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

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Disclosure

Il Prof. Giuseppe Pugliese dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- ✓ Partecipazioni a Congressi: Astra-Zeneca, Laboratori Guidotti, Sanofi, Takeda;
- ✓ Relazioni / moderazioni / partecipazioni a board retribuite: Astra-Zeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dome, Mylan, Sigma-Tau, Takeda.

Il Prof. Giuseppe Pugliese 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.).

Agenda

- ✓ General considerations
- ✓ Treatment with SGLT2 inhibitors and renal outcomes
- ✓ Treatment with SGLT2 inhibitors in CKD patients
- ✓ Placing SGLT2 inhibitors in the therapeutic algorithm
- ✓ Mechanisms of nephroprotection with SGLT2 inhibitors

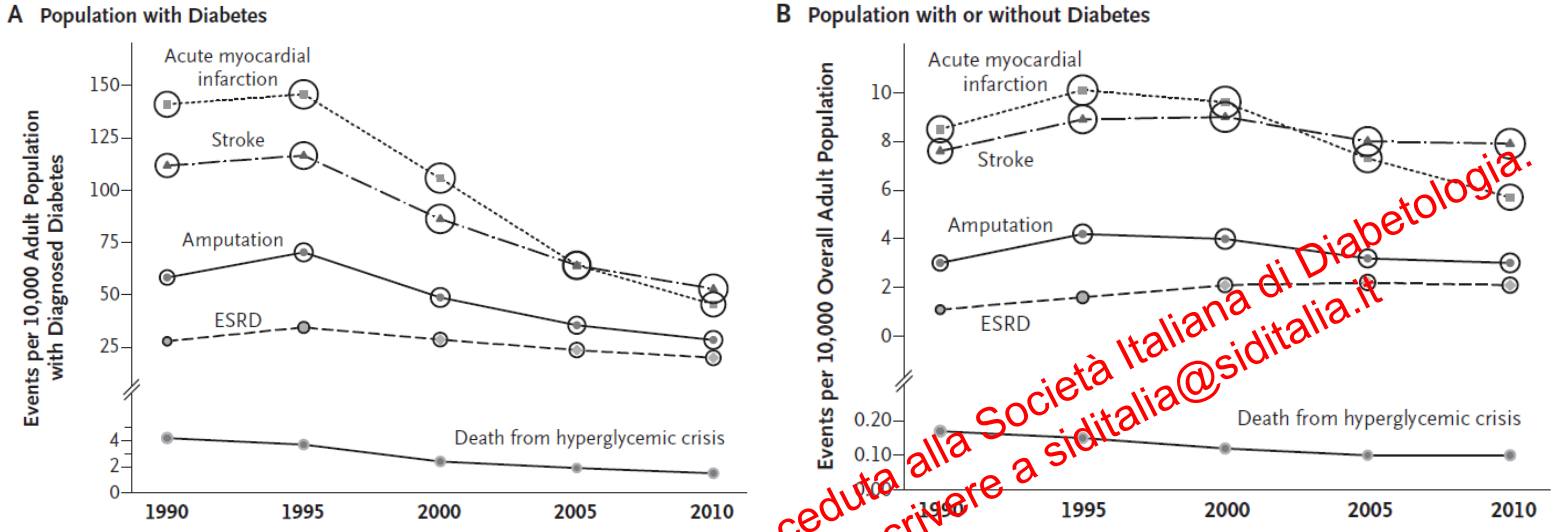
Domanda 1

Cosa aggiungono secondo voi gli SGLT2 inibitori in termini di nefro-protezione nel paziente diabetico?

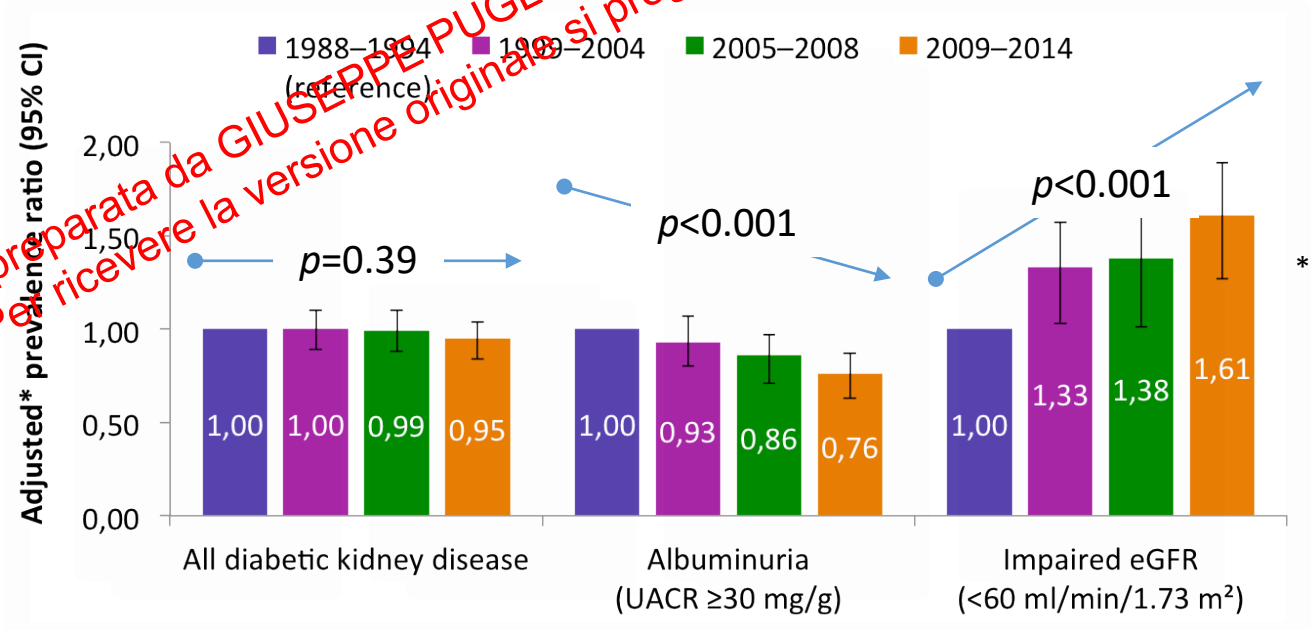
Opzioni di risposta

A. offrono la possibilità di combinare la nefro-protezione con il controllo della glicemia
B. rappresentano una possibile alternativa ad altri farmaci ad azione nefro-protettiva
C. non aggiungono molto rispetto ad altri trattamenti quali i bloccanti del RAS
D. possono colmare un vuoto nel nostro armamentario terapeutico

Unmet needs in diabetic nephropathy

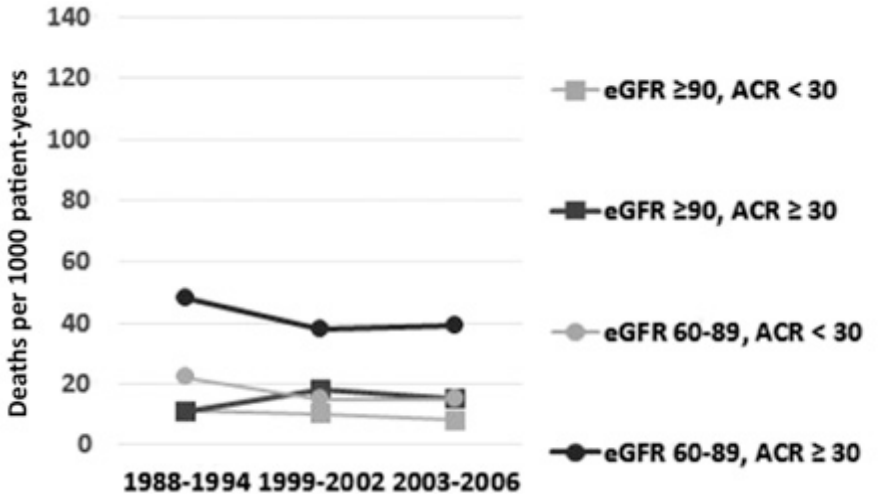


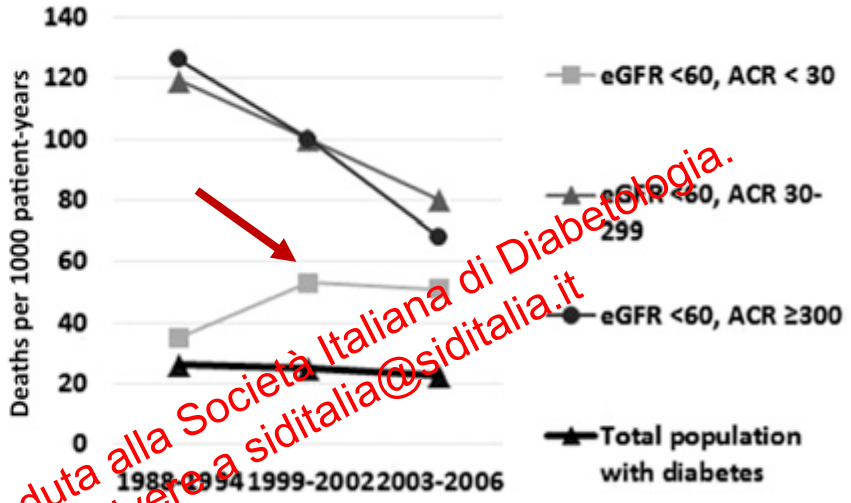
Gregg EW et al. N Engl J Med. 2014;370:1514–1523



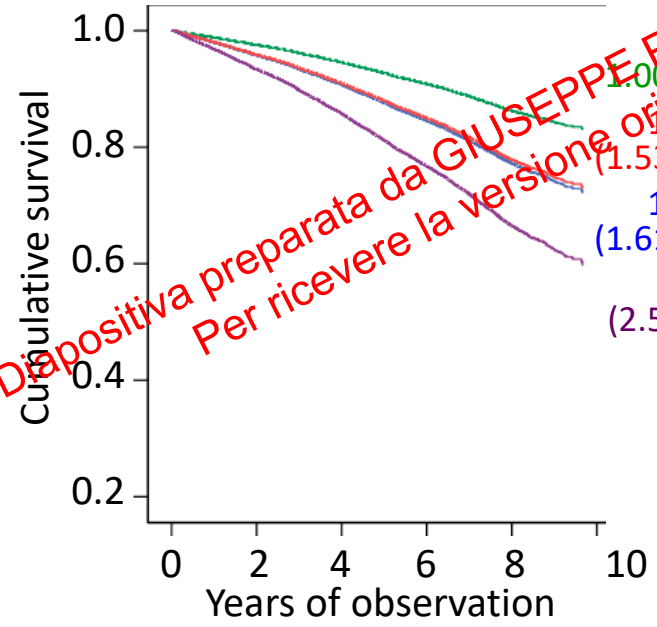
Afkarian M et al. JAMA. 2016;316:602–610

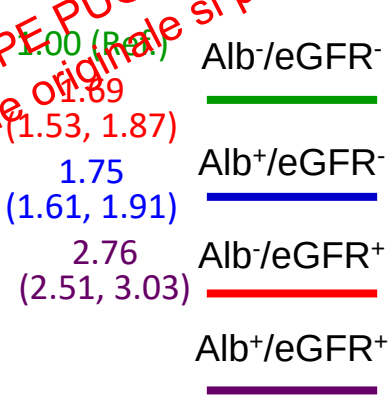
Unmet needs in diabetic nephropathy

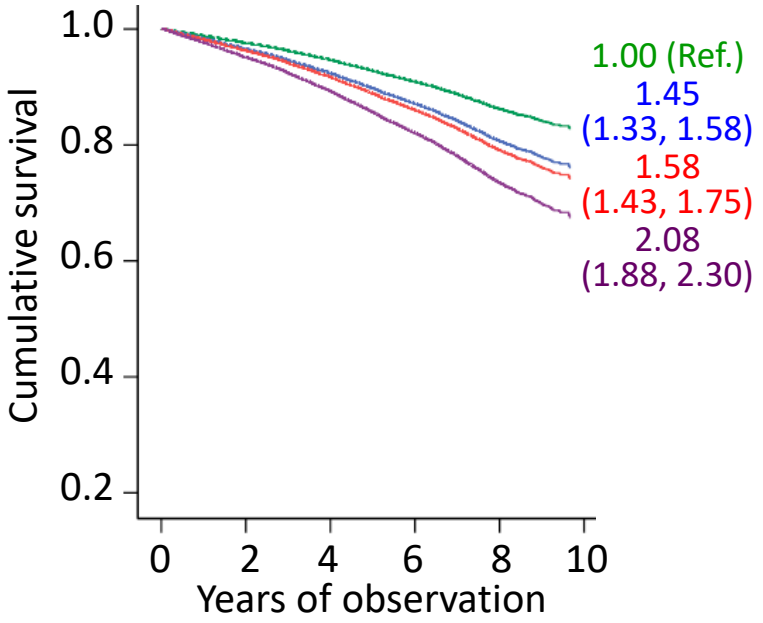




Kramer H et al. Diabetes Care. 2018;41:775–781

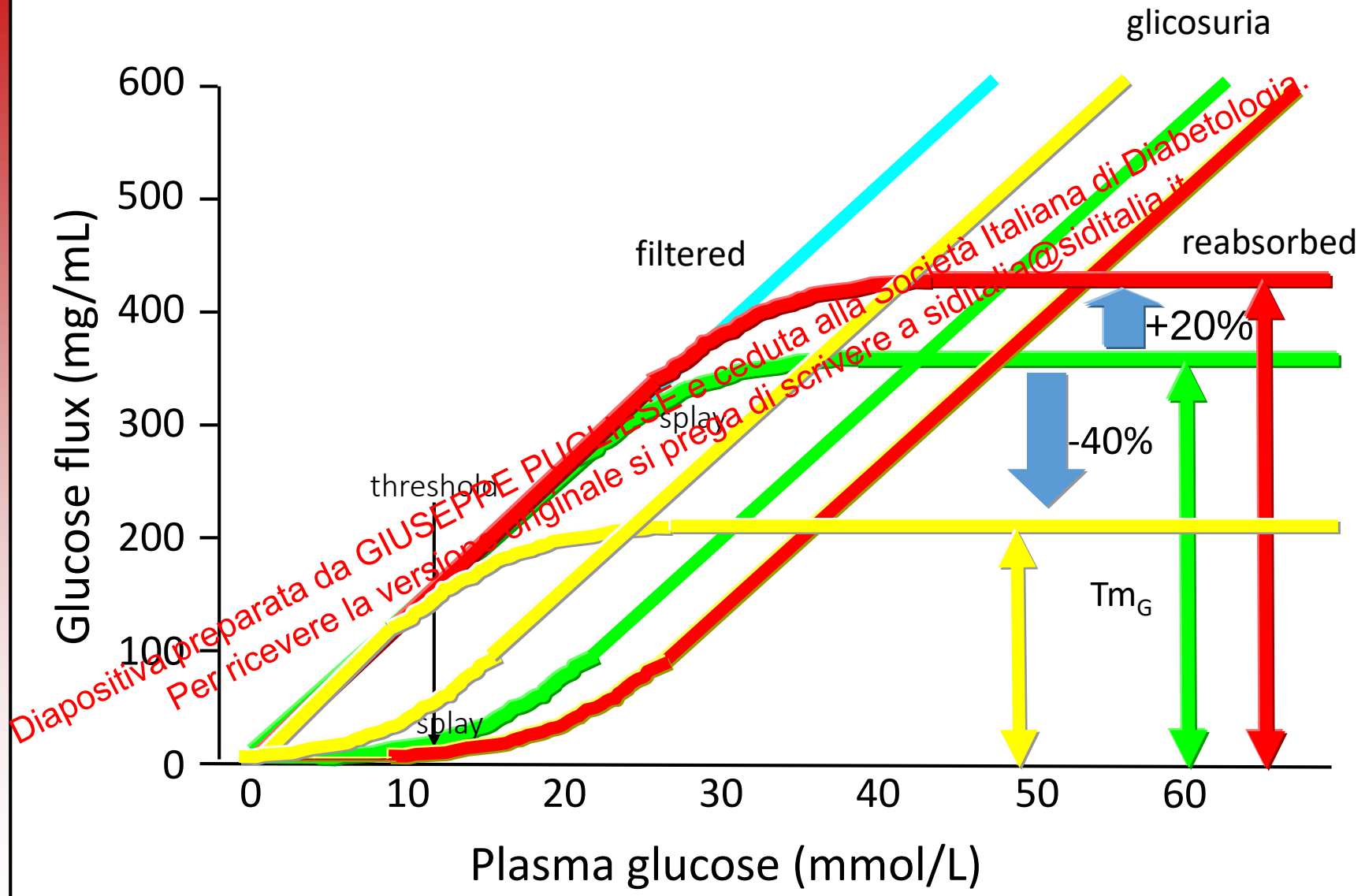






Penno G et al. Diabetologia. 2018; Jul 21

Mechanism of action of SGLT2 inhibitors



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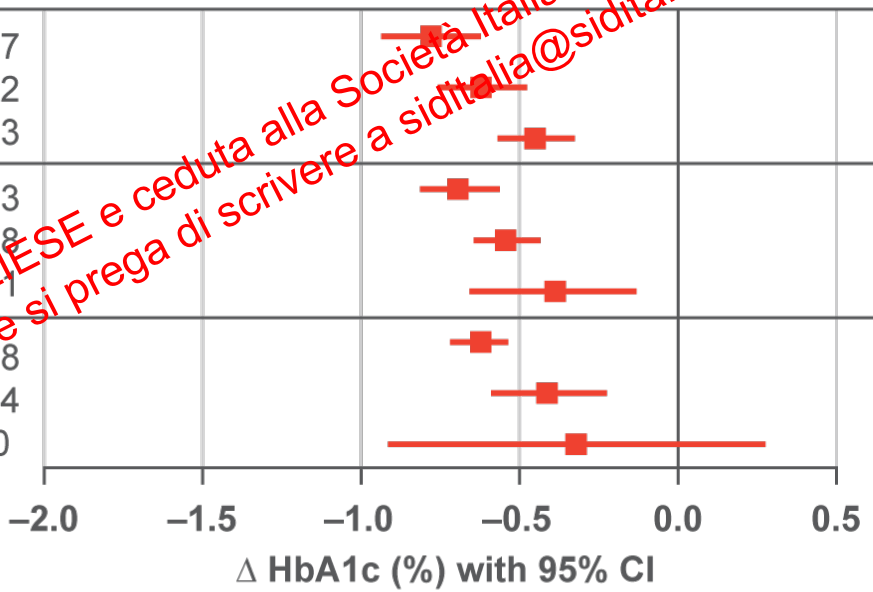
HbA_{1c}- and eGFR-dependent effect of SGLT2 inhibitors

