Inibitori del SGLT2 e Nefropatia Diabetica

Parma, 20 ottobre 2017

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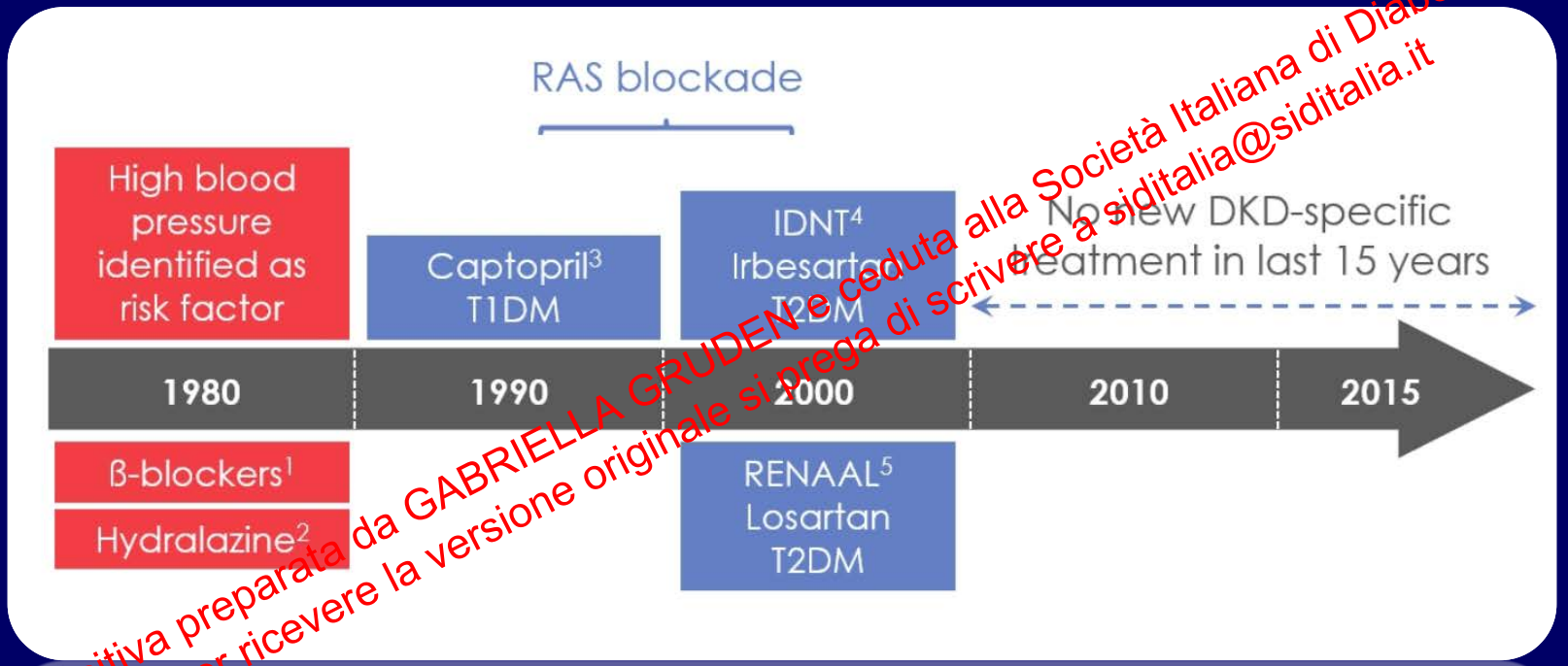
OUTLINE

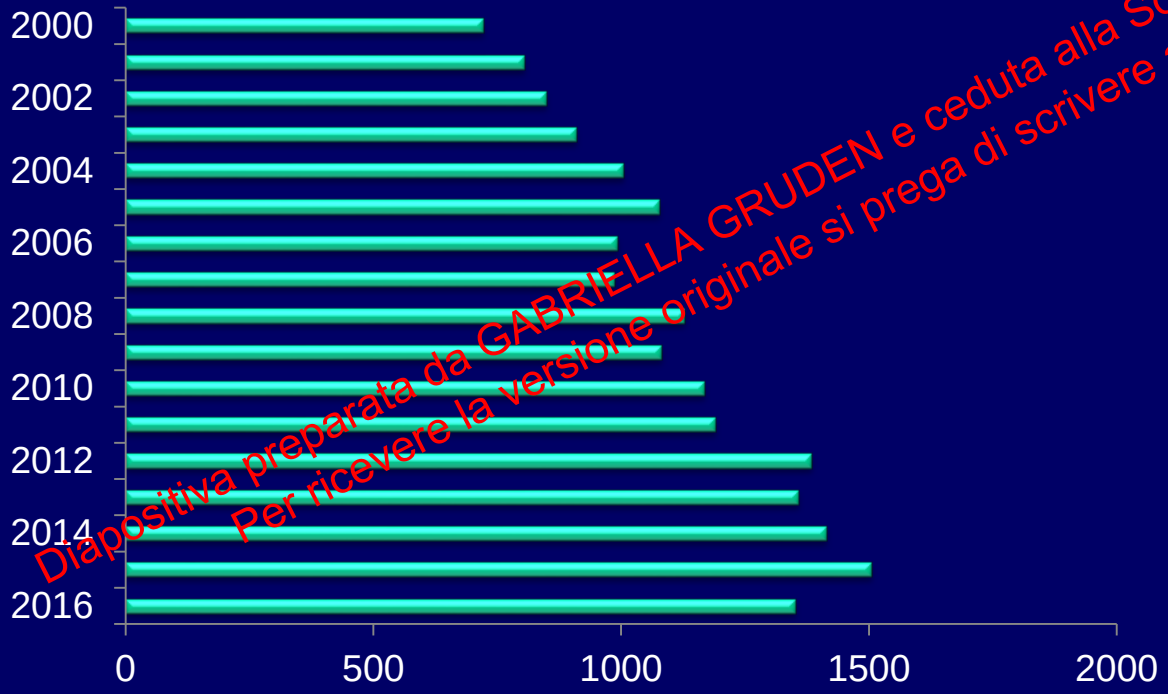
- Premessa
- Studi clinici
  - Efficacia: outcome renali
  - Effetti avversi
- Meccanismi

NEFROPATIA DIABETICA

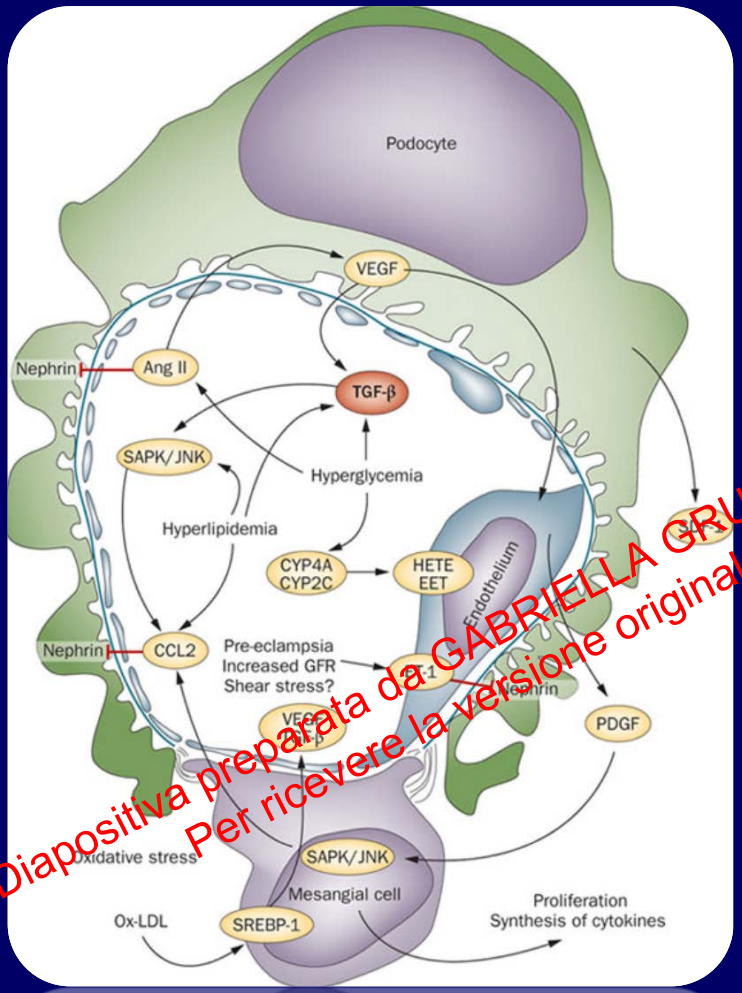


PUBBLICAZIONI 2000-2016: Nefropatia Diabetica

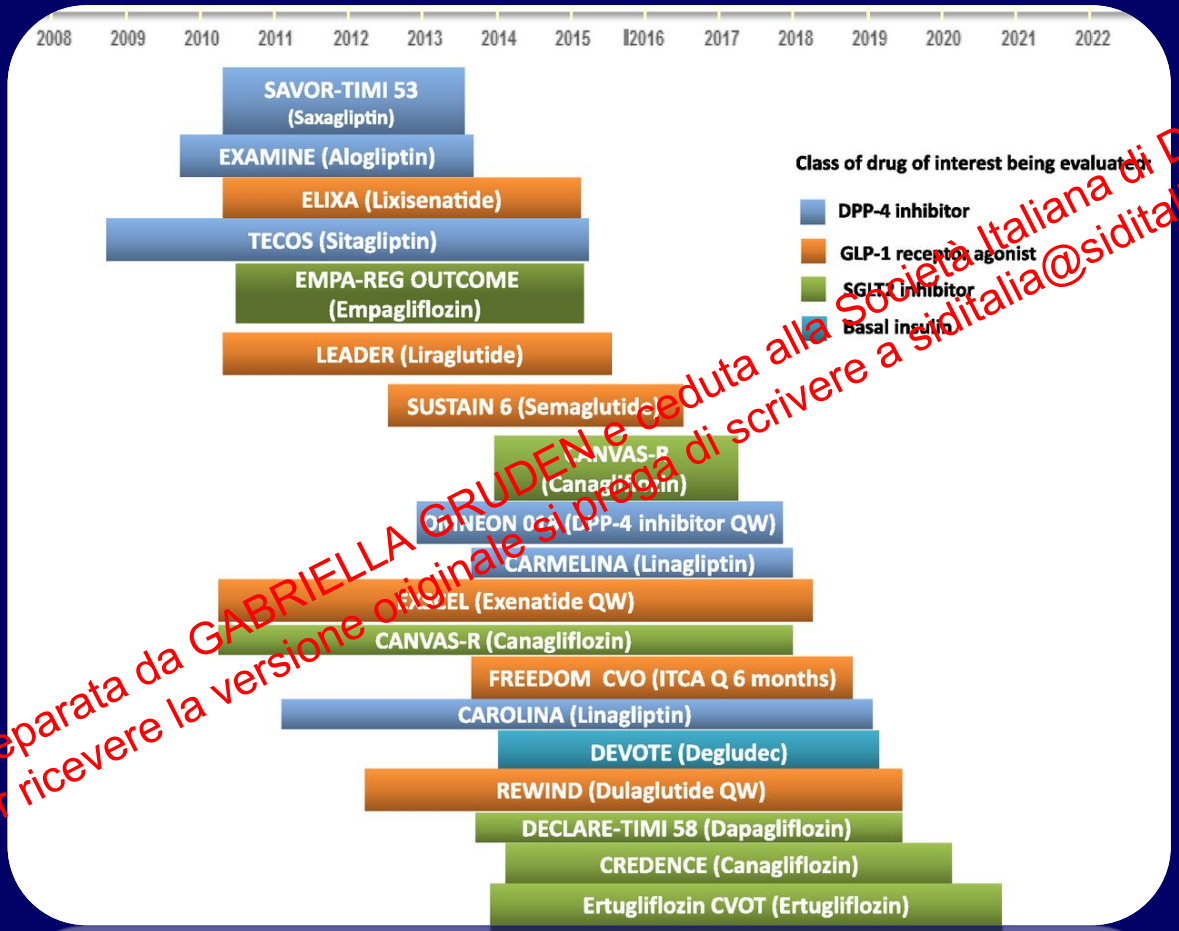
PubMed: keyword nefropatia diabetica



MECCANISMI



FDA: TRIALS DI SICUREZZA CV



Mannucci E et al. Diab Care 2016

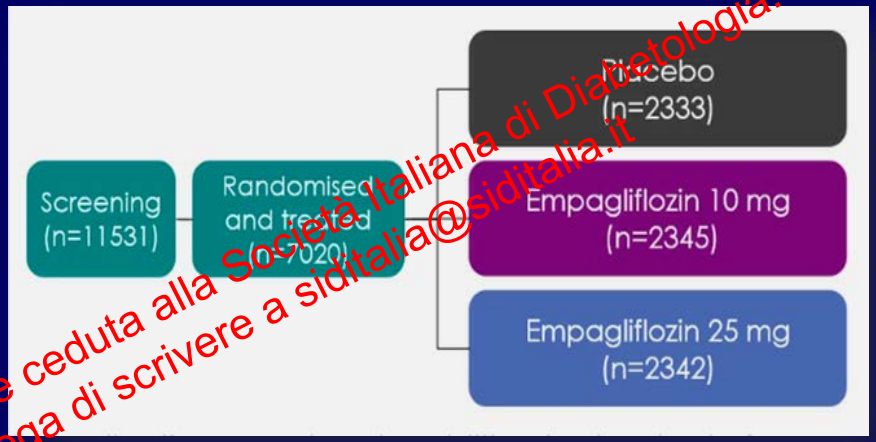
INIBITORI SGLT2: NEFROPROTEZIONE

OUTLINE

- Premessa
- Studi clinici
  - Efficacia su outcome renali
  - Effetti avversi
- Meccanismi

EMPA REG OUTCOME

RCT doppio cieco multicentrico con outcome CV



In aggiunta a terapia standard

Criteri di inclusione
- Adulto con DM2
- BMI≤ 45 Kg/m2
- HbA1c 7-10%
- Nota patologia CV

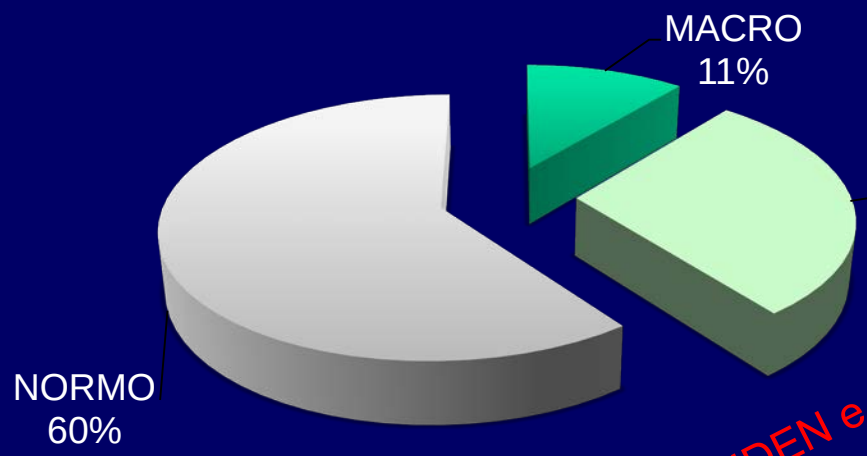
Criteri di esclusione
- eGFR <30 ml/min/1.73 m^2

