



IL CROSS-TALK *cuore-rene* FISIOPATOLOGIA ED
ASPETTI CLINICI

MILANO 15 OTTOBRE 2019



**Effetti nefroprotettivi degli SGLT2 inibitori:
meccanismi ed evidenze cliniche**

Gian Paolo Fadini

Università di Padova

Diapositiva preparata da GIAN PAOLO FADINI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

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

- Abbott
- AstraZeneca
- Boehringer
- Lilly
- MSD
- Mundipharma
- Novartis
- Novonordisk
- Sanofi

Diapositiva preparata da GIAN PAOLO FADINI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Effetti nefroprotettivi degli SGLT2 inibitori:

Evidenze cliniche

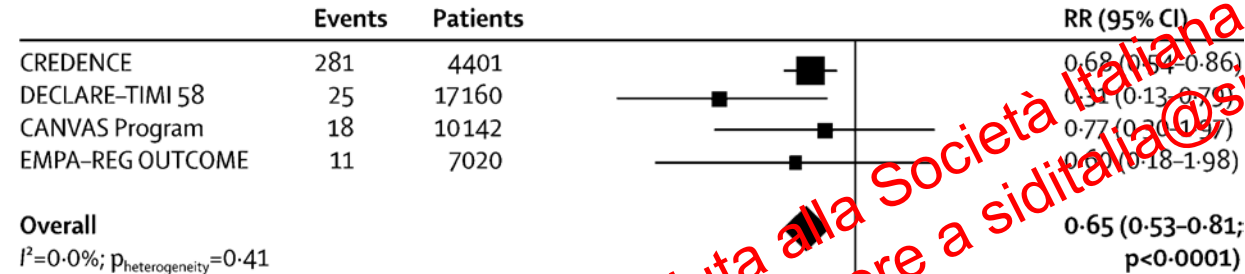
Diapositiva preparata da GIAN PAOLO FADINI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

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

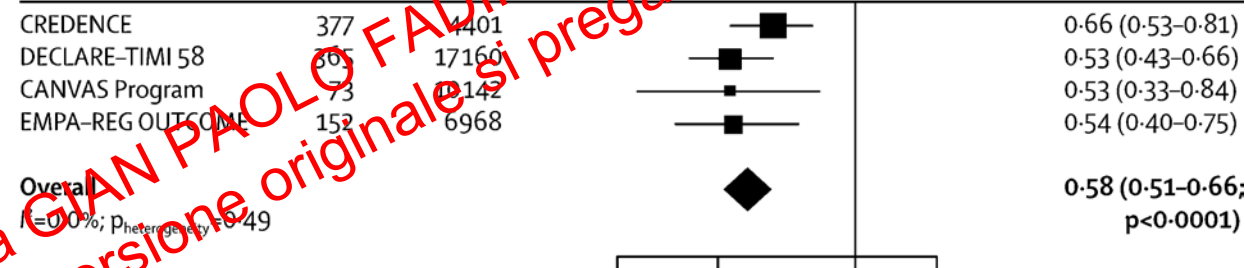
Lancet Diabetes Endocrinol 2019

Brendon L Neuen, Tamara Young, Hidde J L Heerspink, Bruce Neal, Vlado Perkovic, Laurent Billot, Kenneth W Mahaffey, David M Charytan, David C Wheeler, Clare Arnott, Severine Bompont, Adeera Levin, Meg J Jardine

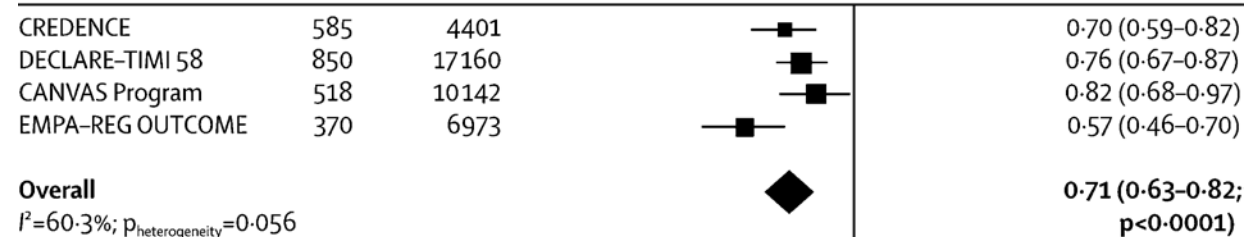
A ESKD



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

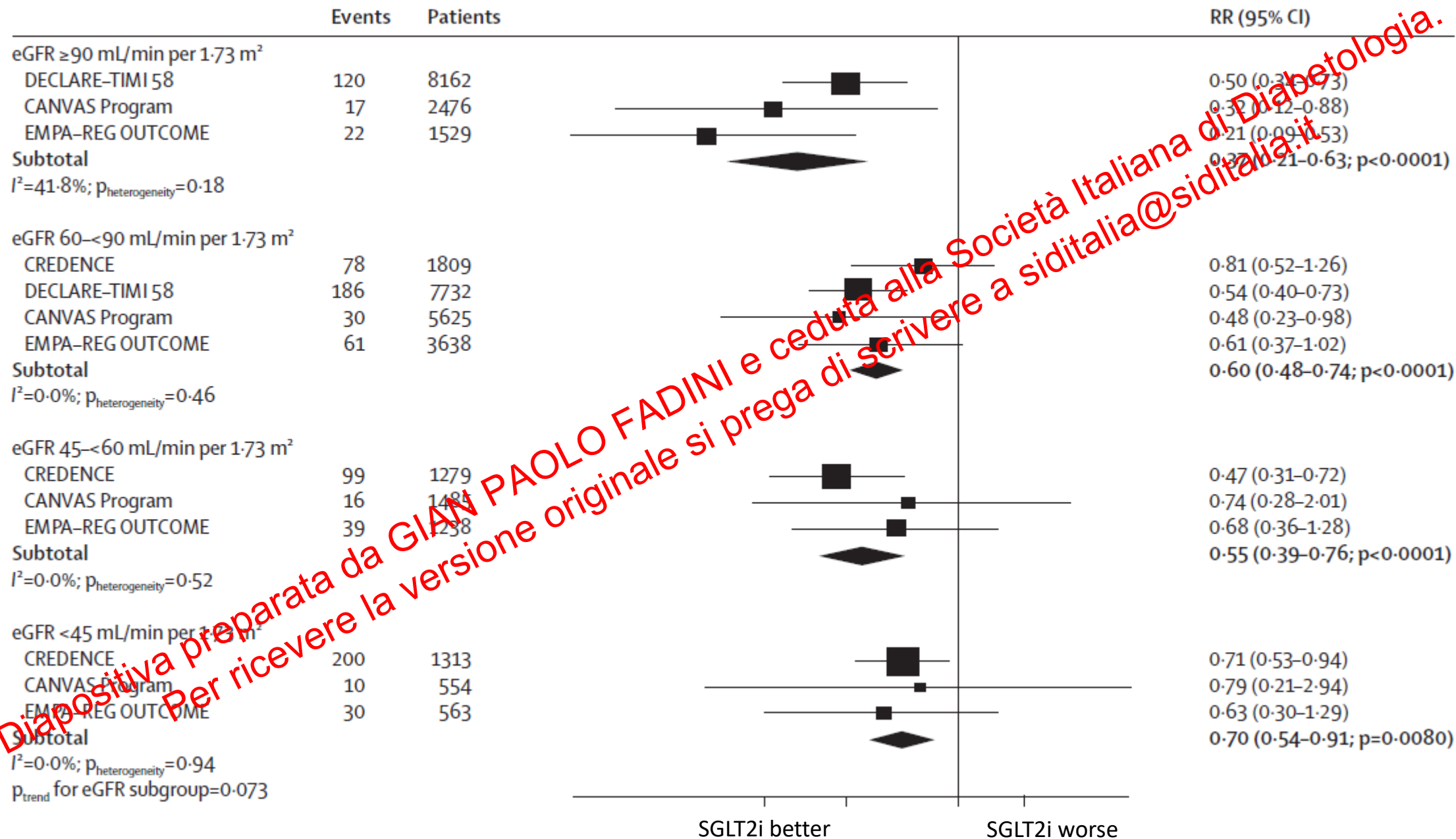


C Substantial loss of kidney function, ESKD, or death due to cardiovascular or kidney disease



