SGLT2 inibitori e rene: prima e dopo lo studio CREDENCE

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ROMA
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SGLT2 INIBITORI

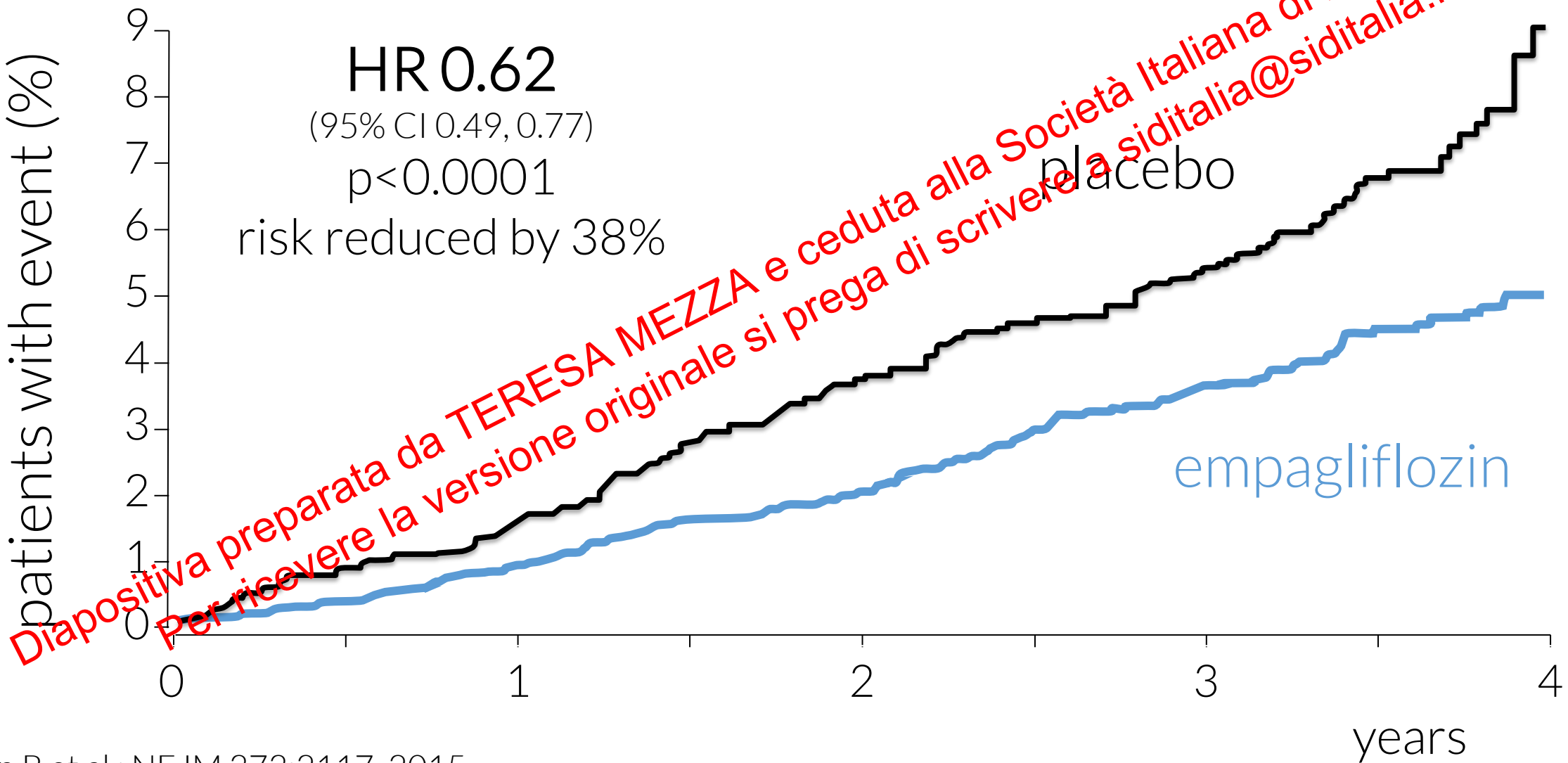
e progressione della **malattia renale** nel **diabete tipo 2**

La dottoressa Mezza Teresa dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- MSD
- Novonordisk
- Mundipharma

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, [illegible]rgici, ecc.).