Outcome Primario
3 punti-MACE: morte CV, IMA o ictus non fatali

Sponsorizzato

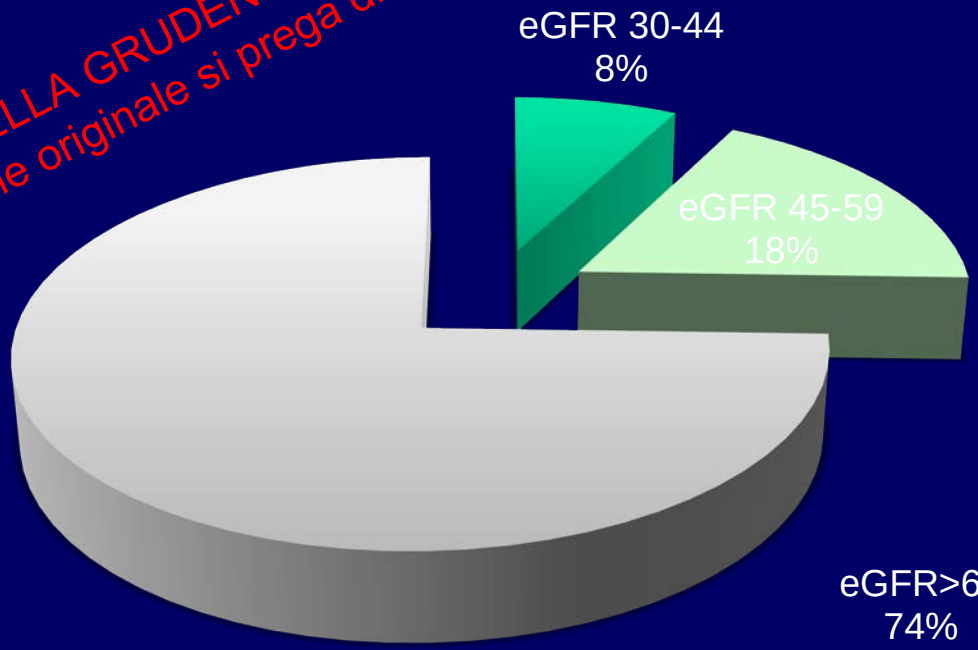
Zinman B et al. N Engl J Med 2015

EMPA REG OUTCOME



ALBUMINURIA

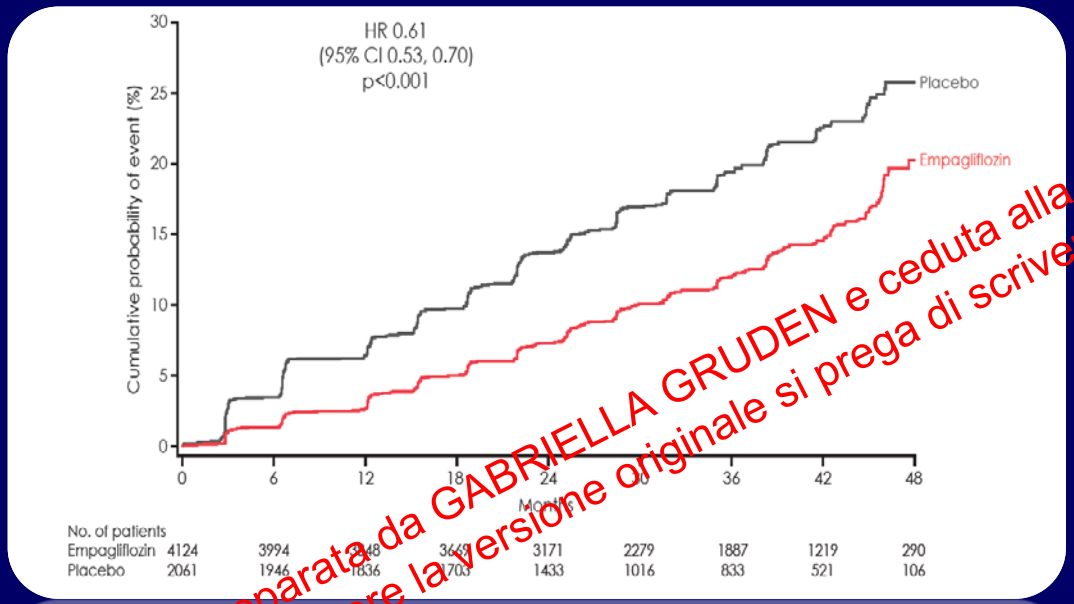
eGFR

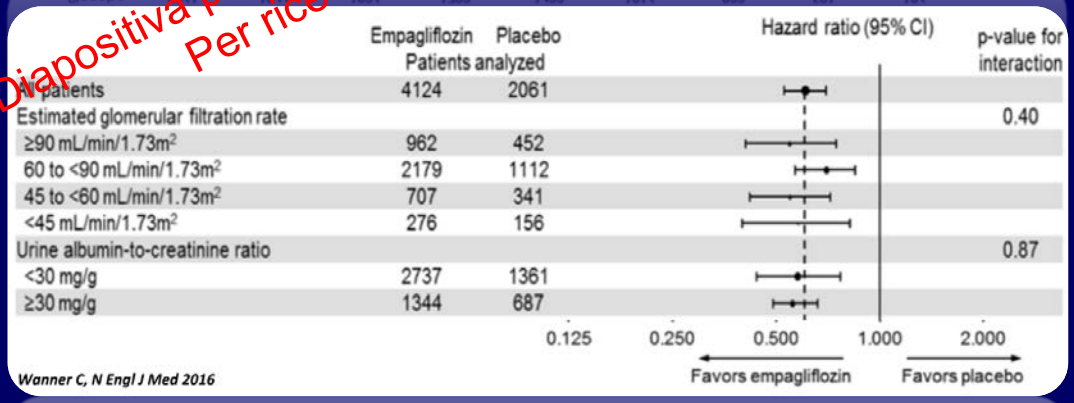


EMPA REG OUTCOME RENAL

Esordio o Progressione della Nefropatia

End-point secondario pre-specificato





-39% RR

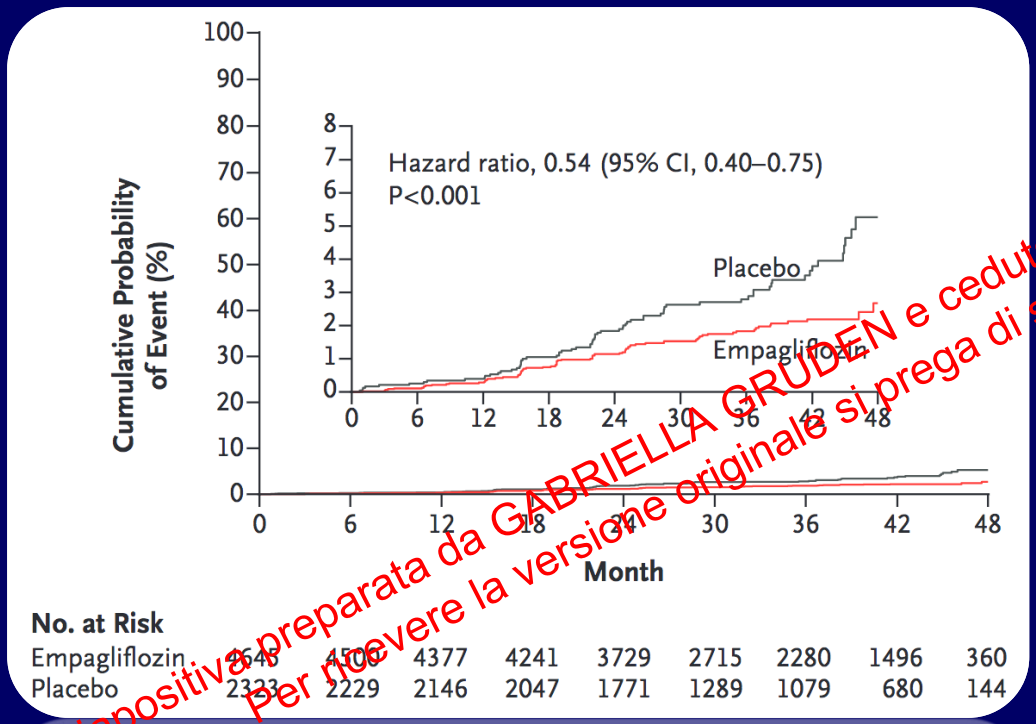
Outcome Renale

- Macroalbuminuria
- Raddoppio Cr
- RRT
- Morte renale

Wanner C et al NEJM 2016

EMPA-REG OUTCOME

PROGRESSIONE CKD: *Analisi post-hoc*



-46% RR

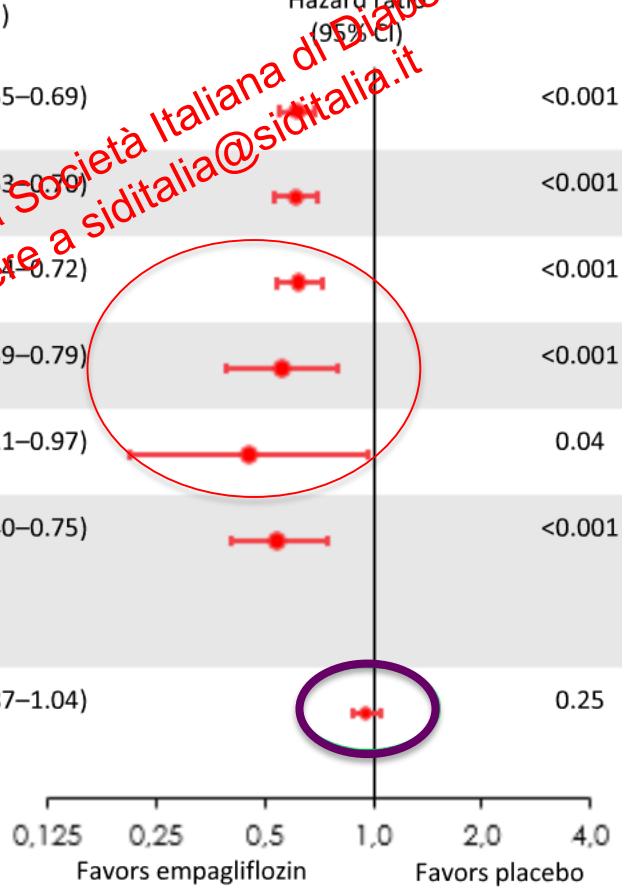
Outcome Renale

- Raddoppio Cr
- RRT
- Morte renale

Wanner C et al NEJM 2016

EMPA-REG OUTCOME
RENAL OUTCOMES

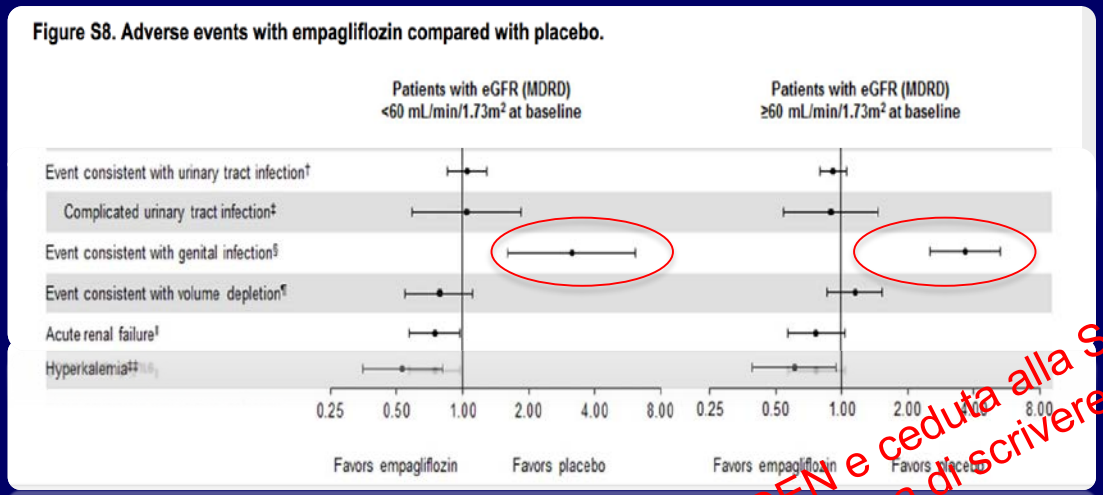
	Empagliflozin		Placebo			
	no. with event /analyzed (%)	rate/ 1000 pt-yr	no. with event/ analyzed (%)	rate/ 1000 pt-yr	Hazard Ratio (95% CI)	p-value
Incident or worsening nephropathy or CV death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (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	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine*	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	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine*, initiation of renal replacement therapy, or death due to 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 normoalbuminuria at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25



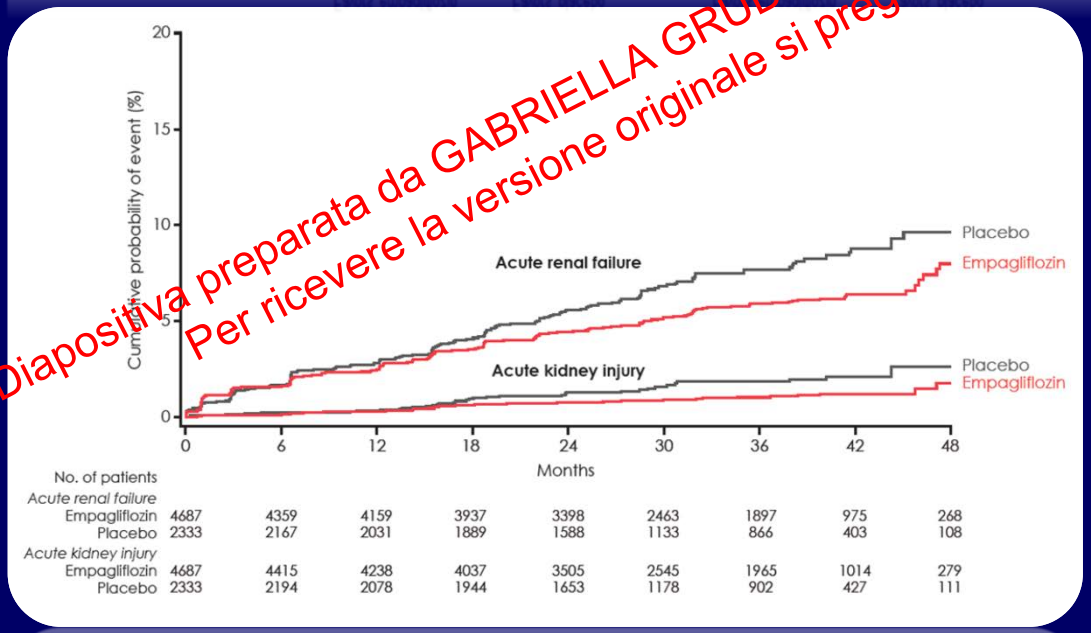
Cox regression analyses in patients treated with ≥1 dose of study drug.
Analyses were prespecified except for the composite of doubling of serum creatinine, initiation of renal replacement therapy, or death due to renal disease.
*Accompanied by eGFR [MDRD] ≤45 ml/min/1.73m^2.

Wanner C, N Engl J Med 2016

EFFETTI AVVERSI RENALI



INFEZIONI GENITALI



AKI - AKF

Wanner C et al NEJM 2016

POOL ANALYSIS: 15 TRIALS EMPA IN CKD

Pooled analysis: identification of patients with CKD

15 randomized, placebo-controlled, Phase I–III clinical trials
(including EMPA-REG OUTCOME®)
plus 4 extension studies

↓

12,620 patients with T2DM randomized (1:1:1) to:
- placebo (n=4203)
- empagliflozin 10 mg (n=4221)
- empagliflozin 25 mg (n=4196)

↓

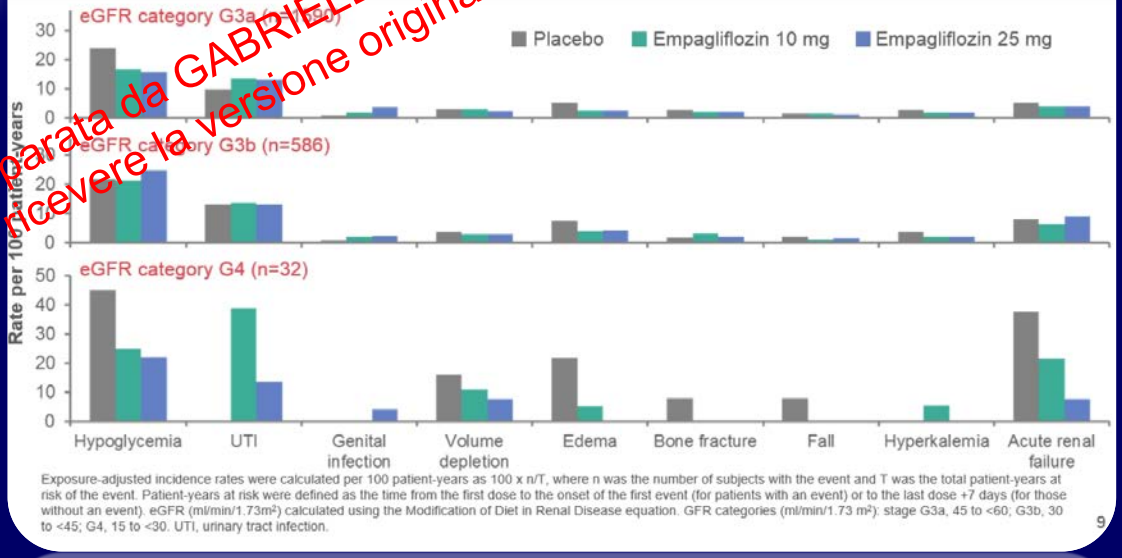
Overall, 2208 patients had baseline eGFR <60 ml/min/1.73m²:
- CKD G3a (n=1590)
- CKD G3b (n=586)
- CKD G4 (n=32)

Pooled analysis of all patients has been published: Kohler S *et al. Adv Ther* 2017;34:1707.
Four patients were excluded because no eGFR measurement was available.
GFR categories (ml/min/1.73 m²): stage G3a, 45 to <60; G3b, 30 to <45; G4, 15 to <30.

Proportion by category of eGFR and UACR at baseline

Baseline UACR data were missing for 4 patients in the placebo group, 10 in the EMPA 10 mg group, and 6 in the EMPA 25 mg group. GFR categories (ml/min/1.73 m²): stage G3a, 45 to <60; G3b, 30 to <45; G4, 15 to <30. Albuminuria: UACR <30 mg/g; microalbuminuria: UACR ≥30 to ≤300 mg/g; macroalbuminuria: UACR >300 mg/g.
eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; SD, standard deviation; UACR, urine albumin-creatinine ratio.

Incidence of other selected adverse reactions



Exposure-adjusted incidence rates were calculated per 100 patient-years as 100 x n/T, where n was the number of subjects with the event and T was the total patient-years at risk of the event. Patient-years at risk were defined as the time from the first dose to the onset of the first event (for patients with an event) or to the last dose +7 days (for those without an event). eGFR (ml/min/1.73m²) calculated using the Modification of Diet in Renal Disease equation. GFR categories (ml/min/1.73 m²): stage G3a, 45 to <60; G3b, 30 to <45; G4, 15 to <30. UTI, urinary tract infection.