0.3 0.5 1.0 1.5
Favours SGLT2 inhibitor Favours placebo

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

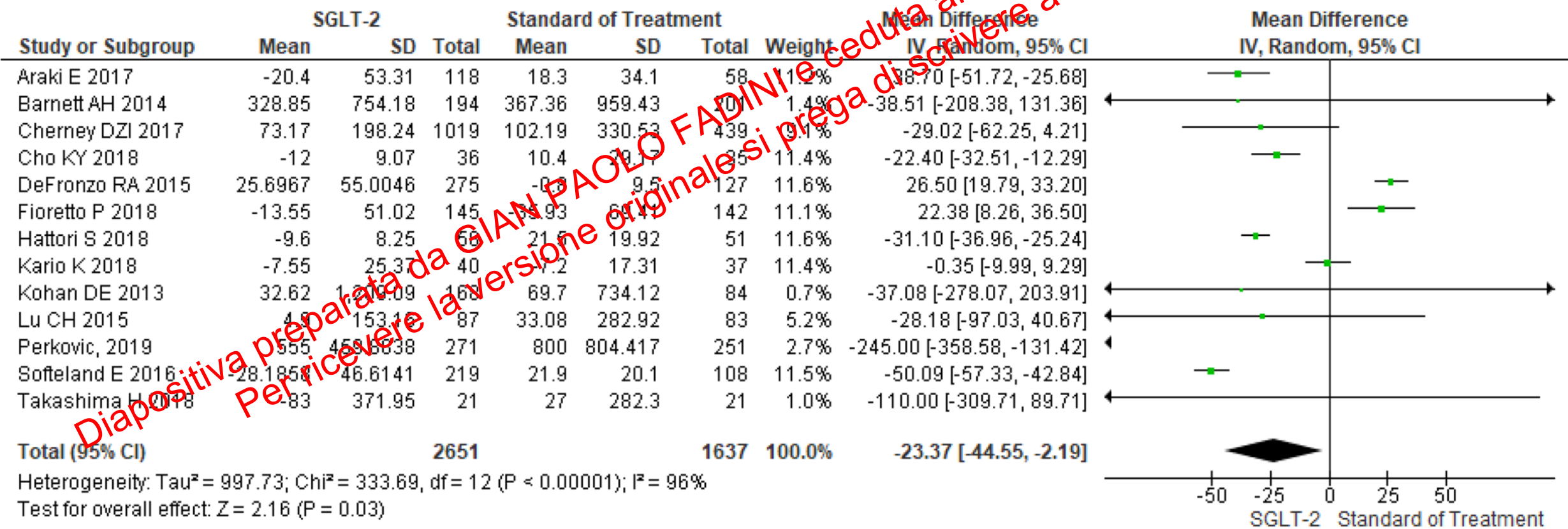


SGLT-2 inhibitors and microvascular outcomes in patients with type 2 diabetes

A systematic review and meta-analysis

Dorsey-Trevino et al. JEI 2019

Urine Albumin to Creatinine Ratio

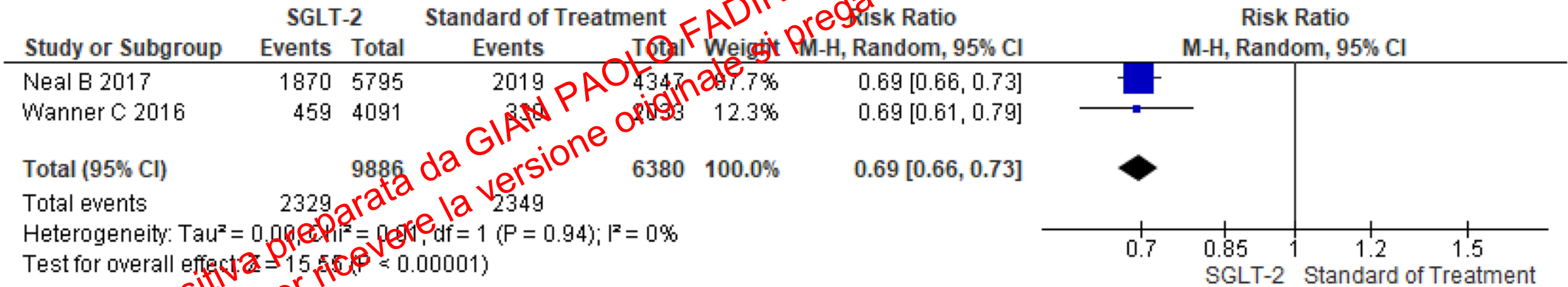


SGLT-2 inhibitors and microvascular outcomes in patients with type 2 diabetes

A systematic review and meta-analysis

Dorsey-Trevino et al. JEI 2019

Progression of Albuminuria

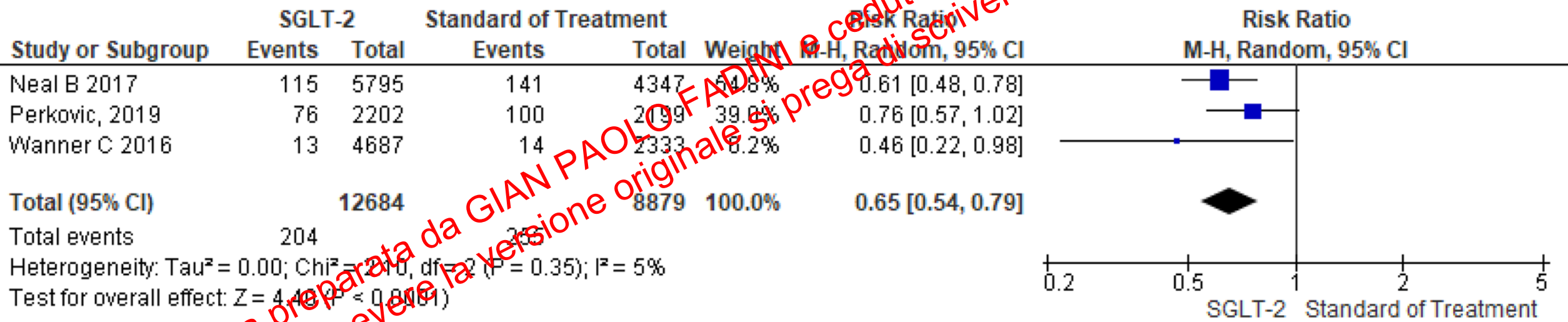


SGLT-2 inhibitors and microvascular outcomes in patients with type 2 diabetes

A systematic review and meta-analysis

Dorsey-Trevino et al. JEI 2019

Renal-Replacement Therapy

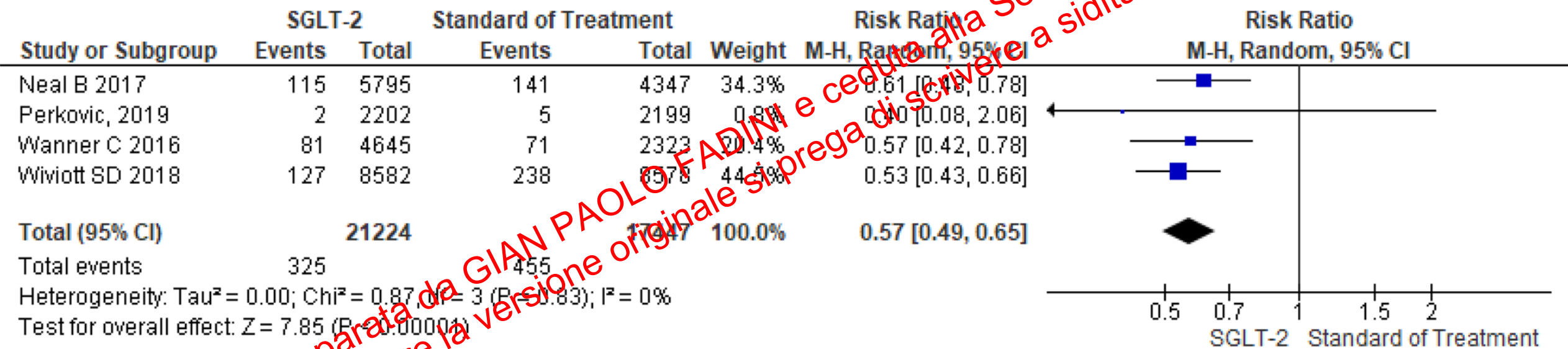


SGLT-2 inhibitors and microvascular outcomes in patients with type 2 diabetes

A systematic review and meta-analysis

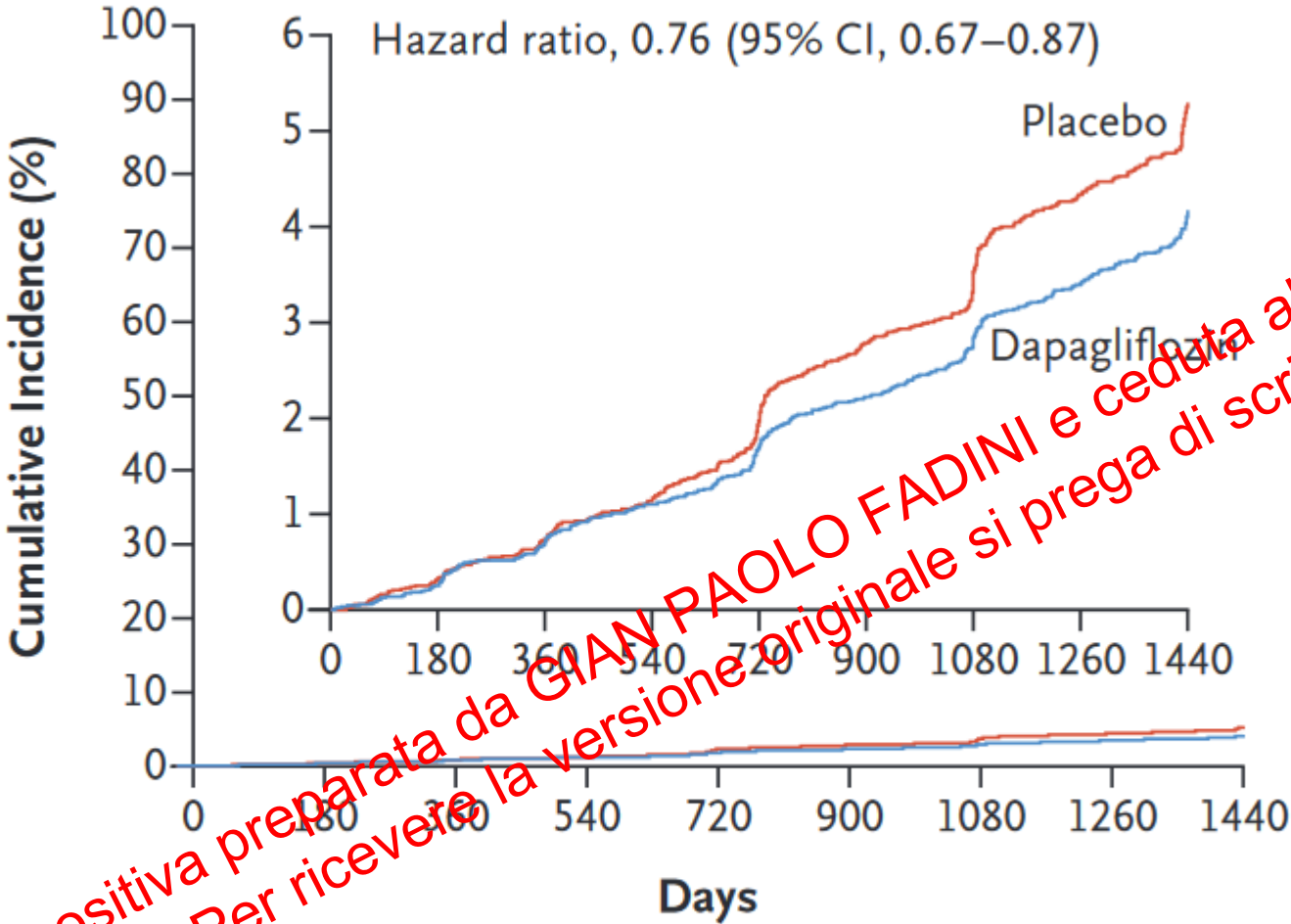
Dorsey-Trevino et al. JEI 2019

Renal Death



DECLARE-TIMI 58

C Renal Composite



Renal composite outcome

- sustained decrease of 40+% in eGFR to <60 ml/min/1.73 m²;
- new end-stage renal disease;
- death from renal or cardiovascular causes

No. at Risk

Placebo	8578	8508	8422	8326	8200	8056	7932	7409	5389
Dapagliflozin	8582	8533	8436	8347	8248	8136	8009	7534	5472