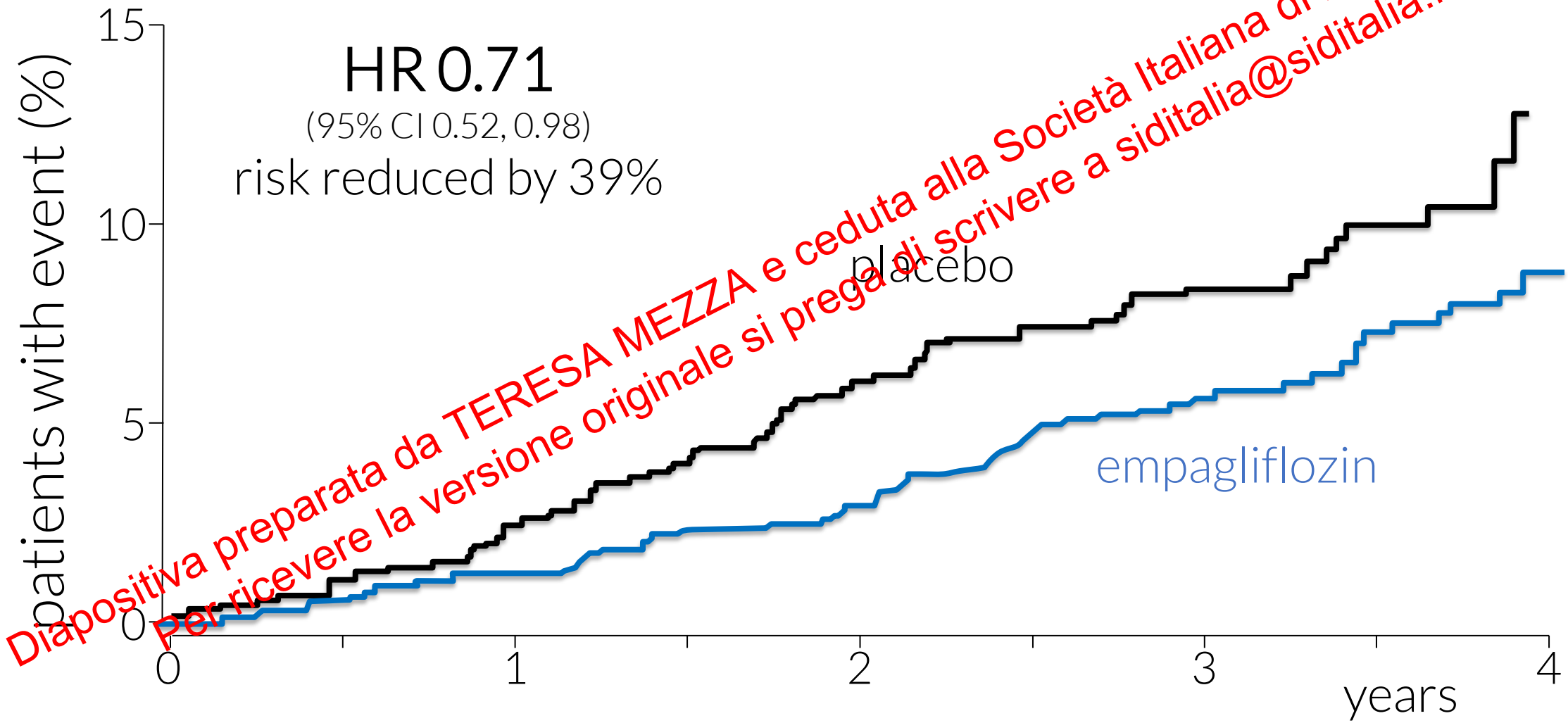
EMPAREG: CV mortality



Zinman B et al.: NEJM 373:2117, 2015

EMPAREG: CV death in CKD

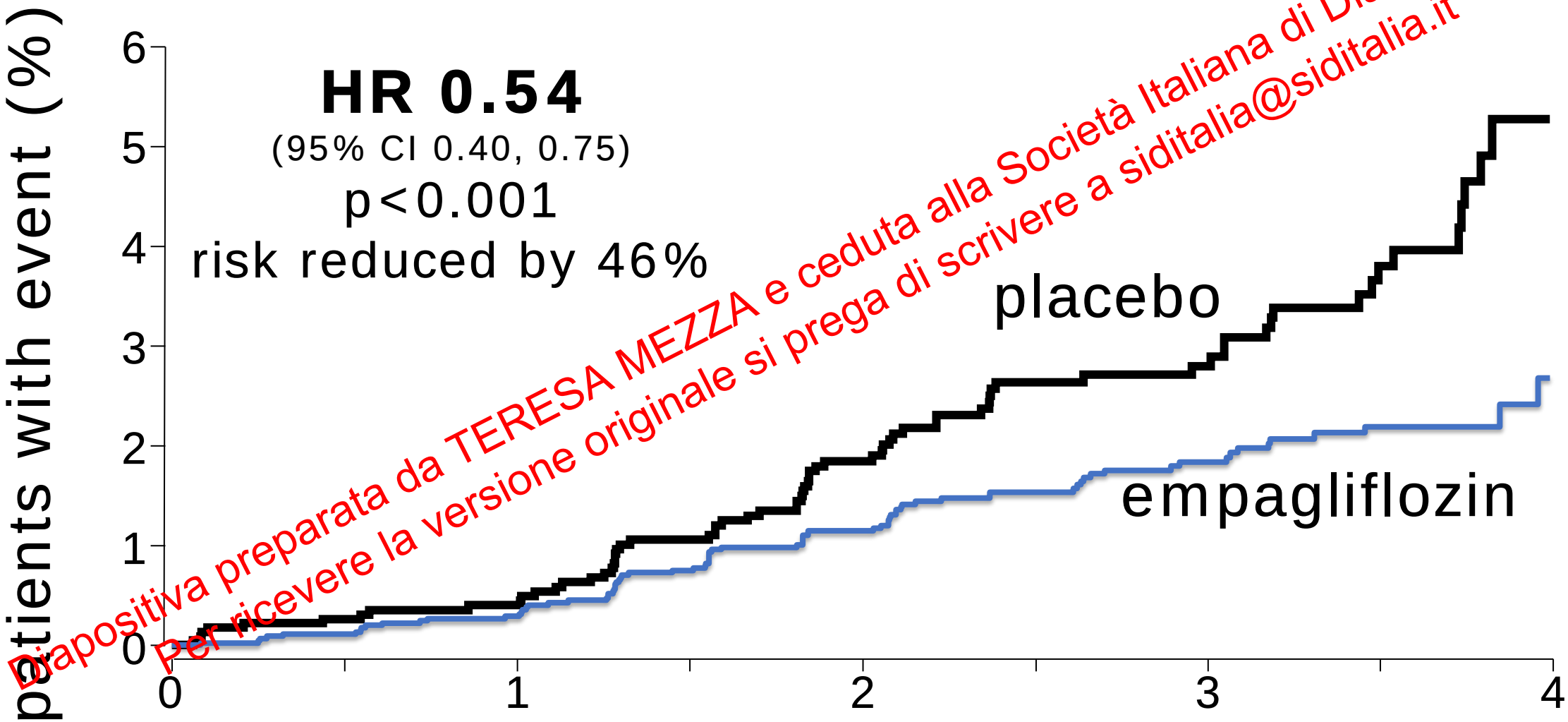
eGFR <60 mL/min/1.73m2 and/or macroalbuminuria (UACR >300 mg/g) at baseline



Wanner C et al. Circulation 137:119, 2018 doi: 10.1161/CIRCULATIONAHA.117.028268

EMPAREG: composite renal

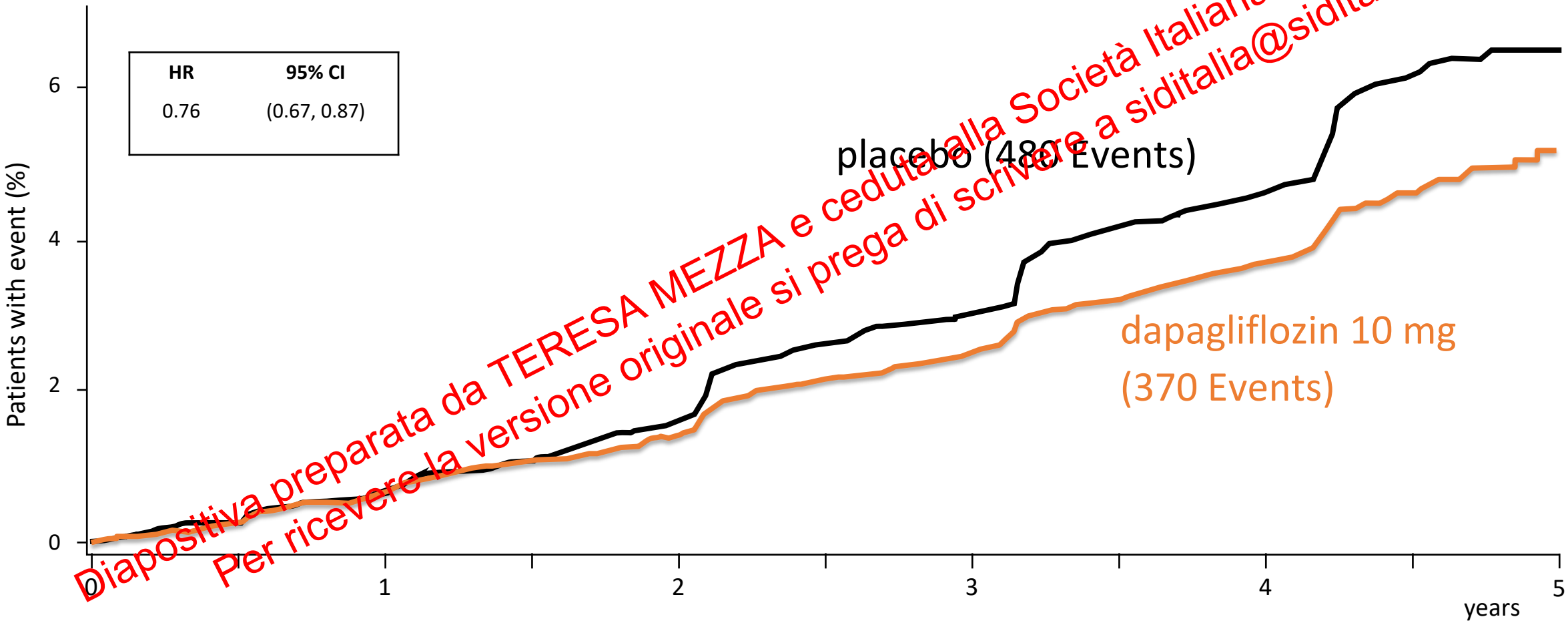
composite of doubling of serum creatinine, initiation of renal-replacement therapy or death from renal disease