Pooled data from 9 phase III studies

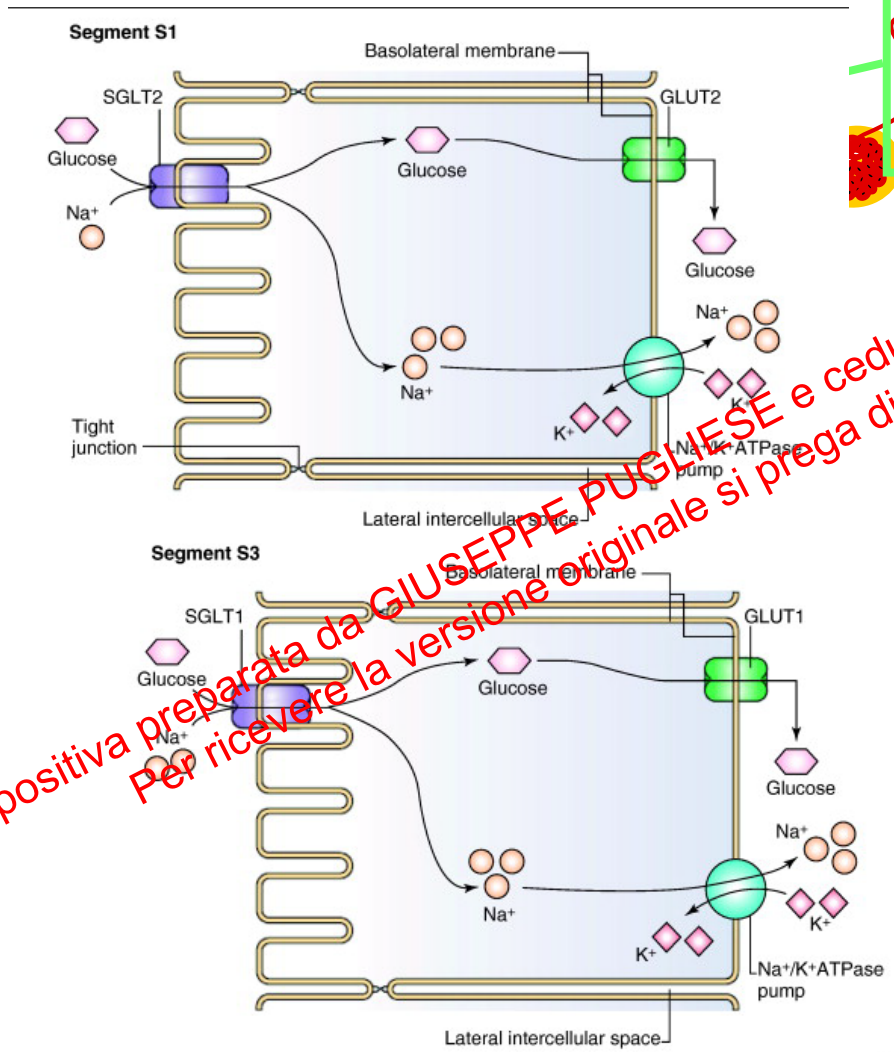
	Baseline Category	Dapa 10 mg N	Pbo N	Difference from Placebo Dapa better ← → Pbo better Δ
HbA1c	≥ 9%	265	347	–0.78
	≥ 8% – < 9%	320	372	–0.62
	< 8%	457	513	–0.45
eGFR (mL/min/1.73m²)	≥ 90	395	443	–0.69
	≥ 60 – < 90	562	688	–0.54
	≥ 30 – < 60	85	101	–0.39
Age (yrs)	< 65	866	988	–0.62
	≥ 65	176	244	–0.41
	≥ 75	16	20	–0.32

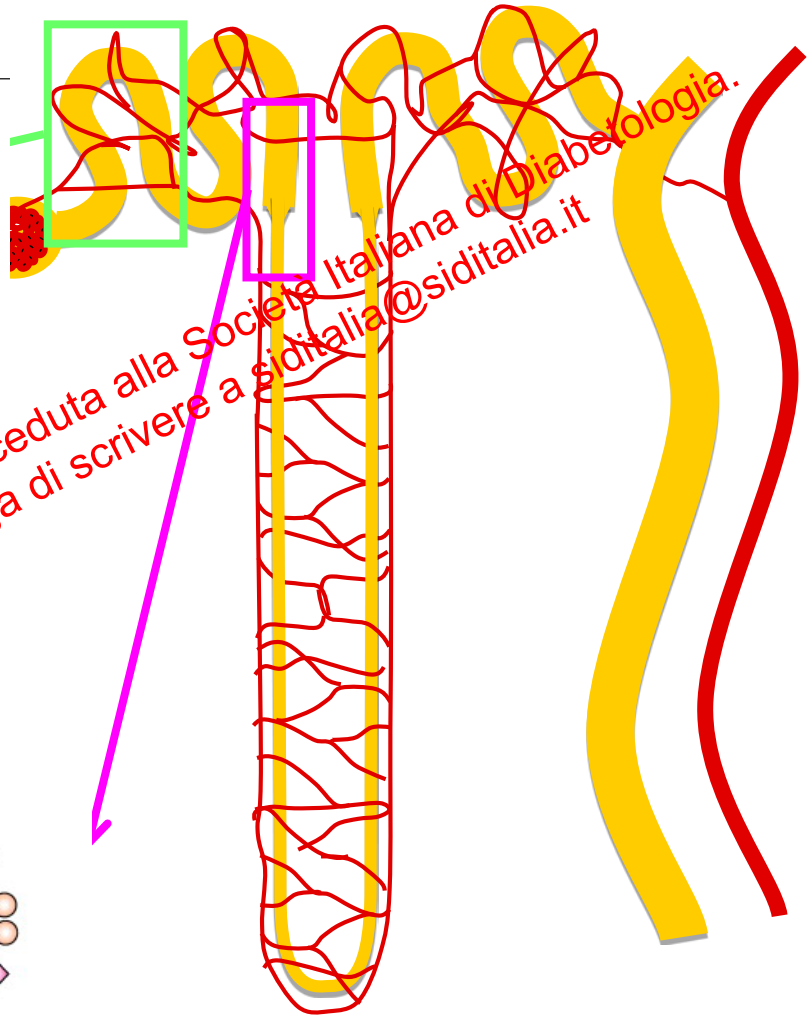


Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF)

FDA Endocrinologic and Metabolic Drugs Advisory Committee: Dapagliflozin BMS-512148. http://tinyurl.com/7kjf5j7

SGLTs in the kidney





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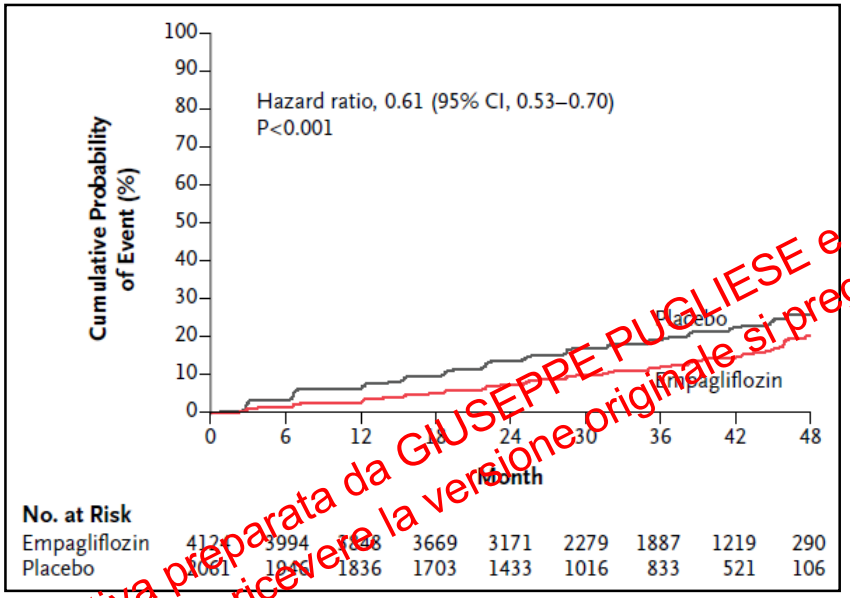
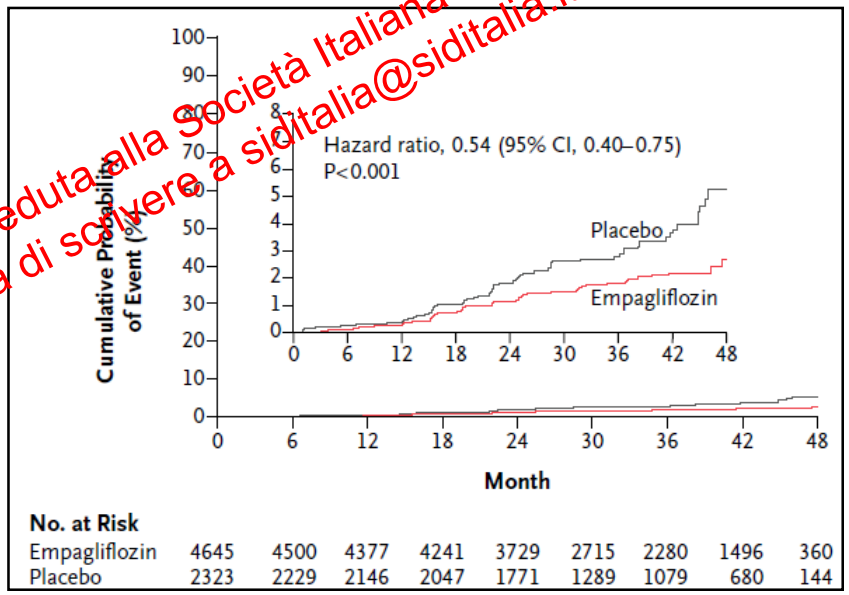
Renal outcomes with SGLT2 inhibitors: empagliflozin

The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial (EMPA-REG OUTCOME) - Chronic Kidney Disease (CKD)

Incident or worsening of nephropathy



Post-hoc renal composite outcome *



* doubling of serum creatinine, initiation of renal-replacement therapy, or death from renal disease

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

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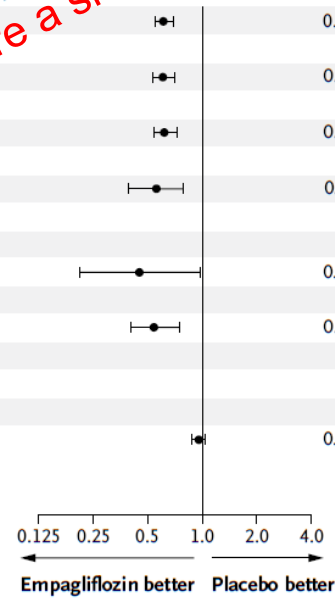
Renal outcomes

Renal Outcome Measure	Empagliflozin: *no. with event/ no. analyzed (%)*	Empagliflozin: *rate/1000 patient-yr*	Placebo: *no. with event/ no. analyzed (%)*	Placebo: *rate/1000 patient-yr*	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	332/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/3687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25



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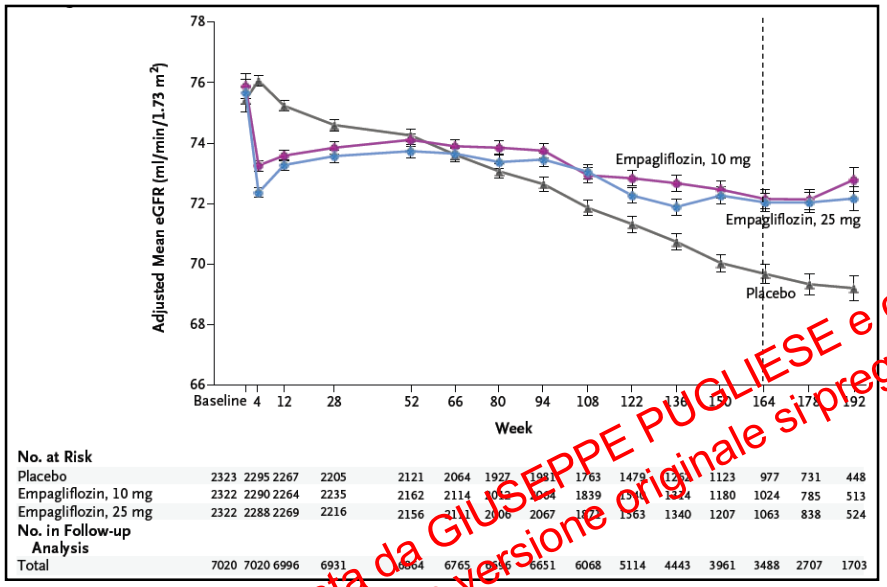
Renal outcomes with SGLT2 inhibitors: empagliflozin

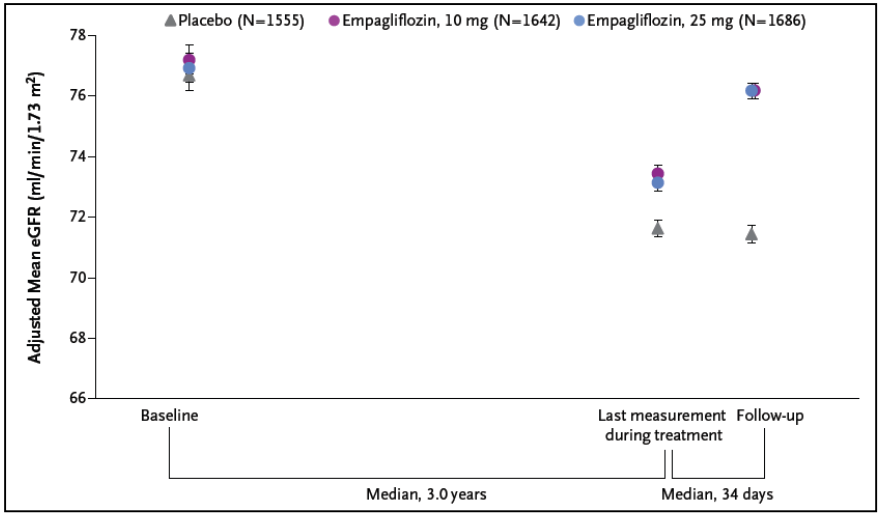
The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial (EMPA-REG OUTCOME) - Chronic Kidney Disease (CKD)

Change in eGFR over 192 weeks



No. at Risk														
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	2052	2064	1839	1544	1324	1180	1024	785	513
Empagliflozin, 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1812	1563	1340	1207	1063	838	524
No. in Follow-up Analysis															
Total	7020	7020	6996	6931	6864	6765	6596	6651	6068	5114	4443	3961	3488	2707	1703

Change in eGFR from baseline to last measurement during treatment & follow-up



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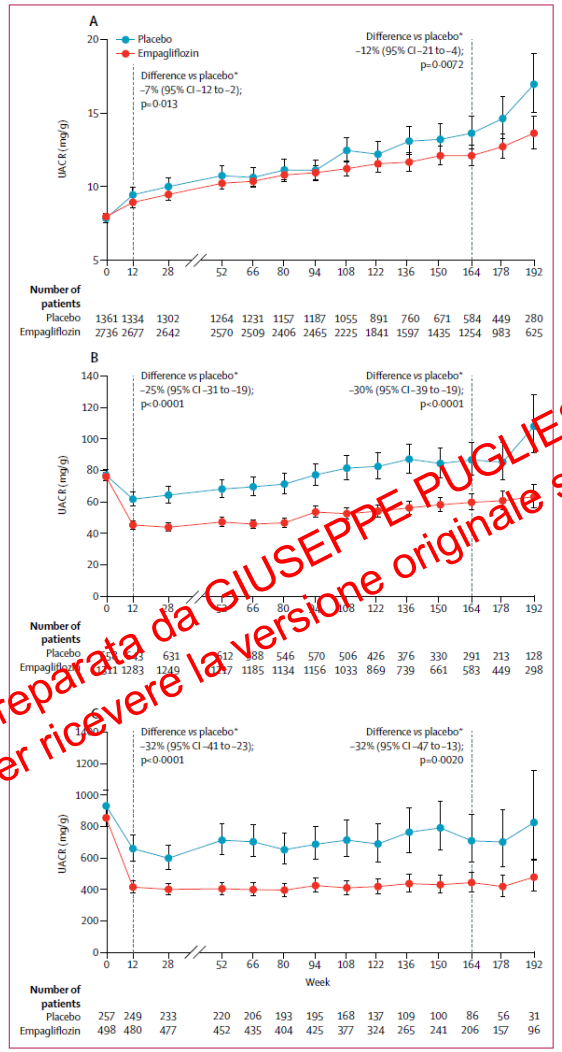
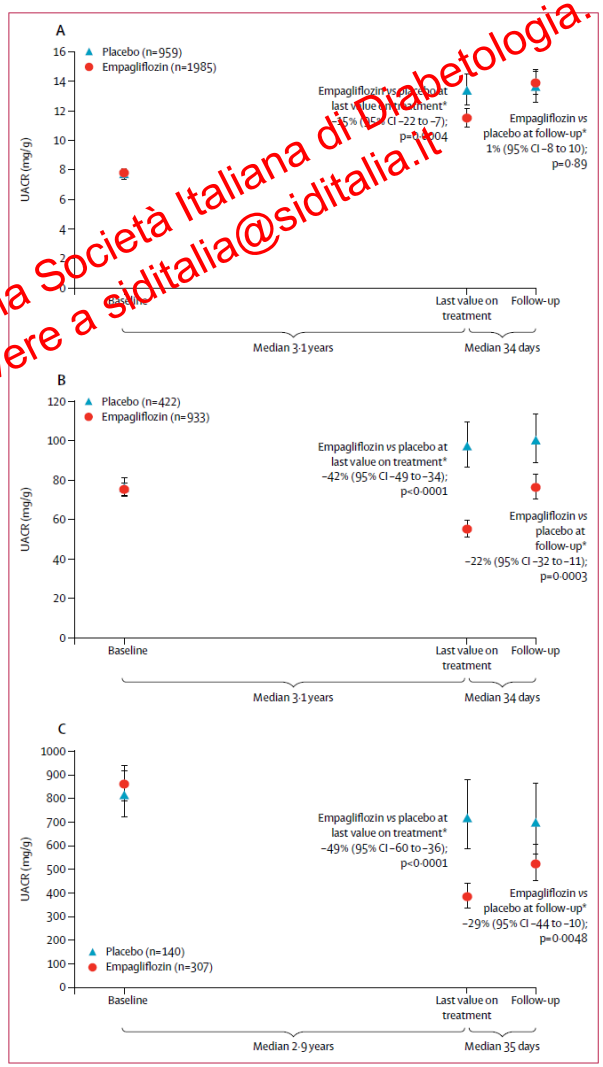
The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial (EMPA-REG OUTCOME) - Chronic Kidney Disease (CKD)

Change in ACR over 192 weeks by albuminuria categories



ACR at baseline to last measurement during treatment and follow-up by albuminuria categories



Cherney DZI et al. Lancet Diabetes Endocrinol. 2017;5:610–621

Renal outcomes with SGLT2 inhibitors: empagliflozin

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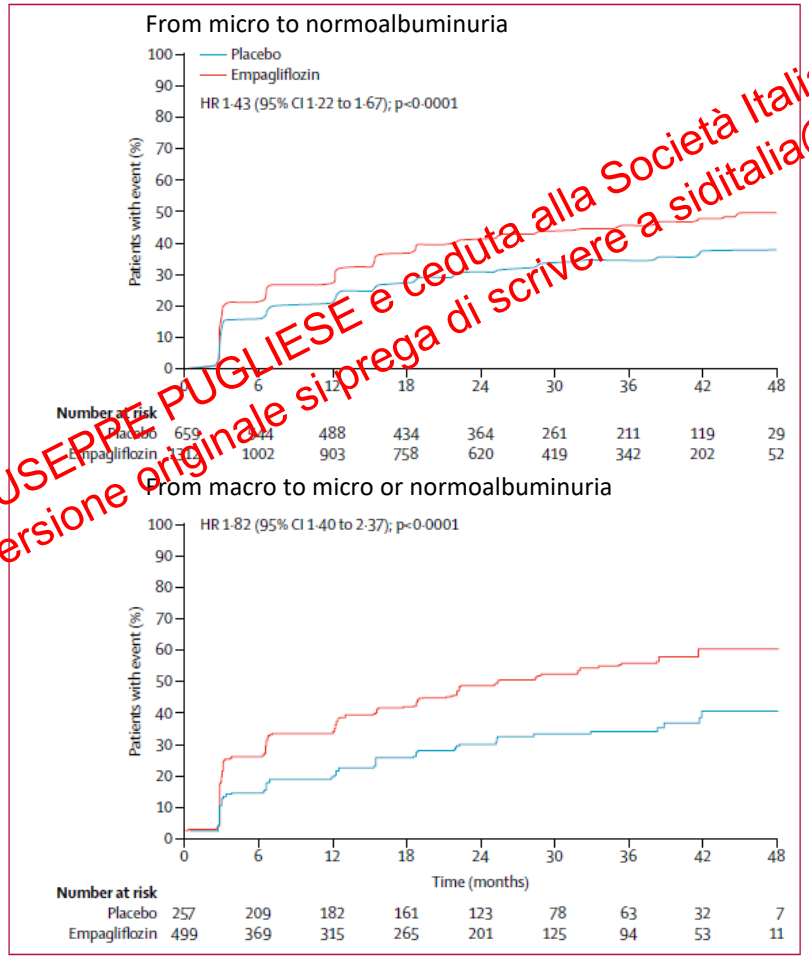
Improvement in albuminuria status