Definitions of Renal and UACR-related Outcomes



Secondary renal composite outcome:^{1,2}

- Sustained confirmed^a decline of at least 40% in eGFR to less than 60 mL/min/1.73m²;
- End-stage renal disease^b;
- Death from renal causes; or
- Death from CV causes

Prespecified, Exploratory, Renal-specific outcome:^{1,2}

- All of the above except death from CV causes

Prespecified, Exploratory UACR variables:³

- Development of sustained macroalbuminuria^c (UACR ≥ 300mg/g) in patients without macroalbuminuria at baseline.
- Development of sustained albuminuria^c (UACR ≥ 30mg/g) in patients without albuminuria at baseline.
- Regression of sustained albuminuria^c
 - Baseline microalbuminuria (UACR 30 to less than 300mg/g) to normoalbuminuria (UACR <30mg/g);
 - Baseline macroalbuminuria to microalbuminuria;
 - The previous 2 combined

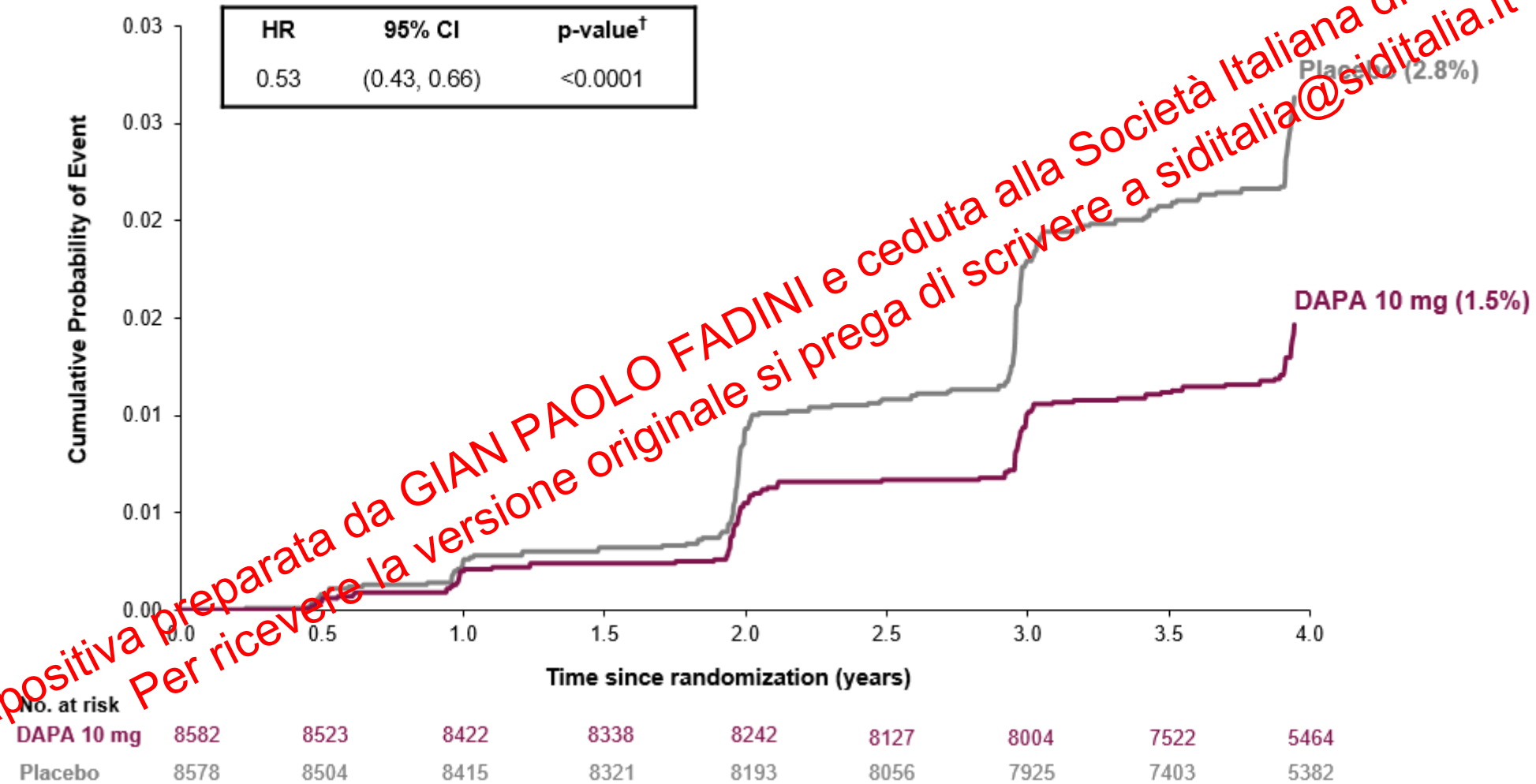
^a2 tests at least 4 weeks apart; ^bdefined as dialysis for at least 90 days, kidney transplantation, or confirmed sustained eGFR <15mL/min/1.73 m²; ^cConfirmation required that albuminuria be present at 2 consecutive visits. Time to onset was based on the first of the 2 laboratory assessments with albuminuria.

CV = cardiovascular; eGFR = estimated glomerular filtration rate; UACR = urinary albumin-to-creatinine ratio.