Wanner C et al. N Engl J Med 2016;doi:10.1056/NEJMoa1515920

DECLARE: composite renal

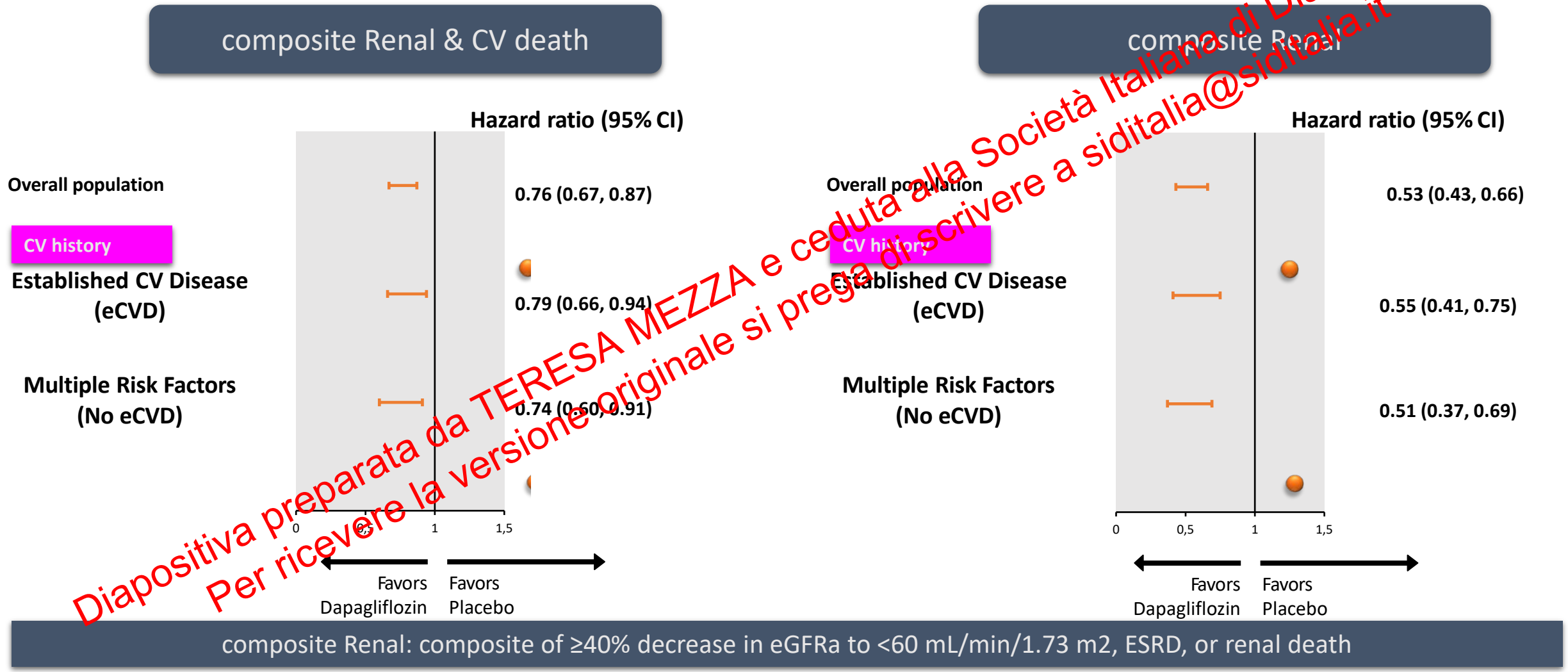
composite of ≥40% decrease in eGFRa to <60 mL/min/1.73 m2, ESRD, or renal death



Renal composite endpoint defined as confirmed sustained eGFR decrease ≥40% to eGFR <60 mL/min/1.73 m2 using CKD-EPI equation and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15 mL/min/1.73 m2) and/or renal or CV death.

Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018

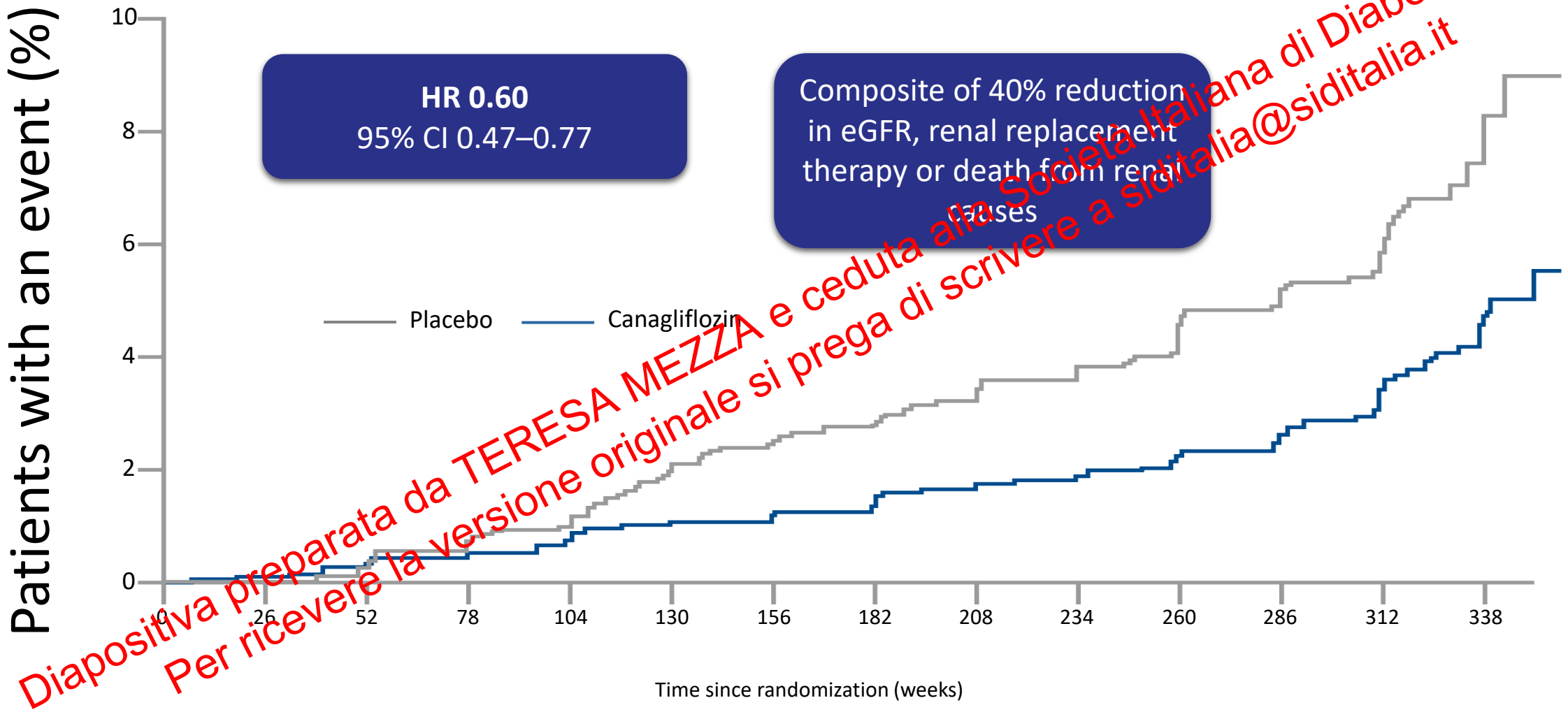
DECLARE: renal endpoints per CV history



CV, cardiovascular; eCVD, established CV disease; HF, heart failure; hHF, hospitalized heart failure; SGLT-2i, SGLT co-transporter 2 inhibitor; T2D, type 2 diabetes

Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018

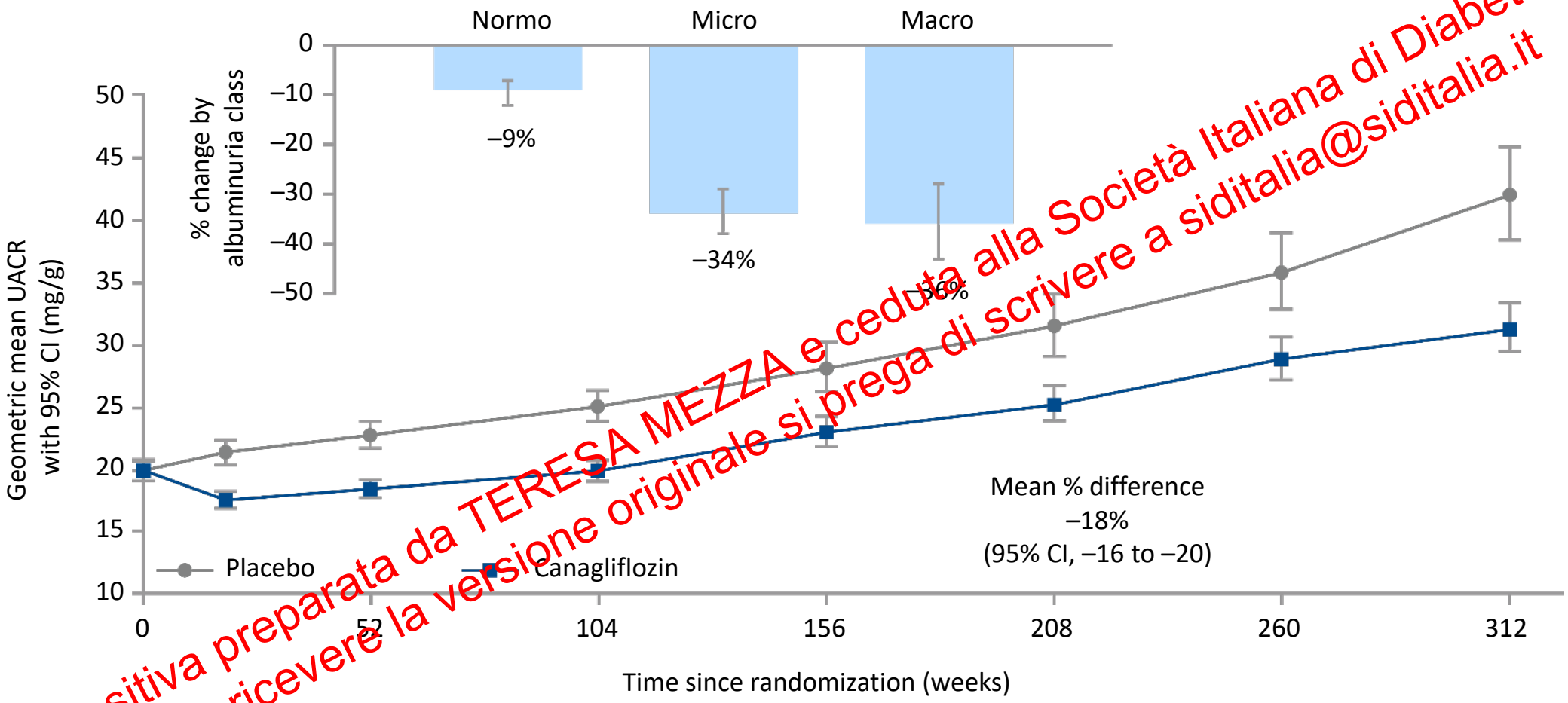
Canagliflozin reduced risk of renal composite events[1,a]