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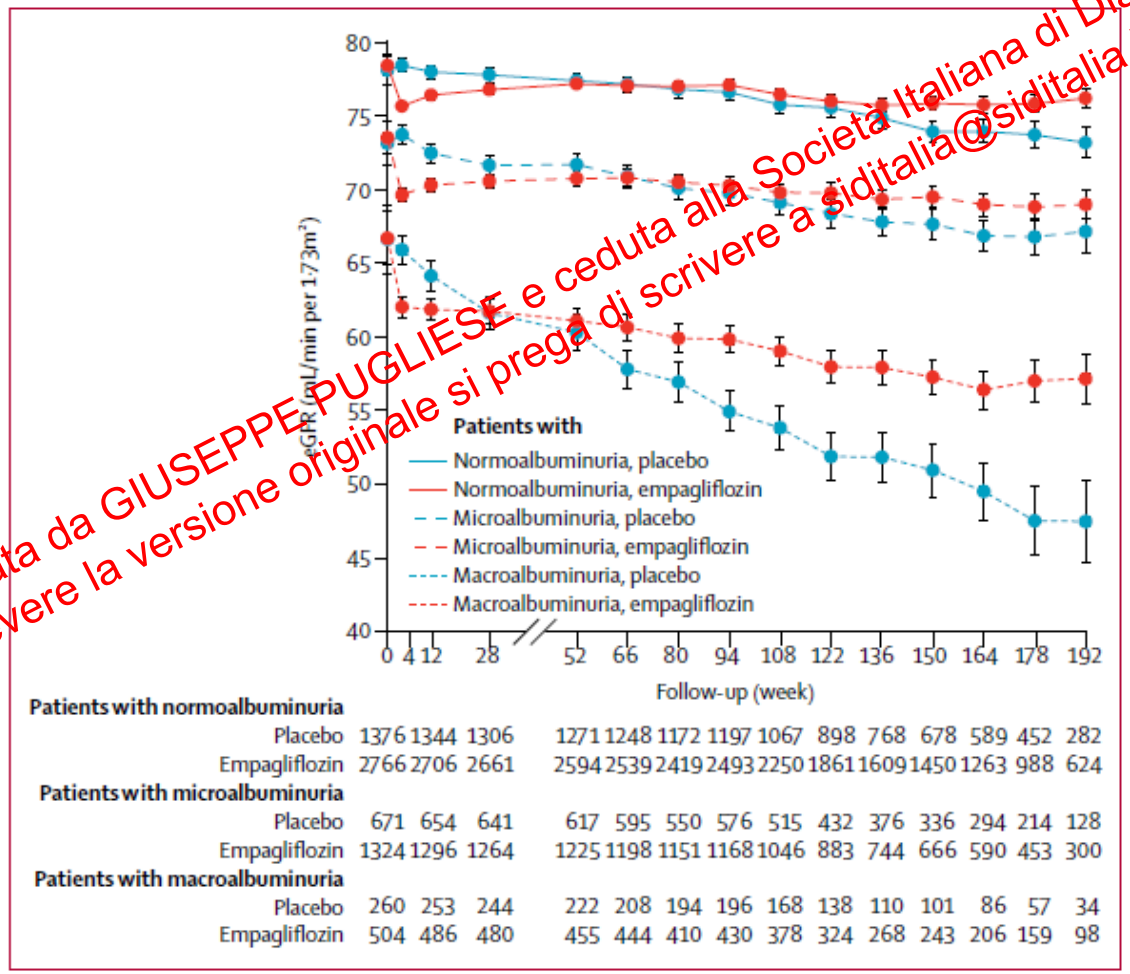


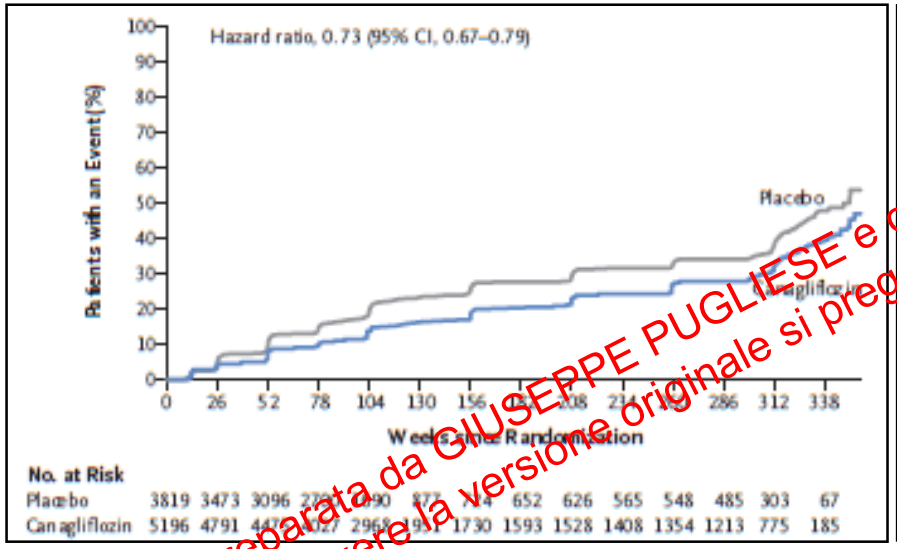
Patients with normoalbuminuria														
Placebo	1376	1344	1306	1271	1248	1172	1197	1067	898	768	678	589	452	282
Empagliflozin	2766	2706	2661	2594	2539	2419	2493	2250	1861	1609	1450	1263	988	624
Patients with microalbuminuria														
Placebo	671	654	641	617	595	550	576	515	432	376	336	294	214	128
Empagliflozin	1324	1296	1264	1225	1198	1151	1168	1046	883	744	666	590	453	300
Patients with macroalbuminuria														
Placebo	260	253	244	222	208	194	196	168	138	110	101	86	57	34
Empagliflozin	504	486	480	455	444	410	430	378	324	268	243	206	159	98

Cherney DZI et al. Lancet Diabetes Endocrinol. 2017;5:610–621

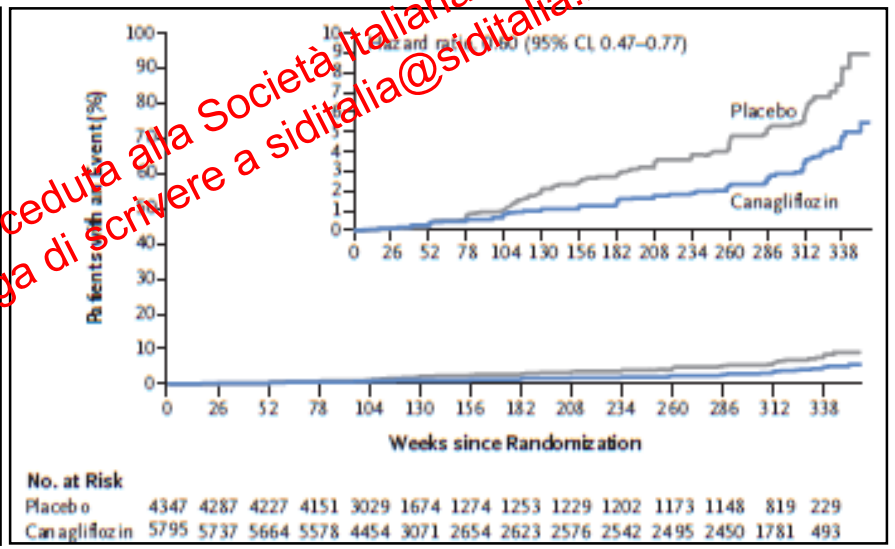
Renal outcomes with SGLT2 inhibitors: canagliflozin

The Canagliflozin Cardiovascular Assessment Study (CANVAS) Program CANVAS and CANVAS-Renal (CANVAS-R)

Progression of albuminuria*



Composite renal outcome*



* >30% increase in albuminuria or change from either normo to micro or macroalbuminuria or from micro to macroalbuminuria

* 40% reduction in eGFR, initiation of renal-replacement therapy, or death from renal disease

Neal B et al. N Engl J Med. 2017; Jun 12

Renal outcomes with SGLT2 inhibitors: canagliflozin

The Canagliflozin Cardiovascular Assessment Study (CANVAS) Program CANVAS and CANVAS-Renal (CANVAS-R)

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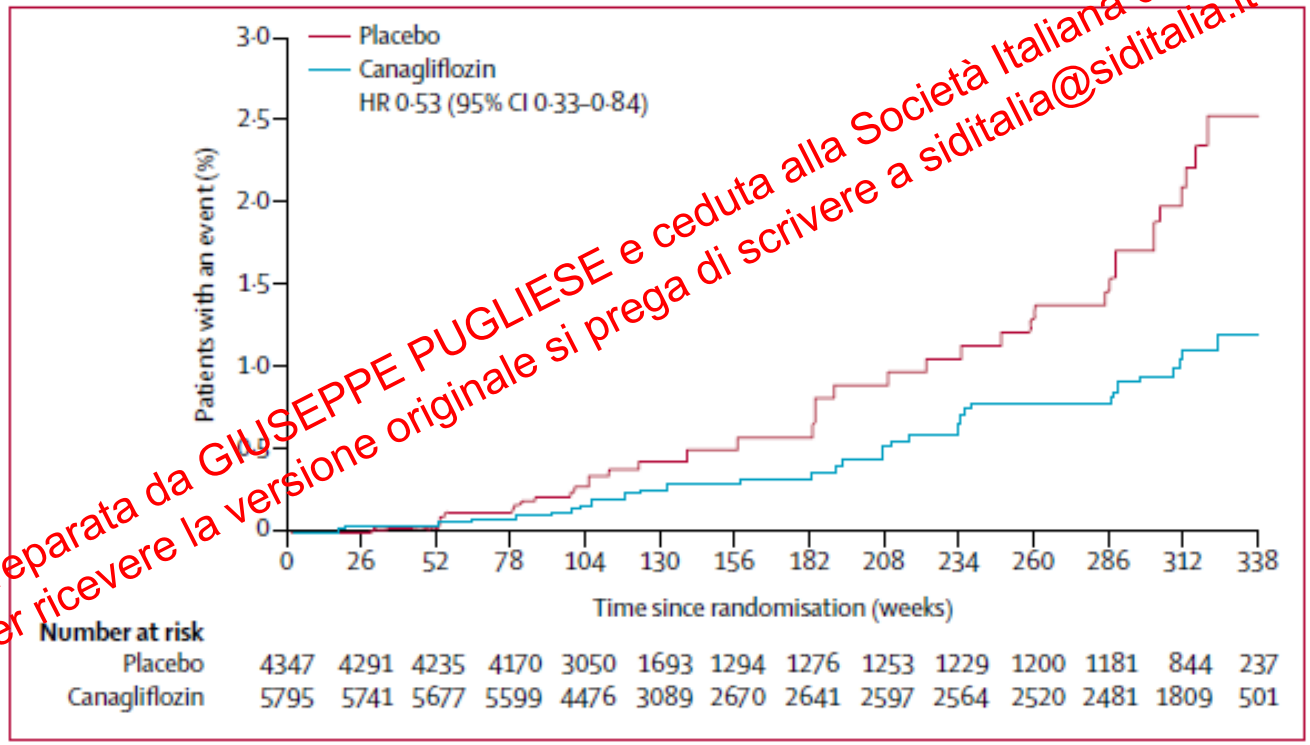


* Doubling of serum creatinine, ESRD, or death from renal disease

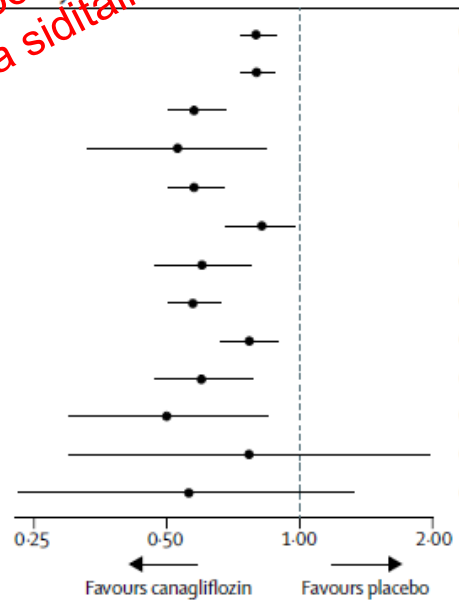
Perkovic V et al. Lancet Diabetes Endocrinol. 2018;6:691–704

Renal outcomes with SGLT2 inhibitors: canagliflozin

The Canagliflozin Cardiovascular Assessment Study (CANVAS) Program CANVAS and CANVAS-Renal (CANVAS-R)

Renal outcomes

	Number of participants with an event	Canagliflozin participants with an event per 1000 patient-years	Placebo participants with an event per 1000 patient-years	Hazard ratio (95% CI)
New-onset albuminuria	1990	100·4	130·8	0·80 (0·73–0·88)
New-onset microalbuminuria	1935	96·7	120·3	0·80 (0·73–0·87)
New-onset macroalbuminuria	636	22·6	27·6	0·58 (0·50–0·68)
dSCr, ESKD, or death from renal causes	72	1·5	2·8	0·53 (0·33–0·84)
dSCr, ESKD, death from renal causes, or new-onset macroalbuminuria	698	25·1	27·4	0·58 (0·50–0·67)
dSCr, ESKD, or death from renal or cardiovascular causes	518	13·2	15·8	0·82 (0·68–0·97)
40% reduction in eGFR, ESKD, or death from renal causes	249	5·5	9·0	0·60 (0·47–0·77)
40% reduction in eGFR, ESKD, death from renal causes, or new-onset macroalbuminuria	847	18·6	33·3	0·57 (0·50–0·66)
40% reduction in eGFR, ESKD, or death from renal or cardiovascular causes	679	16·9	21·6	0·77 (0·66–0·89)
40% eGFR reduction	239	5·3	8·7	0·60 (0·47–0·78)
dSCr	60	1·2	2·4	0·50 (0·30–0·84)
ESKD	18	0·4	0·6	0·77 (0·30–1·97)
ESKD or death from renal causes	21	0·4	0·8	0·56 (0·23–1·32)



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Renal outcomes with SGLT2 inhibitors: canagliflozin

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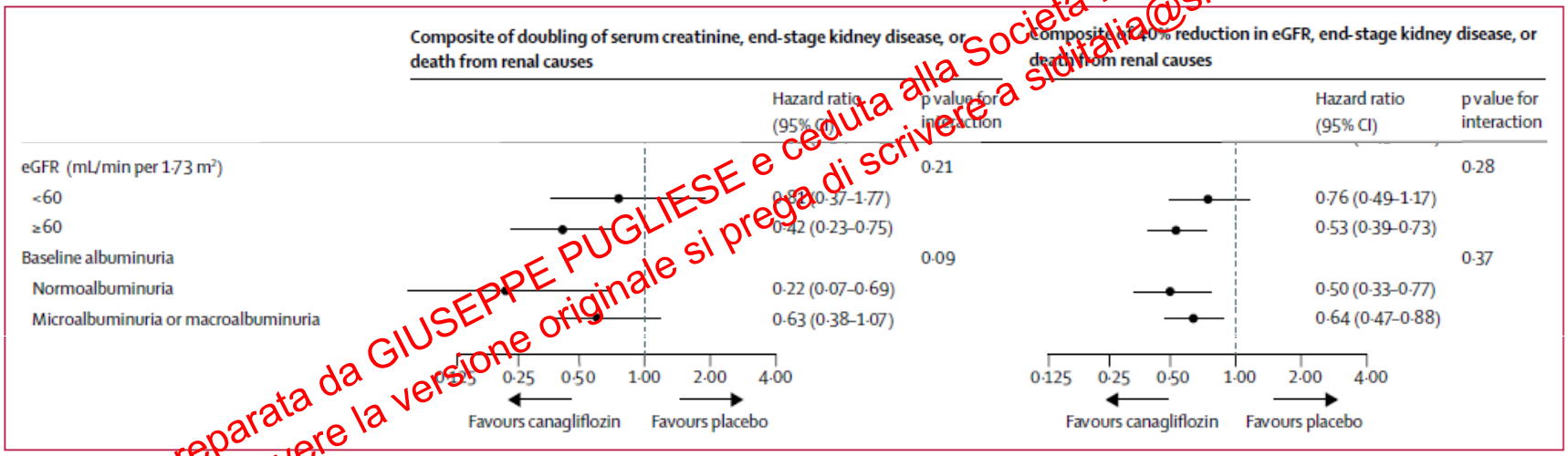
Renal outcomes by subgroups



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Renal outcomes with SGLT2 inhibitors: canagliflozin

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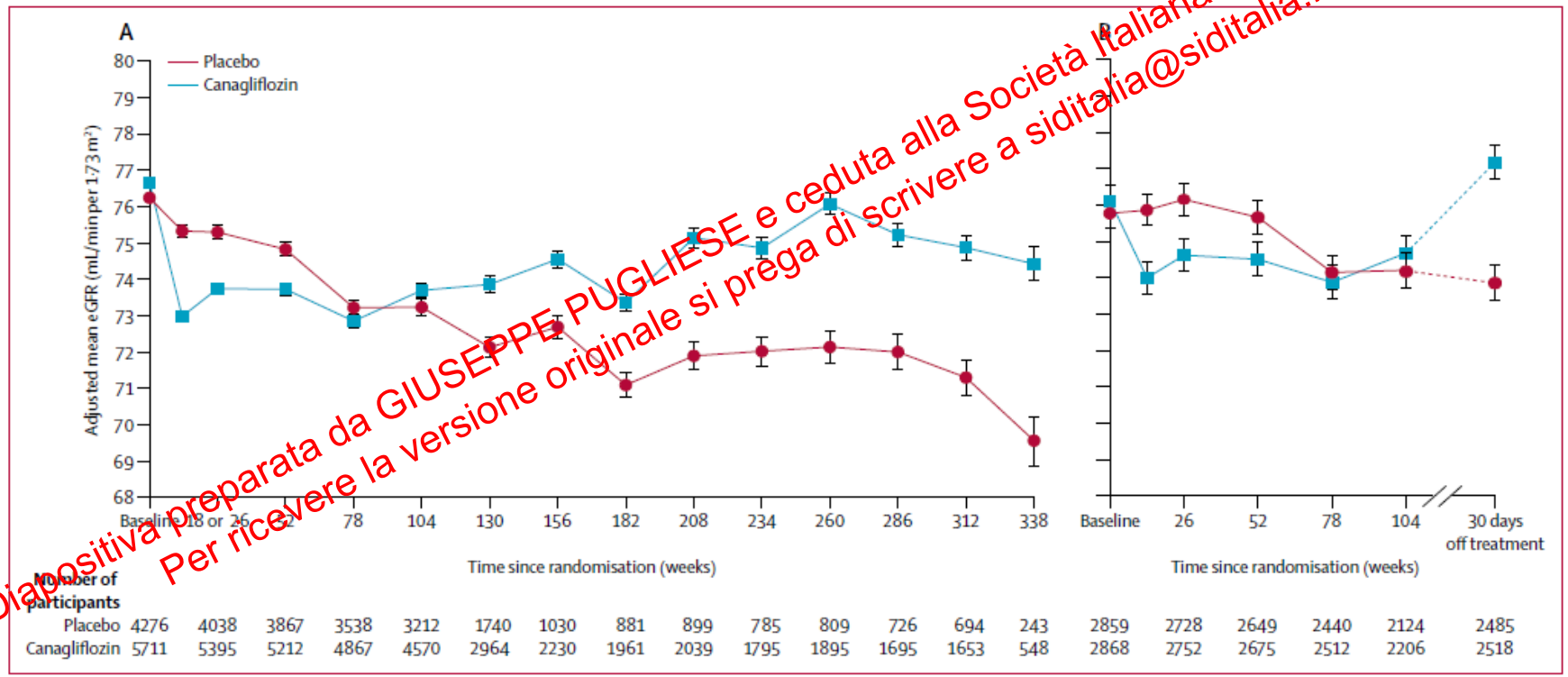
Change in eGFR over time