1. Wiviott SD et al. *N Engl J Med*. 2019;380:347-357; 2. Mosenzon O et al. Online ahead of print. *Lancet Diabetes Endocrinol*. 2019; 3. Raz I et al. Presented at: ADA 79th Scientific Sessions; June 7-11, 2019; San Francisco, CA 244-OR.

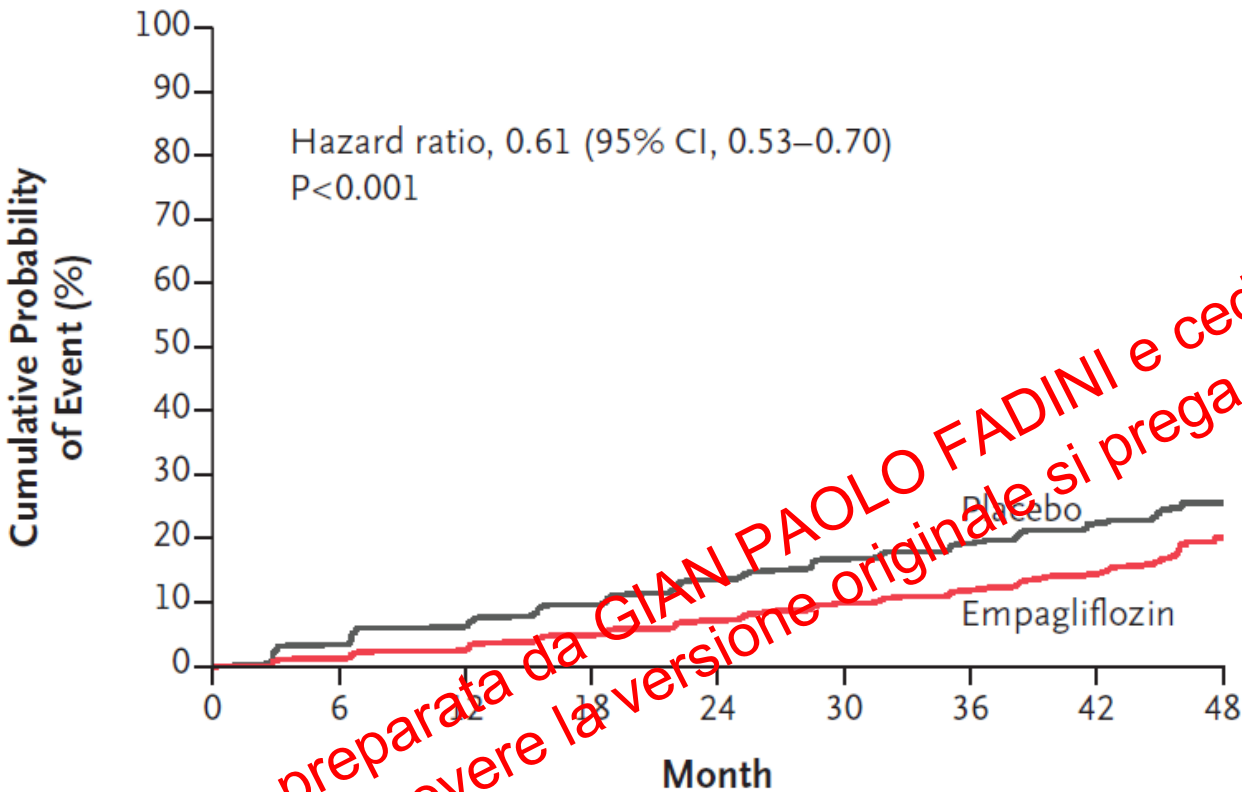
DECLARE-TIMI 58

Renal-specific Outcome
Decrease eGFR $\geq 40\%$, ESRD or Renal Death



EMPA-REG Outcome trial

A Incident or Worsening Nephropathy



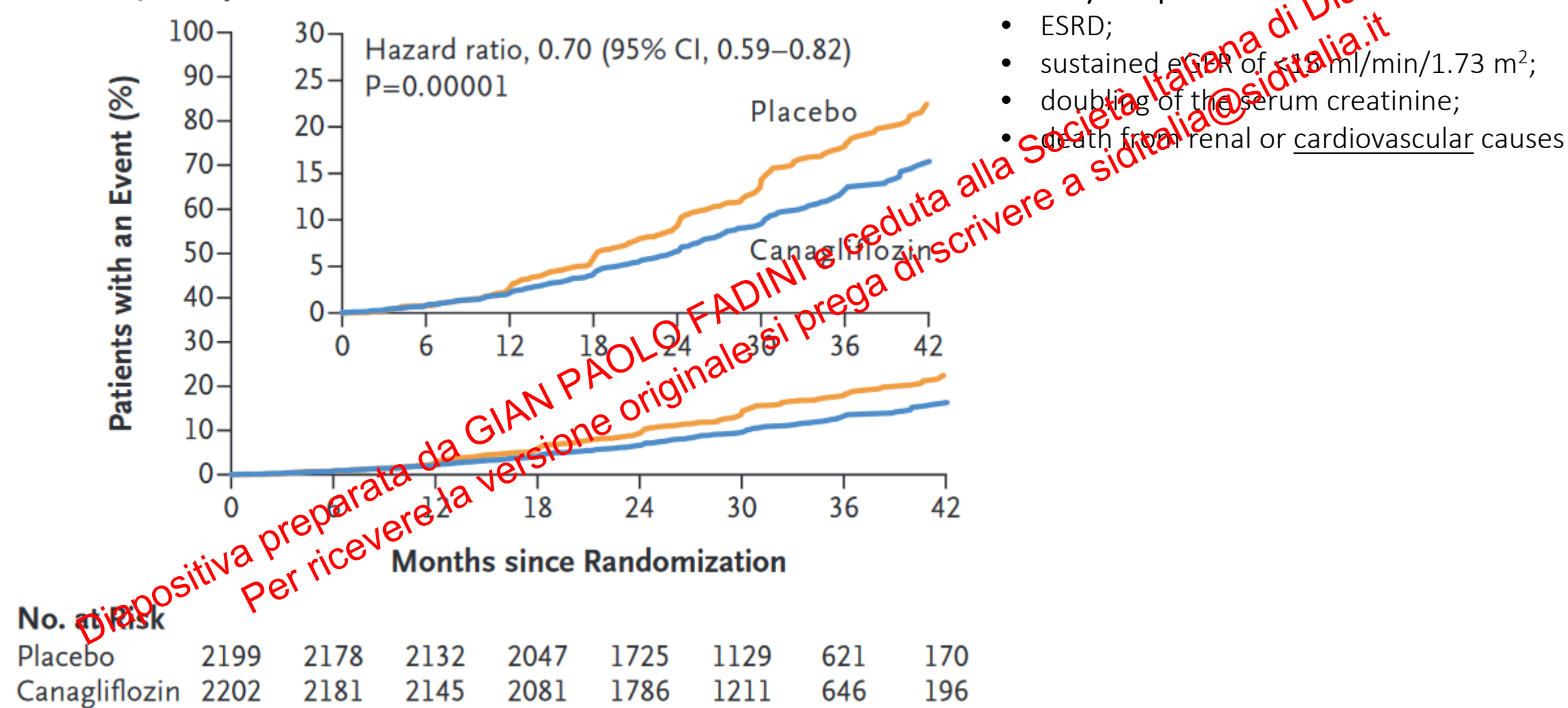
- Incident or worsening nephropathy
- Progression to macroalbuminuria
 - doubling of the serum creatinine + eGFR ≤ 45
 - the initiation of renal-replacement therapy
 - death from renal disease