[a]Intention-to-treat analysis. Exploratory outcome, no *p*-value is reported, only nominal effect estimate is given
CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio

1. Neal B *et al. N Engl J Med* 2017;377:644

Change in Urine Albumin-to-Creatinine Ratio (UACR)[1]

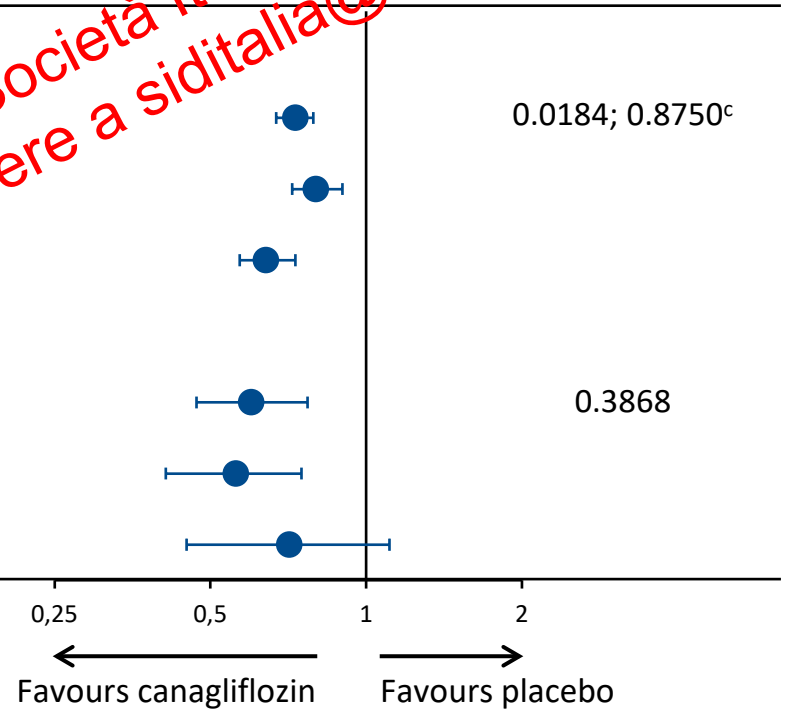


Mixed model for repeated measures (MMRM) analysis, excluding those below detection level

1. Presented at the American Diabetes Association 77th Scientific Sessions, June 12 2017, San Diego, CA, USA.

Renal outcomes across CANVAS trials1

	Per 1000 patient-years			
	Canagliflozin	Placebo	HR (95% CI)	*p*-value for interaction
Progression of albuminuria[a]				
All patients	89.38	128.71	0.73 (0.67, 0.79)	0.0184; 0.8750[c]
CANVAS	84.96	106.32	0.80 (0.72, 0.90)	
CANVAS-R	99.80	153.01	0.64 (0.57, 0.73)	
Composite renal endpoint[b]				
All patients	5.54	9.03	0.60 (0.47, 0.77)	0.3868
CANVAS	5.55	9.91	0.56 (0.41, 0.75)	
CANVAS-R	5.50	7.87	0.71 (0.45, 1.11)	



[a]Defined as >30% increase in albuminuria and a change from normoalbuminuria to microalbuminuria or macroalbuminuria, or from microalbuminuria to macroalbuminuria; [b] Defined as 40% reduction in eGFR, renal replacement therapy or death from renal causes; [c] Gail-Simon test is a test of qualitative interaction (i.e. to investigate whether the direction of the treatment effect is different between subgroups)

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio

1. Neal B *et al. N Engl J Med* 2017;377:644 (supplementary appendix)

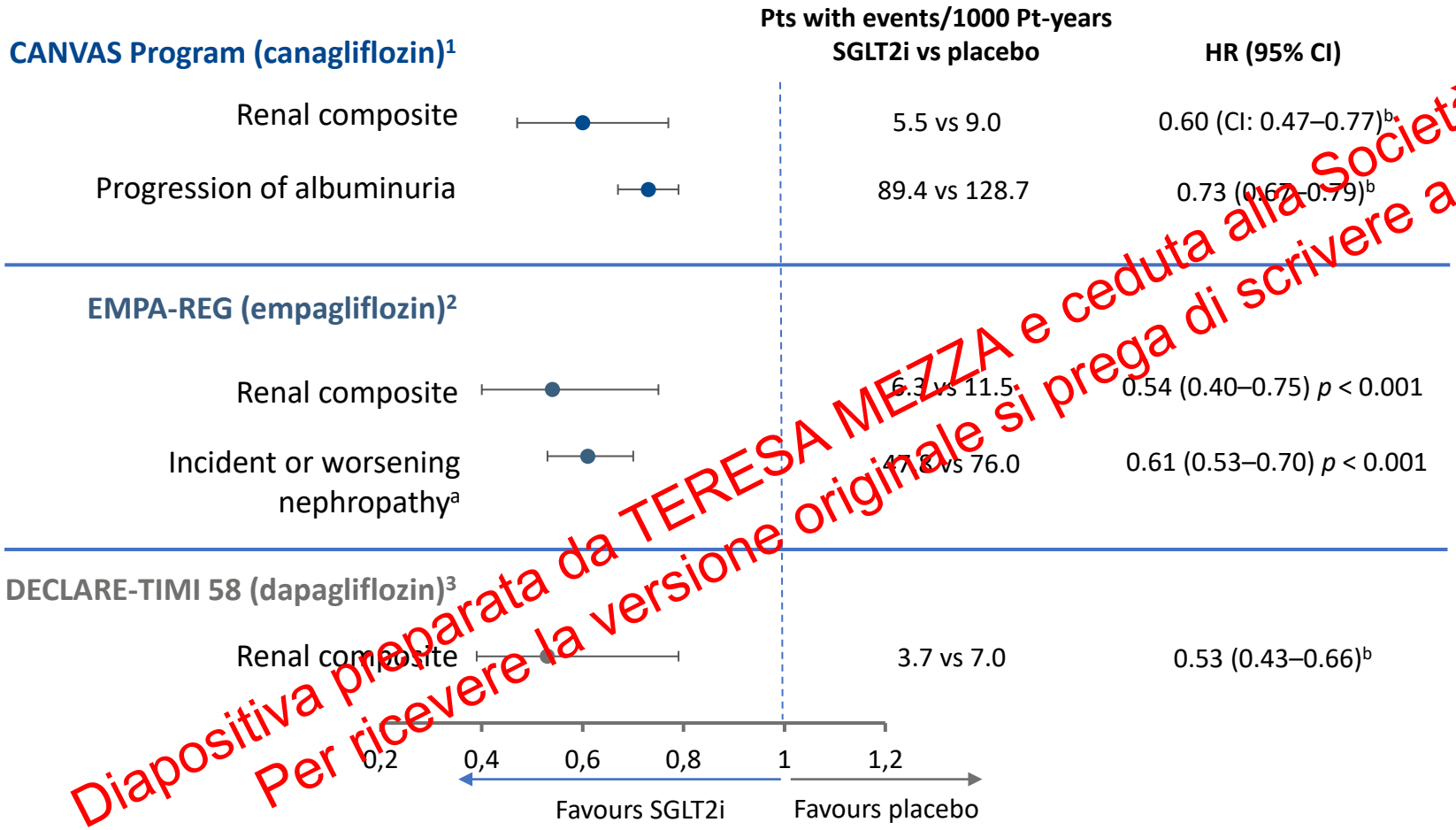
SGLT2 inibitors: CVOTs in type 2 diabetes