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Renal outcomes with SGLT2 inhibitors: canagliflozin

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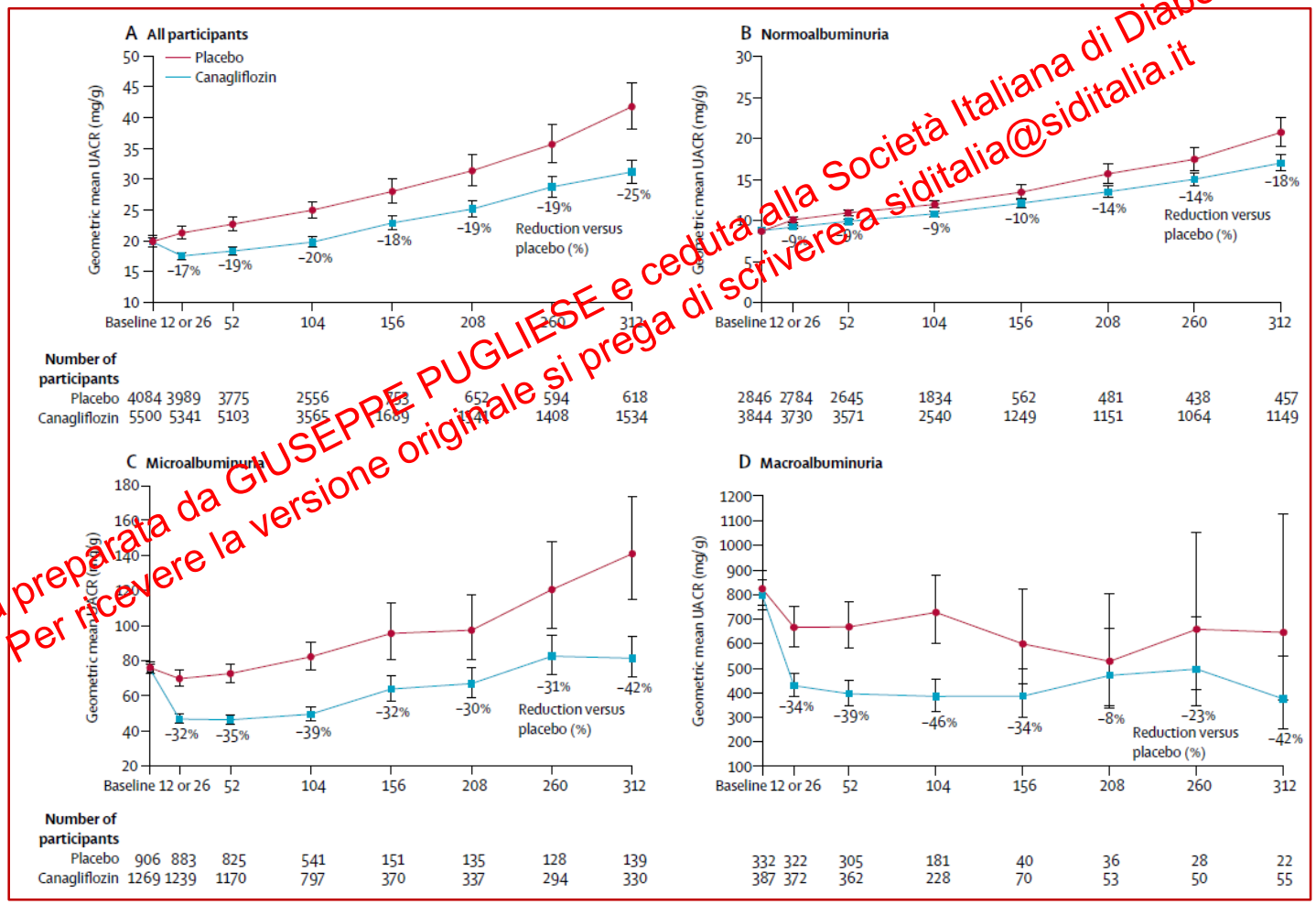
Change in ACR over time and by albuminuria categories



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Renal outcomes with SGLT2 inhibitors: canagliflozin

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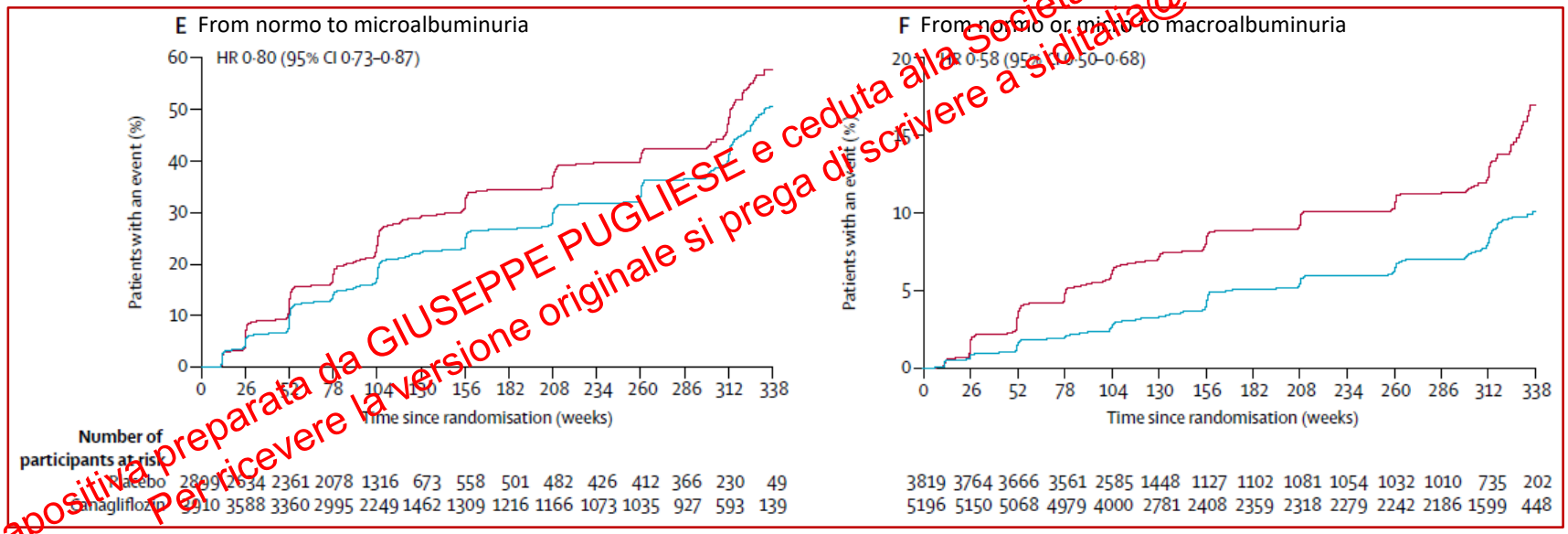
Improvement in albuminuria status



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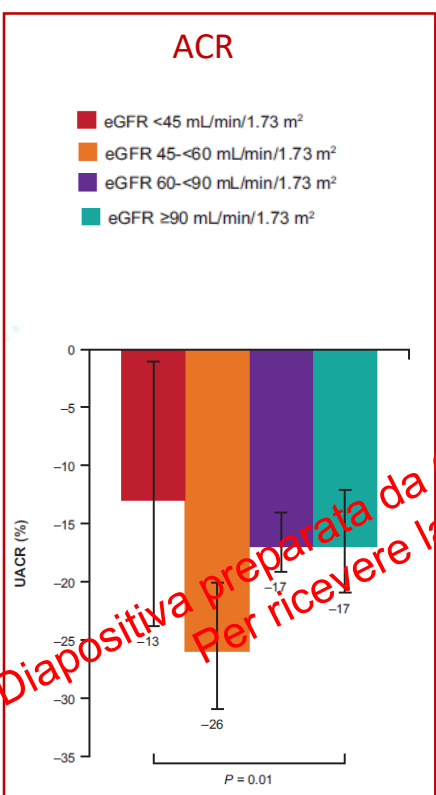
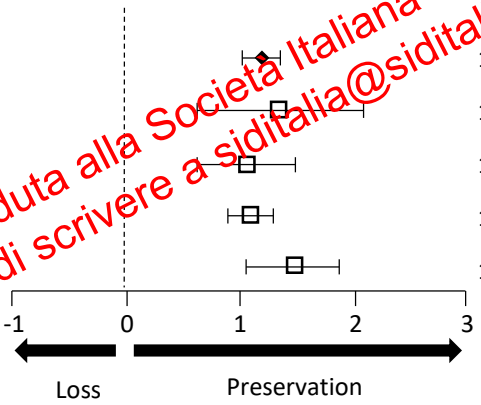
Renal outcomes by eGFR category

ACR



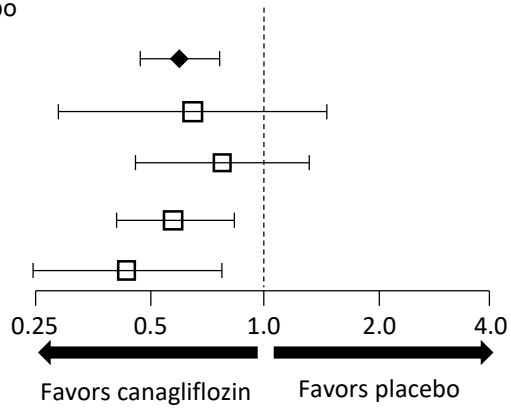
eGFR

	Annual change from week 6/13			Interaction P value
	Canagliflozin	Placebo	HR (95% CI)	
All	0.33±0.05	-0.85±0.07	1.18 (1.02, 1.35)	0.59
<45	0.26±0.23	-1.09±0.30	1.35 (0.62, 2.09)	
45-<60	0.19±0.14	-0.86±0.17	1.05 (0.62, 1.48)	
60-<90	0.36±0.06	-0.73±0.08	1.09 (0.89, 1.29)	
≥90	0.31±0.12	-1.16±0.17	1.47 (1.05, 1.88)	



Renal composite*

	Patients with an event per 1000 patient-years			Interaction P value
	Canagliflozin	Placebo	HR (95% CI)	
All	5.5	9.0	0.60 (0.47, 0.77)	0.59
<45	13.5	18.4	0.65 (0.29, 1.48)	
45-<60	10.6	13.9	0.78 (0.46, 1.31)	
60-<90	4.6	7.4	0.58 (0.41, 0.84)	
≥90	3.8	8.1	0.44 (0.25, 0.78)	

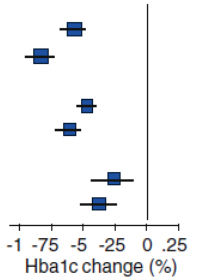


* 40% eGFR reduction, ESRD, or death from renal disease

Neuen B et al. Circulation. 2018 Jun 25

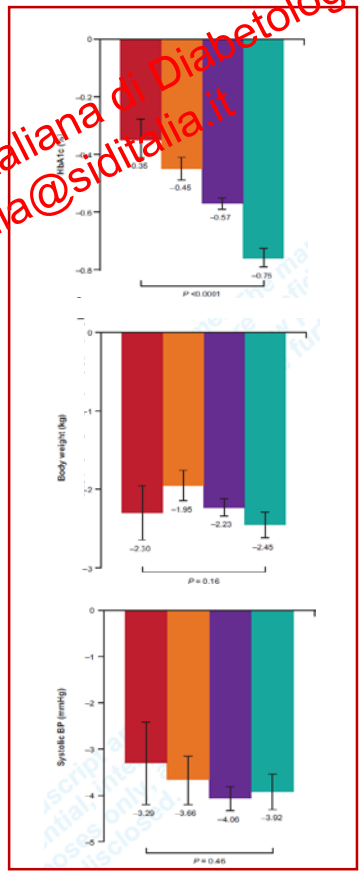
Maintenance of BP (and weight)-lowering effect in CKD patients

	Placebo patients	SGLT2i patients	Change	95%CI	
Hba1c					
eGFR>90 ml/min/1.73 m²					
Dapagliflozin	671	723	-0.57	-0.68	-0.47
Empagliflozin	343	348	-0.84	-0.95	-0.72
eGFR 60-90 ml/min/1.73 m²					
Dapagliflozin	1233	1251	-0.47	-0.54	-0.40
Empagliflozin	516	518	-0.60	-0.70	-0.51
*eGFR 30-60 ml/min/1.73 m²**					
Dapagliflozin	274	252	-0.27	-0.43	-0.11
Empagliflozin	239	234	-0.38	-0.52	-0.24
Body Weight					
eGFR>90 ml/min/1.73 m²					
Dapagliflozin	671	723	-2.3	-2.7	-1.9
Empagliflozin	343	348	-1.9	-2.3	-1.5
eGFR 60-90 ml/min/1.73 m²					
Dapagliflozin	1233	1251	-1.8	-2.0	-1.5
Empagliflozin	516	518	-2.0	-2.3	-1.7
eGFR<60 ml/min/1.73 m²					
Dapagliflozin	274	252	-2.1	-2.6	-1.5
Empagliflozin	239	234	-1.4	-1.8	-0.9
Systolic Blood Pressure					
eGFR>90 ml/min/1.73 m²					
Dapagliflozin	671	723	-3.4	-4.7	-2.1
Empagliflozin	343	348	-3.2	-4.9	-1.5
eGFR 60-90 ml/min/1.73 m²					
Dapagliflozin	1233	1251	-2.6	-3.6	-1.6
Empagliflozin	516	518	-4.0	-5.4	-2.6
eGFR<60 ml/min/1.73 m²					
Dapagliflozin	274	252	-4.3	-6.8	-1.8
Empagliflozin	239	234	-5.5	-7.6	-3.4



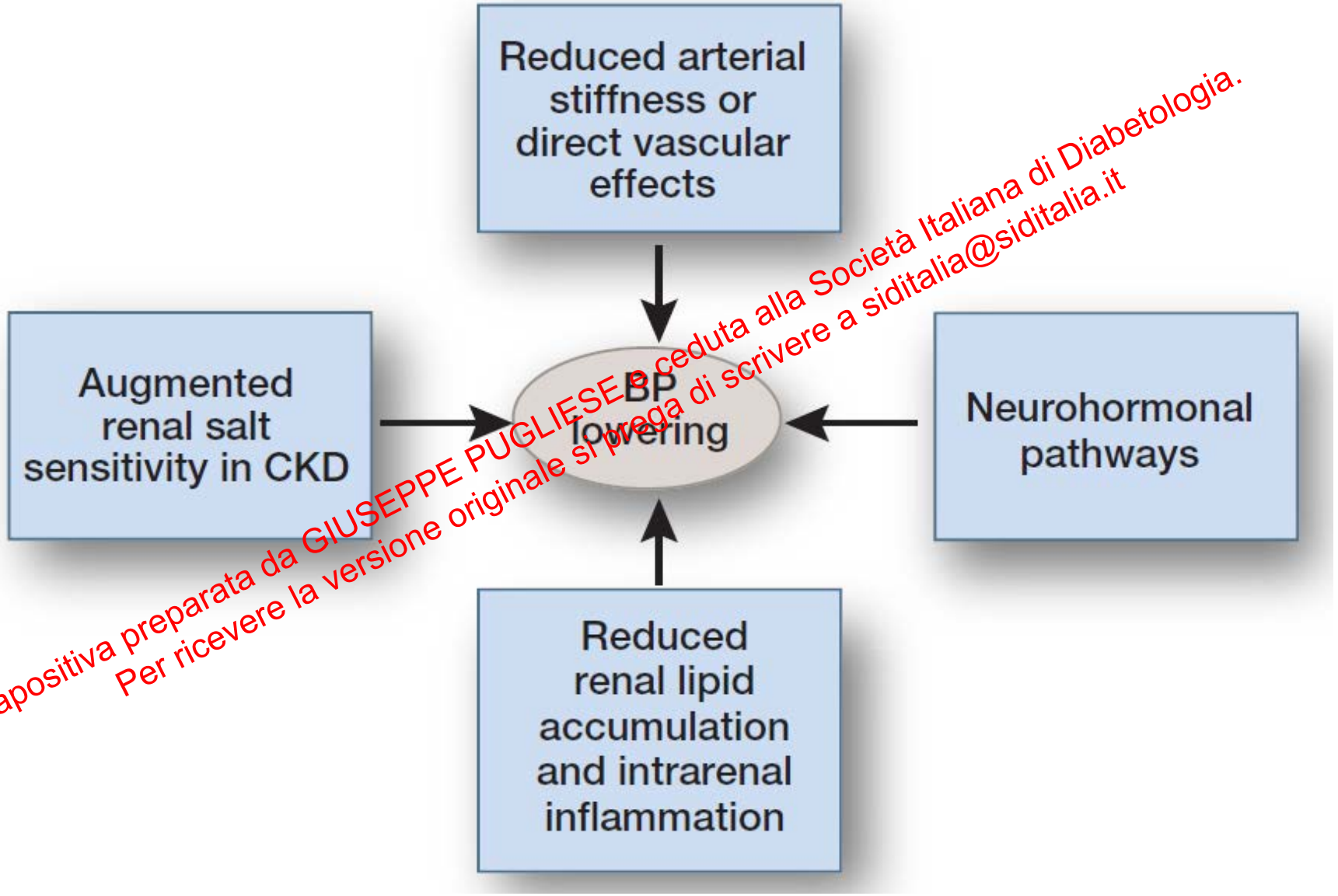
*eGFR ranges from 45–60 in the Dapagliflozin group

Canagliflozin



Cherney DZI et al. Kidney Int. 2018;93:231–244
Petrykiv S et al. Clin J Am Soc Nephrol. 2017;12:751–759
Neuen B et al. Circulation. 2018 Jun 25

Mechanisms for maintenance of BP-lowering effect in CKD patients



Chan CW & Tang SCW. Kidney Int. 2018;93:22–24

Domanda 2

Qual è secondo voi il principale evento avverso che può compromettere l'efficacia nefro-protettiva degli SGLT2 inibitori?