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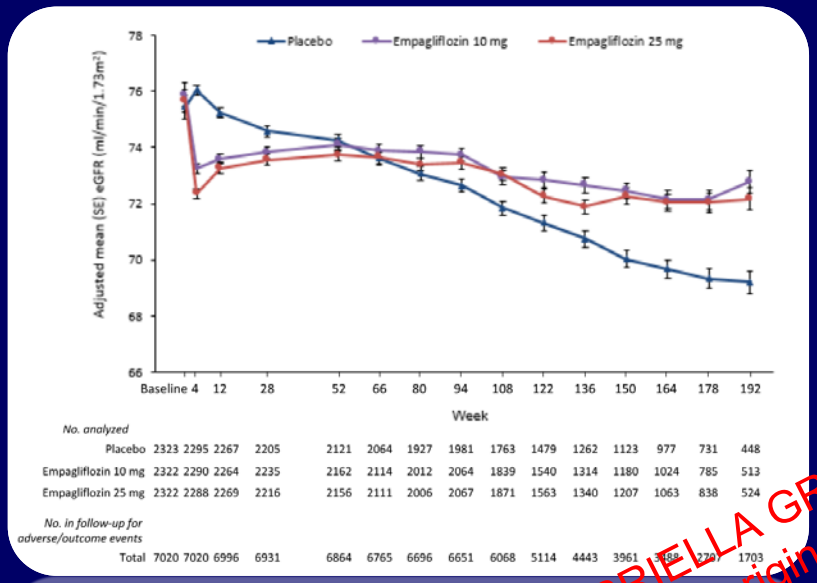
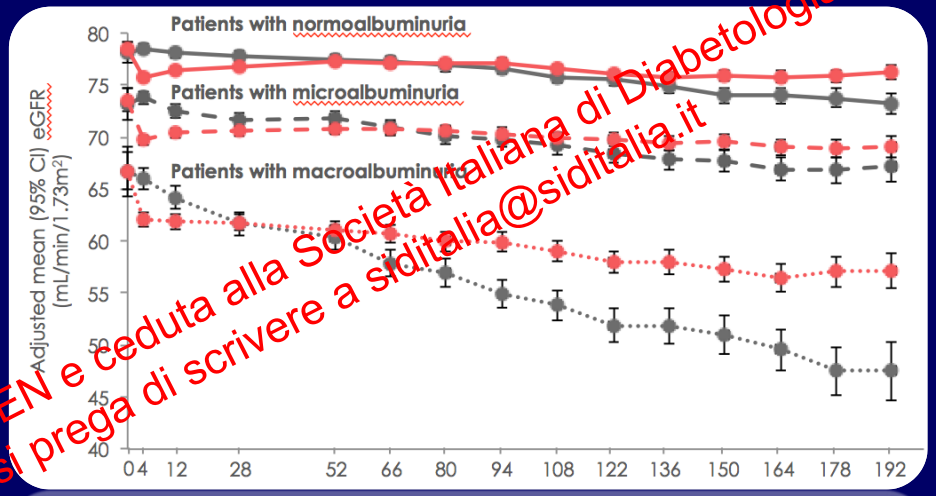
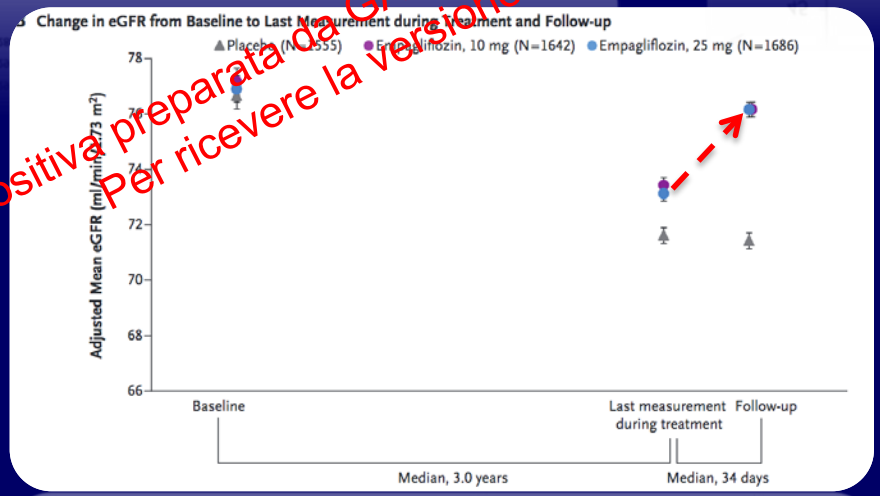
Tuttle K et al EASD 2017

EMPA-REG OUTCOME: eGFR

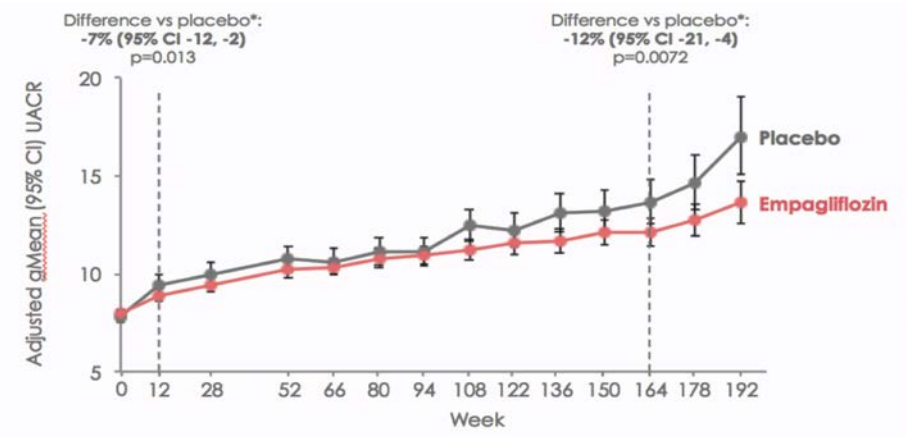


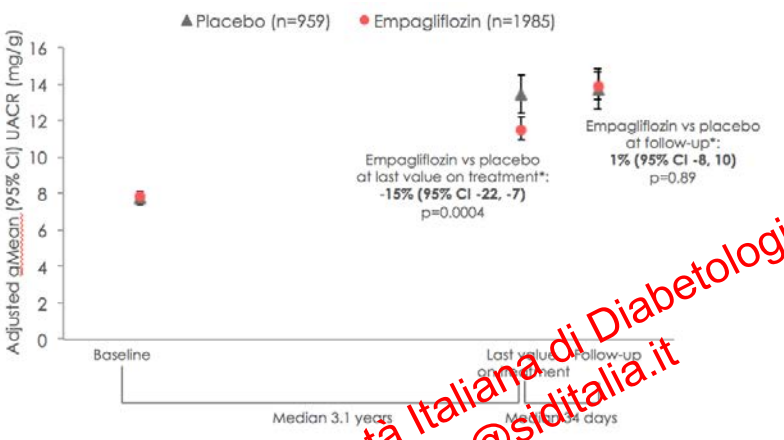




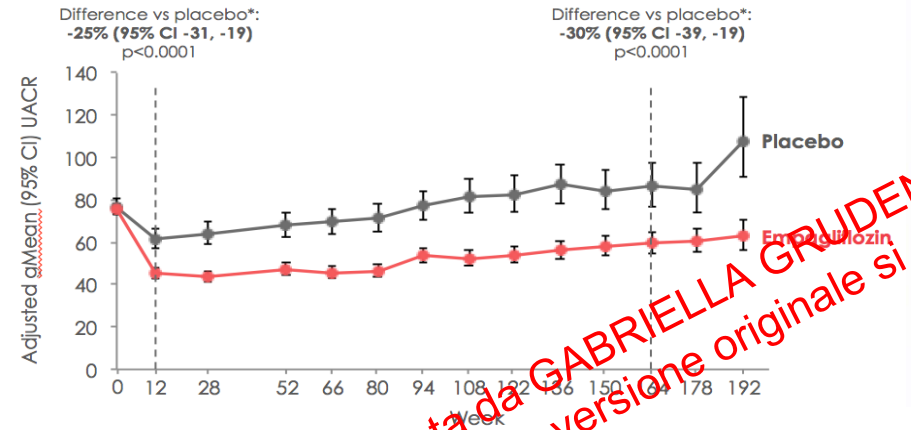
Wanner C et al NEJM 2016

DZI Cherney et Lancet Diab Endocrinol 2017

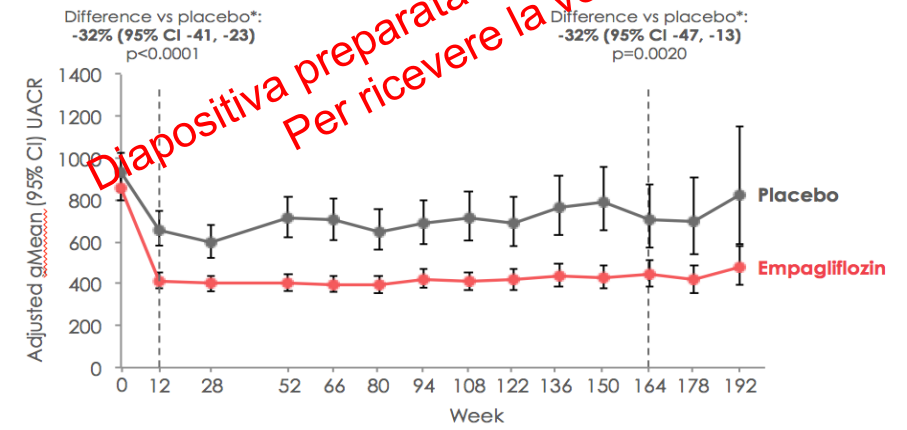


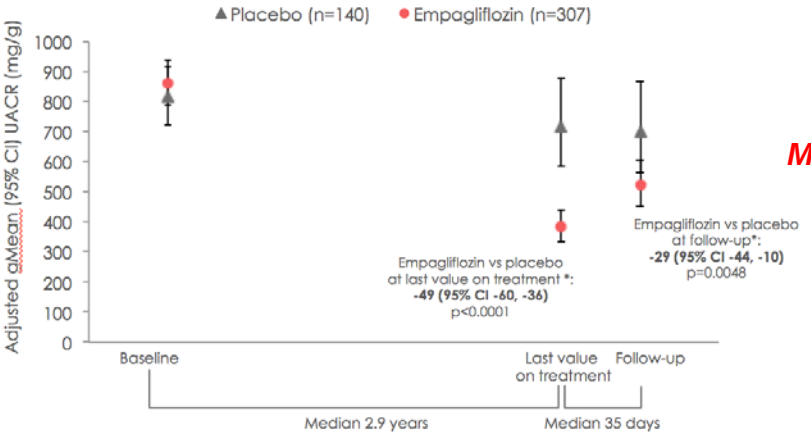


NORMO



MICRO

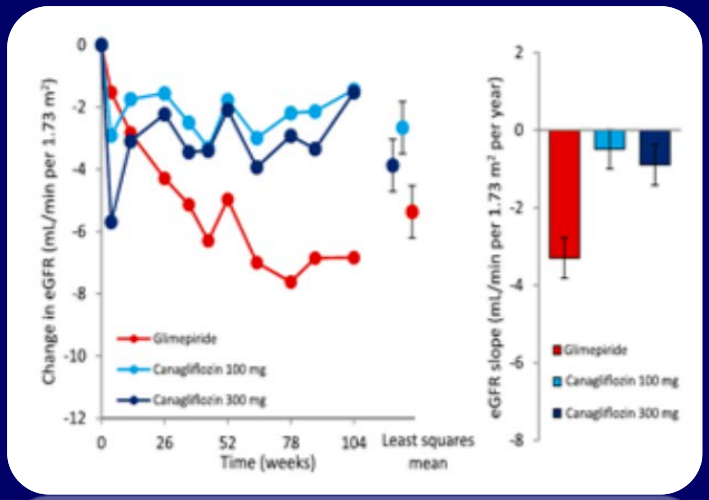


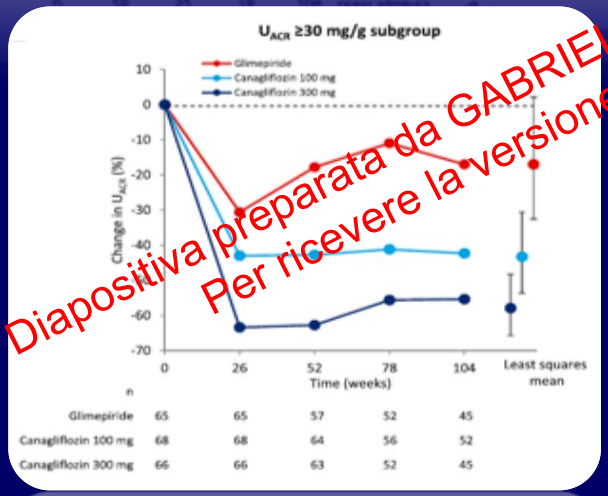


MACRO

Cherney et Lancet Diab Endocrinol 2017

CANAGLIFLOZIN: eGFR

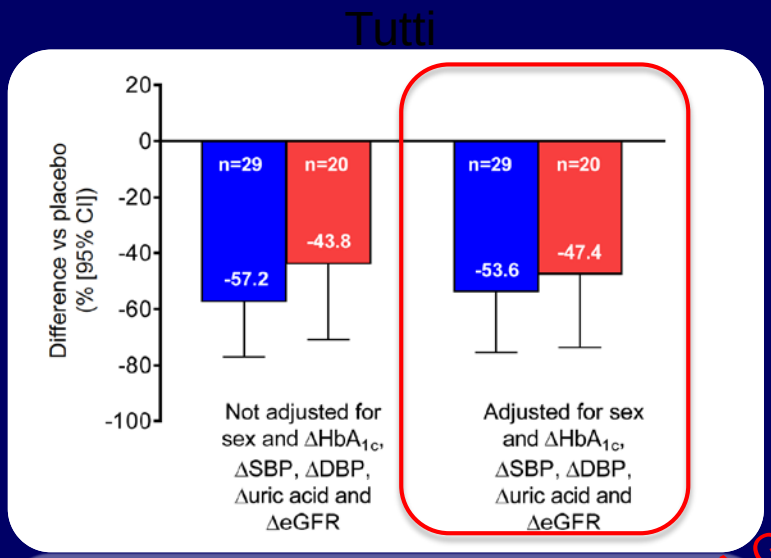


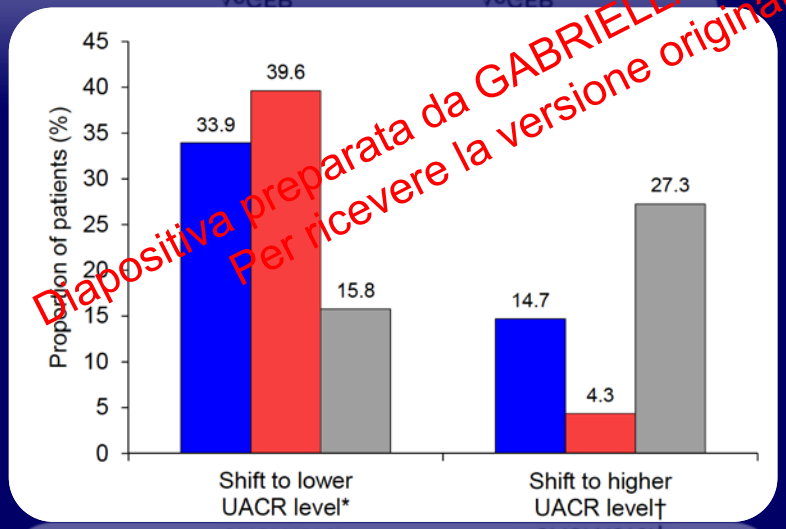


- 1450 DM2
- Metformina
  - Cana 100/300 mg o SU (glimepiride)
  - FU 2 aa
  - Indipendente da glicemia
- Limiti
  - Eventi non aggiudicati
  - 2 yrs FU
  - No eGFR post-terapia
  - Non placebo (effetto SU)

Heerspink HJ, J Am Soc Nephrol 2017

DAPAGLIFLOZIN RENAL STUDY: AER



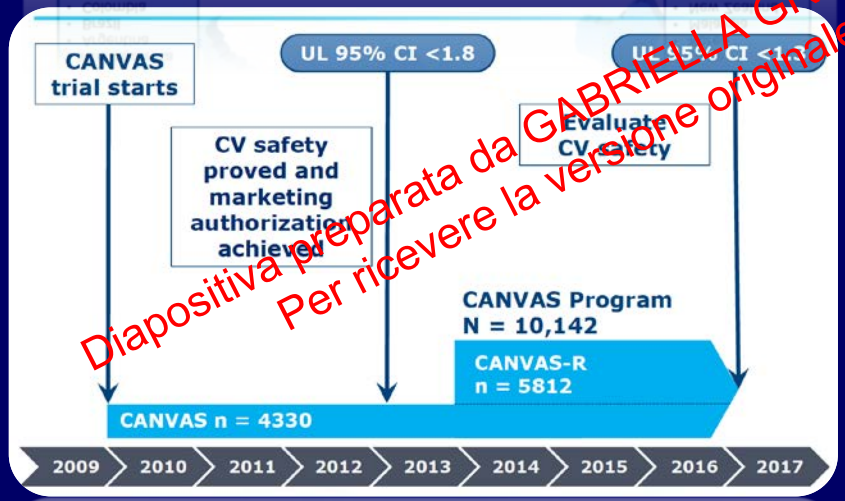


- 166 DM2 e CKD-3 e ACR >30g/g
- Dapagliflozin 10 mg o 5 mg o placebo
- 104 w

- Limiti
  - Post-hoc
  - Limitato numero casi

Fioretto P et al Diabetologia 2016

CANVAS PROGRAM



Criteri di inclusione

- Adulto con DM2
- HbA1c 7-10.5%
- Età >30 e CVD oppure età >50 e 2 FdR CV*

Criteri di esclusione

- eGFR <30 ml/min/1.73 m^2

*Diabetes duration ≥10 years, SBP >140 mmHg on ≥1 medication, current smoker, micro- or macroalbuminuria, or HDL cholesterol <1 mmol/L.