No. at Risk

Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

CREDENCE

A Primary Composite Outcome



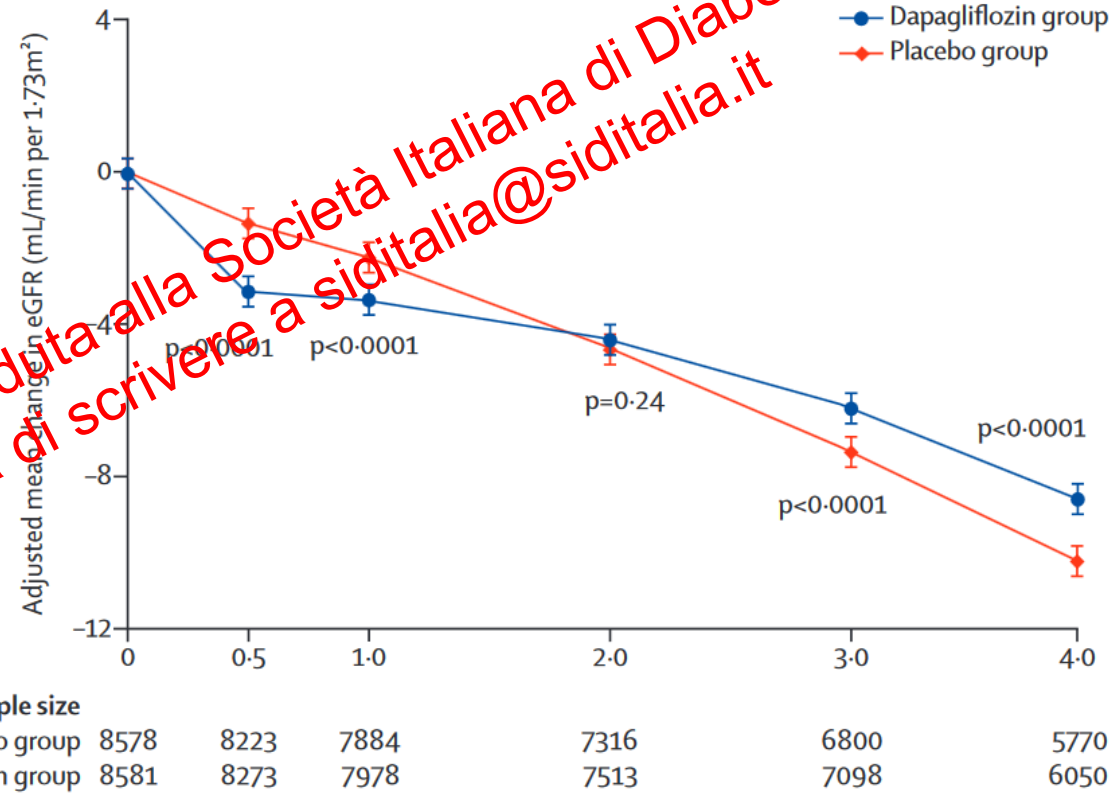
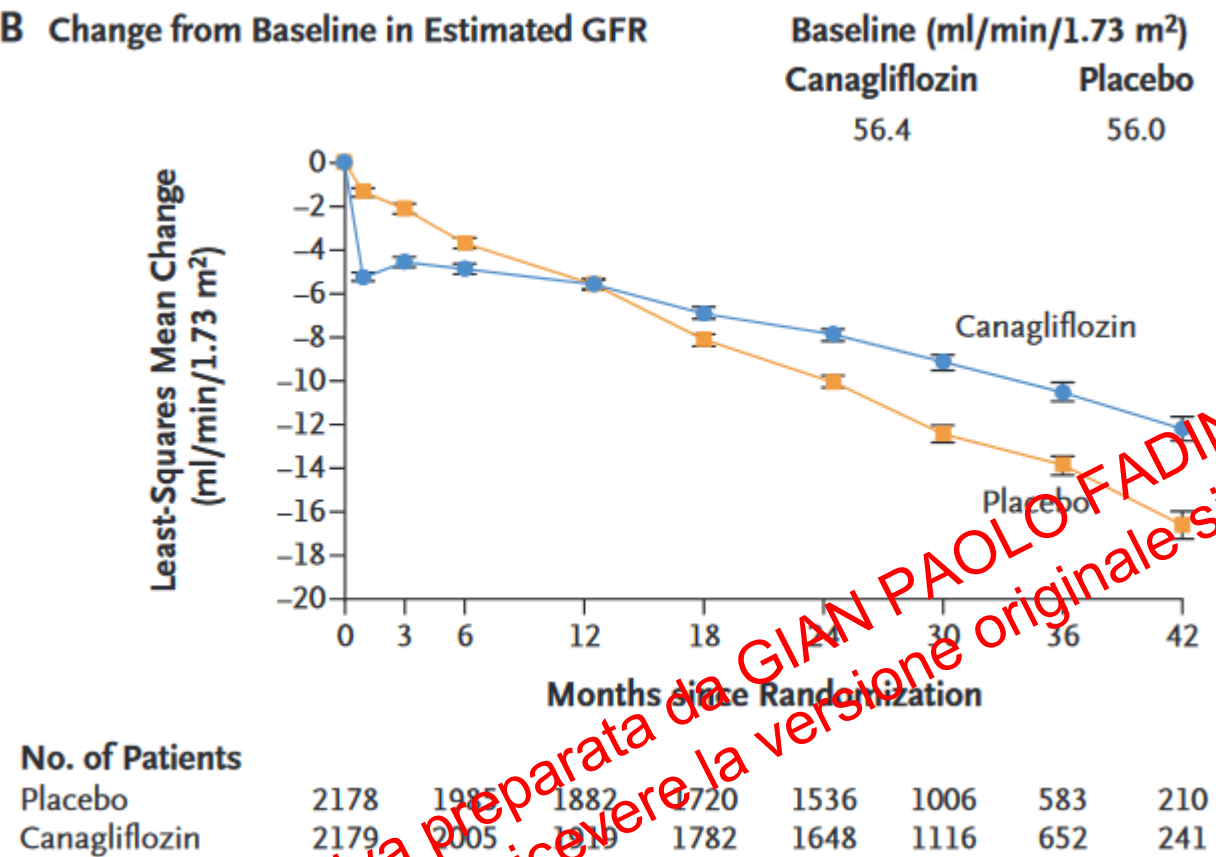
CREDENCE vs DAPA-CKD

	CREDENCE	DAPA-CKD
Clinical trials identifier	NCT02065791	NCT03036150
Design	Randomized placebo-controlled double-blind trial	Randomized placebo-controlled double-blind trial
Study Population	Type 2 diabetes UACR 300–3500 mg/g eGFR 30–90 ml/min/1.73m ²	Chronic kidney disease UACR 300–3500 mg/g eGFR 30–75 ml/min/1.73m ²
Primary endpoint	Composite of end-stage renal disease, doubling of serum creatinine, renal or cardiovascular death	Composite of end-stage renal disease, $\geq 50\%$ eGFR decline, renal or cardiovascular death
Secondary endpoints	-Cardiovascular death -All-cause death -Cardiovascular composite endpoint (myocardial infarction, stroke, CV death) -Renal composite endpoint (end-stage renal disease, doubling of serum creatinine, renal death)	-All-cause death First occurrence of: -End-stage renal disease, $\geq 50\%$ eGFR decline, renal death -Cardiovascular death or hospitalization for heart failure
Number of patients	4404	4000
Anticipated trial completion	June 2019	November 2020

CREDENCE

DECLARE-TIMI 58

B Change from Baseline in Estimated GFR

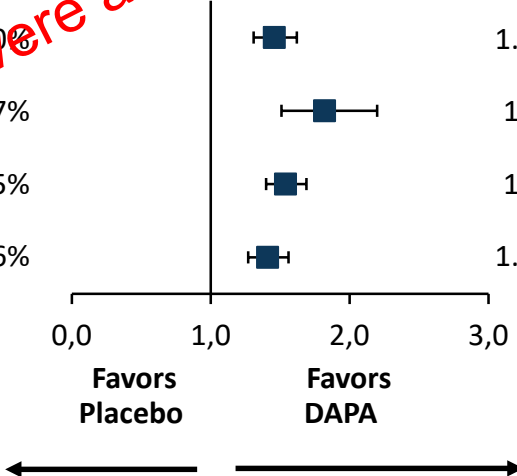


Diapositiva preparata da GIAN PAOLO FADINI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Improvement of Albuminuria Category from Baseline

Endpoints	Dapagliflozin		Placebo		Hazard Ratio (95% CI)	Cox p-value
	n/N (%)	KM Event Rate	n/N (%)	KM Event Rate		
Improvement from baseline						
Micro to Normo	774/2017 (38.4)	38.90%	576/2013 (28.4)	29.0%	1.46 (1.31, 1.62)	<0.0001
Macro to Normo/Micro	282/594 (47.5)	48.10%	175/595 (30.4)	31.7%	1.82 (1.51, 2.2)	<0.0001
Macro to Normo/Micro or Micro to Normo	1056/2611 (40.4)	41.60%	751/2588 (29.0)	29.5%	1.54 (1.4, 1.69)	<0.0001
Micro/Macro to Normo	809/2611 (31.0)	31.50%	604/2588 (23.3)	23.6%	1.41 (1.27, 1.56)	<0.0001

Definitions of Albuminuria Categories



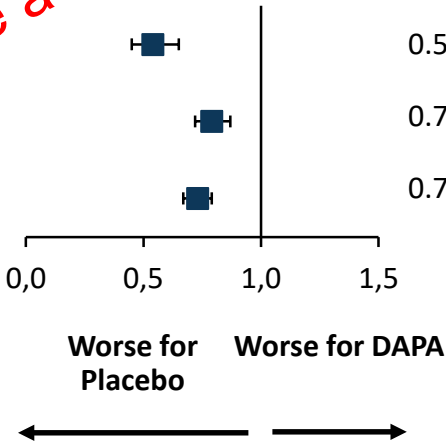
0,0 1,0 2,0 3,0

Favors Placebo Favors DAPA

Definitions of Albuminuria Categories	
Macroalbuminuria	UACR ≥300 mg/g
Microalbuminuria	UACR ≥30 to <300 mg/g
Normoalbuminuria	UACR <30 mg/g