Opzioni di risposta

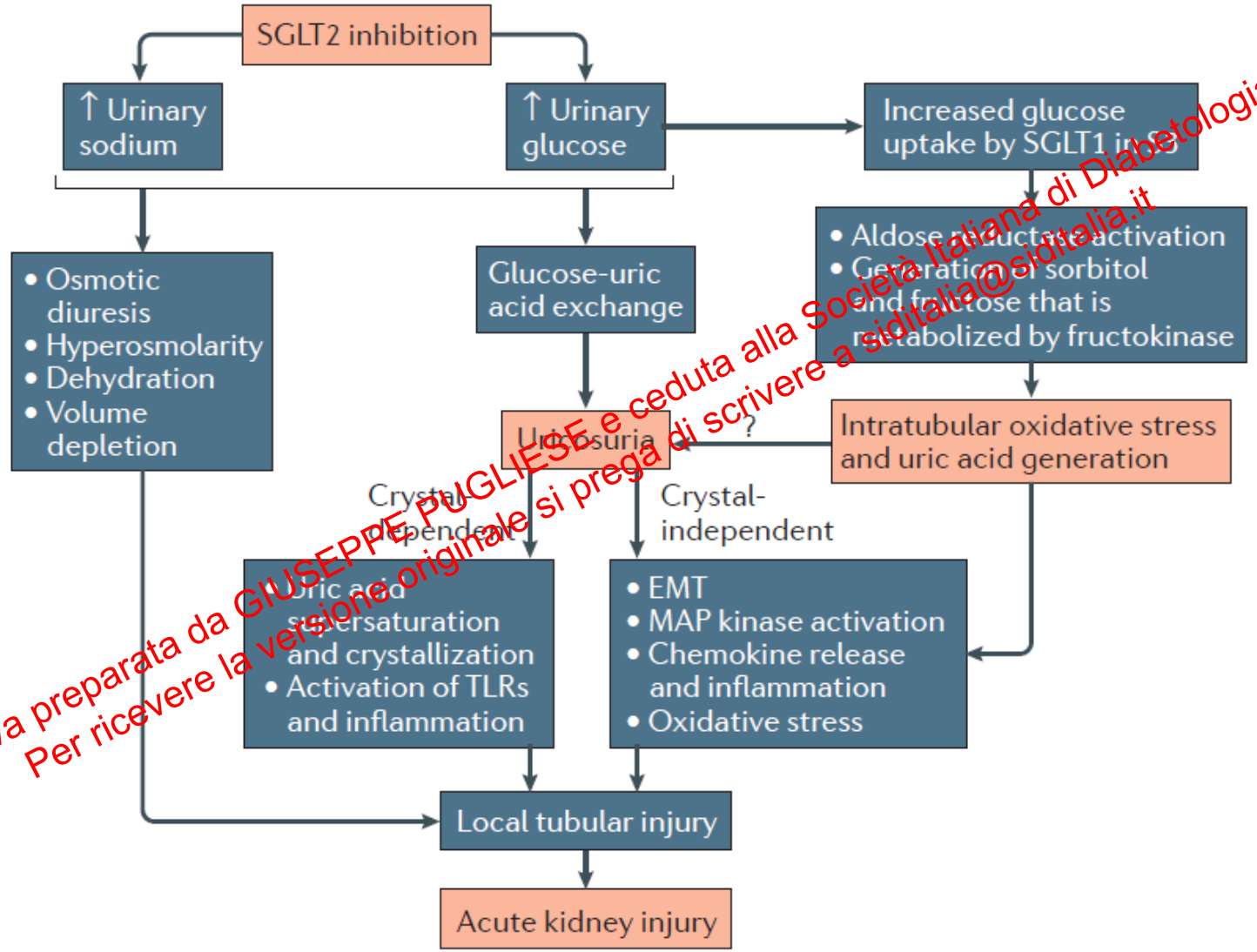
A. infezioni urinarie

B. chetoacidosi

C. acute kidney injury

D. fratture

Mechanisms for AKI under SGLT2 inhibition



Hahn K et al. Nat Rev Nephrol. 2016;12:711–712

Safety issues with SGLT2 inhibitors: empagliflozin

The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial (EMPA-REG OUTCOME) - Chronic Kidney Disease (CKD)

Event	Patients with Baseline eGFR of 59 ml per Minute per 1.73 m^2 or Less				Patients with Baseline eGFR of 60 ml per Minute per 1.73 m^2 or More			
	Placebo (N=607)		Empagliflozin (N=1212)		Placebo (N=1726)		Empagliflozin (N=3473)	
	no. (%)	*rate per 100 patient-yr*	*no. (%)*	*rate per 100 patient-yr*	*no. (%)*	*rate per 100 patient-yr*	*no. (%)*	*rate per 100 patient-yr*
Any adverse event	577 (95.1)	262.3	1107 (91.3)	183.4	1562 (90.5)	159.8	3121 (89.9)	140.1
Severe adverse event†	208 (34.3)	17.3	360 (29.7)	14.0	384 (22.2)	13.9	740 (21.3)	9.1
Serious adverse event†	321 (52.9)	31.7	552 (45.5)	24.9	667 (38.6)	19.6	1237 (35.6)	17.0
Death	40 (6.6)	2.8	68 (5.6)	2.3	79 (4.6)	1.8	108 (3.1)	1.2
Adverse event leading to discontinuation	167 (27.5)	12.6	278 (22.9)	10.4	286 (16.6)	6.9	535 (15.4)	6.2
Confirmed hypoglycemic adverse event‡								
Any	233 (38.4)	22.9	391 (32.3)	17.9	417 (24.2)	11.7	912 (26.3)	12.8
Requiring assistance	18 (3.0)	1.3	23 (1.9)	0.8	18 (1.0)	0.4	40 (1.2)	0.4
Event consistent with urinary tract infection								
Any§	132 (21.7)	10.4	278 (22.9)	11.0	291 (16.9)	7.5	564 (16.2)	6.9
Complicated¶	17 (2.8)	1.2	37 (3.1)	1.3	24 (1.4)	0.6	45 (1.3)	0.5
Event consistent with genital infection‖	10 (1.6)	0.7	64 (5.3)	2.2	32 (1.9)	0.7	237 (6.8)	2.7
Event consistent with volume depletion**	49 (8.1)	3.6	81 (6.7)	2.8	66 (3.8)	1.6	158 (4.5)	1.8
Acute renal failure††	87 (14.3)	6.5	136 (11.2)	4.9	68 (3.9)	1.6	110 (3.2)	1.2
Acute kidney injury	22 (3.6)	1.6	26 (2.1)	0.9	15 (0.9)	0.4	19 (0.5)	0.2
Diabetic ketoacidosis‡‡	1 (0.2)	0.1	2 (0.2)	0.1	0	0	2 (0.1)	<0.1
Thromboembolic event§§	7 (1.2)	0.5	13 (1.1)	0.4	13 (0.8)	0.3	17 (0.5)	0.2
Bone fracture¶¶	32 (5.3)	2.3	57 (4.7)	2.0	59 (3.4)	1.4	122 (3.5)	1.4
Hyperkalemia‖‖	42 (6.9)	3.0	47 (3.9)	1.6	36 (2.1)	0.8	46 (1.3)	0.5

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

Safety issues with SGLT2 inhibitors: canagliflozin

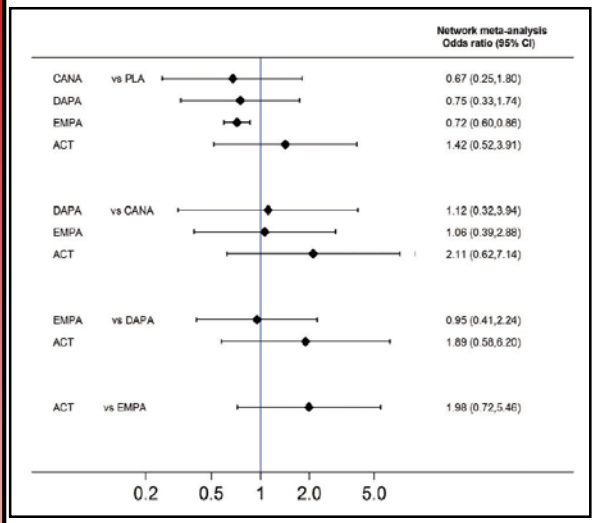
The Canagliflozin Cardiovascular Assessment Study (CANVAS) Program CANVAS and CANVAS-Renal (CANVAS-R)

Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
All serious adverse events	104.3	120.0	0.04
Adverse events leading to discontinuation	35.5	32.8	0.07
Serious and nonserious adverse events of interest recorded in the CANVAS Program			
Acute pancreatitis (adjudicated)	0.5	0.1	0.03
Cancer			
Renal cell	0.6	0.2	0.17
Bladder	1.0	1.1	0.74
Breast	3.1	2.6	0.65
Photosensitivity	1.0	0.3	0.07
Diabetic ketoacidosis (adjudicated)	0.6	0.3	0.14
Amputation	6.3	3.4	<0.001
Fracture (adjudicated)‡			
All	15.4	11.9	0.02
Low trauma	11.6	9.2	0.06
Venous thromboembolic events	1.7	1.7	0.63
Infection of male genitalia§	34.9	10.8	<0.001
Serious and nonserious adverse events of interest collected in CANVAS alone¶			
Osmotic diuresis	34.5	13.3	<0.001
Volume depletion	26.0	18.5	0.009
Hypoglycemia	50.0	46.4	0.20
Acute kidney injury	3.0	4.1	0.33
Hyperkalemia	6.9	4.4	0.10
Urinary tract infection	40.0	37.0	0.38
Mycotic genital infection in women	68.8	17.5	<0.001
Severe hypersensitivity or cutaneous reaction	8.5	6.1	0.17
Hepatic injury	7.4	9.1	0.35
Renal-related (including acute kidney injury)	19.7	17.4	0.32

Neal B et al. N Engl J Med. 2017;377:644–657

AKI with SGLT2 inhibitors

Meta-analysis of RCTs



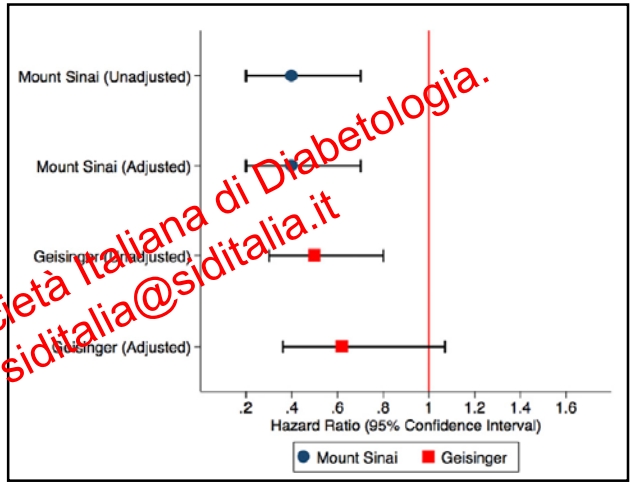
Tang H et al. Diabetes Obes Metab. 2017;19:1106–1115

Meta-analysis of RCTs

Event	N	OR (95% CI)	*P*
AKI	13510	0.80 (0.67–0.96)	0.014

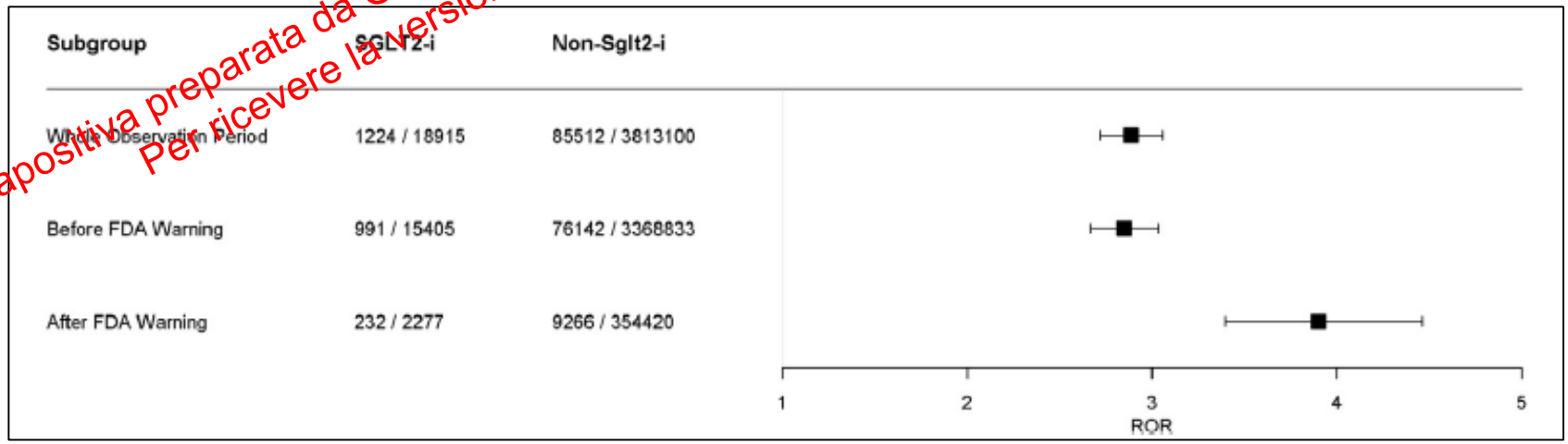
Zhang XL et al. J Am Heart Assoc. 2018;7:e007165

Mount Sinai CKD registry and Geisinger Health System cohort



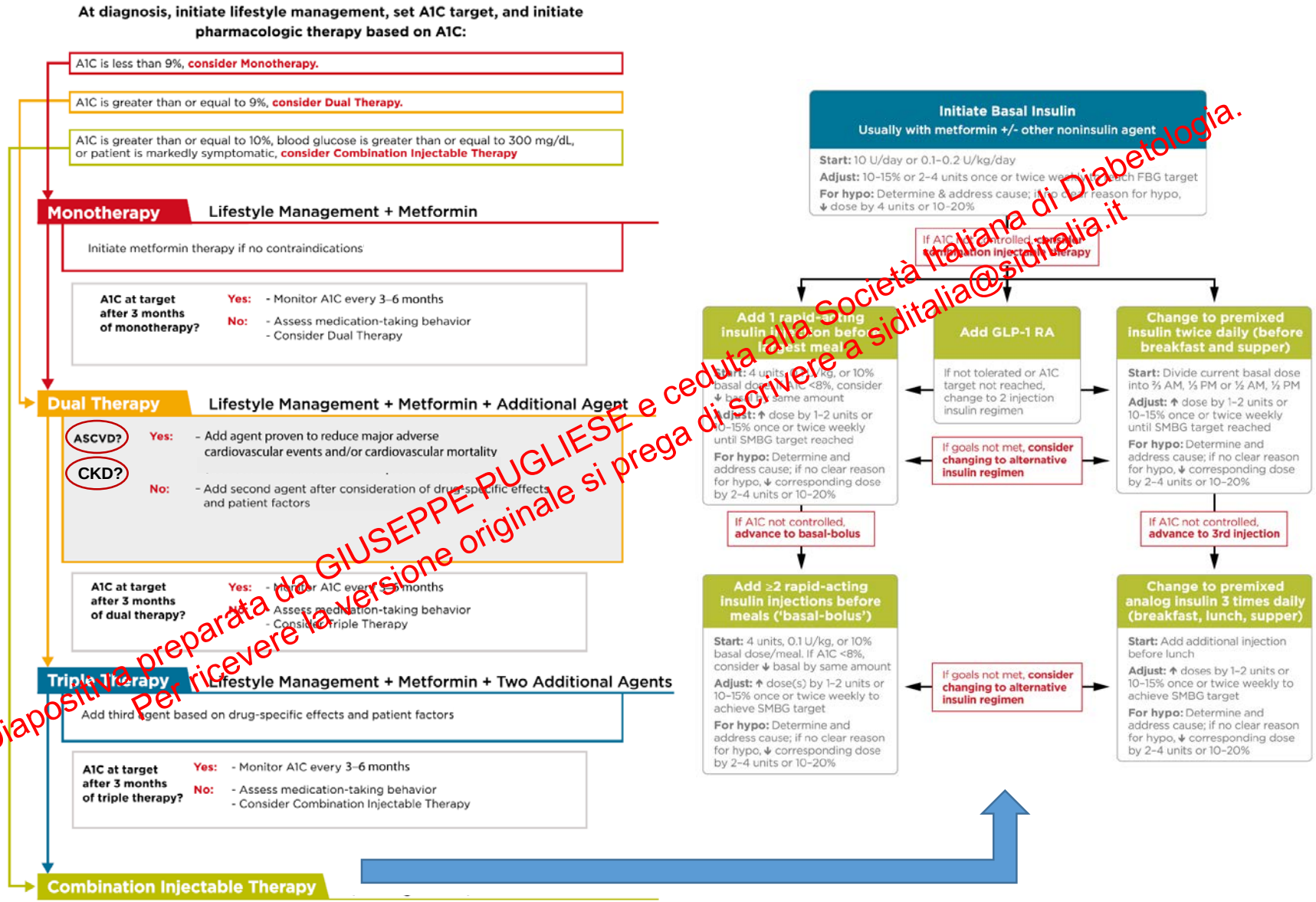
Nadkarni GN et al. Diabetes Care. 2017;40:1479–1485

FDA adverse event report system database



Perlman A et al. Nutr Metab Cardiovasc Dis. 2017;27:1108–1113

Therapeutic algorithm for type 2 diabetes



ADA. Standard of Medical Care in Diabetes, 2018

Domanda 3

Quali studi ulteriori sono secondo voi necessari per legittimare l'uso degli SGLT2 inibitori per la nefroprotezione nel paziente diabetico?

Opzioni di risposta

A. studi di confronto con farmaci ad azione nefroprotettiva

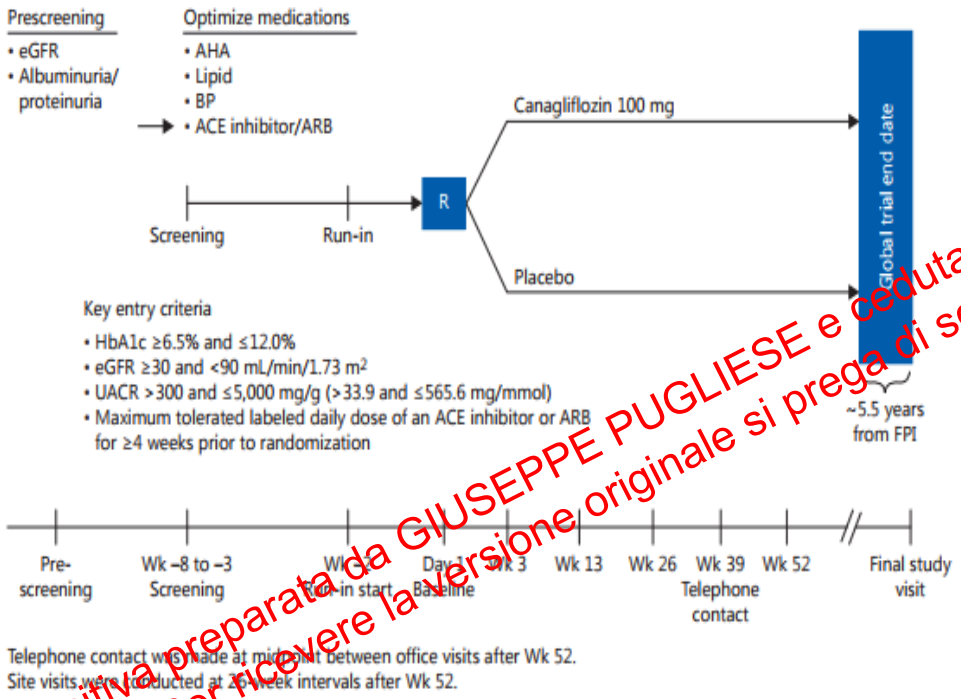
B. studi di efficacia in cui l'outcome renale sia l'endpoint primario

C. studi di sicurezza in pazienti con ridotta funzione renale

D. studi di efficacia in prevenzione primaria

Ongoing trials with primary renal endpoints

The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) Study



Anticipated targets:

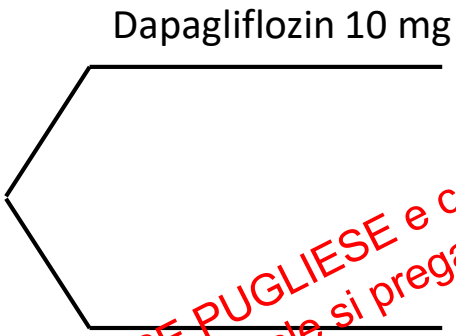
- 4,401 randomized
- Event-driven
- Duration 5.5 years

- Primary endpoint: composite of ESRD, doubling of serum creatinine, and renal or CV death.
- Secondary endpoints:
  - Renal composite of ESRD, doubling of serum creatinine, and renal death;
  - HF composite of CV death and hospitalization for congestive heart failure;
  - CV composite of CV death, nonfatal acute myocardial infarction or stroke hospitalization for congestive heart failure or unstable angina;
  - CV death;
  - All-cause death.

Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT02065791

Ongoing trials with primary renal endpoints

A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (Dapa-CKD)



Population:

- Diabetic and non-diabetic pts.
- CKD stage 2-4
- UACR ≥200 mg/g

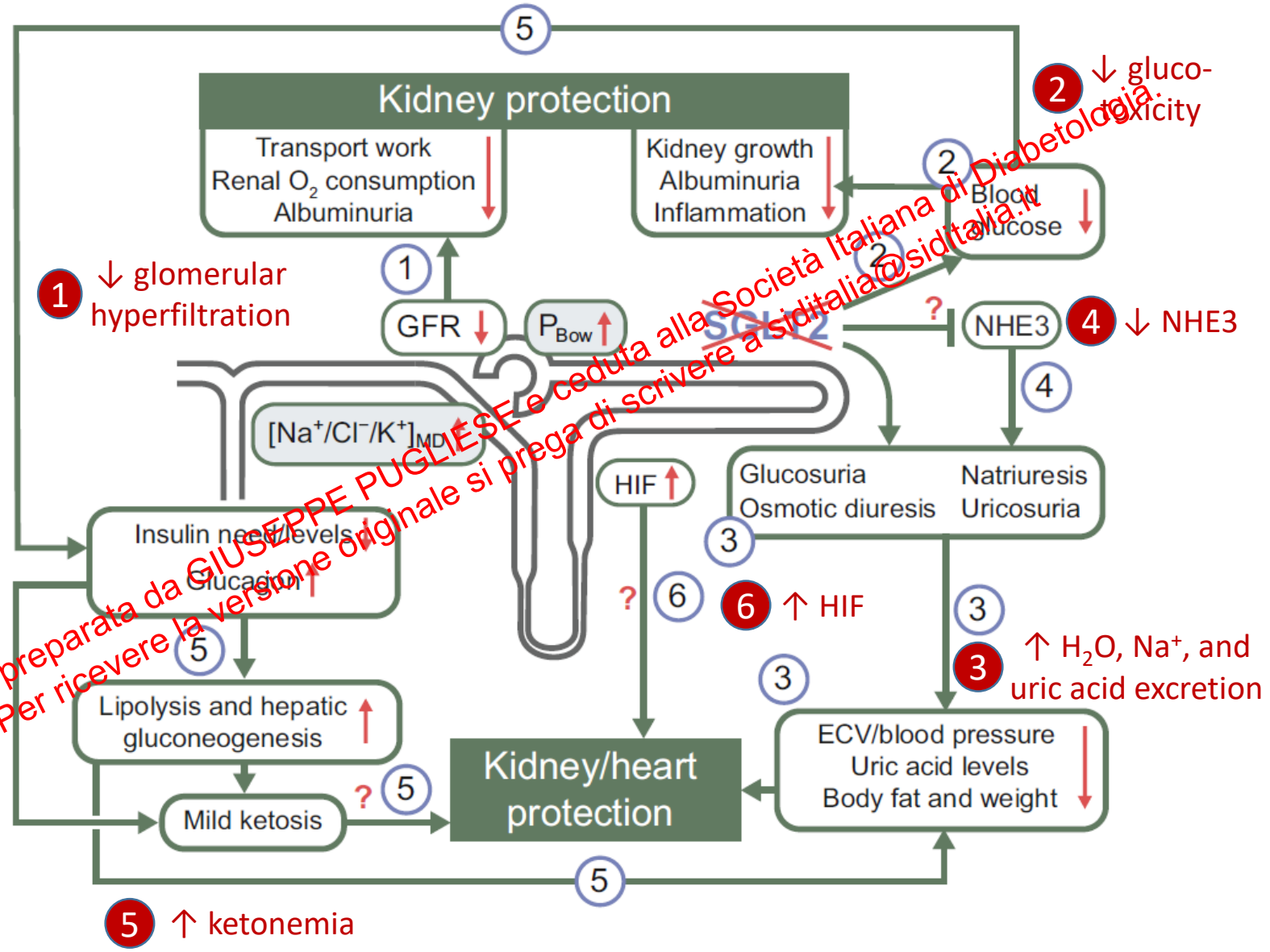
- Primary endpoint: composite of ESRD, 50% eGFR decline, and renal or CV death
- Secondary endpoints:
  - Renal composite of ESRD, 50% eGFR decline, and renal death;
  - HF composite of CV death and hospitalization for congestive heart failure;
  - All-cause death.

Anticipated targets:

- 4,000 randomized
- Event-driven
- Duration 45 months

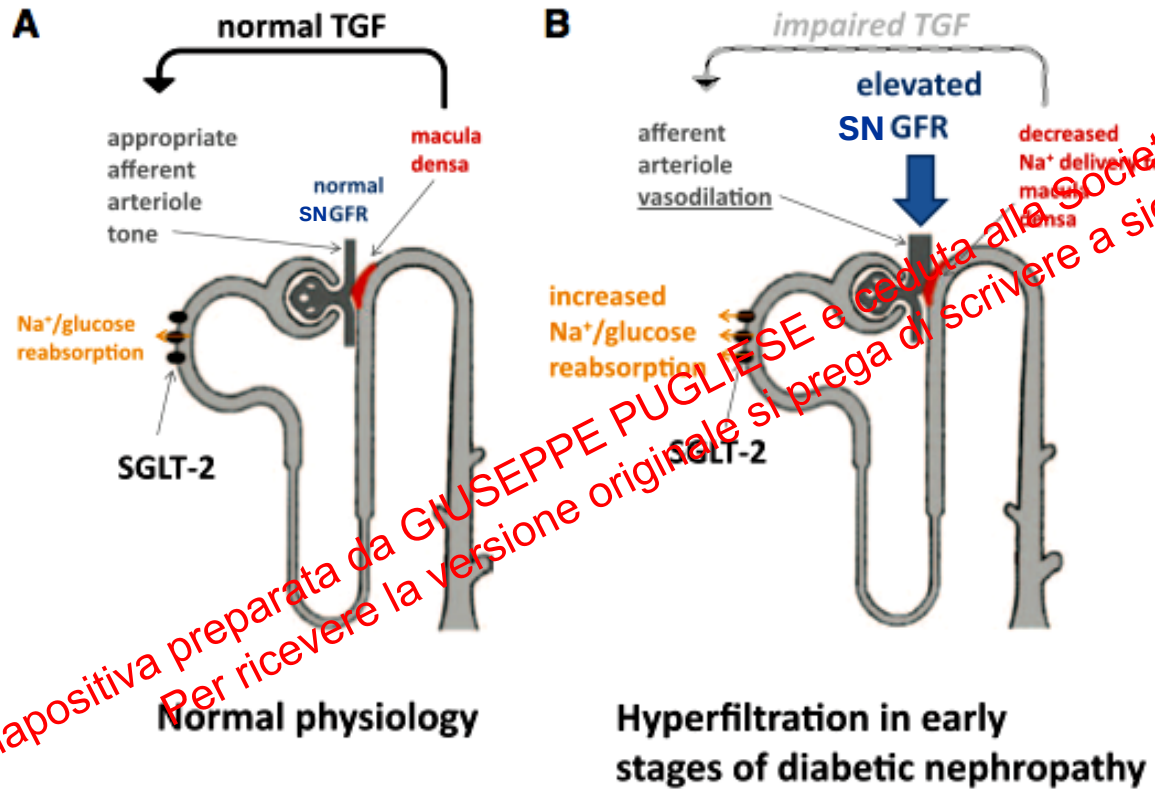
Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT03036150

Mechanisms of renal protection with SGLT2 inhibitors



Vallon V & Thomson SC. Diabetologia. 2017;60:215–225

Glomerular hyperfiltration in diabetes



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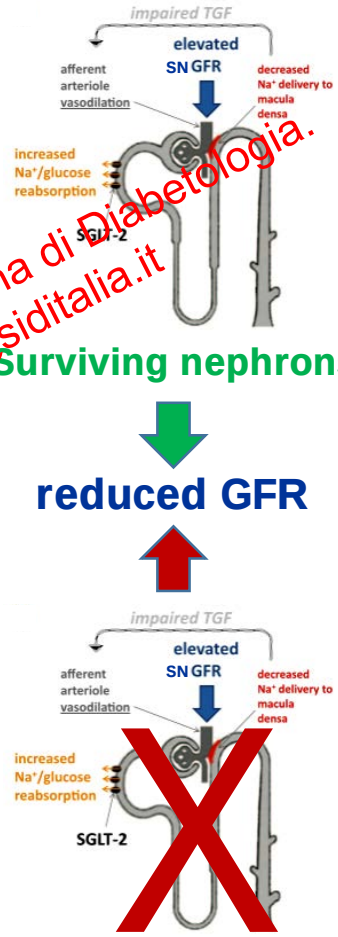
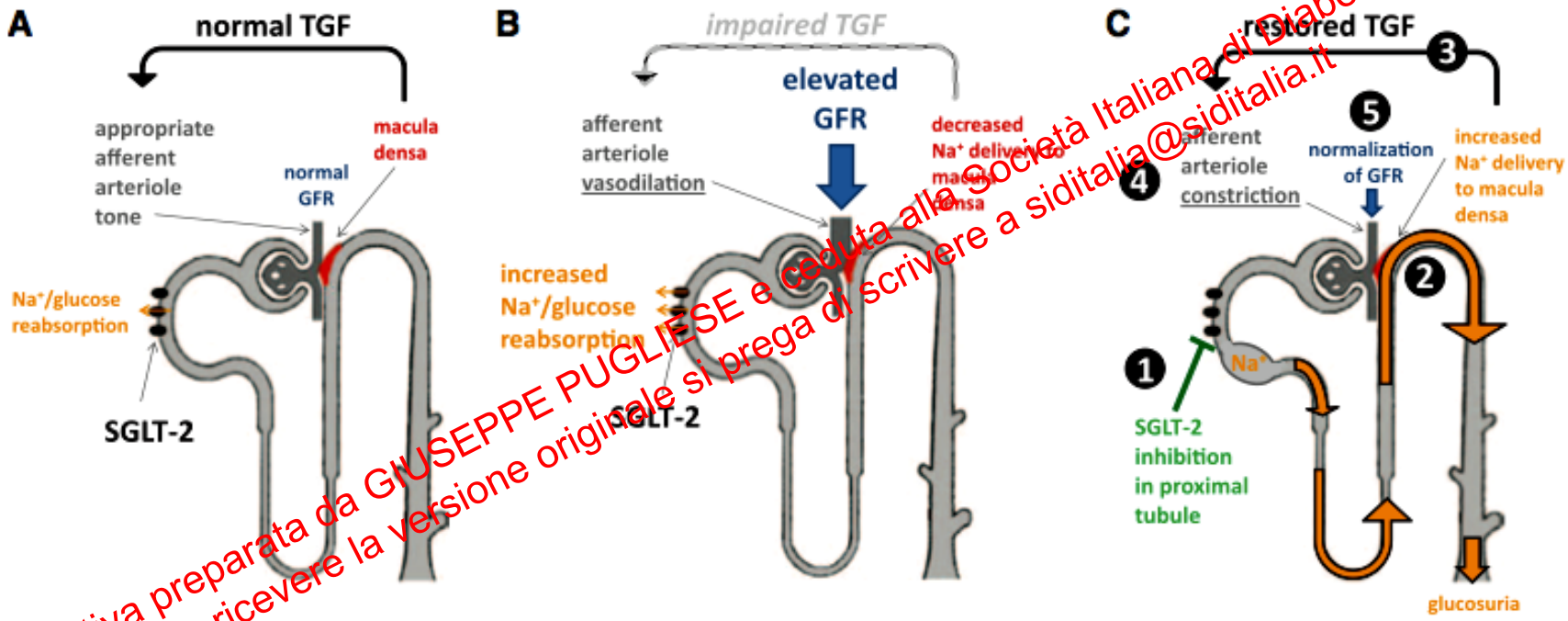


Hyperfiltration in residual nephrons in late stages of diabetic nephropathy

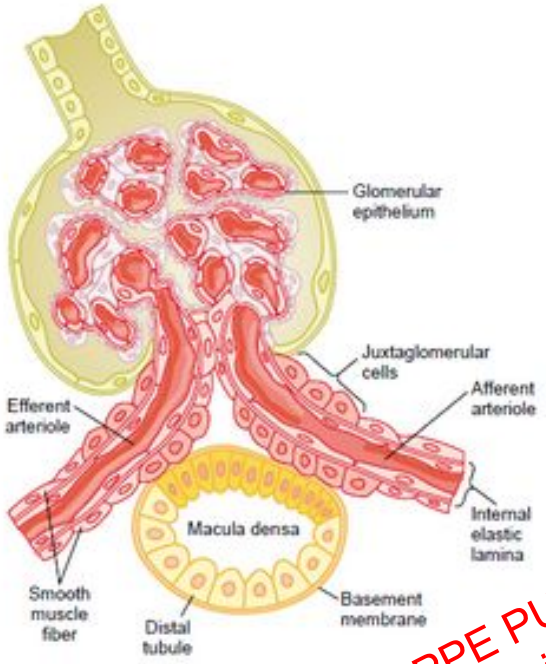
Cherney D et al. Circulation. 2014;129:587–597

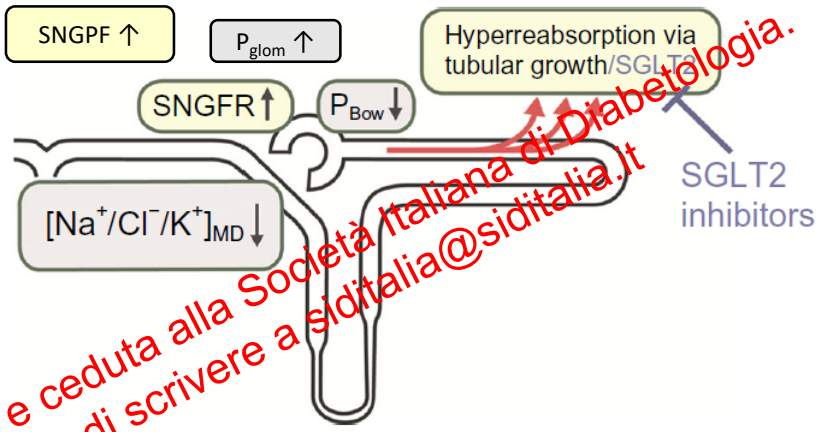
Reduction of glomerular hyperfiltration with SGLT2 inhibitors



Cherney D et al. Circulation. 2014;129:587–597

Reduction of glomerular hyperfiltration with SGLT2 inhibitors



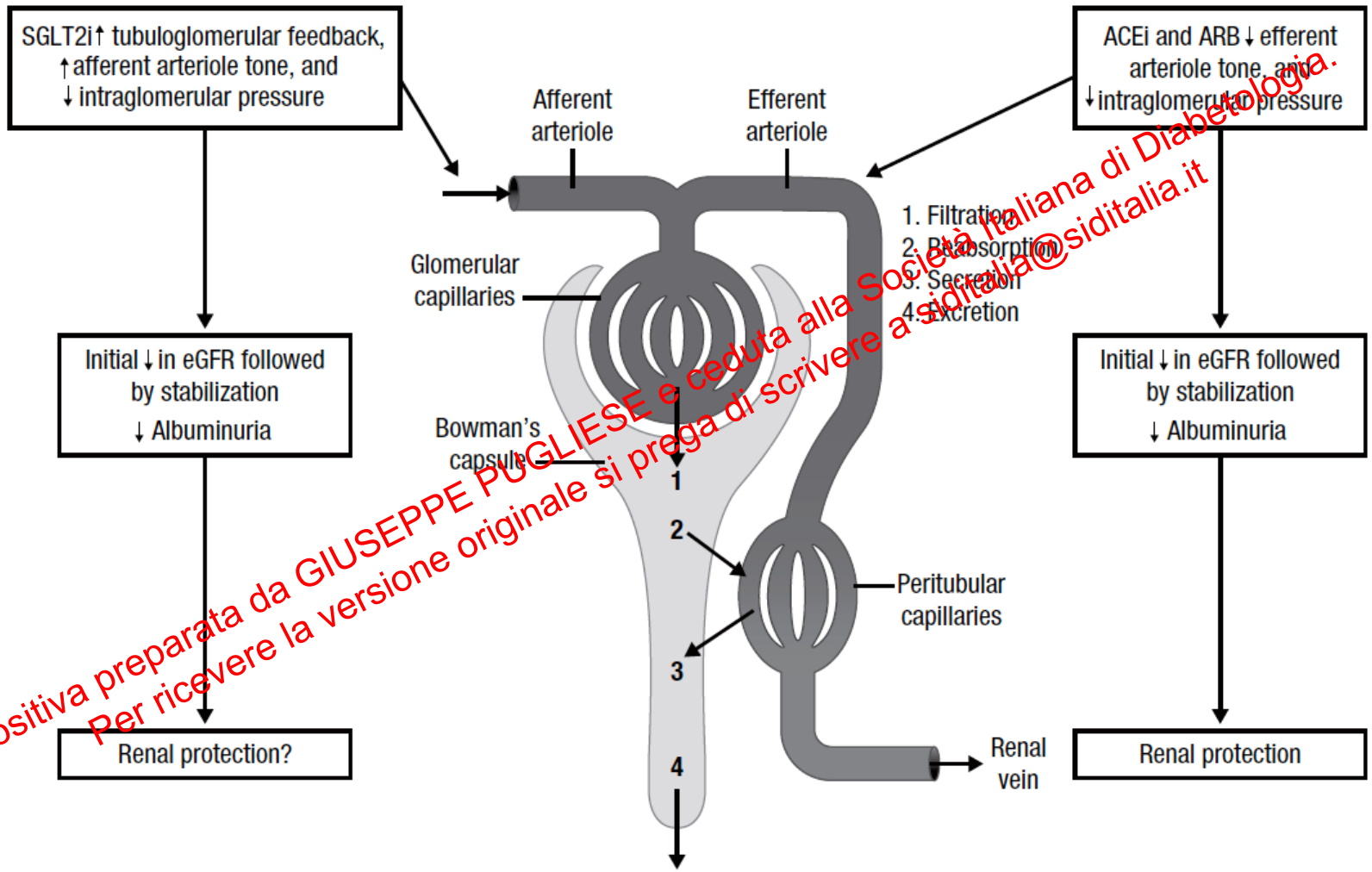


Vallon V & Thomson SC. Diabetologia. 2017;60:215–225

	Placebo (n = 25)	Dapagliflozin 10 mg (n = 24)	Hydrochlorothiazide 25 mg (n = 26)
Extracellular volume related parameters			
NT-ProBNP, ng/l			
Baseline, median (25th–75th percentile)	33.0 (20–42)	22.0 (12–52)	20.0 (13–45)
Change at week 12, median (IQR)	3.0 (30.0)	19.0 (32.0)	−3.0 (21.0)
Plasma renin activity, × 10^{-2} pmol/l/h			
Baseline, median (25th–75th percentile)	2.84 (0.71–17.8)	2.13 (1.19–4.03)	2.37 (1.42–9.48)
Change at week 12, median (IQR)	−0.23 (8.53)	0.71 (12.1)	3.08 (9.01)
Serum aldosterone, pmol/l			
Baseline, median (25th–75th percentile)	277.4 (221.9–360.6)	374.5 (249.7–499.3)	332.9 (249.7–457.7)
Change at week 12, median (IQR)	−55.5 (221.9)	55.5 (152.6)	55.5 (166.4)