Neal B et al. NEJM 2017

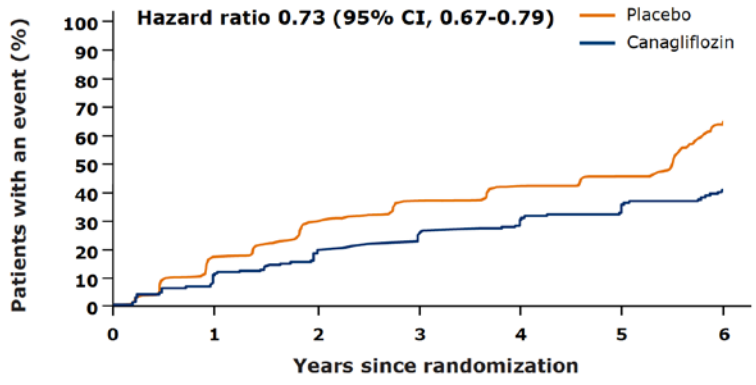
CANVAS PROGRAM

	Canagliflozin (n = 5795)	Placebo (n = 4347)
Mean eGFR, mL/min/1.73 m²	**77**	**76**
≥90 mL/min/1.73 m², %	*25*	*24*
60 to <90 mL/min/1.73 m², %	*56*	*54*
45 to <60 mL/min/1.73 m², %	*14*	*16*
<45 mL/min/1.73 m², %	*5*	*6*
Median albumin:creatinine ratio, mg/g	**12.4**	**12.4**
Normoalbuminuria (<30 mg/g), %	*70*	*70*
Microalbuminuria (30 to 300 mg/g), %	*23*	*22*
Macroalbuminuria (>300 mg/g), %	*7*	*8*
Cardioprotective agents		
RAAS inhibitor	80	80
Statin	75	75
Antithrombotic	73	74
Beta blocker	52	55
Diuretic	44	45

Popolazione a basso rischio renale

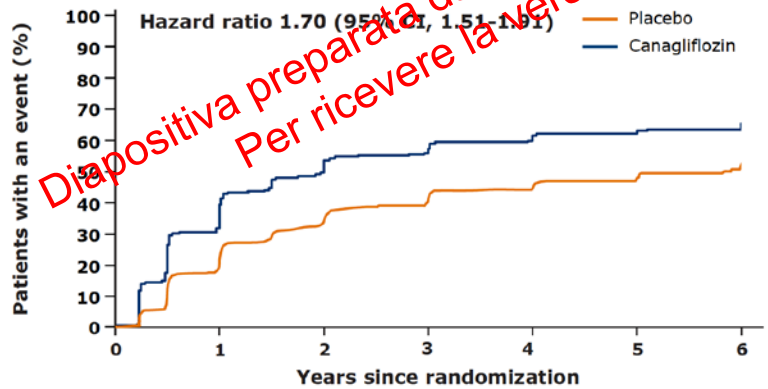
CANVAS: AER

Progression of Albuminuria



No. of patients							
Placebo	3819	3096	1690	724	626	548	303
Canagliflozin	5196	4475	2968	1730	1528	1354	775

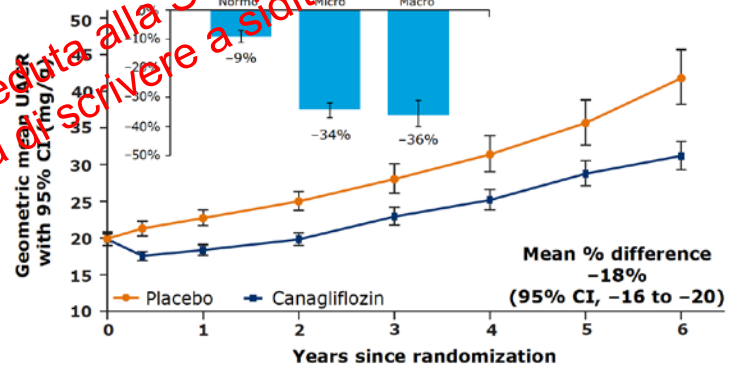
Regression of Albuminuria



No. of patients							
Placebo	1257	913	426	163	144	123	59
Canagliflozin	1679	1009	518	276	227	198	112

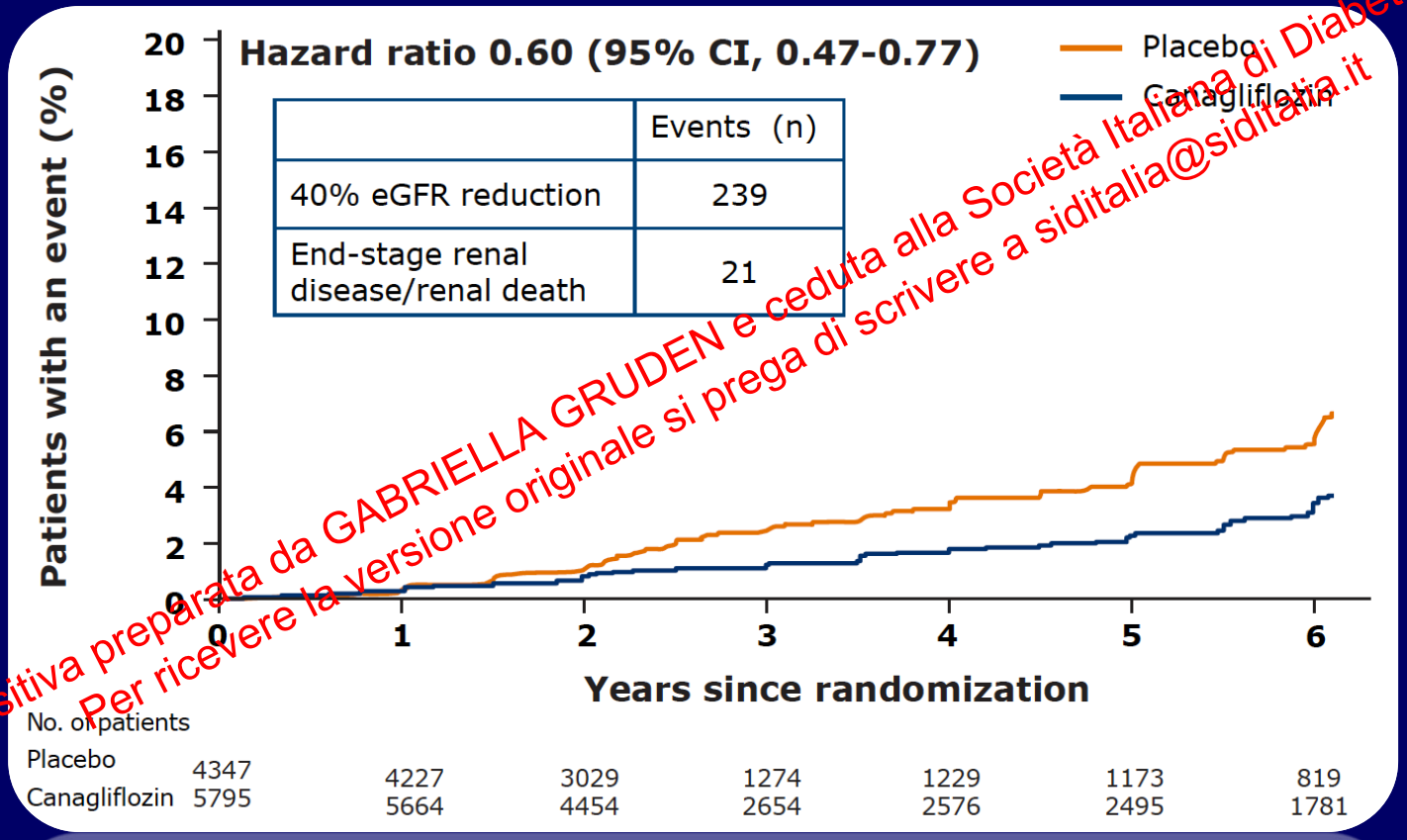
Change in Albumin:Creatinine Ratio (UACR)

Percent Change in UACR per Albuminuria Class (inset)



No. of patients							
Placebo	4084	3775	2556	753	652	594	618
Canagliflozin	5500	5103	3565	1689	1541	1408	1534

ENDPOINT RENALE COMPOSITO



Neal B et al. N Engl J Med 2017

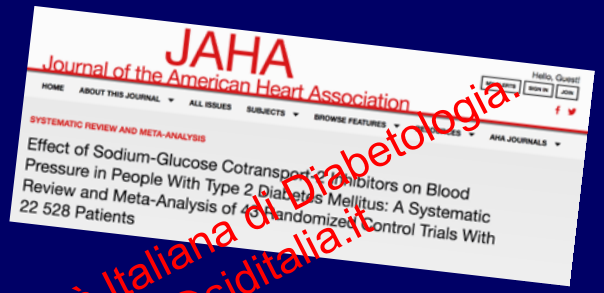
MECCANISMI DI EFFETTO

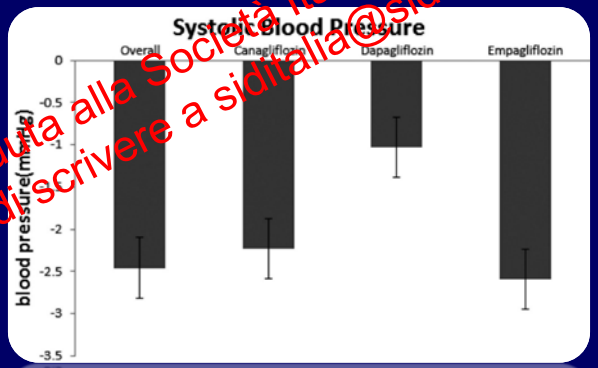
- Fattori di rischio
- Emodinamico-TGF
- RAS-mediato
- Meccanismi di danno
- Fibroblasti ^{EP}

