapianto renale.
- **FU 5.5 anni**

Future outlook – Dual SGLT2 and RAAS inhibition



Clinical implications:

- Decreased glomerular pressure
- Reduction in albuminuria
- Renal protection suggested

- Decreased glomerular pressure
- Reduction in albuminuria
- Renal protection proven in clinical trials

- Potential for normalisation of intraglomerular pressure
- Potential additive intraglomerular pressure reduction
- Potential for long-term renal protection

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 Empaglifozine e Canaglifozin) 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,in aggiunta al trattamento con ACEi/ARBs, nel paziente diabetico con albuminuria e, per il momento, con eGFR > 60 ml/min.