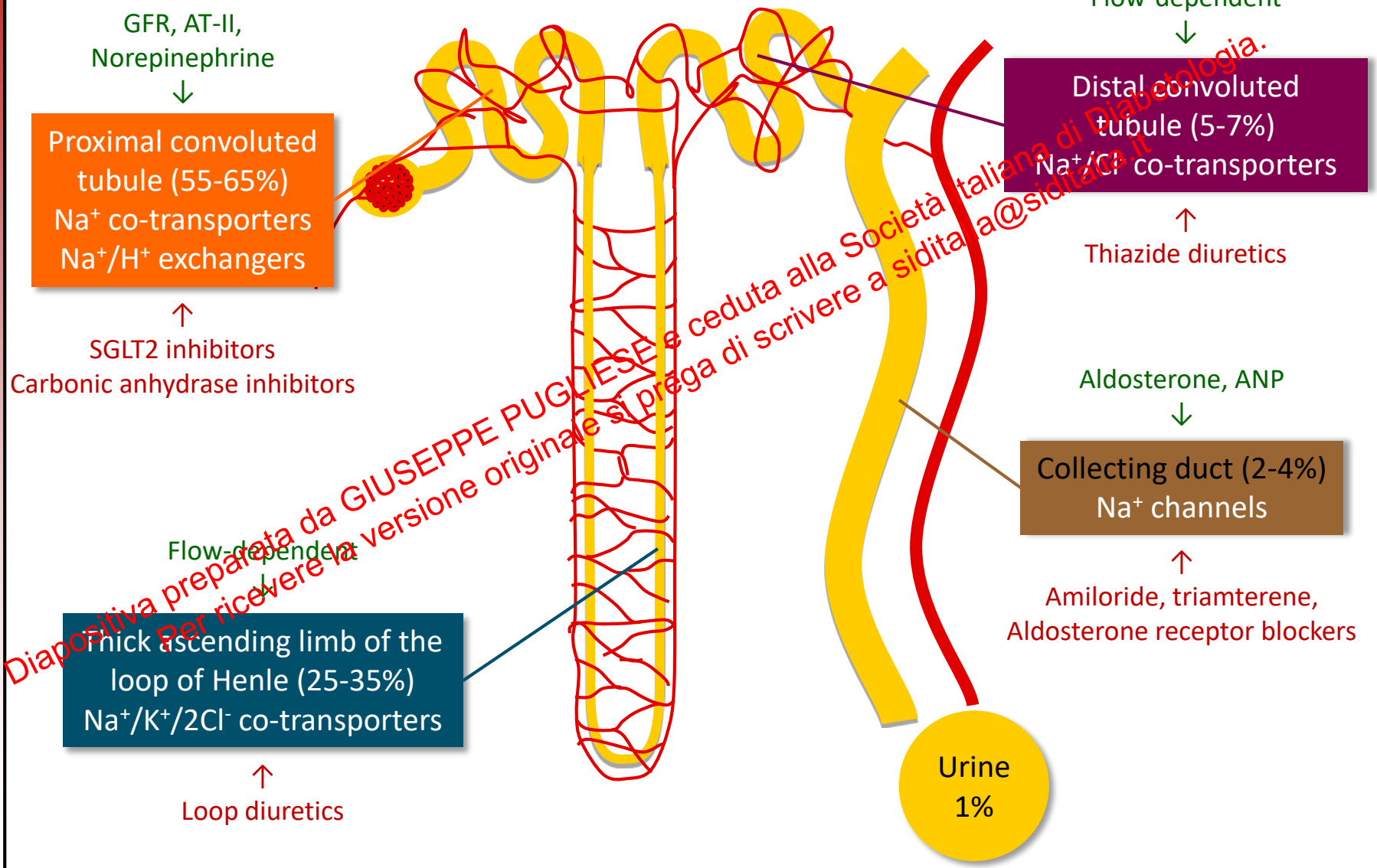
Heerspink IJL et al. Diabetes Obes Metab. 2013;15:853–862

Complementary actions of SGLT2 inhibitors and RAS blockers

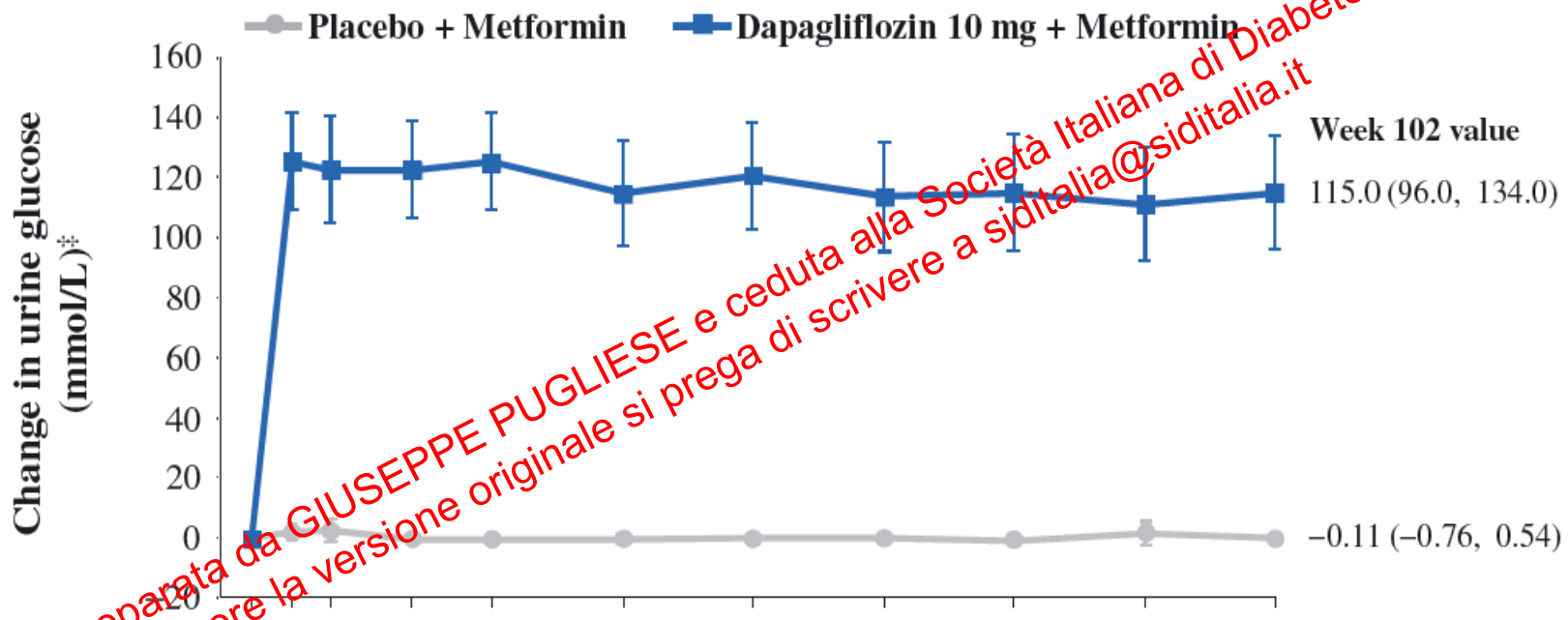


Perkovic V et al. Curr Med Res Opin. 2015;12:2219–2231

Na^+ reabsorption in the kidney



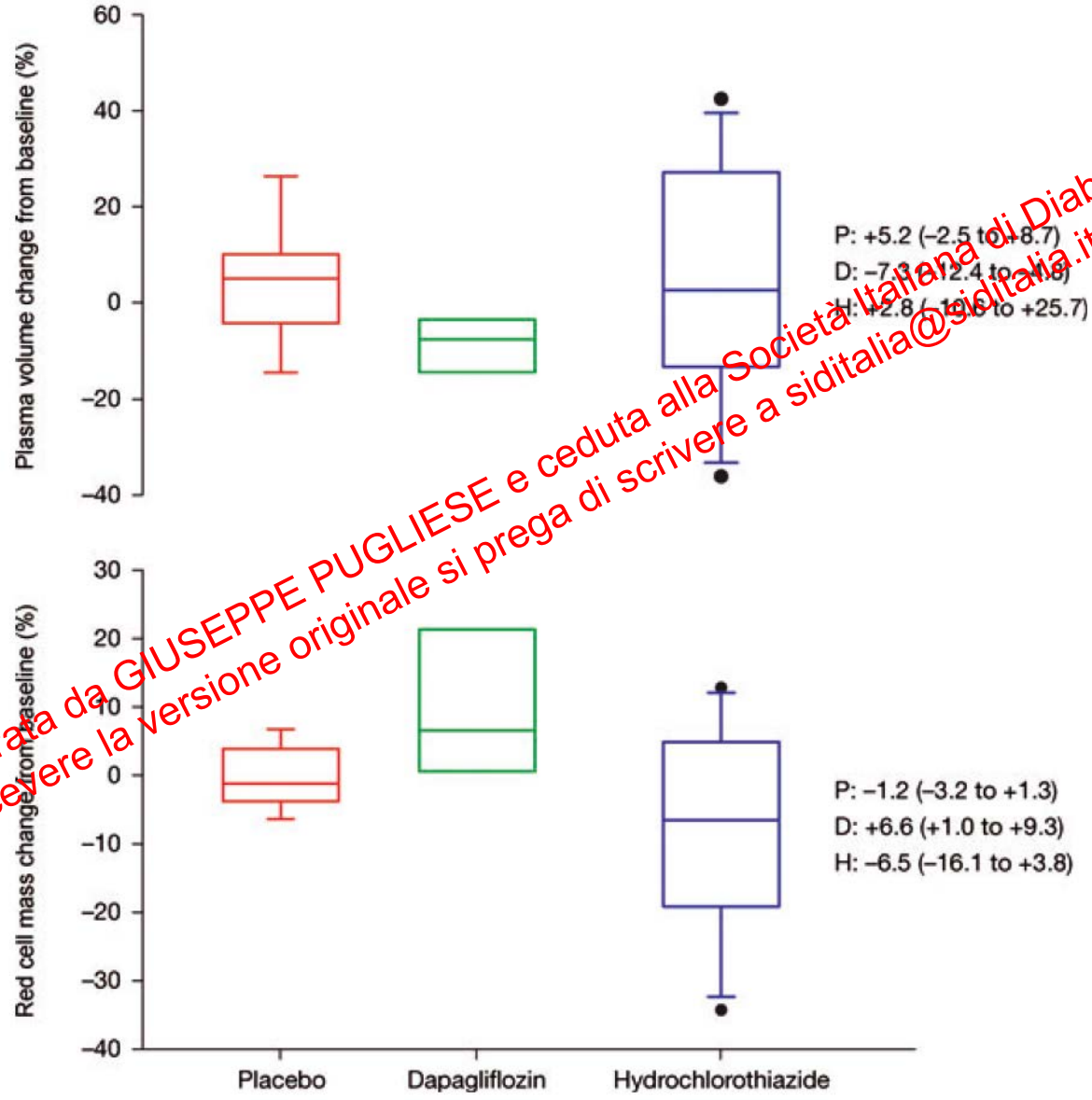
Sustained increase in urinary glucose excretion with SGLT2 inhibitors



Sample size per time point											Baseline value
PBO + MET	91	89	89	86	83	86	83	81	78	71	70	1.25 mmol/L
DAPA 10 mg + MET	91	87	85	83	83	83	81	77	72	69	67	1.72 mmol/L

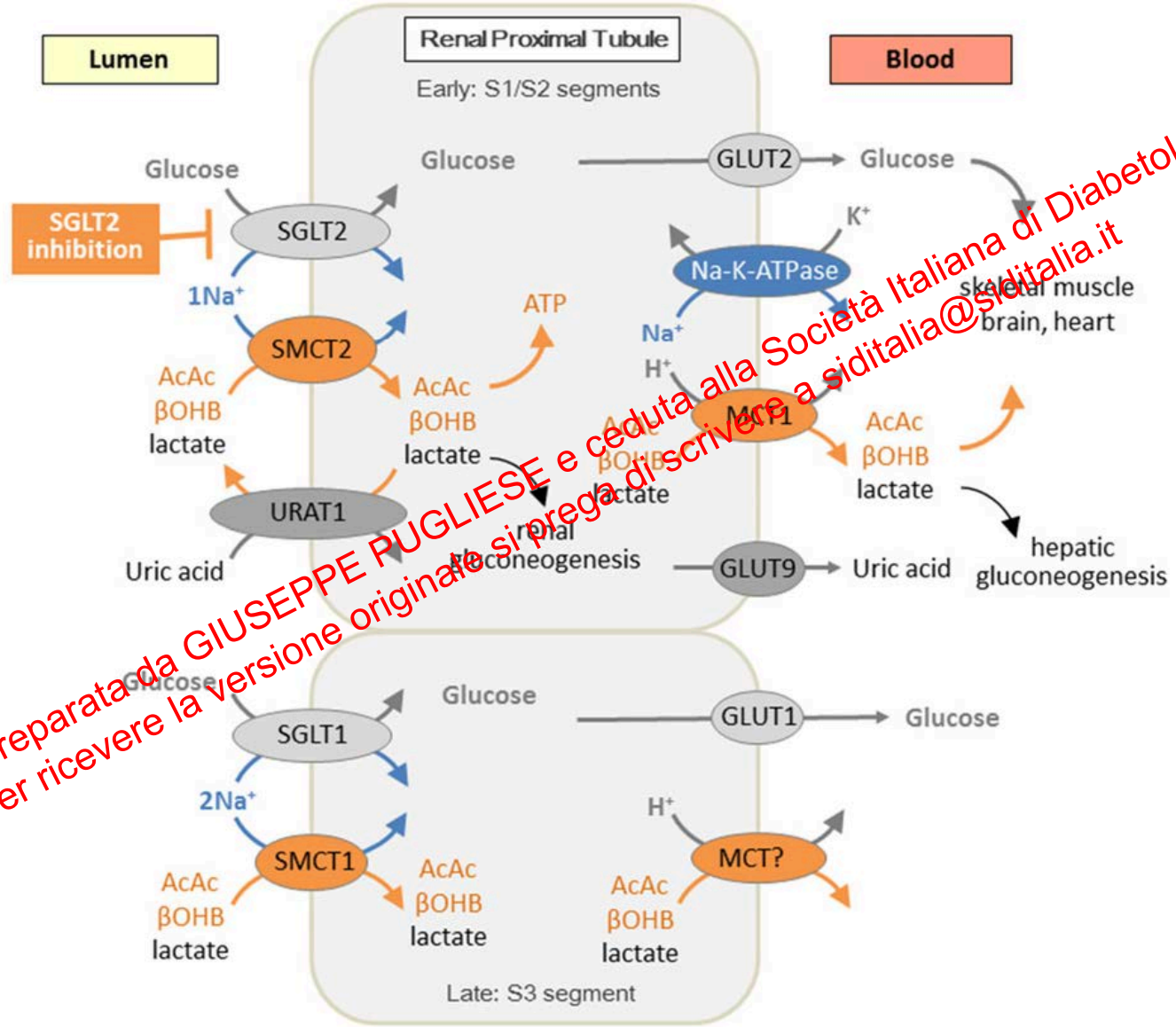
Bolinder J et al. Diabetes Obes Metab. 2014;16:159–169

Sustained reduction in plasma volume with SGLT2 inhibitors



Heerspink IJL et al. Diabetes Obes Metab. 2013;15:853–862

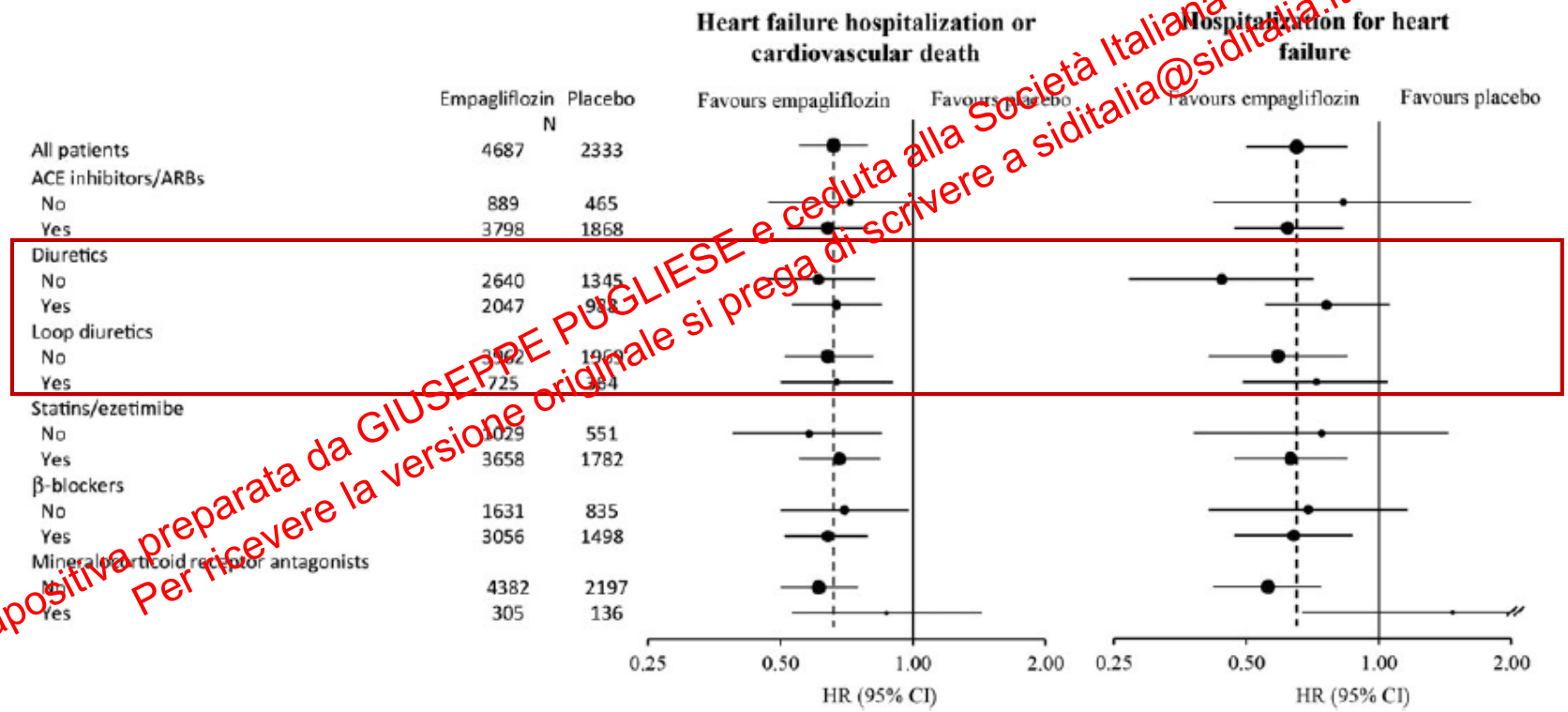
Increased urate excretion with SGLT2 inhibitors