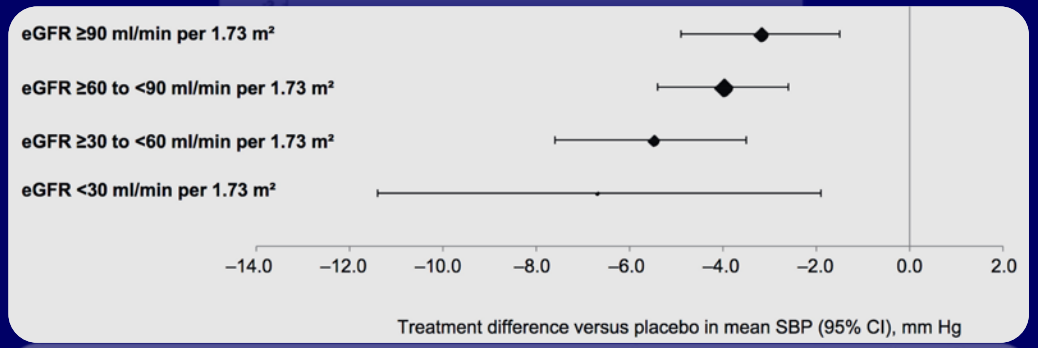
EFFETTO SU FATTORI DI RISCHIO

- ↓ HbA1c
- ↓ SBP
- ↓ Body weight
- ↓ Uric acid

↓ Danno renale

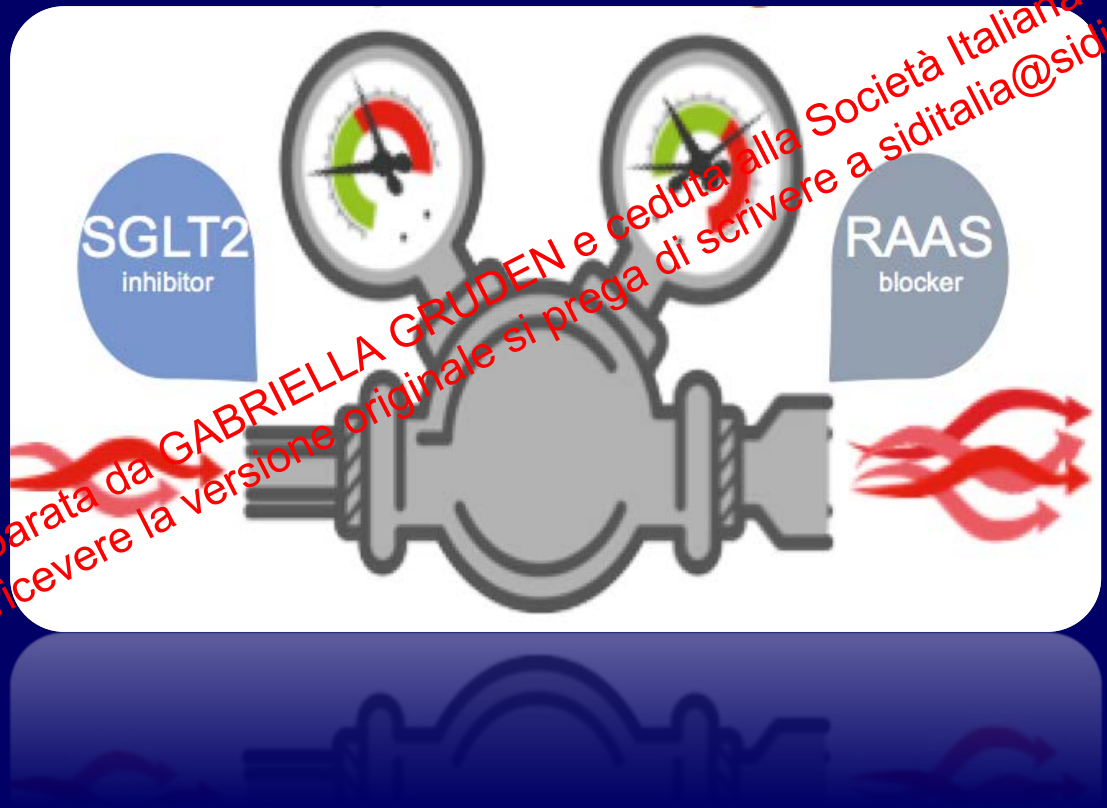






Cherney DZI, Kidney Int. 2017

EFFETTO SU EMODINAMICA GLOMERULARE



DIABETE ED EMODINAMICA GLOMERULARE

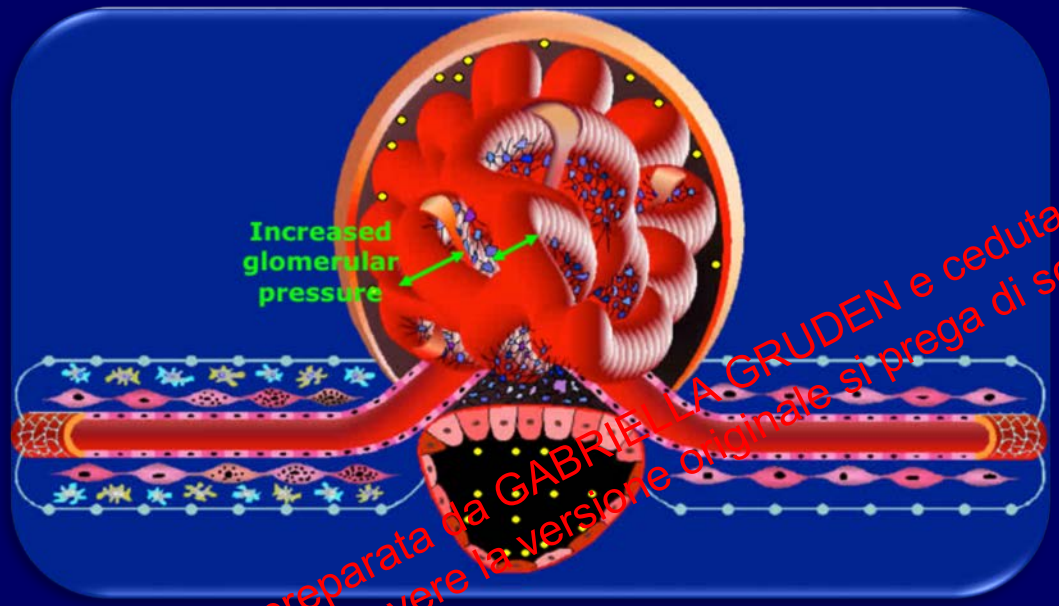
Vasodilatazione
A afferente

Vasocostrizione
A efferente

Aumento P_{GC} e
SN-FR

Danno
Glomerulare

DANNO GLOMERULARE

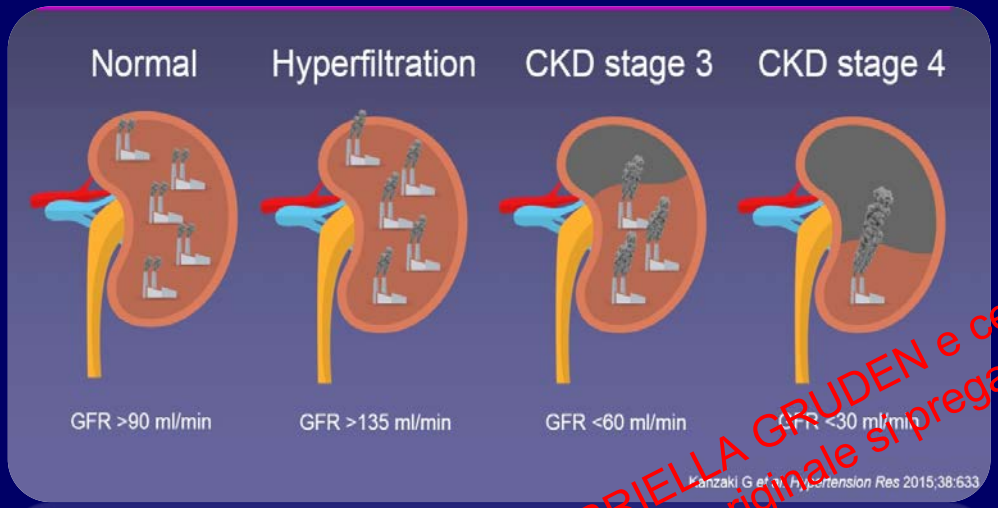


Stretch

Produzione di matrice extracellulare

Podocita: perdita di nefrina, apoptosi podocita

IPERFILTRAZIONE E DANNO RENALE



Meccanismo di inesorabile progressione del danno renale

Vasodilatazione
A afferente

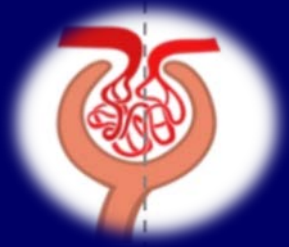
Vasocostrizione
A efferente

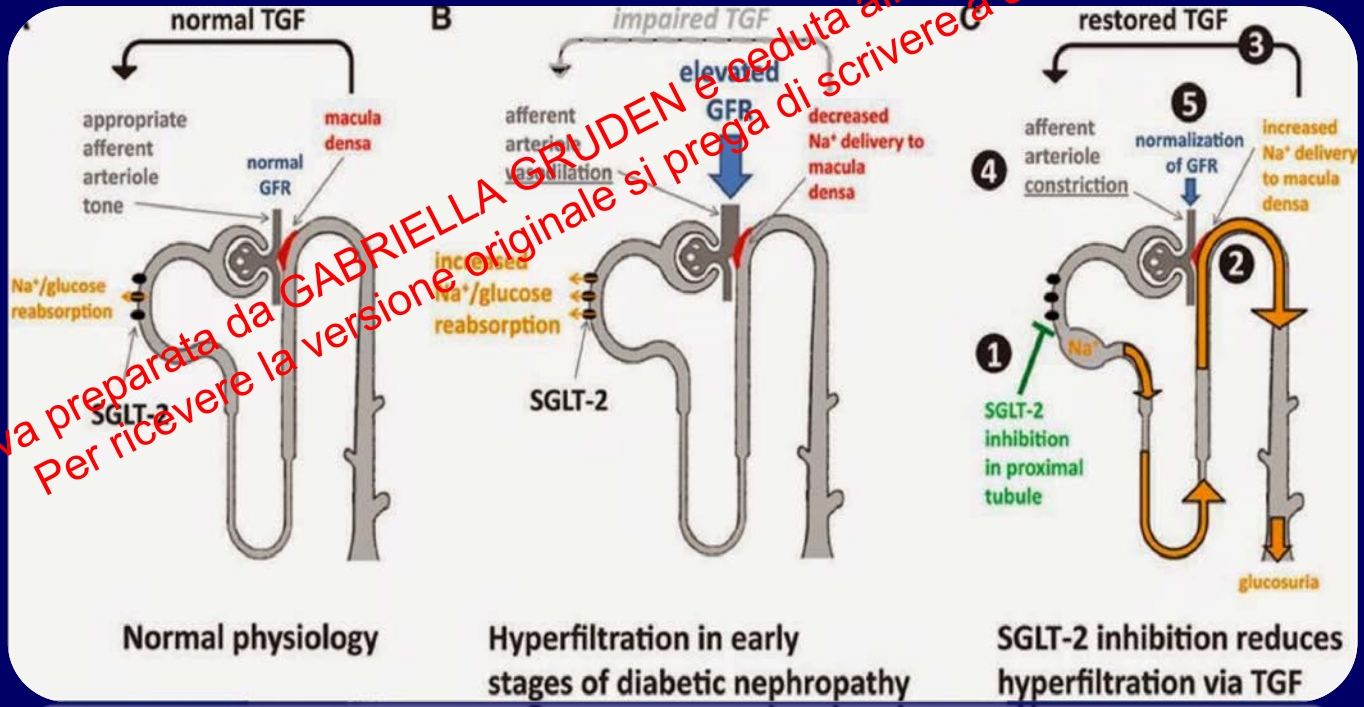
SGLT2i

ARB/ACE i

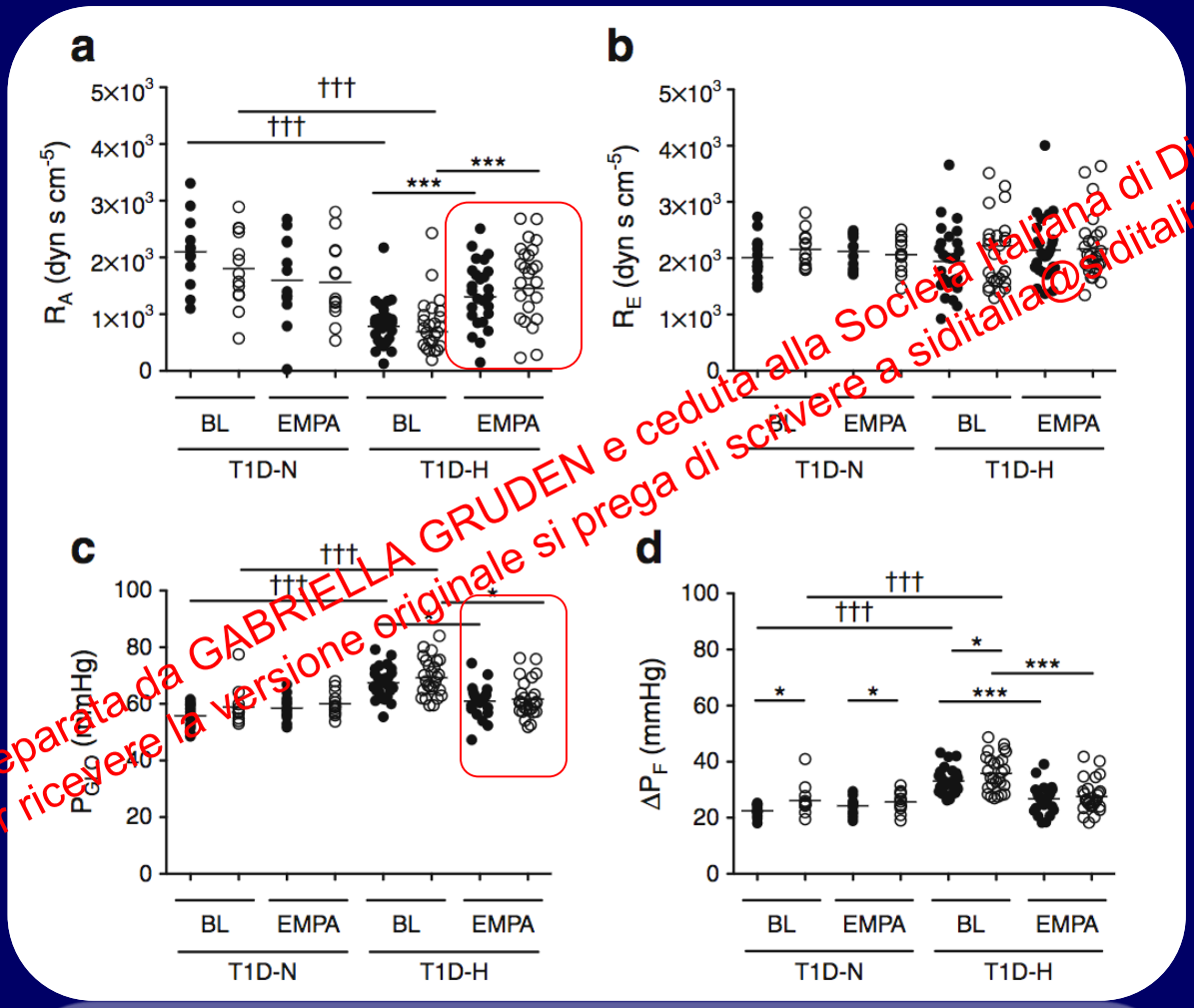
TGF

RAS



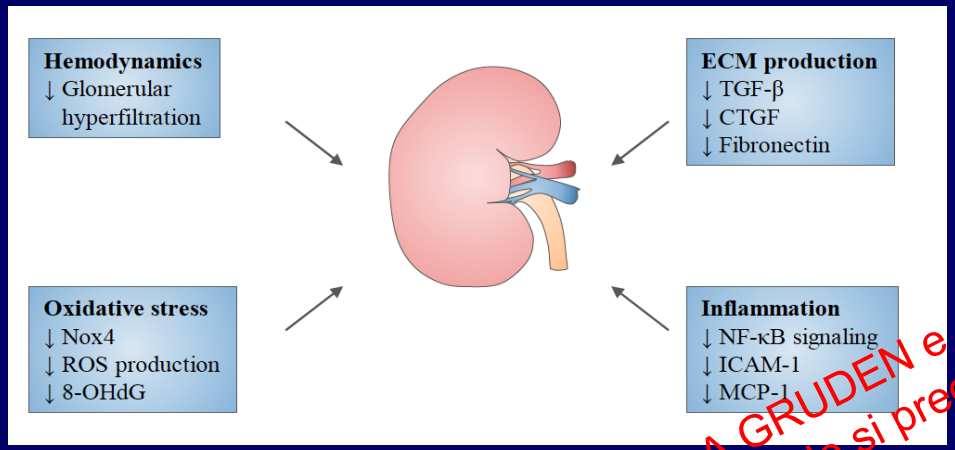


SGLT2-i Emodinamica Renale Pazienti DM1



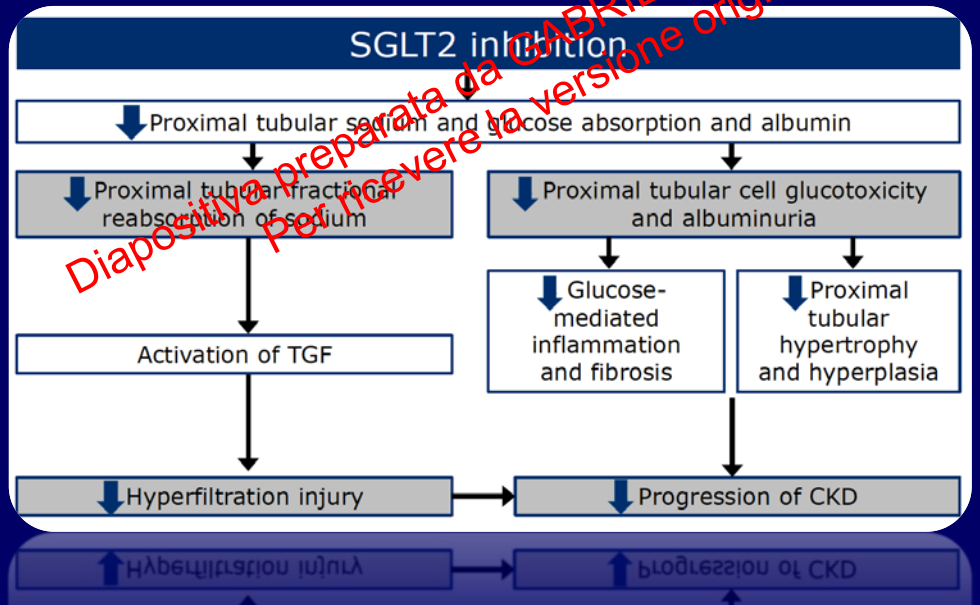
Škrtić M et al Diabetologia 2014

EFFETTO MECCANISMI
(FIBROSI, STRESS OSSIDATIVO, INFIAMMAZIONE)



RIDUZIONE:

- FIBROSI
- STRESS OSSIDATIVO
- INFIAMMAZIONE



TUBULO RENALE
GLUCOTOSSICITA’

STUDI SPERIMENTALI: SGLT2-i

Study	Model	Drug/Dose/Duration	Major Effects
Malatiali et al. [29]	STZ-diabetic rats	phlorizin, 800 mg/kg, 6 days (initial dose: 400 mg/kg)	↓ Glomerular hyperfiltration, ↓ Kidney size, ↓ Oxidative stress
Osorio et al. [30]	STZ-diabetic rats	phlorizin, 400 mg/kg, 30 days	↓ Oxidative stress
Vallon et al. [27]	Akita mice	empagliflozin, 300 mg/kg, 15 weeks	↓ Glomerular hyperfiltration, ↓ Albuminuria, ↓ Kidney Weight, ↓ Inflammation
Gembardt et al. [31]	BTBR ob/ob mice	empagliflozin, diet containing 300 ppm of empagliflozin, 12 weeks	↓ Albuminuria, ↓ Glomerular hypertrophy, ↓ Inflammation, ↓ Mesangial matrix expansion
	BTBR ob/ob mice with hypertension (angiotensin-II infusion)	empagliflozin, 300 ppm, 12 weeks	↓ Albuminuria
Ojima et al. [32]	STZ-diabetic rats	empagliflozin, 10 mg/kg, 4 weeks	↔ Albuminuria, ↓ AGE/RAGE, ↓ Oxidative stress, ↓ Inflammation, ↓ Fibrotic gene markers, ↓ Tubular injury
Gangadharan Komala et al. [38]	eNOS-deficient-STZ-diabetic mice	empagliflozin, 10 mg/kg, 19 weeks	↔ Albuminuria, ↔ Glomerulosclerosis, ↔ Interstitial fibrosis, ↔ TGF-β, ↔ Fibronectin, ↔ MCP-1
Gallo et al. [39]	db/db mice	empagliflozin, 10 mg/kg, 10 weeks	↔ Albuminuria ↓ Profibrotic gene markers, ↓ Fibronectin, ↓ TGF-β
Kojima et al. [34]	T2DN rats (McWi strain)	luseogliflozin, 10 mg/kg, 3 weeks	↔ Proteinuria ↓ Glomerulosclerosis
Terami et al. [35]	db/db mice	dapagliflozin, 0.1 mg/kg or 1.0 mg/kg, 12 weeks	↓ Albuminuria, ↓ Oxidative stress, ↓ Inflammation
Hatanaka et al. [36]	Akita mice	dapagliflozin, 1.0 mg/kg, 12 weeks	↓ Albuminuria, ↓ Oxidative stress, ↓ Macrophage infiltration
Nagata et al. [37]	db/db mice	tofogliflozin, Diet containing 0.005% or 0.015% of tofogliflozin, 8 weeks	↓ Albuminuria, ↓ Glomerular hypertrophy
Wang et al. [23]	db/db mice	JNJ39933673, Diet containing 0.07 g/kg of JNJ39933673, 12 weeks	↓ Albuminuria, ↓ Mesangial expansion, ↓ Podocyte injury, ↓ Renal lipid accumulation

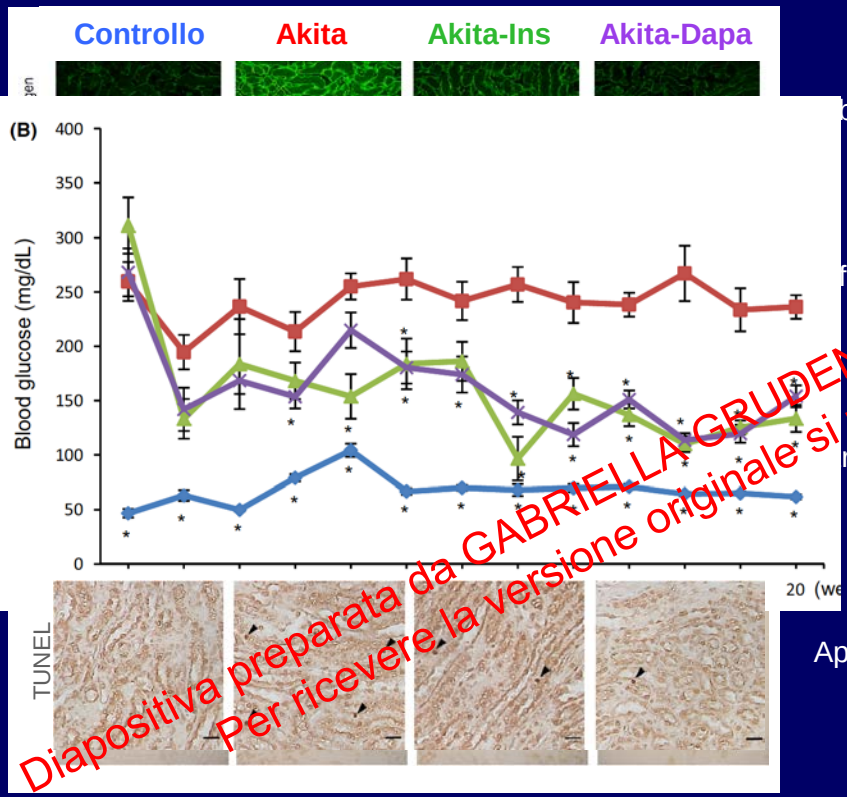
Stress ossidativo

Infiammazione

Fibrosi

- Inconsistenti (modello animale, farmaco, dose, durata)
- Non controllati

Dapagliflozin: Danno Tubulo Interstiziale



brosi interstizio

fiammazione

ress ossidativo

Apoptosi

- Controllo
- Akita
- Akita + Dapa
- Akita + Insulina

Hatanaka et al Pharmacol Res Perspec 2016

SGLT2-i – FIBROBLASTI^{EP}

Aumento Hct: emoconcentrazione, eritropoiesi (EP)

Fibroblasti^{EP} ⇄ Miofibroblasti

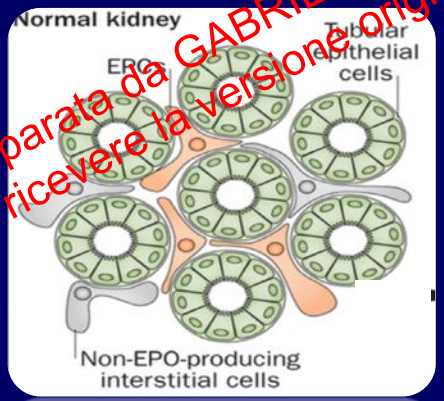
↓ ↓

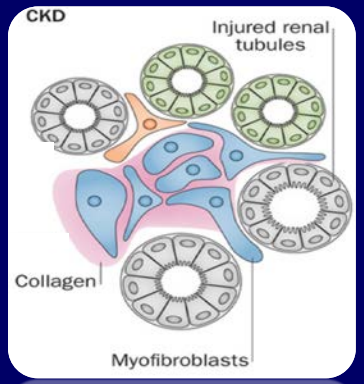
Eritropoiesi

Fibrosi interstiziale

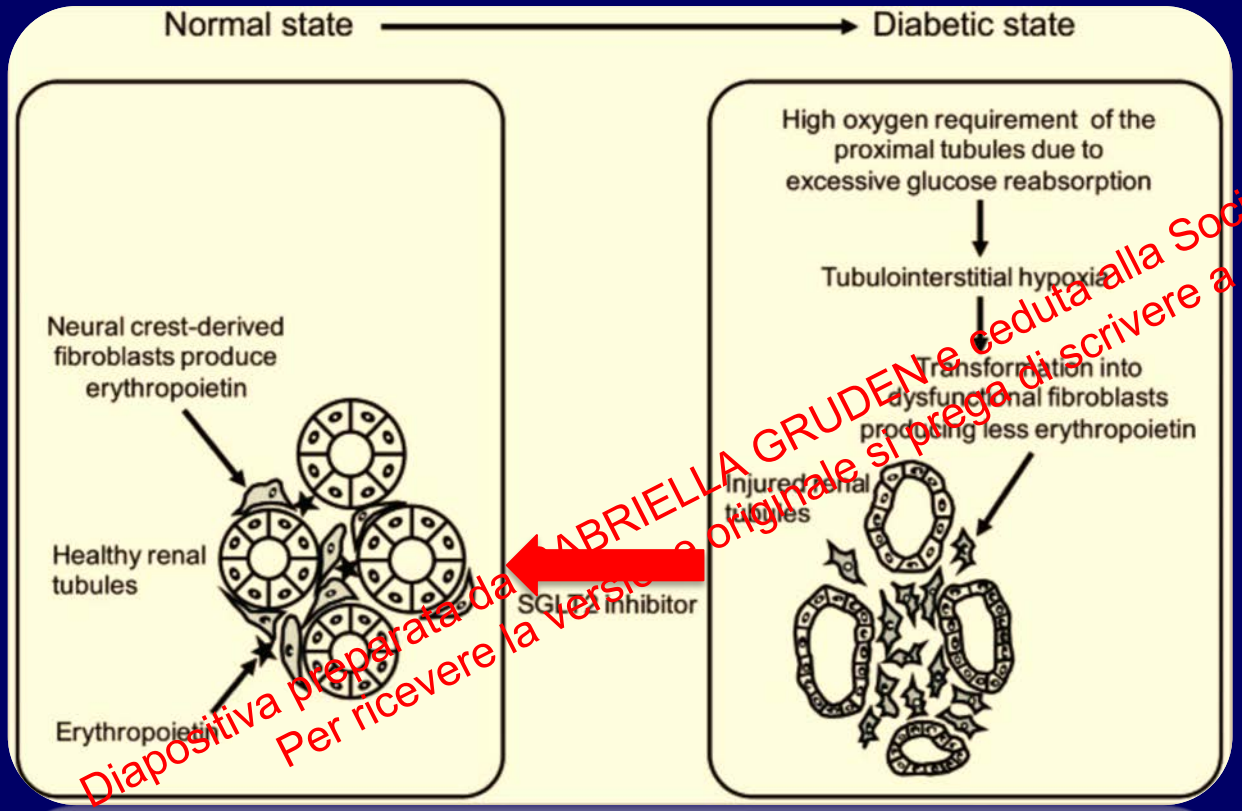
↓

ESRF





SGLT2-i – FIBROBLASTI^{EP}



Diabete

- Riassorbimento Na-Glucoso TP
- Elevato consumo O2
- Ipossia tubulo-interstiziale
- Fibroblasti^{EP} → miofibroblasti