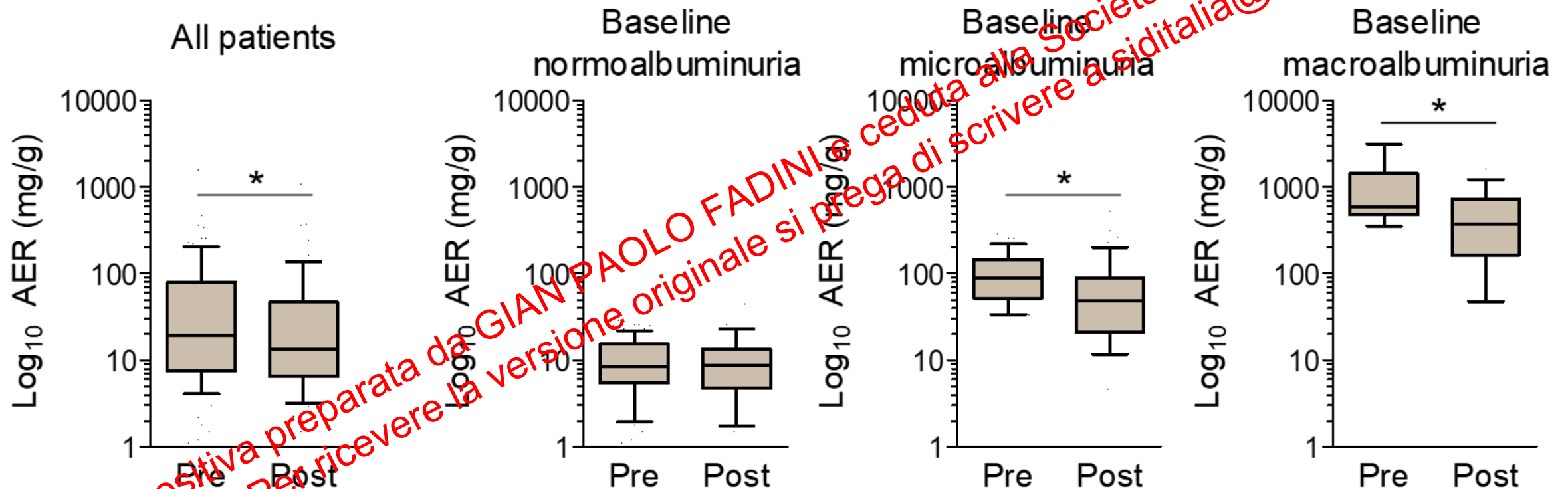
Deterioration of Albuminuria Category from Baseline

Endpoints	Dapagliflozin		Placebo		Hazard Ratio (95% CI)	Cox p-value
	n/N (%)	KM Event Rate	n/N (%)	KM Event Rate		
Deterioration from baseline						
Normo/Micro to Macro	181/7836 (2.3)	2.30%	330/7838 (4.2)	4.2%		0.54 (0.45, 0.65) <0.0001
Normo to Micro/Macro	772/5819 (13.3)	13.30%	959/5825 (16.5)	16.3%		0.79 (0.72, 0.87) <0.0001
Normo to Micro/Macro or Micro to Macro	928/7836 (11.8)	11.90%	1243/7838 (15.9)	15.8%		0.73 (0.67, 0.79) <0.0001



Definitions of Albuminuria Categories	
Macroalbuminuria	UACR ≥300 mg/g
Microalbuminuria	UACR ≥30 to <300 mg/g
Normoalbuminuria	UACR <30 mg/g

Improvement of Albuminuria in RWE



Effetti nefroprotettivi degli SGLT2 inibitori:

Meccanismi

Diapositiva preparata da GIAN PAOLO FADINI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Glycaemic control

SGLT2i



- Acts independently of insulin mechanisms to reduce HbA_{1c} via the kidney
- Works regardless of β -cell function
- Has a low propensity for hypoglycaemia

Weight loss



- Urinary excretion of ~70 g glucose/day with SGLT2i corresponds to loss of 280 kcal/day^{*1}
(1 g glucose = ~4 kcal)
- 1 lb of body fat equates to ~3500 calories²

Blood pressure reduction



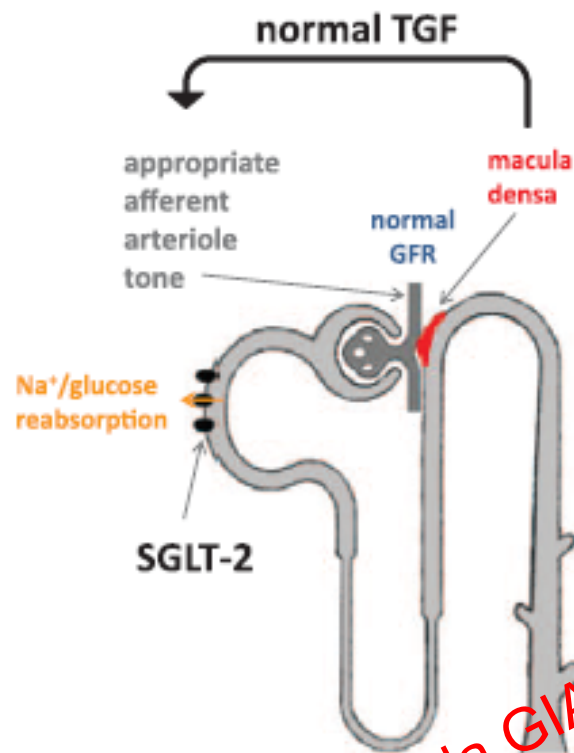
- SGLT2i is associated with significant reductions in SBP, which is likely to be due in part to the effect of increased diuresis^{†1}

Effetti nefroprotettivi degli SGLT2 inibitori

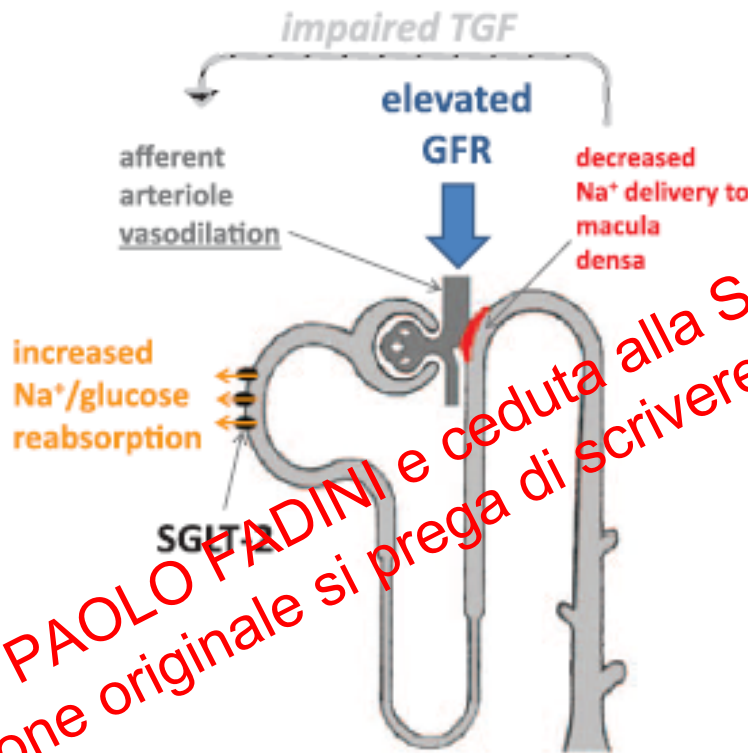
Meccanismi

- Miglioramento simultaneo di glicemia, peso, pressione

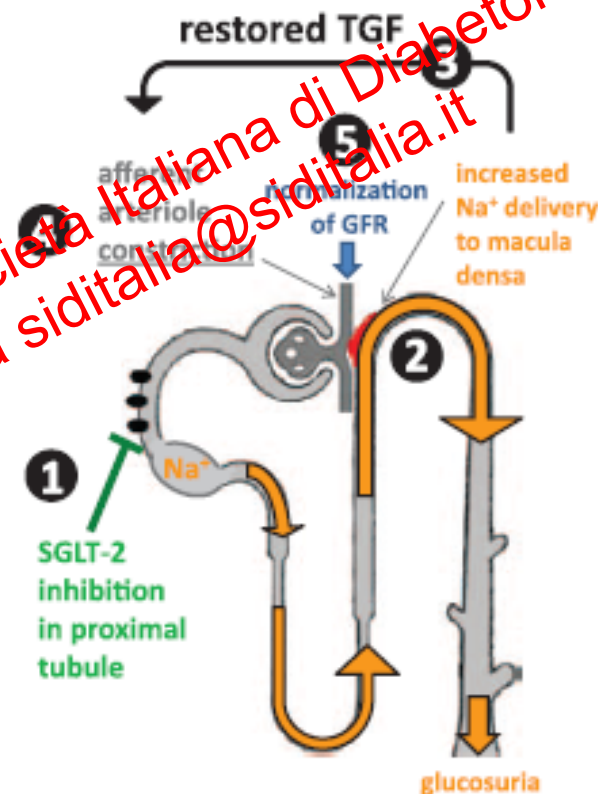
Diapositiva preparata da GIAN PAOLO FADINI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it