Qiu H et al. Diabetes Metab Res Rev. 2017;33:e2886

Loop diuretic sparing effect of SGLT2 inhibitors

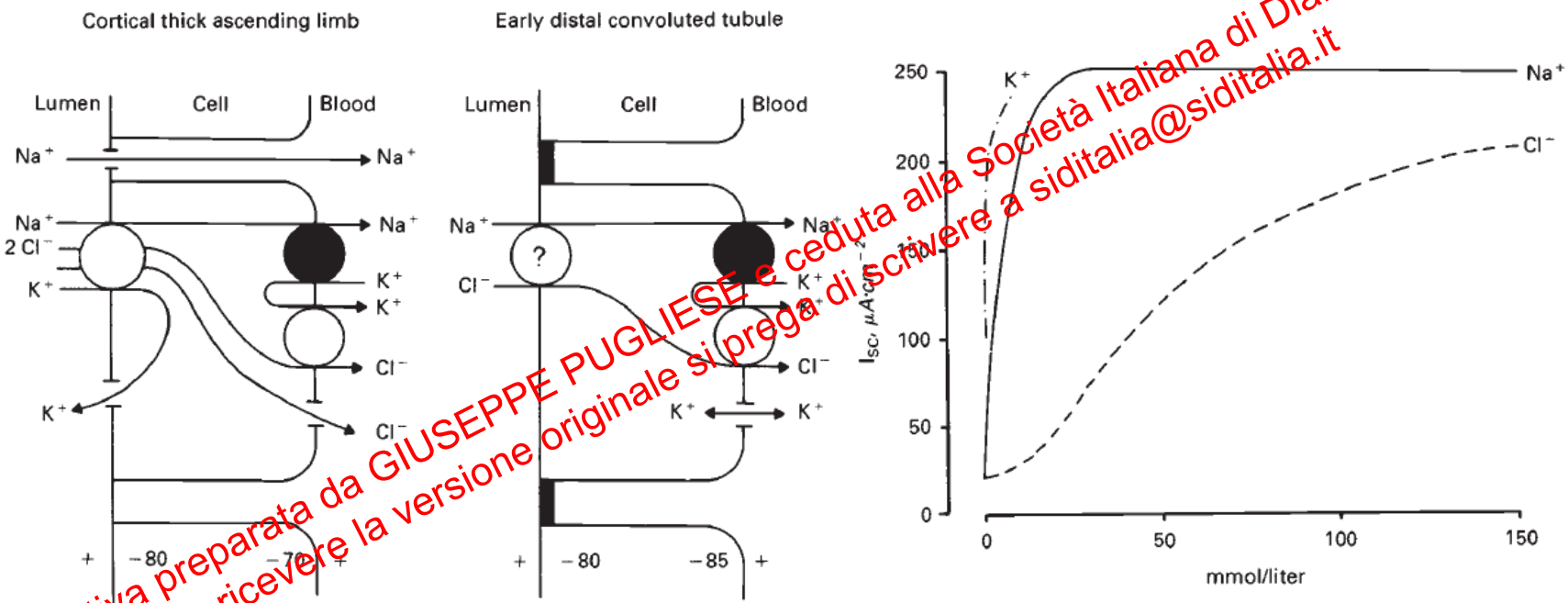
The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial (EMPA-REG OUTCOME)



Fitchett D et al. Eur Heart J. 2016;37:1526–1534

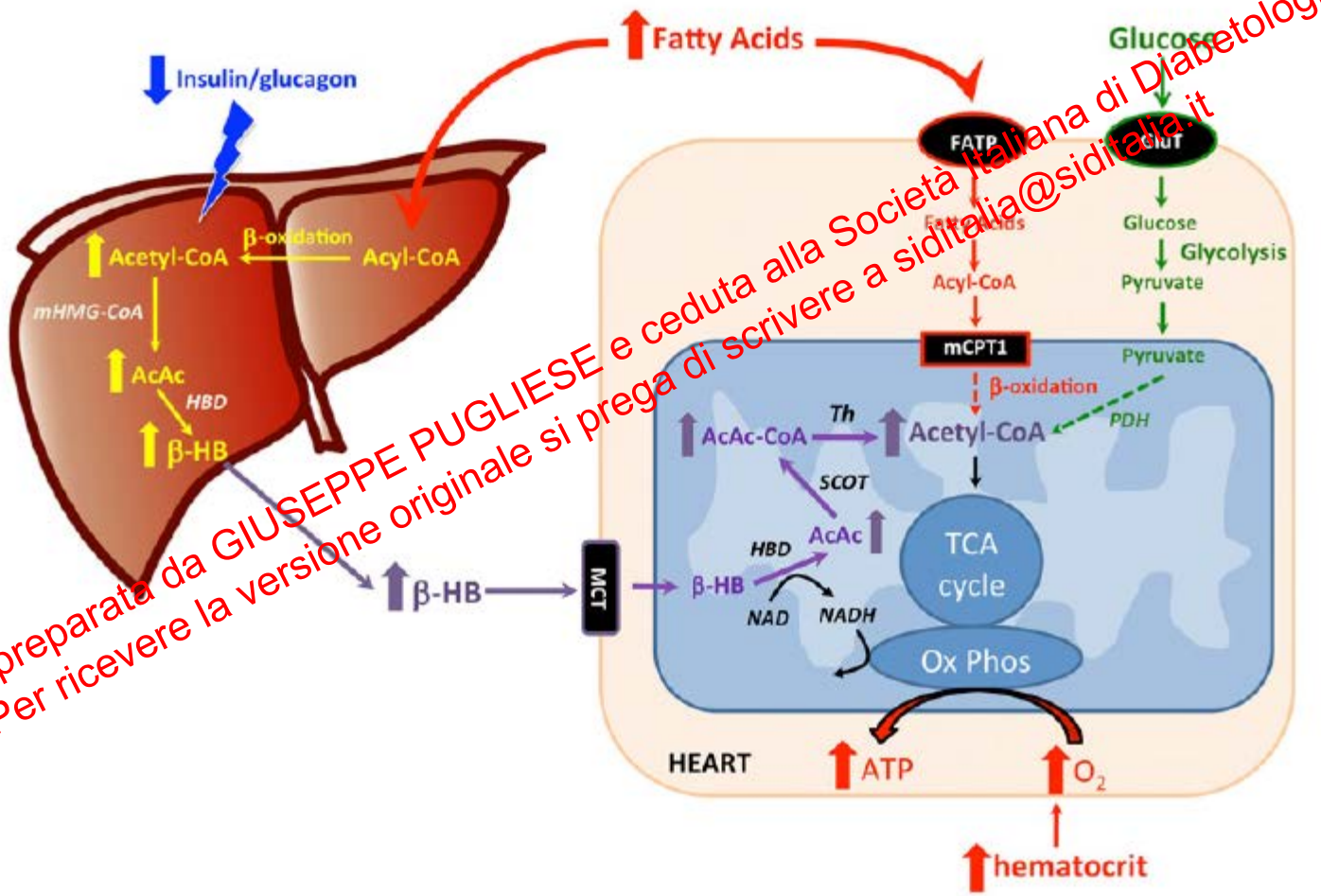
Reduced chloride concentration and NKCC inhibition

NKCC = Na-K-2Cl co-transporter



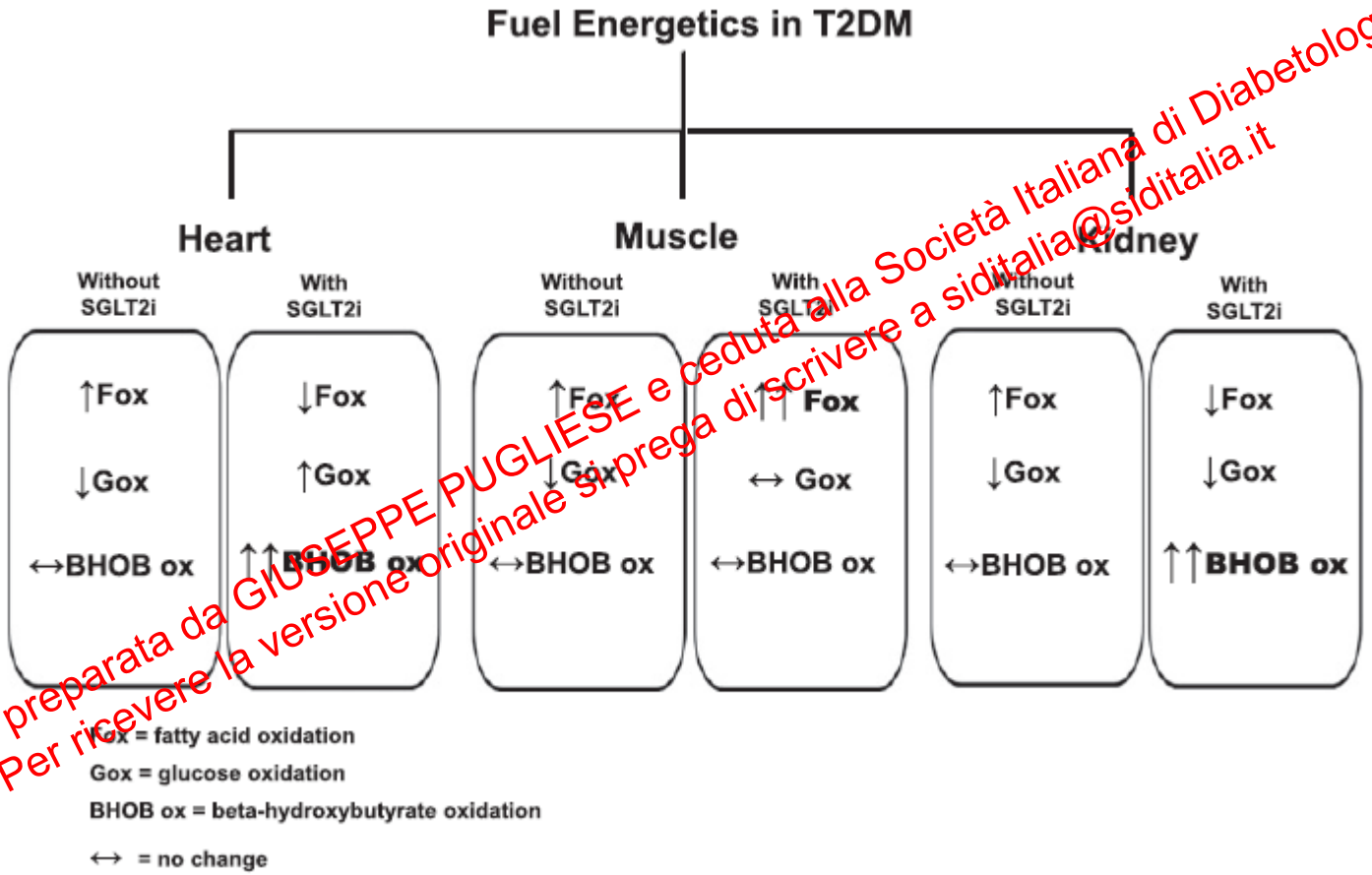
Greger R et al. Kidney Int. 1987;31:590–596

The thrifty substrate



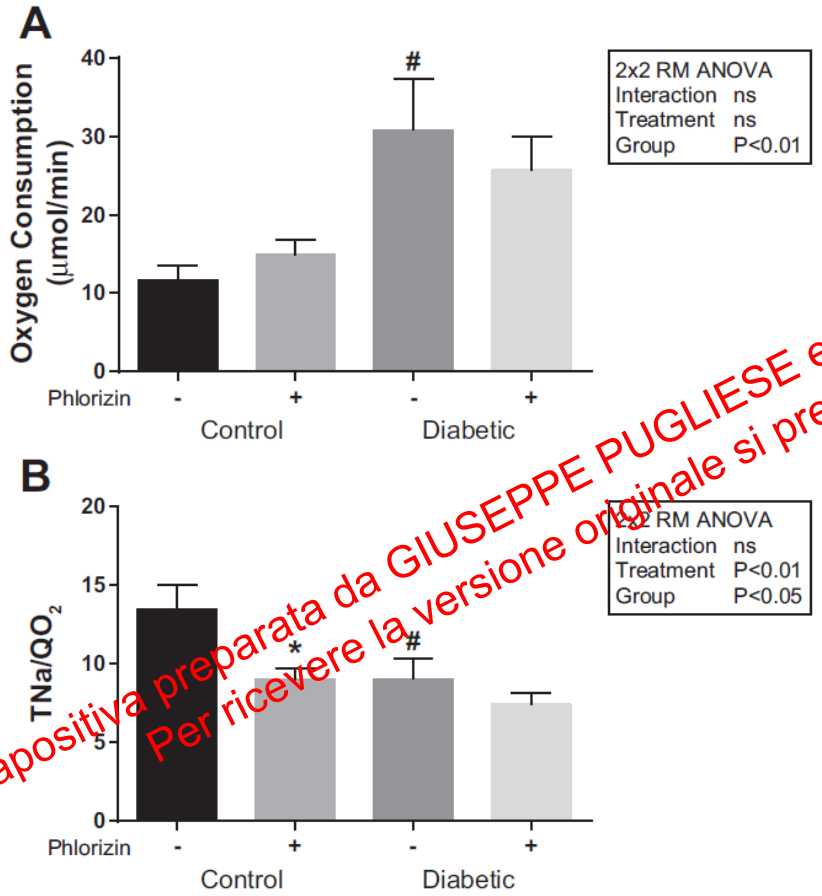
Ferrannini E et al. Diabetes Care. 2016; 39:1108–1114

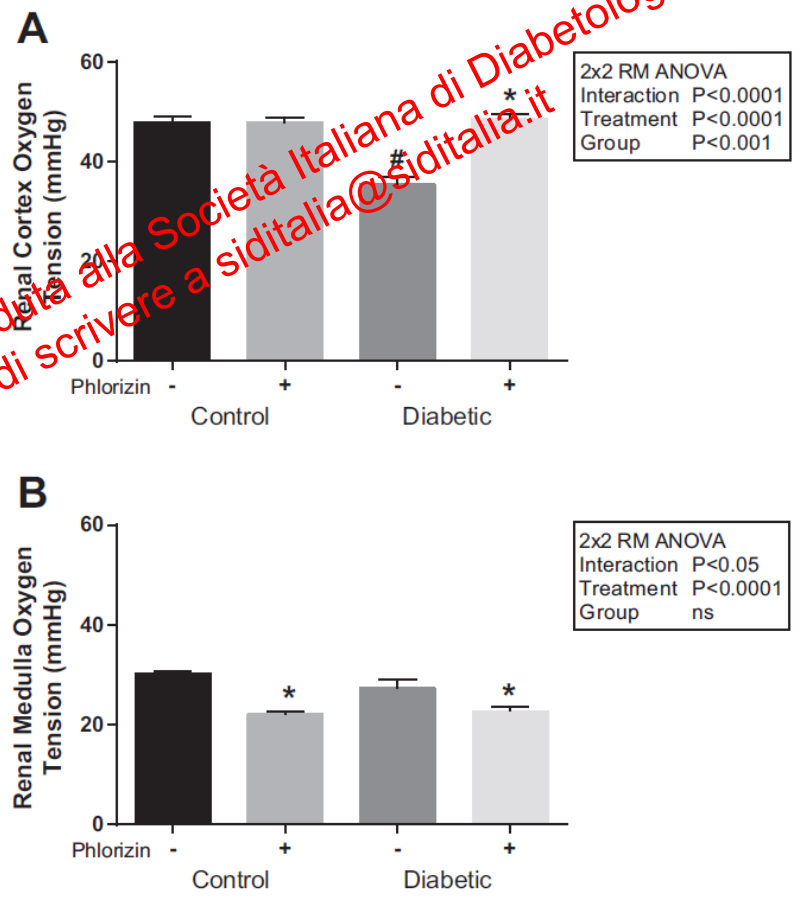
Shift in fuel energetics with SGLT2 inhibitors



Mudaliar S et al. Diabetes Care. 2016; 39:1115–1122

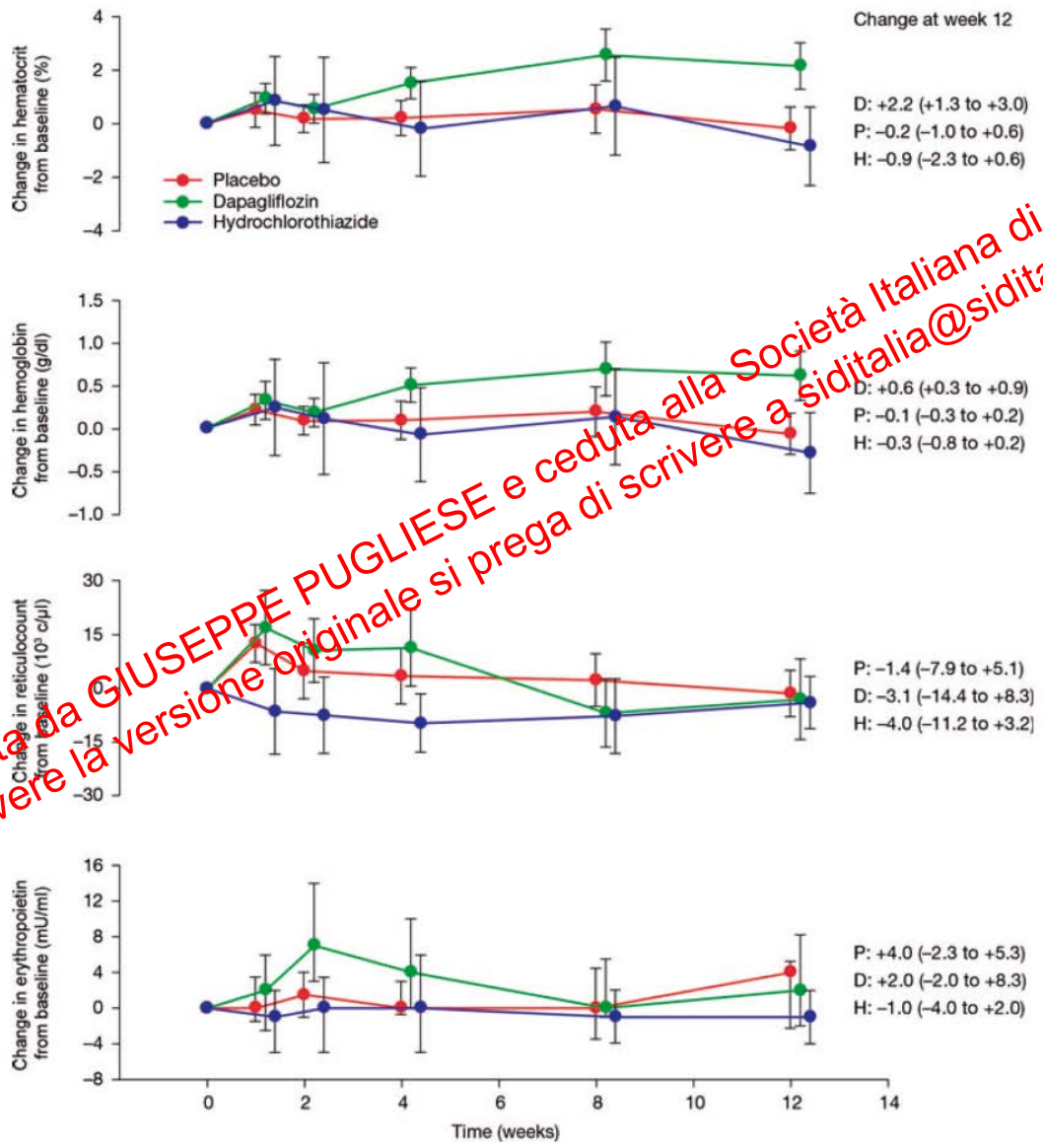
Hypoxia-dependent effects of SGLT2 inhibitors





O'Neill J et al. Am J Physiol Renal Physiol. 2015;309:F227–F234

Increased hematocrit with SGLT2 inhibitors



Heerspink IJL et al. Diabetes Obes Metab. 2013;15:853–862

Conclusions

- ✓ There is an unmet need for effective measures for nephroprotection in diabetic patients.
- ✓ Trials with SGLT2 inhibitors have shown promising effects of these agents on renal outcomes, including decrease of both albuminuria and eGFR decline.
- ✓ Treatment with SGLT2 inhibitors in CKD patients is less effective in reducing blood glucose, but not blood pressure levels and appears equally effective in improving cardiovascular and renal outcomes.
- ✓ Safety concerns with respect to nephroprotection include increased risk of AKI, which is mainly related to volume depletion and may be prevented by appropriate management of diuretic therapy.
- ✓ Further studies, including the ongoing trials with primary renal endpoints, are required for recommending SGLT2 inhibitors as nephroprotective agents in diabetic (and non-diabetic) individuals.
- ✓ Multiple mechanisms seems to be involved in nephroprotection with SGLT2 inhibitors, including reduced glomerular hyperfiltration and glucose-toxicity, volume depletion, urate excretion, shift in fuel energetics, and hypoxia-dependent effects.