SGLT2-i

SGLT2-i – Nefropatia Diabetica

- Effetto protettivo
- Trial renali dedicati

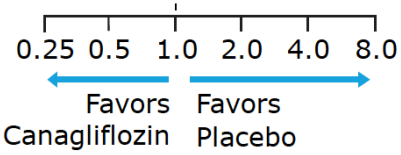
Name Of the Study	DECLARE	VERTIS	CREDENCE	DAPA-CKD	EMPAGLIFLOZIN RENAL
Clinical trial registration	NCT01730534	NCT01986881	NCT02065791	NCT03036150	TBA
Intervention	Dapagliflozin versus placebo	Ertugliflozin versus placebo	Canagliflozin versus placebo	Dapagliflozin versus placebo	Empagliflozin versus placebo
Patient population	DM2, high CV risk	DM2, established vascular disease	DM2, high CV risk	DM2 and nonpatients with diabetes, high CV risk	DM2 and nonpatients with diabetes, high CV risk
Kidney function inclusion criteria	eGFR≥30 ml/min per 1.73 m^2	eGFR≥30 ml/min per 1.73 m^3	30≥ eGFR≤90 ml/min per 1.73 m^2 (CKD 2 and 3)	30≥ eGFR≤90 ml/min per 1.73 m^3 (CKD 2 and 3)	30≥ eGFR≤90 ml/min per 1.73 m^4 (CKD 2 and 3)
Number of patients	17,276	8000 (estimated)	4461	4000 (estimated)	TBA
Prespecified renal endpoints	Time to first event of renal composite endpoint: Confirmed sustained ≥40% decrease in eGFR to eGFR<60 ml/min per 1.73 m^2 and/or ESRD and/or renal or CV death	Time to composite of renal death, renal dialysis/transplant, or ≥2×increase in baseline serum creatinine	Time to the first occurrence of an event in the primary composite endpoint (primary) ESRD, doubling of serum creatinine, renal or CV	Time to the first occurrence of any of the components of the composite: ≥50% sustained decline in eGFR or reaching ESRD or CV death or renal death	TBA

CANVAS PROGRAM: EFFETTI AVVERSI

	Event rate per 1000 patient-years		Hazard ratio (95% CI)
	Canagliflozin	Placebo	
Female genital mycotic infection (n = 196)	69	18	4.37 (2.78-6.88)
Urinary tract infection (n = 440)	40	37	1.09 (0.89-1.34)

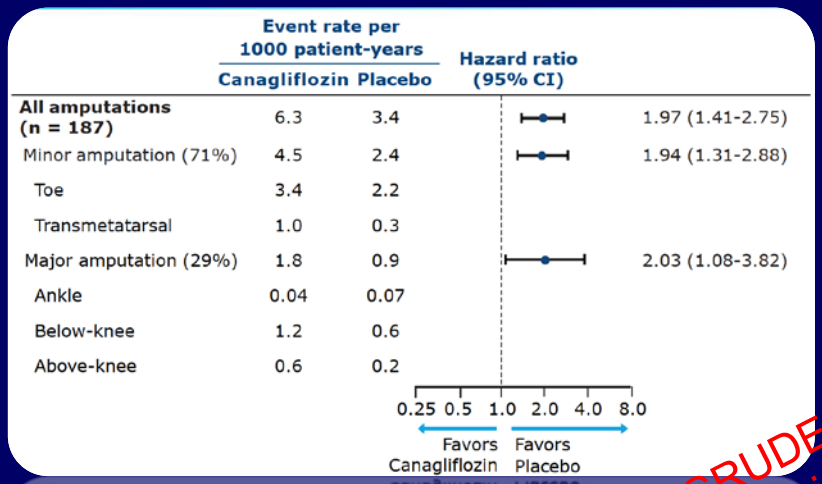
Renal Safety

	Event rate per 1000 patient-years		Hazard ratio (95% CI)
	Canagliflozin	Placebo	
Serious renal-related (n = 83)	2.5	3.3	0.76 (0.49-1.19)
Serious acute kidney injury (n = 58)	1.6	2.5	0.68 (0.45-1.02)
Serious hyperkalemia (n = 15)	0.4	0.6	0.75 (0.27-2.11)



Neal B et al. N Engl J Med 2017

CANVAS PROGRAM: EFFETTI AVVERSI

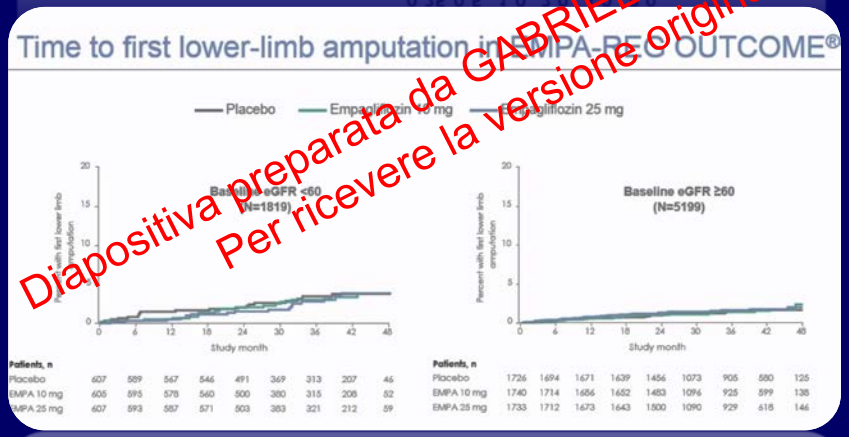


Amputation Risk Factors - Multivariate Analysis

Risk Factor at Baseline	Hazard Ratio	95% CI
Amputation	20.9	(14.2-30.8)
Peripheral vascular disease*	3.1	(2.2-4.5)
Male	2.3	(1.6-3.5)
Neuropathy	2.1	(1.6-2.9)
HbA1c >8%	1.9	(1.4-2.6)
Canagliflozin treatment	1.8	(1.3-2.5)
Presence of CV disease	1.5	(1.0-2.3)

- Predictors of amputation risk are similar in both arms
- Canagliflozin treatment, independent of the risk factors, increased amputation risk

*Predictive on univariate analysis: nephropathy, insulin use, retinopathy, loop diuretic, eGFR, diabetes duration
Factors assessed but not significantly predictive: non-loop diuretic, smoking, SBP, hemoglobin, age

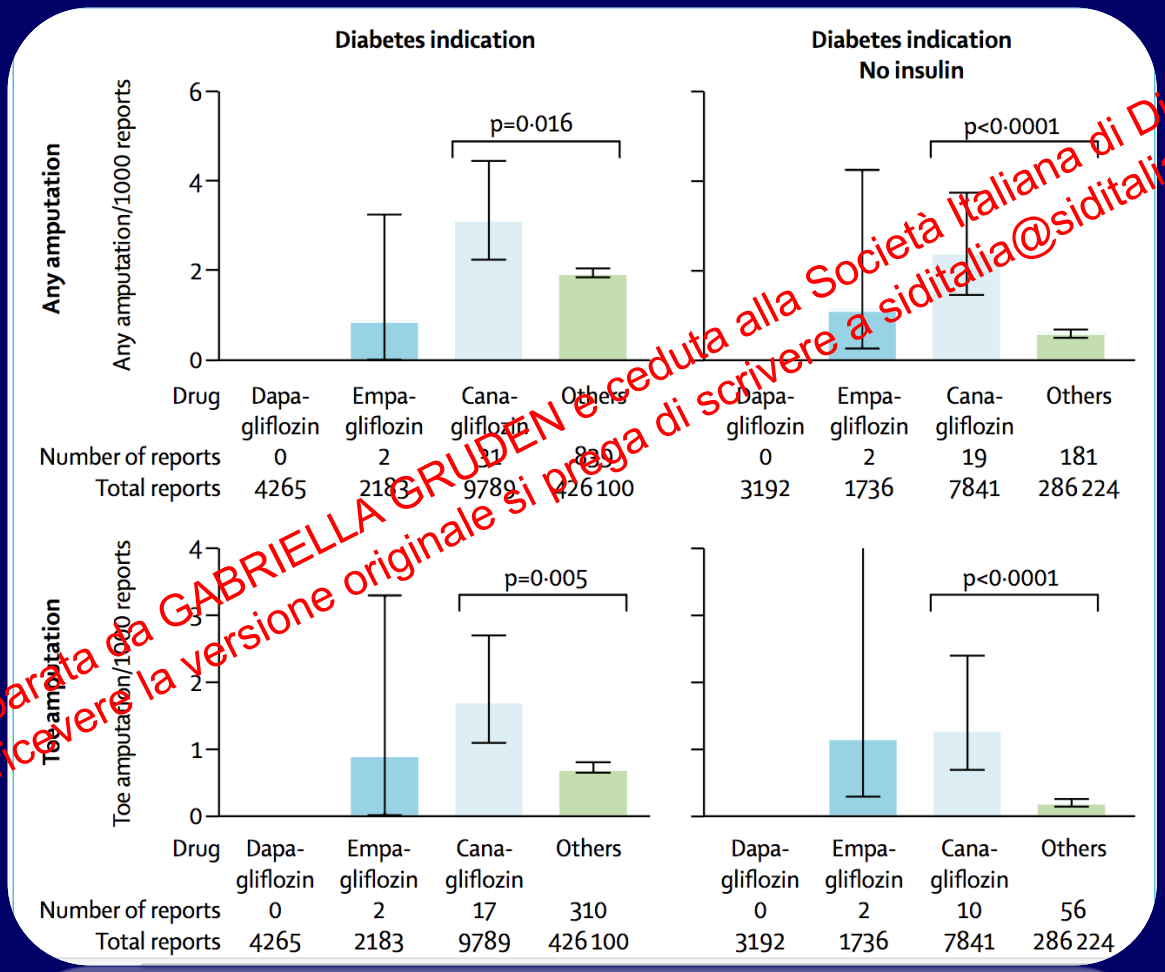


Amputation	Placebo/comparator-controlled 30-study pool	
	Control (N=4629; 4177 patient-years)	Dapagliflozin total (N=9195; 8059 patient-years)
Patients with lower-limb amputation, n (%)	7 (0.2)	8 (0.1)

Neal B et al. N Engl J Med 2017

Joubbour S Diabetes Obes Metab. 2017

Amputations in the US FDA Adverse Event Reporting System

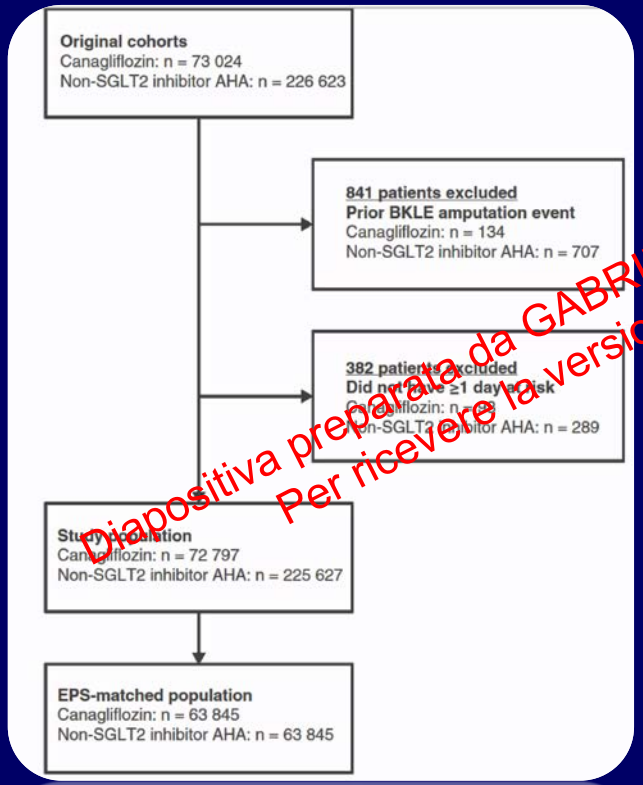


Fadini GP et al Lancet Diab Endocrinol 2017

Amputazioni e Canagliflozin Real World Data

Risk of lower extremity amputations in people with type 2 diabetes mellitus treated with sodium-glucose co-transporter-2 inhibitors in the USA: A retrospective cohort study

Zhong Yuan MD, PhD[1] | Frank J. DeFalco BA[2] | Patrick B. Ryan PhD[1] | Martijn J. Schuemie PhD[1] | Paul E. Stang PhD[1] | Jesse A. Berlin ScD[3] | Mehul Desai MD[2] | Norm Rosenthal MD[2]



Overall					
SGLT2 inhibitors	119 567	225	140 145	171	1.22
Canagliflozin	73 024	139	95 422	131	1.26
Dapagliflozin	39 117	76	38 541	37	0.96
Empagliflozin	24 433	55	17 930	85	1.39
Non-SGLT2 inhibitor AHA	226 623	722	161 366	330	1.87
High CV risk					
SGLT2 inhibitors	25 781	120	29 650	61	2.03
Canagliflozin	15 850	75	20 594	41	1.99
Dapagliflozin	8045	46	7829	10	1.28
Empagliflozin	5186	22	4098	14	3.42
Non-SGLT2 inhibitor AHA	68 483	357	58 903	194	3.29
Non-high CV risk					
SGLT2 inhibitors	93 786	105	110 095	110	1.00
Canagliflozin	57 174	64	74 827	79	1.06
Dapagliflozin	31 072	30	30 712	27	0.88
Empagliflozin	18 865	33	13 831	11	0.80
Non-SGLT2 inhibitor AHA	178 140	365	224 503	336	1.50

Incidenza di amputazione BKLE
1.18 vs. 1.12 per 1000 person-years
HR 0.98 [95% CI 0.68-1.41]

Yuan Z Diabetes Obes Metab. 2017

CANVAS: AMPUTAZIONI

- Riduzione outcome primario MACE: shift da hard a soft CV endpoint
- Intention to treat: 30%
- Deplezione di volume

Table 2. Adverse Events.*

Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
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

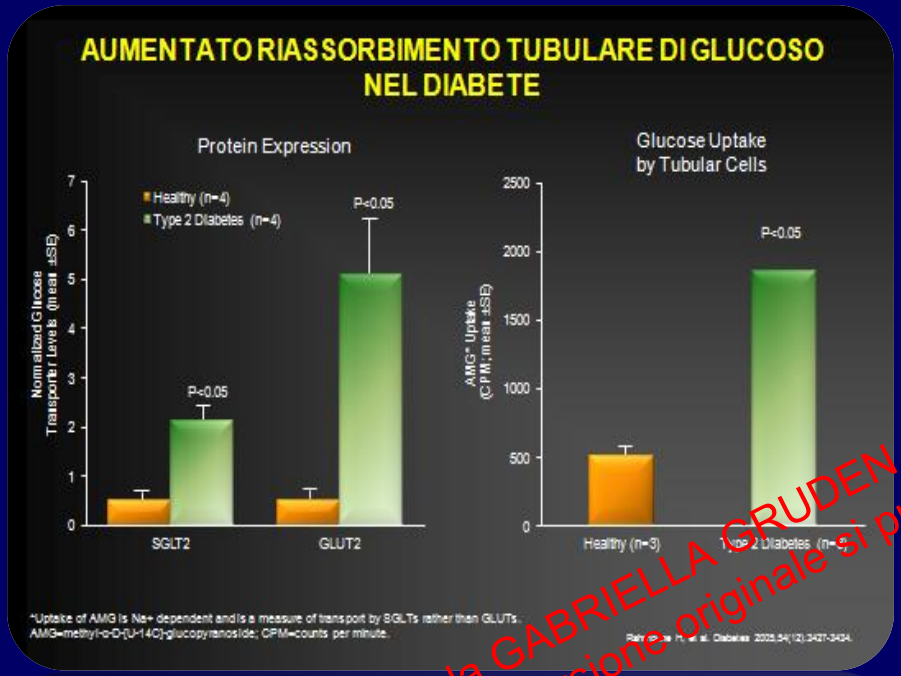
CANVAS

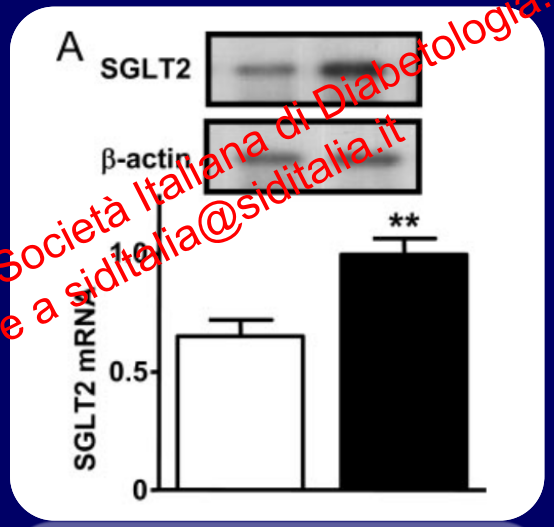
Table 2. Adverse Events.*

Event	Placebo (N=2333)	Empagliflozin, 10 mg (N=2345)	Empagliflozin, 25 mg (N=2342)	Pooled Empagliflozin (N=4687)
	number of patients (percent)			
Event consistent with volume depletion‡‡	115 (4.9)	115 (4.9)	124 (5.3)	239 (5.1)