TRIAL	EMPA-REG empagliflozin	CANVAS Canagliflozin	DECLARE Dapagliflozin	VERTIS Ertugliflozin
Type 2 diabetes %	100	100	100	100
Prior CV disease %	100	65	41	100
Prior Heart failure %	10	14	10	23
3 pt MACE	0.86*	0.86*	0.93	0.97
CV death	0.62*	0.87	0.98	0.92
Hospitalised HF	0.65*	0.67*	0.73*	0.70*
All cause of Death	0.68*	0.87	0.93	

Exploratory renal outcomes in SGLT2i CV outcomes trials

Trials shown had different designs and patient populations, and cannot be compared directly

[b]On the basis of the prespecified hypothesis testing sequence, the renal endpoints are exploratory and are not considered to be statistically significant



Renal composite:[1]
- 40% reduction in eGFR
- requirement for RRT
- renal death

Renal composite:[2]
- doubling of serum creatinine[c]
- requirement for RRT
- renal death

Renal composite:[3]
- 40% reduction in eGFR to < 60 mL/min/1.73 m^2
- end-stage renal disease
- renal death

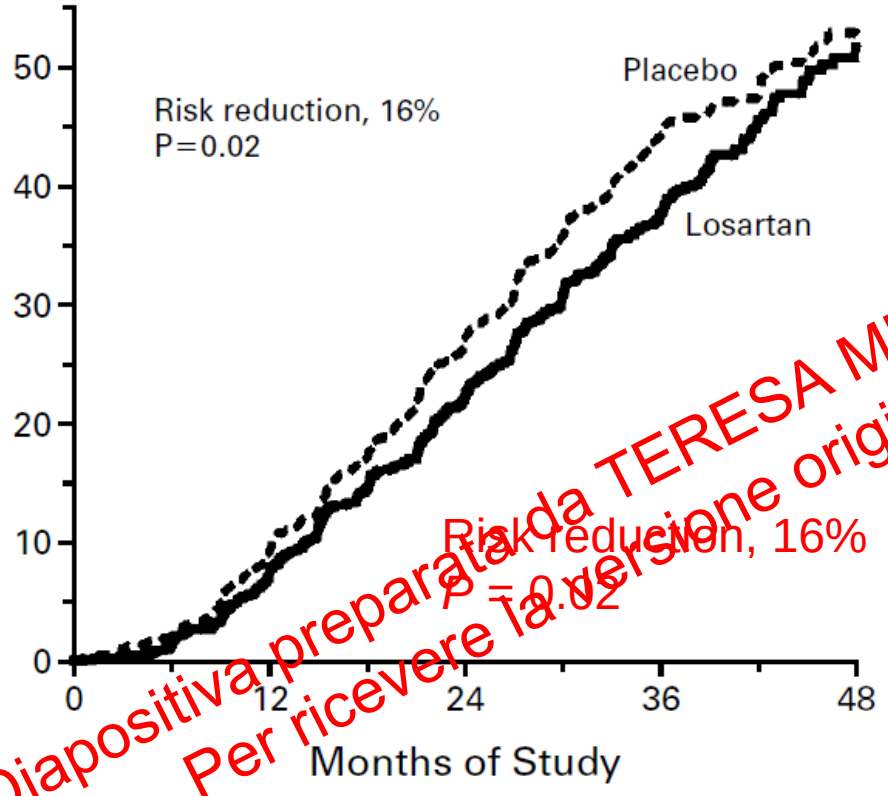
considerazioni su CKD… PRIMA DEL CREDENCE

- ampia efficacia di tutti gli SGLT-2i
- scarse differenze fra i trial nonostante le popolazioni siano diverse
- effetto su outcomes renali «too good to be true»
- tutti i trial hanno eGFR minimo alto
- non efficaci per eGFR ridotti (?)

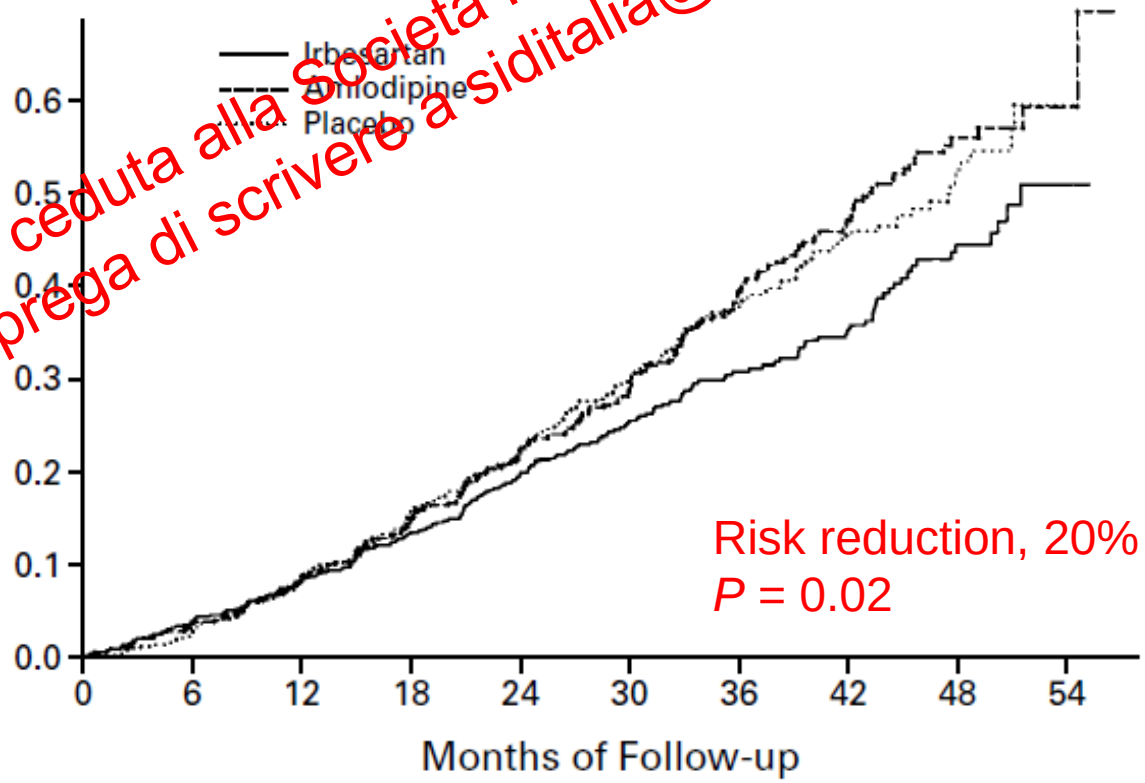
The Only Proven Treatment for Renoprotection in T2DM: RENAAL & IDNT