Normal physiology



Hyperfiltration in early stages of diabetic nephropathy



SGLT-2 inhibition reduces hyperfiltration via TGF

Diapositiva preparata da GIAN PAOLO FADINI e ceduta alla Societa Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Effetti nefroprotettivi degli SGLT2 inibitori

Meccanismi

- Miglioramento simultaneo di glicemia, peso, pressione
- Riduzione dell'iperfiltrazione glomerulare

Diapositiva preparata da GIAN PAOLO FADINI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

a Natriuresis

Tubuloglomerular feedback

- ↓ P_G
- ↑ P_{BOW}
- ↓ Proteinuria

Contraction of plasma volume

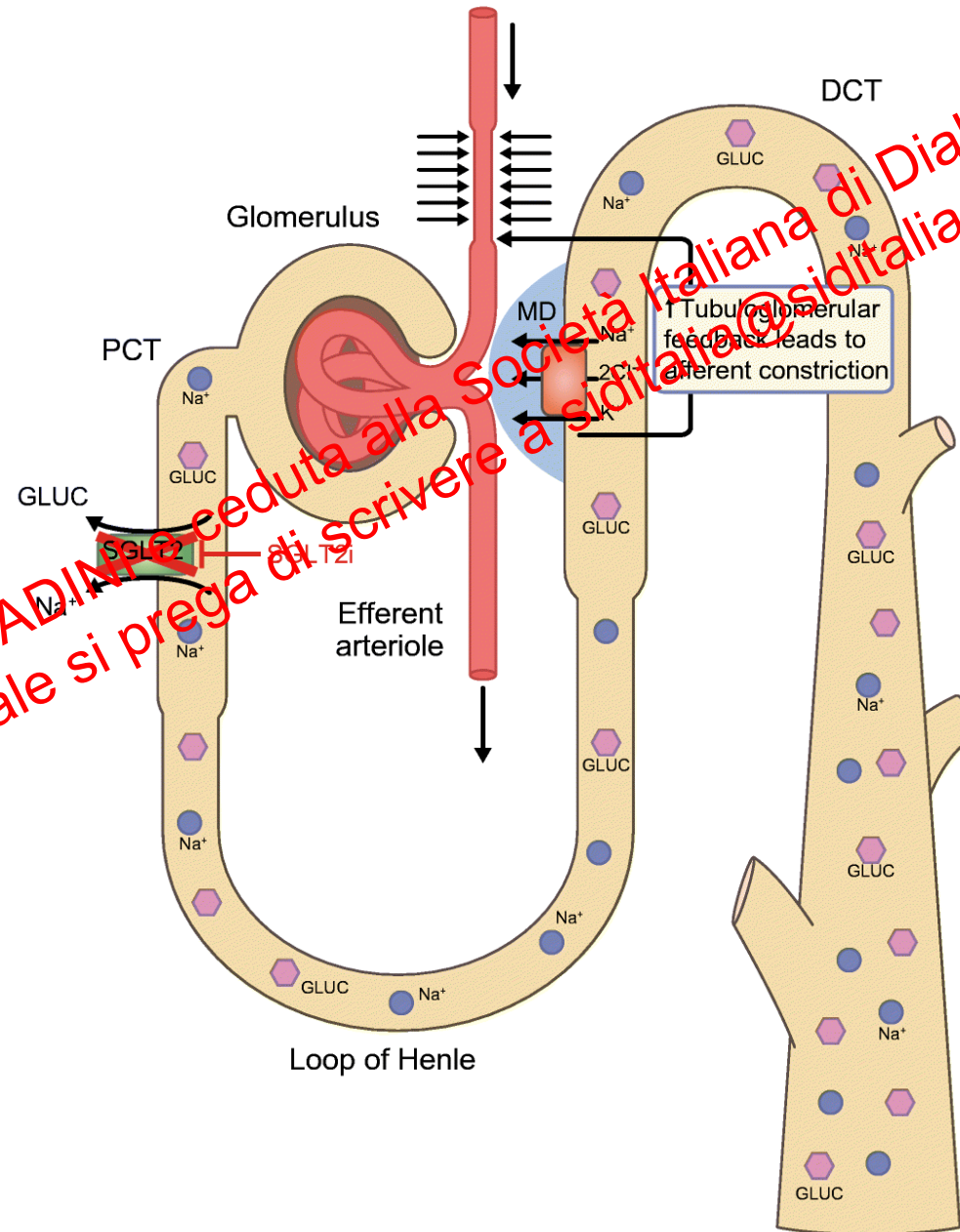
- ↓ Blood pressure
- ↓ Heart failure
- ? Direct/indirect effect on vascular function (e.g. endothelial function)
- ↓ Use of diuretic agents
- ↓ NHE3 activity – additional natriuresis?
- ↑ Erythropoietin leading to ↑ haematocrit
- ↓ Tubular ischaemia/injury/fibrosis
- ↓ Markers of inflammation
- ↓ Oxidative stress

b Glycosuria

- ↓ HbA_{1c}
 - ↓ Body weight
- Metabolic risk and microvascular complication risk

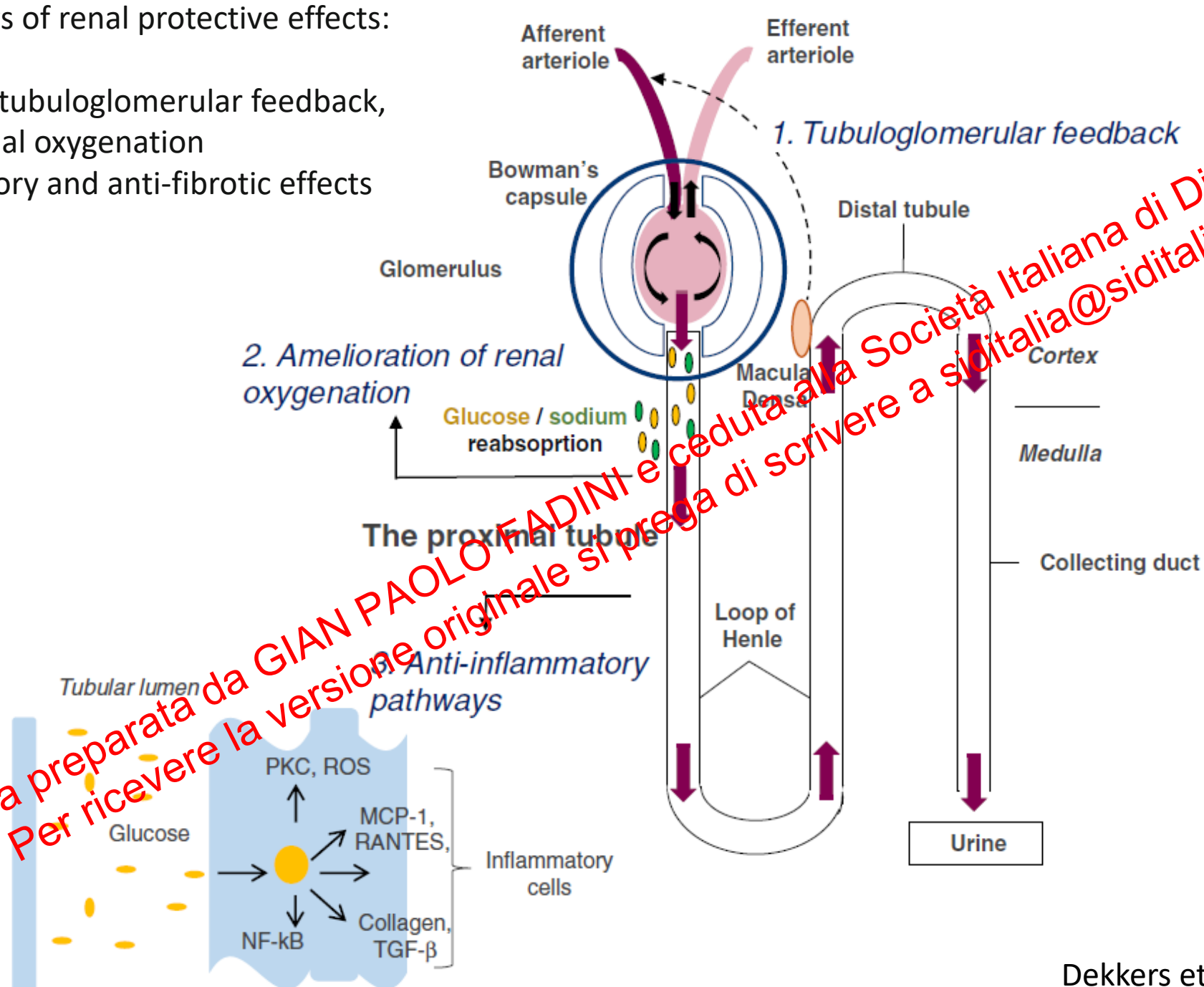
c Natriuresis + Glycosuria

- ↓ Proximal solute reabsorption
- ↓ Energy requirement/utilisation
- ↓ Hypoxia in the kidney