EMPA

SGLT2 & DM





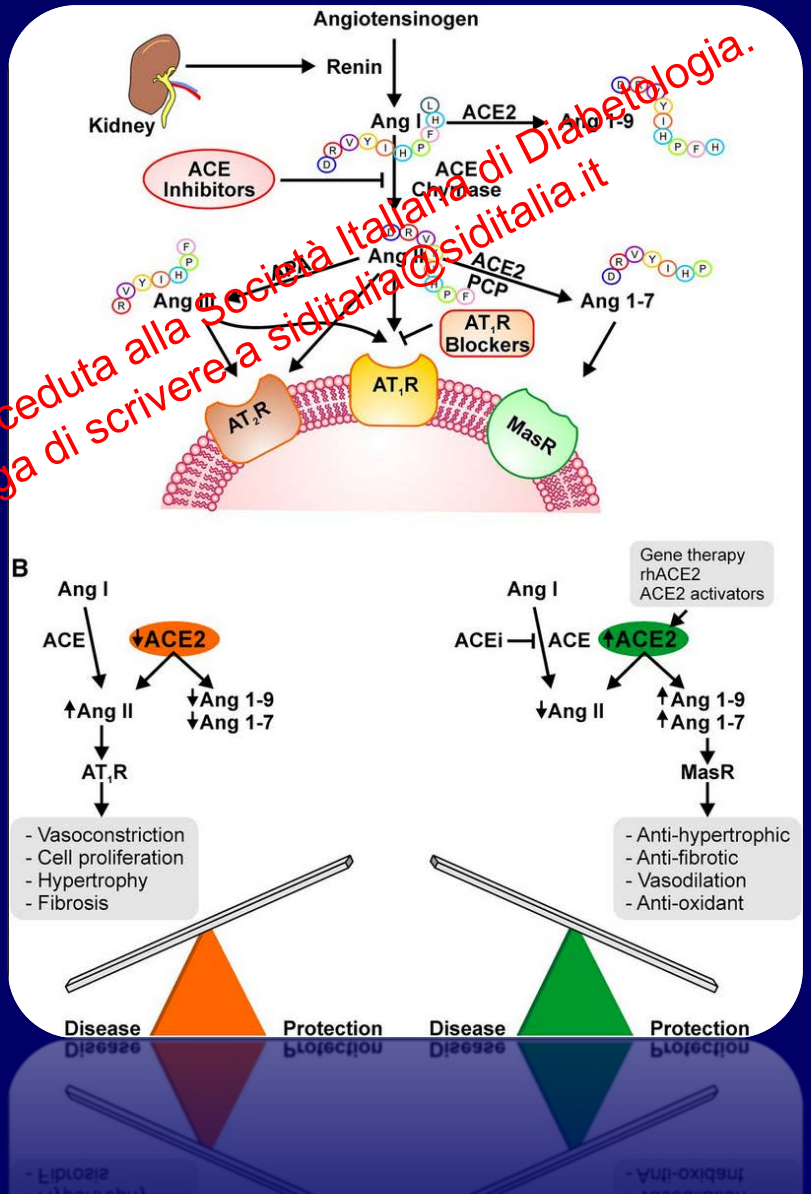
Freitas HS et al. Endocrinology 2008

	SGLT2	GLUT2	SGLT1	GLUT1
Norton L	↓	↓	↑	=
Solini A	↓	↓	=	=
Wang XX	↑			

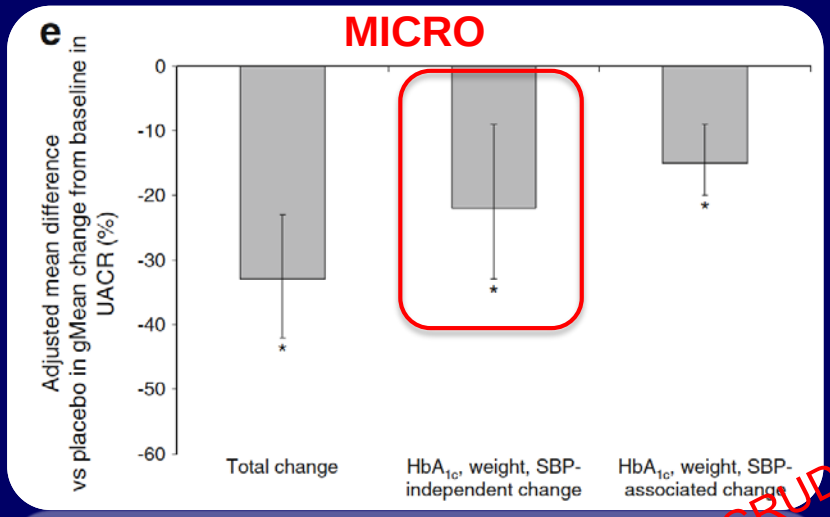
Biopsie renali umane

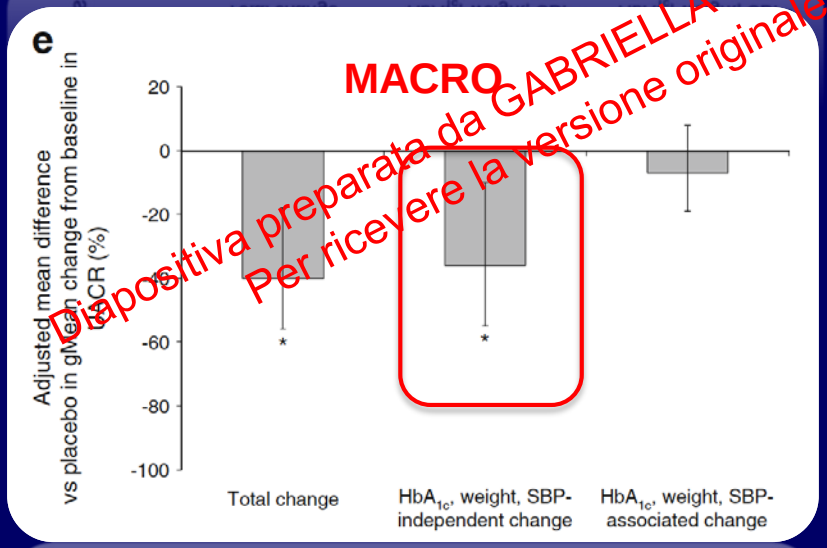
EFFETTO RAS-MEDIATO

- SGLT2-i lieve aumento tono del RAS (diuretico e natriuretico)
- EMPA REG CANVAS 80% pazienti erano trattati con bloccanti del RAS
- Aumento pathway alternative di tipo protettivo (AT2, Ang 1-7)



POOL ANALYSIS: EMPA

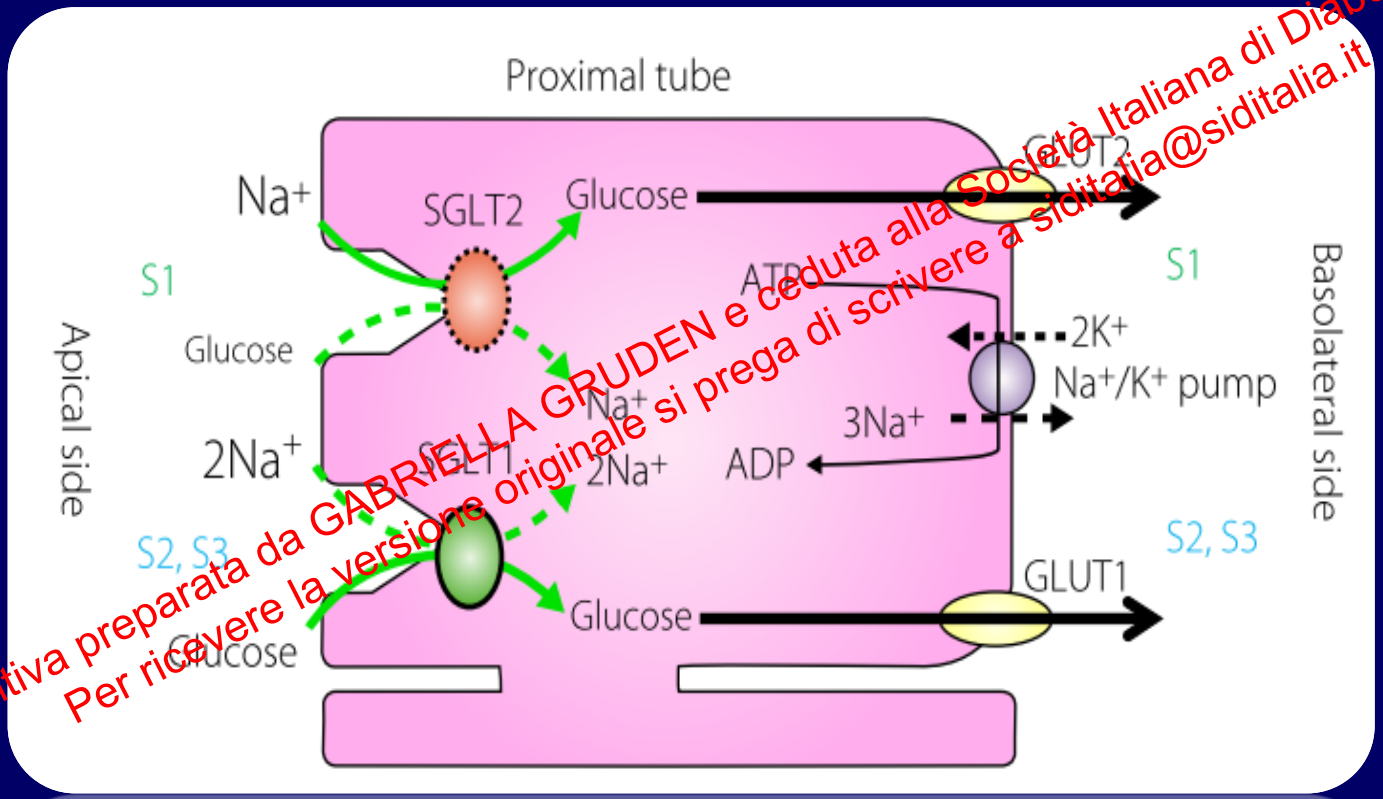




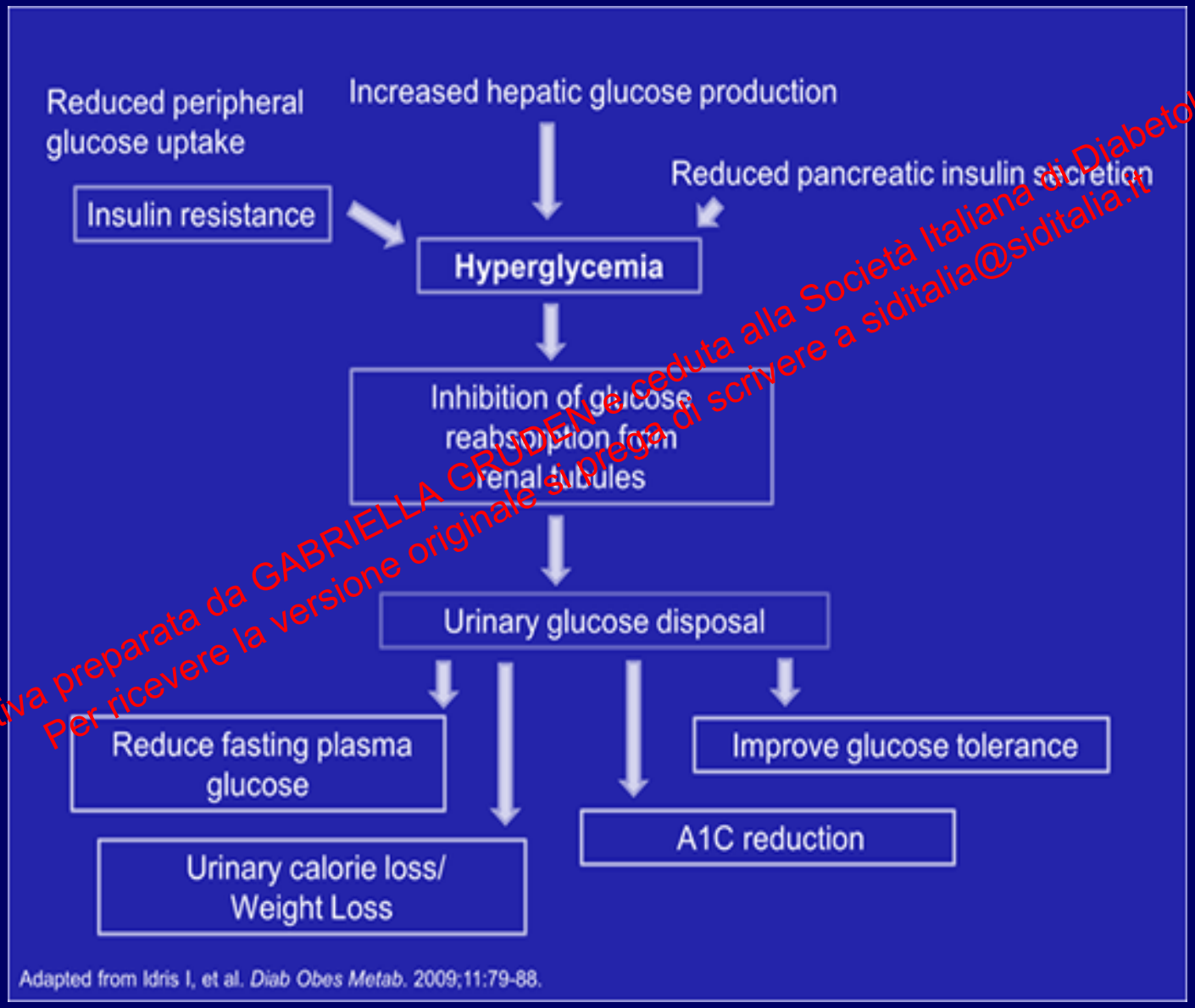
- Pool 5 studi fase III con EMPA
- DM2 con micro/macro
- % change UAER 24 w