Doubling of serum creatinine, ESKD, or death

RENAAL



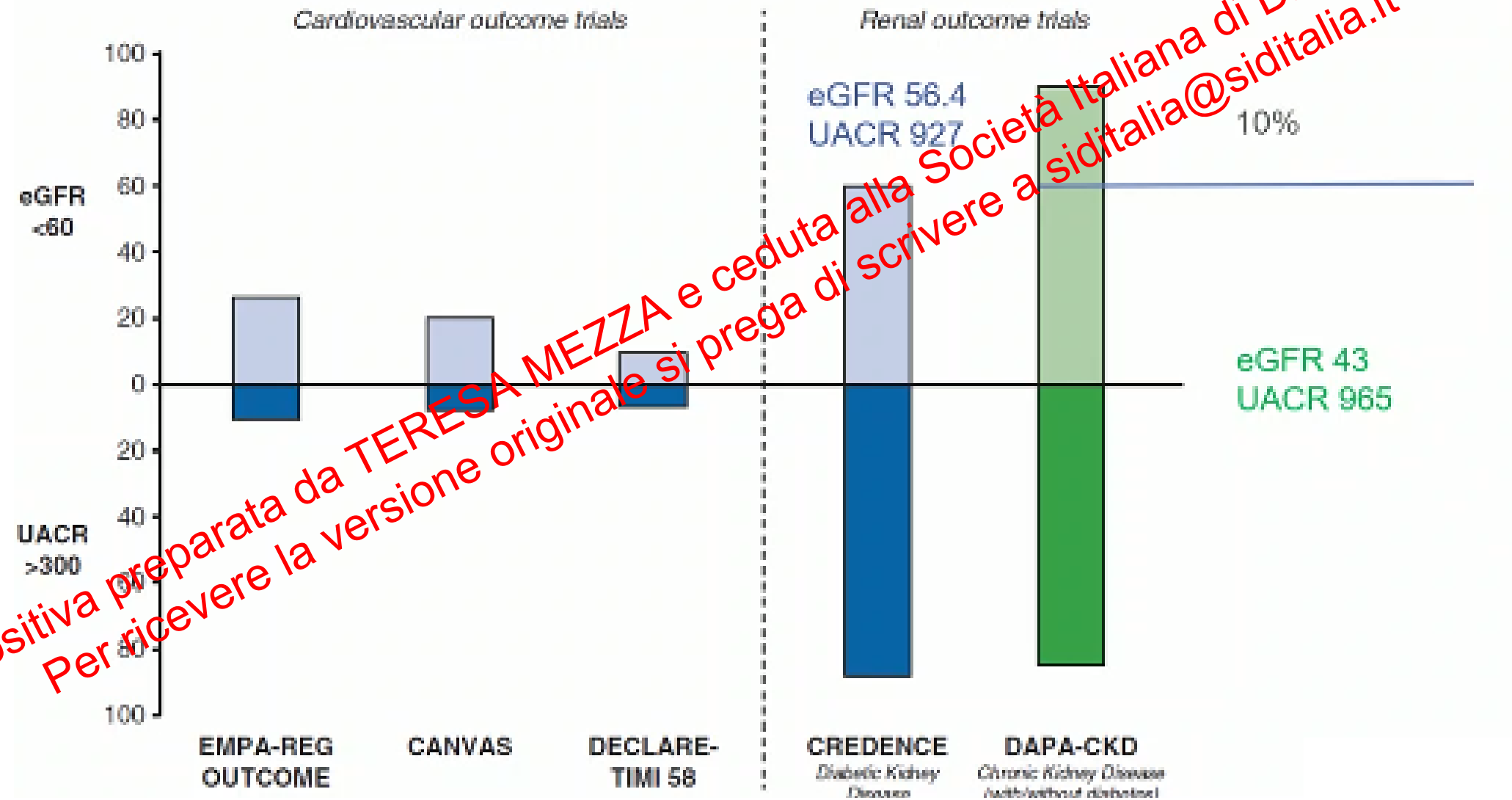
IDNT



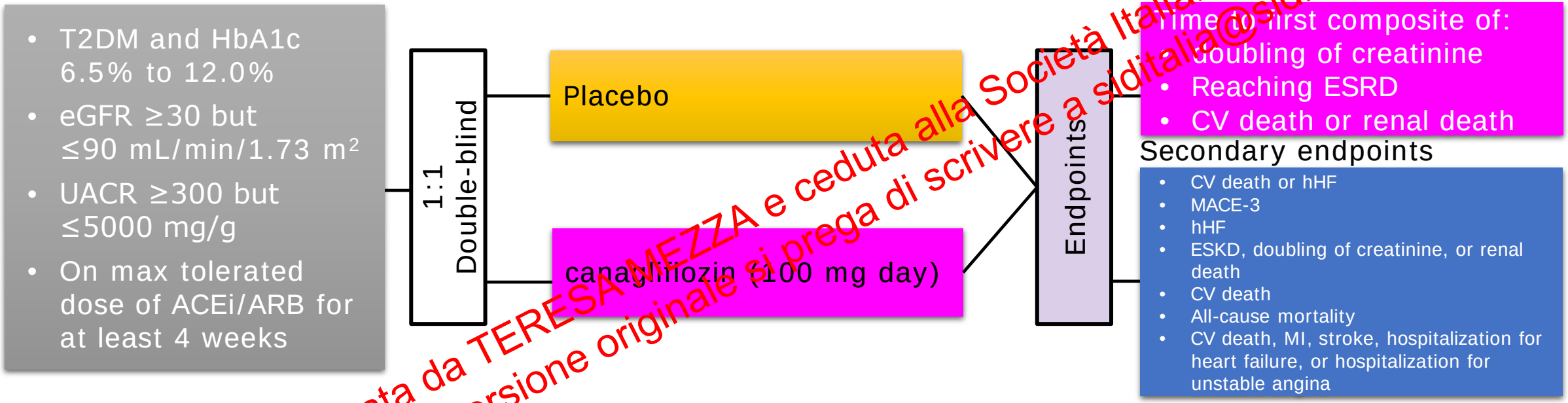
Brenner B, et al. *N Engl J Med*. 2001;345(12):861-869.

Lewis EJ, et al. *N Eng J Med*. 2001;345(12):851-860.

Proportion of patients with eGFR<60 and UACR>300



CREDENCE study design



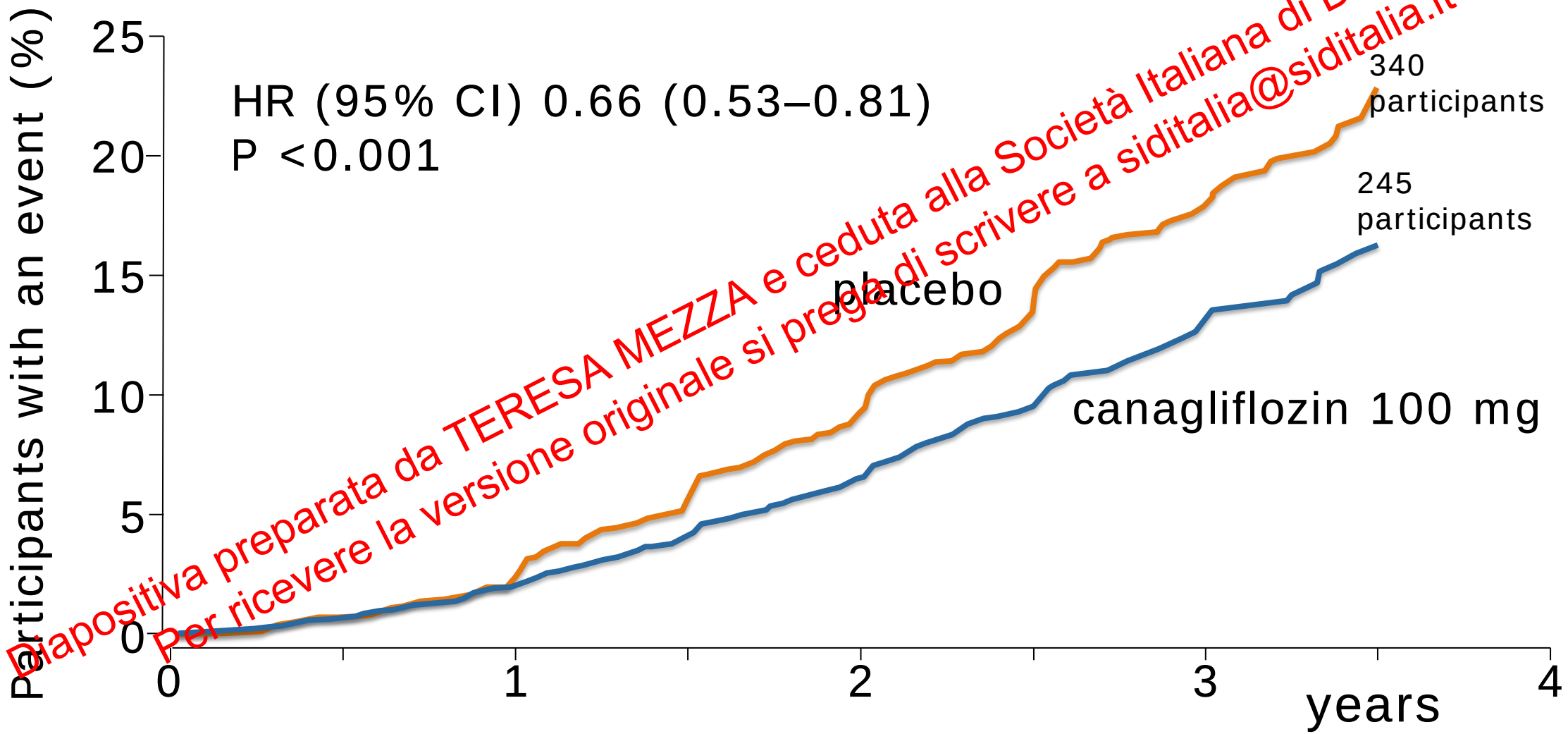
- Follow-up at weeks 3, 13, and 26 (F2F) then every 13 weeks (alternating phone/F2F)
- Participants continued treatment if eGFR was <30 mL/min/1.73 m² until chronic dialysis was initiated or kidney transplant occurred.