Proposed pathways of renal protective effects:

- 1) Restoration of tubuloglomerular feedback,
- 2) Ameliorate renal oxygenation
- 3) Antiinflammatory and anti-fibrotic effects



Diapositiva preparata da GIAN PAOLO FADINI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

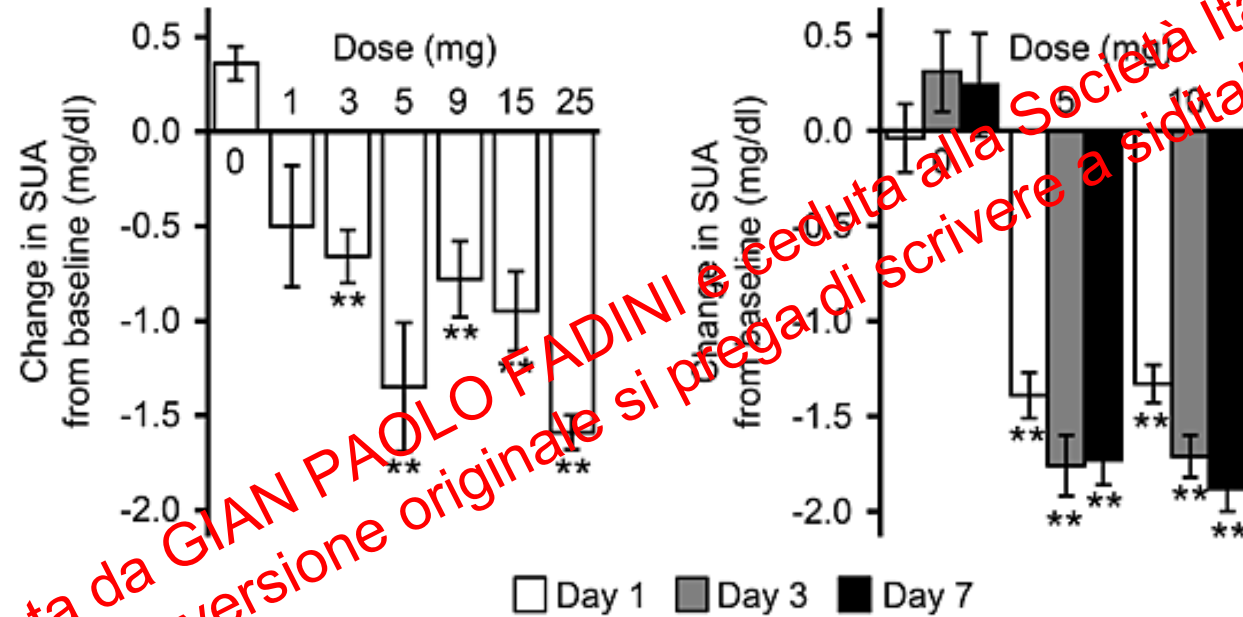
Effetti nefroprotettivi degli SGLT2 inibitori

Meccanismi

- Miglioramento simultaneo di glicemia, peso, pressione
- Riduzione dell'iperfiltrazione glomerulare
- Miglioramento dell'ossigenazione renale

Diapositiva preparata da GIAN PAOLO FADINI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Effetto uricosurico degli SGLT2i



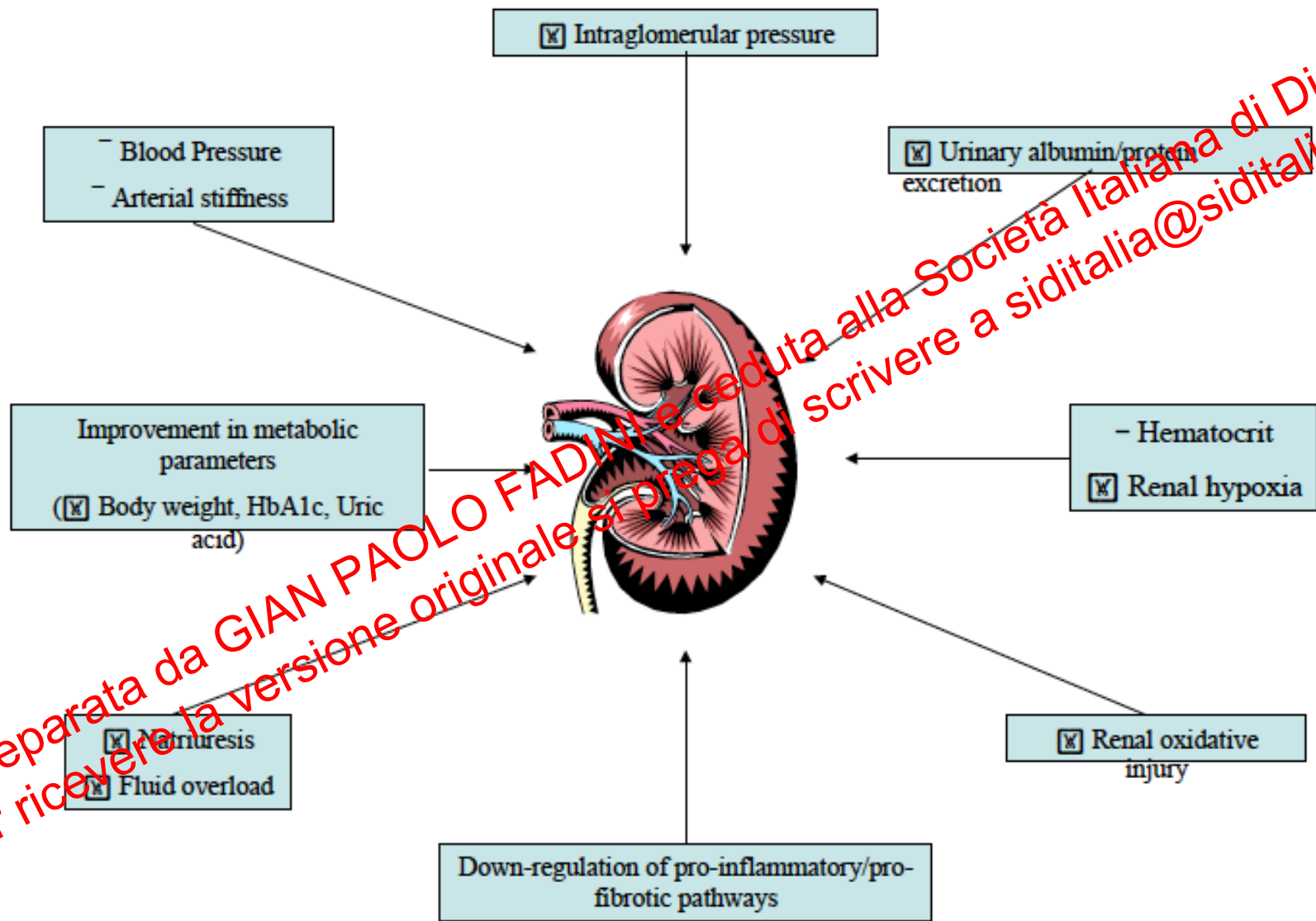
Chino et al. Biopharm Drug Dispos 2014

Effetti nefroprotettivi degli SGLT2 inibitori

Meccanismi

- Miglioramento simultaneo di glicemia, peso, pressione
- Riduzione dell'iperfiltrazione glomerulare
- Miglioramento dell'ossigenazione renale
- Effetto ipouricemizzante

Diapositiva preparata da GIAN PAOLO FADINI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it



Diapositiva preparata da GIAN PAOLO FADINI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Take-home messages

Meccanismi

- Molteplici e non del tutto noti

Evidenze

- Molteplici e solide
 - ✓ Outcome soft e hard
 - ✓ Farmaci diversi
 - ✓ Popolazioni diverse

Diapositiva preparata da GIAN PAOLO FADINI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it