Cherney D et al Diabetologia 2016

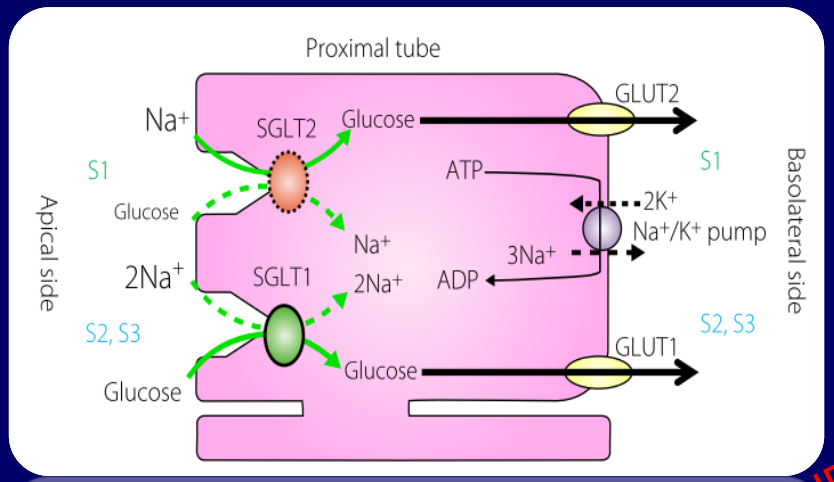
COTRASPORTATORE SODIO-GLUCOSO

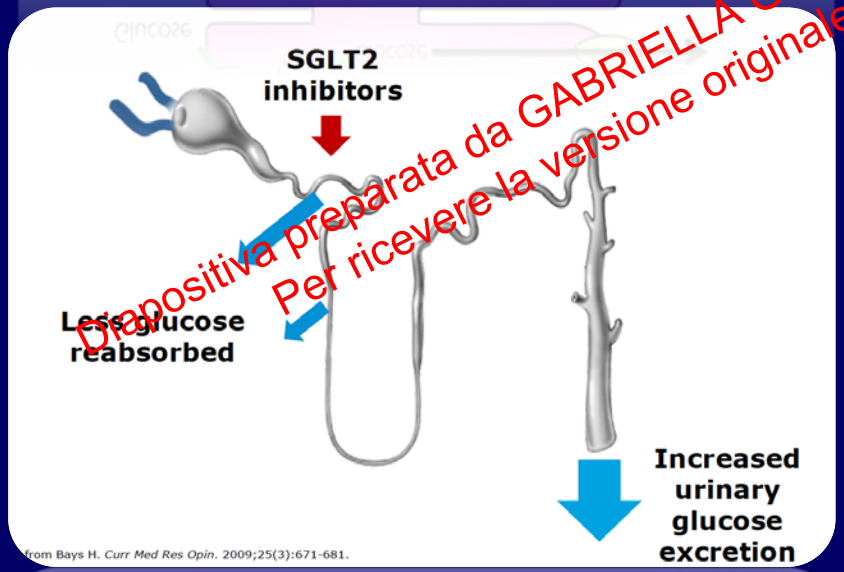


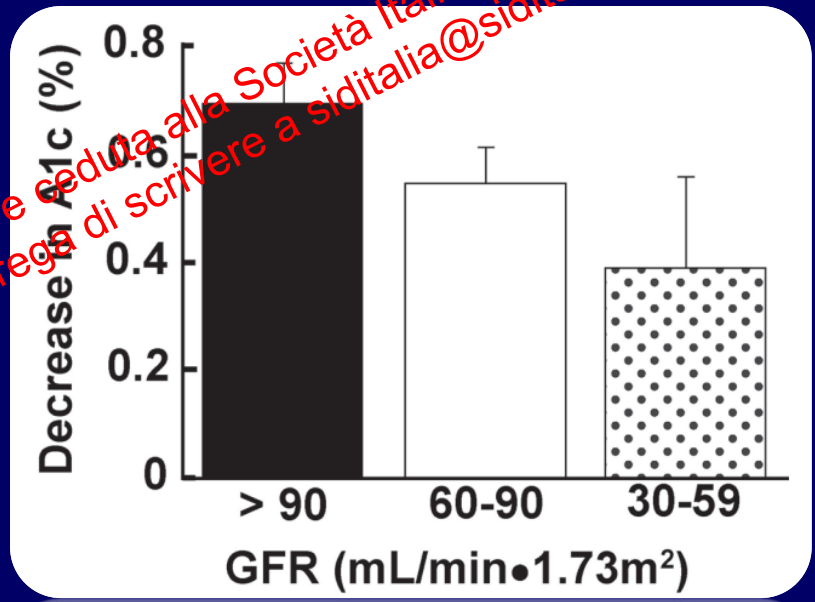
INIBITORI DEL SGLT2



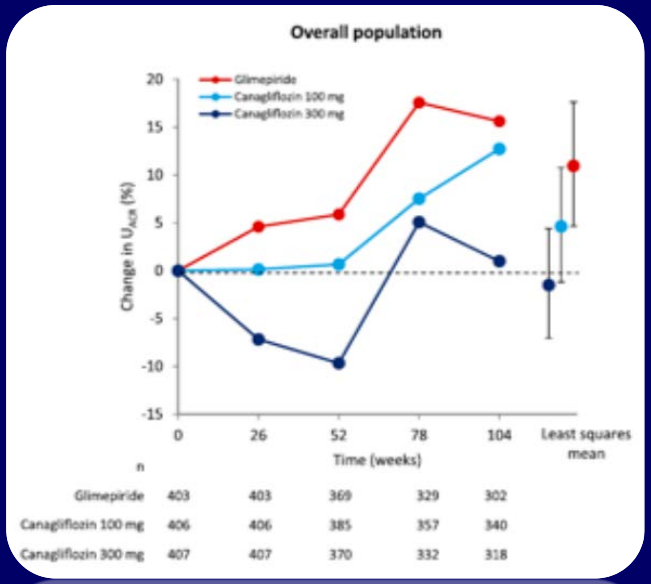
INIBITORI SGLT2







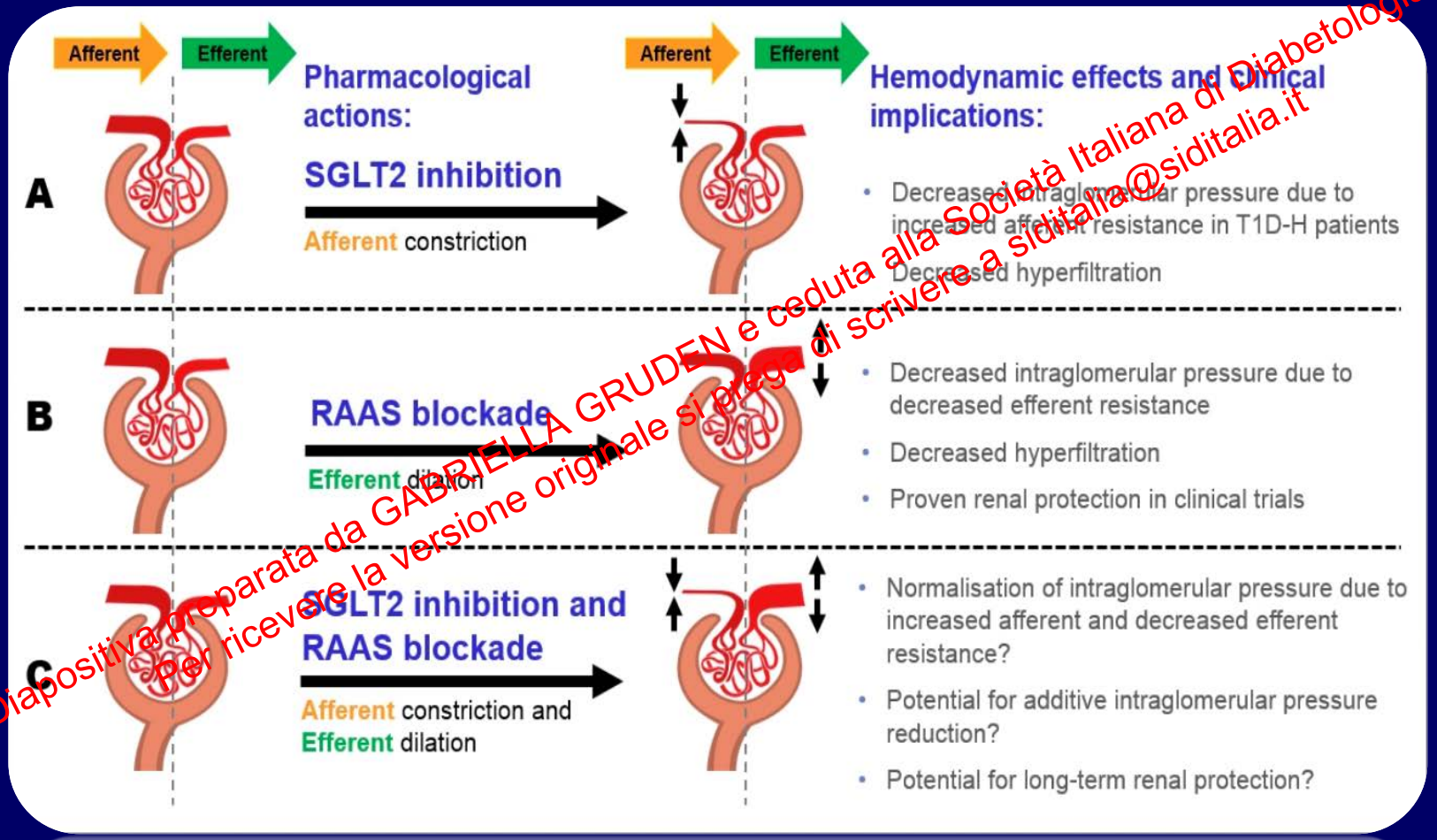
CANAGLIFLOZIN: AER



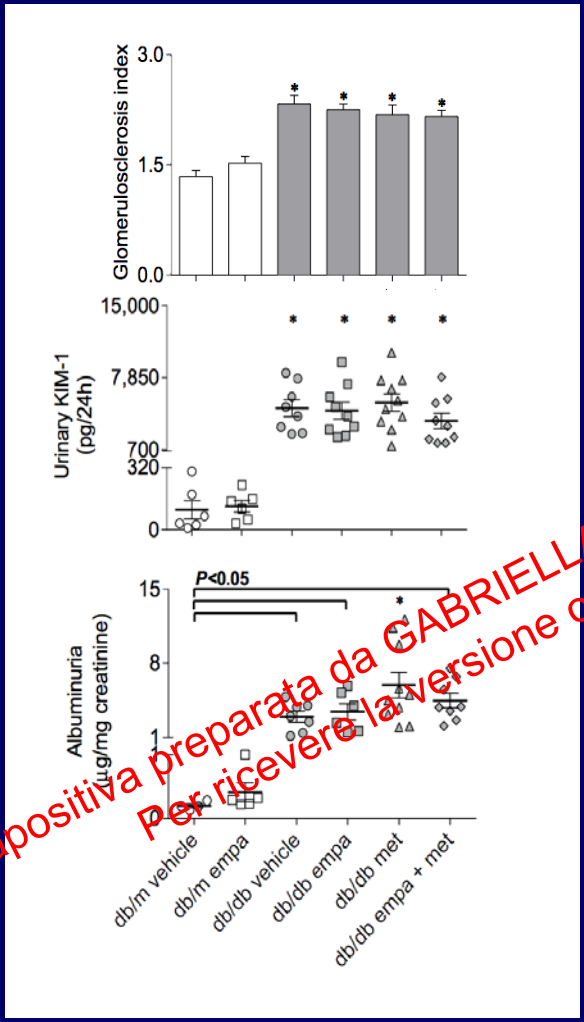
- 1450 DM2
- Metformina
  - Cana 100/300 mg o SU (glimepiride)
  - FU 2 aa
  - Indipendente da glicemia
- Limiti
  - Non dedicato
  - Eventi non aggiudicati
  - 2 yrs FU
  - No eGFR post--T
  - Non placebo (effetto SU)

Heerspink HJ, J Am Soc Nephrol 2017

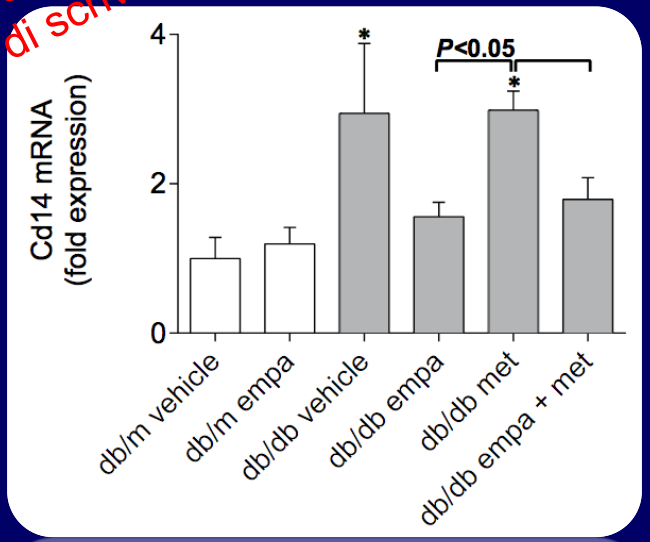
DANNO EMODINAMICO



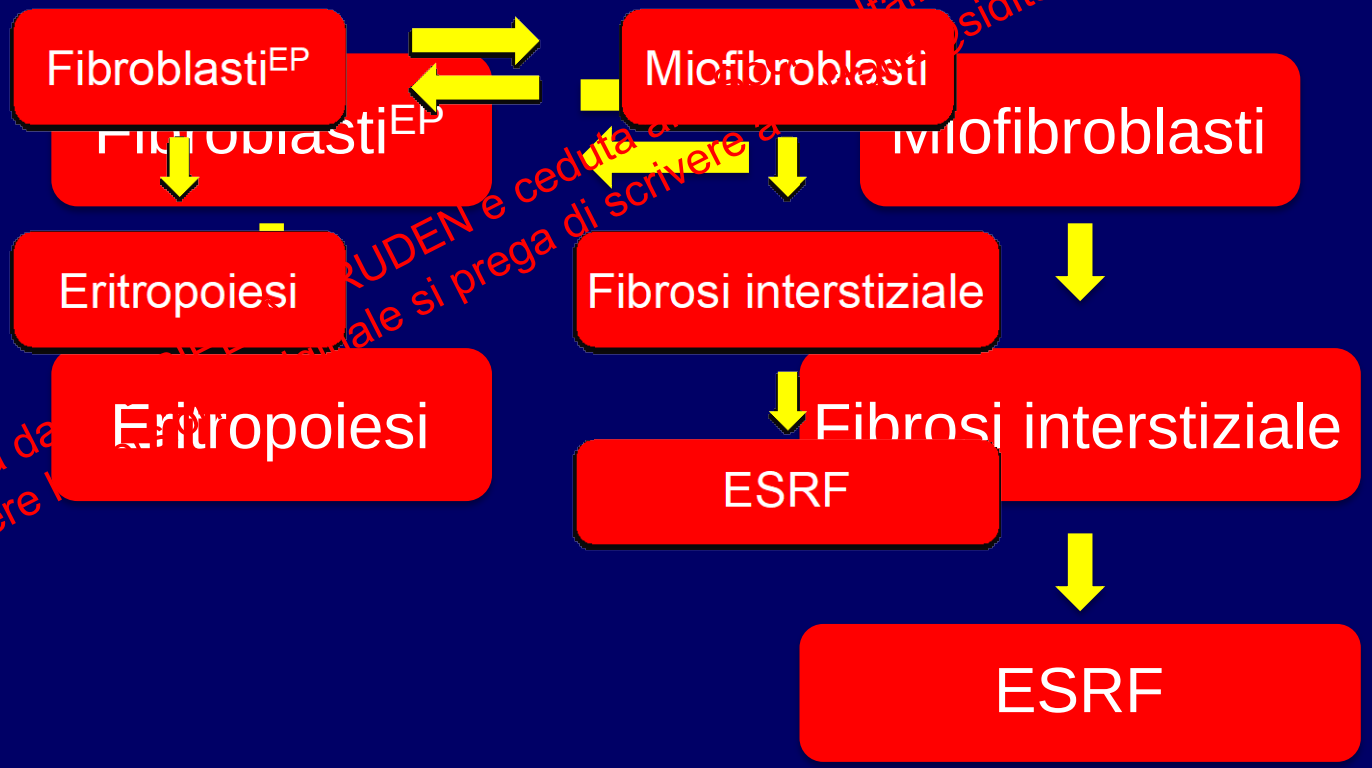
Empagliflozin db/db Mice



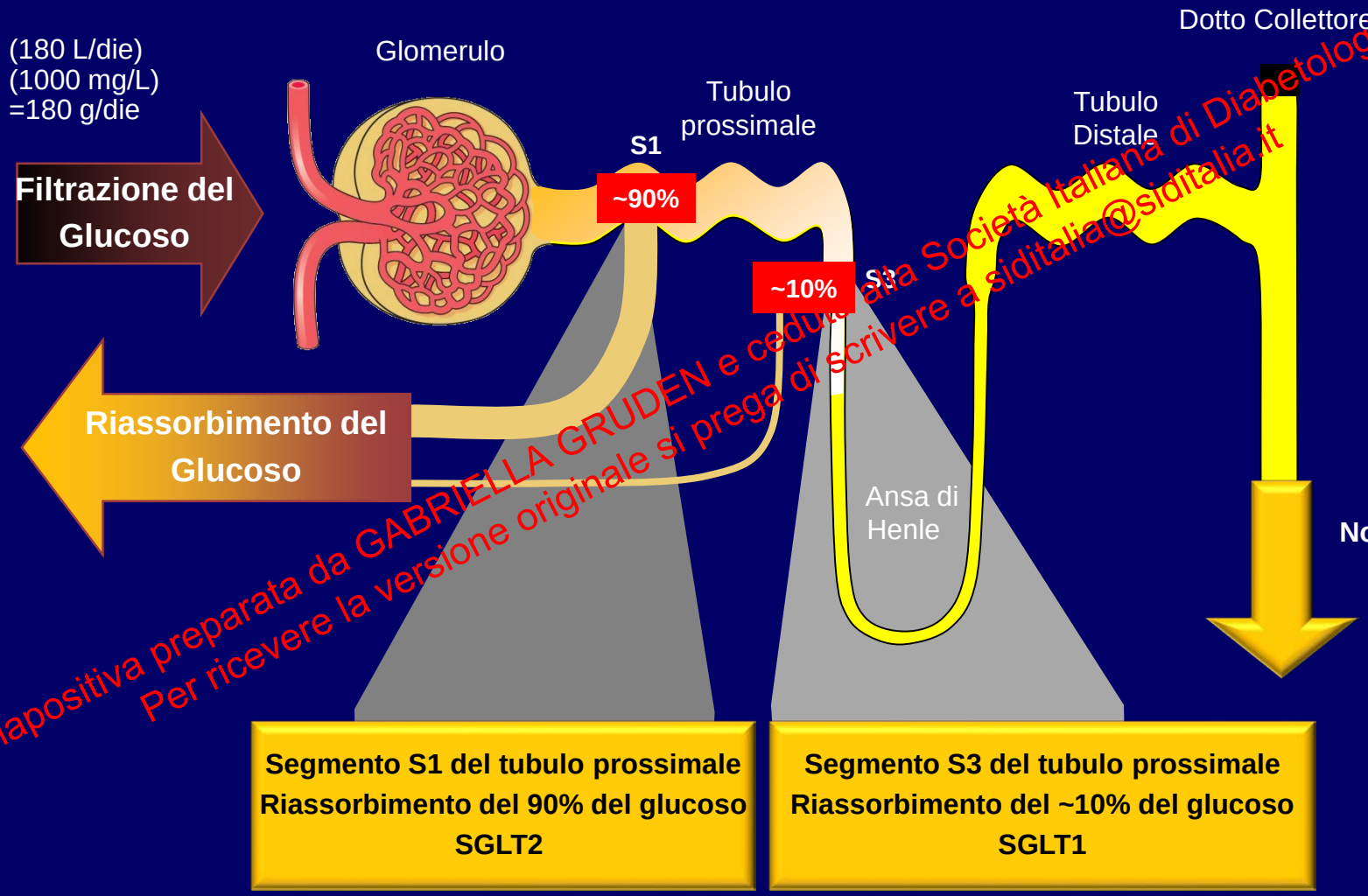
- db/m controllo
- db/db
- db/db empa
- db/db met
- db/db empa+met



Gallo LA Sci Rep 2016



RIASSORBIMENTO RENALE DEL GLUCOSO



Bailey CJ. Trends in Pharmacol Sci 2011;32:63-71.
Chao EC. Core Evidence 2012;7:21-28.