Perkovic V, et al.: NEJM Apr. 14, 2019 doi: 10.1056/NEJMoa1811744

CREDENCE primary endpoint:

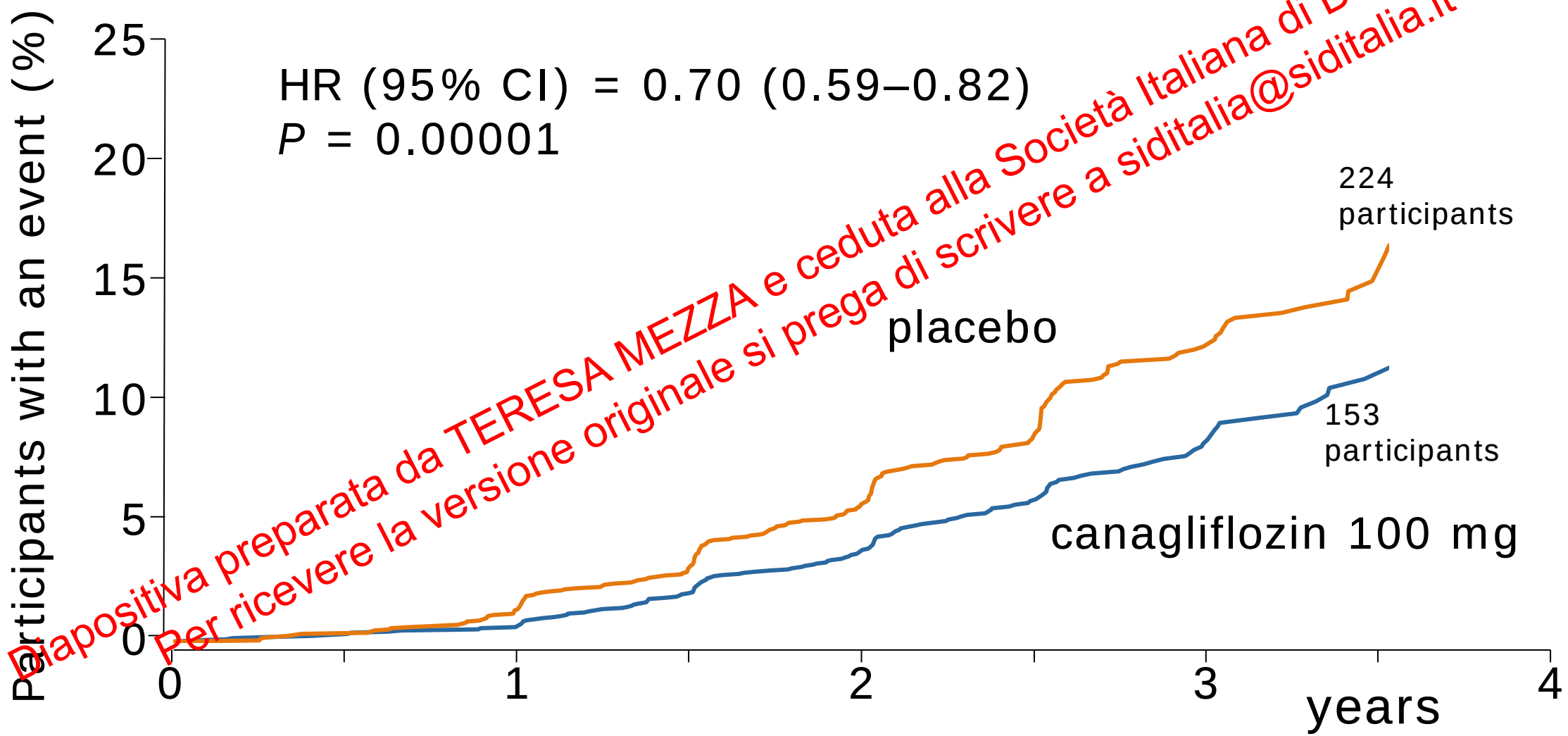
ESKD, Doubling of Creatinine, or Renal or CV Death

T2DM and HbA1c 6.5% to 12.0%; eGFR 30 - 90 mL/min/1.73 m^2; UACR ≥300 but ≤5000 mg/g; ACEi/ARB for at least 4 weeks



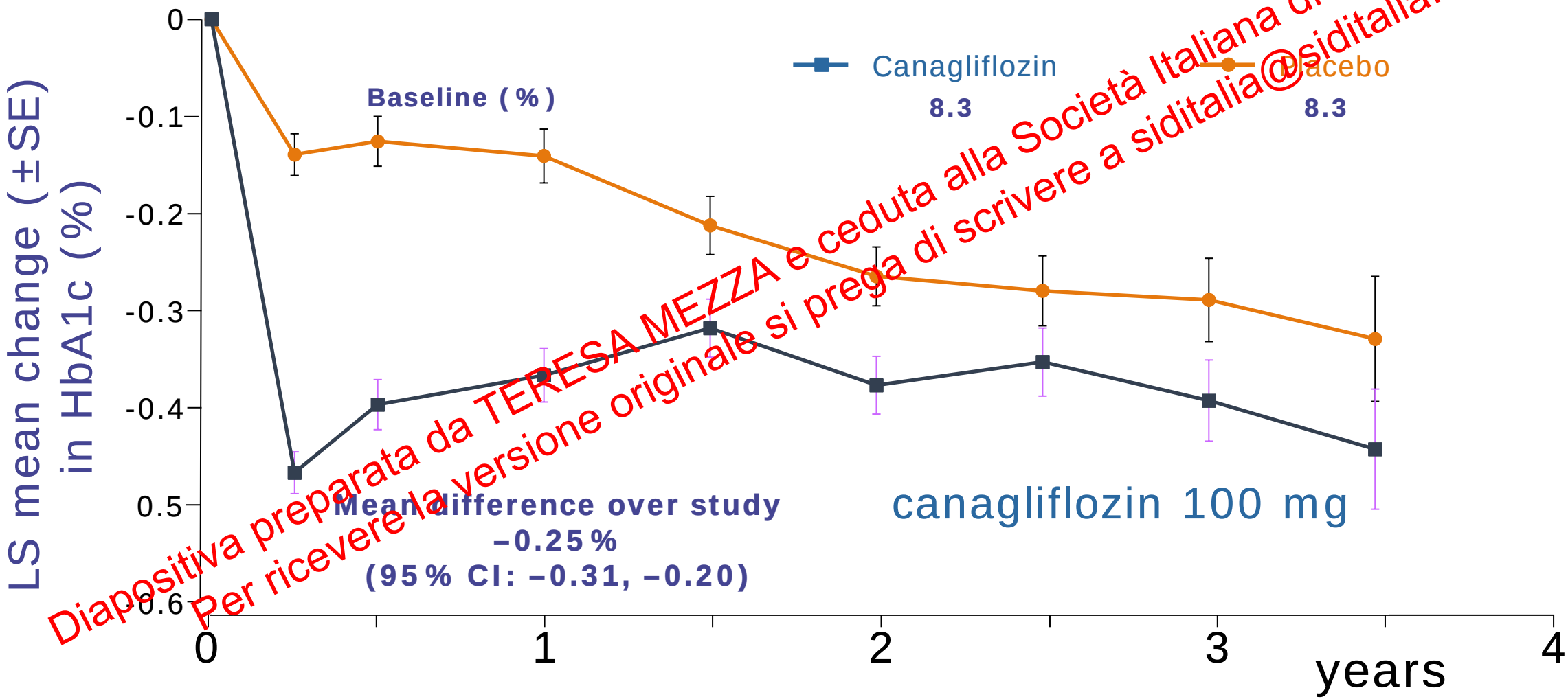
Perkovic V, et al.: NEJM Apr. 14, 2019 doi: 10.1056/NEJMoa1811744

CREDENCE renal endpoint: ESKD, Doubling of Creatinine, or Renal Death



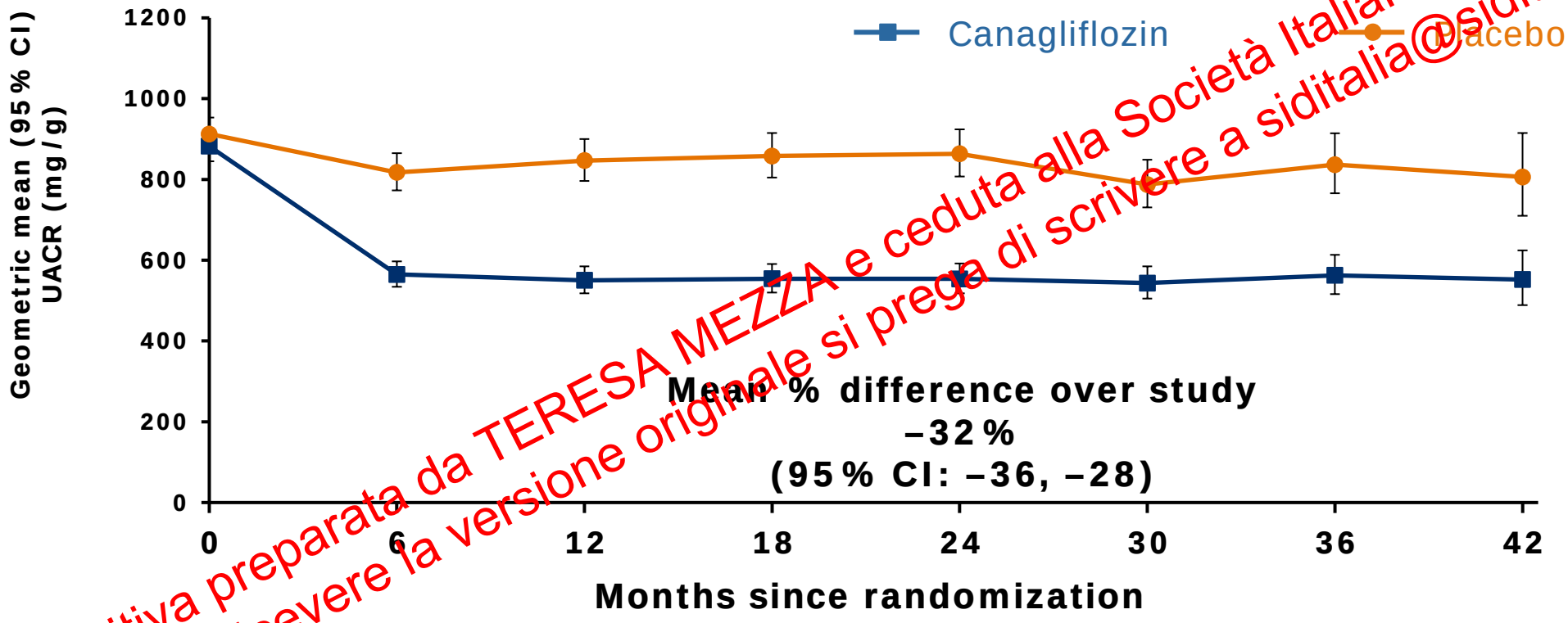
Perkovic V, et al.: NEJM Apr. 14, 2019 doi: 10.1056/NEJMoa1811744

CREDENCE: HbA1c



Perkovic V, et al.: NEJM Apr. 14, 2019 doi: 10.1056/NEJMoa1811744

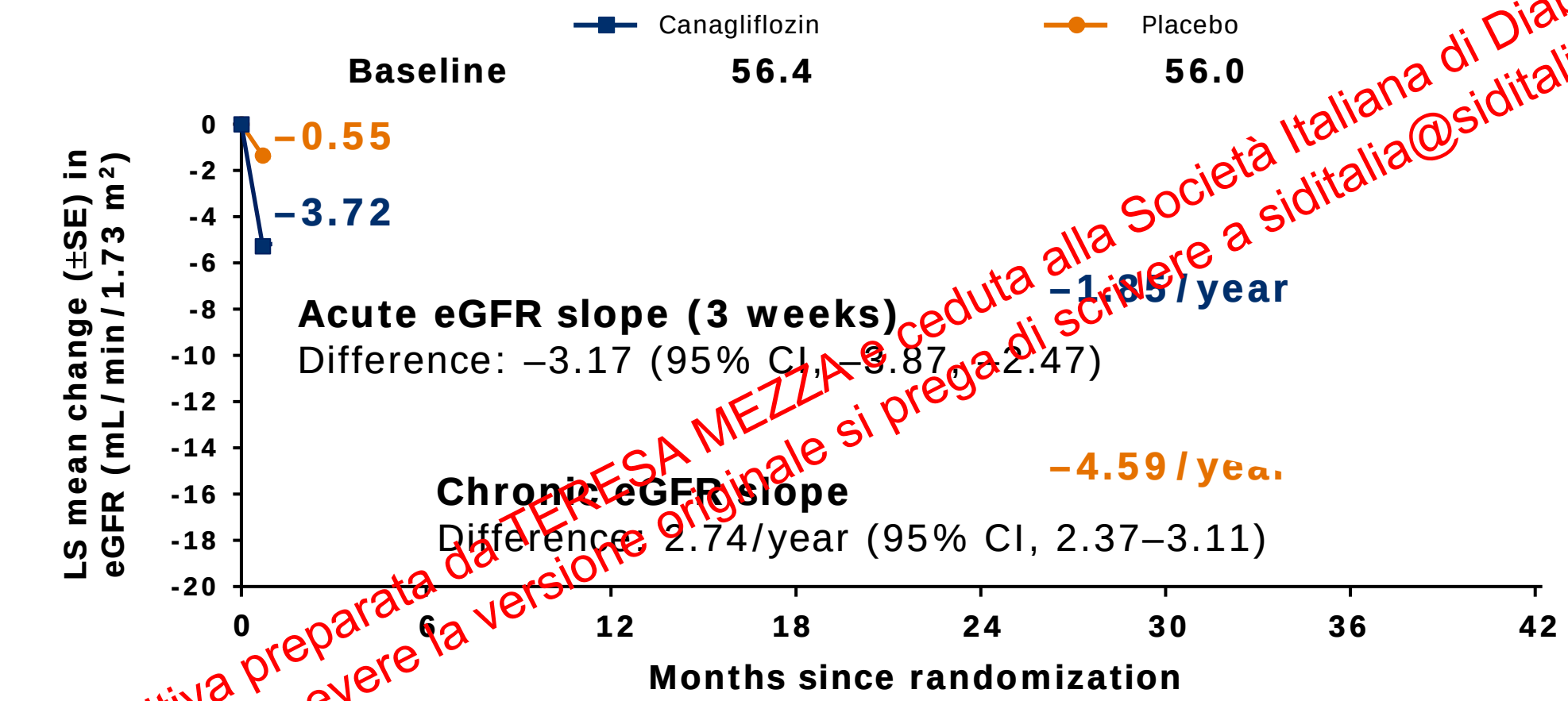
Effects on albuminuria



No. of participants								
Placebo	2113	2061	1986	1865	1714	1158	685	251
Canagliflozin	2114	2070	2019	1917	1819	1245	730	271

ITT analysis

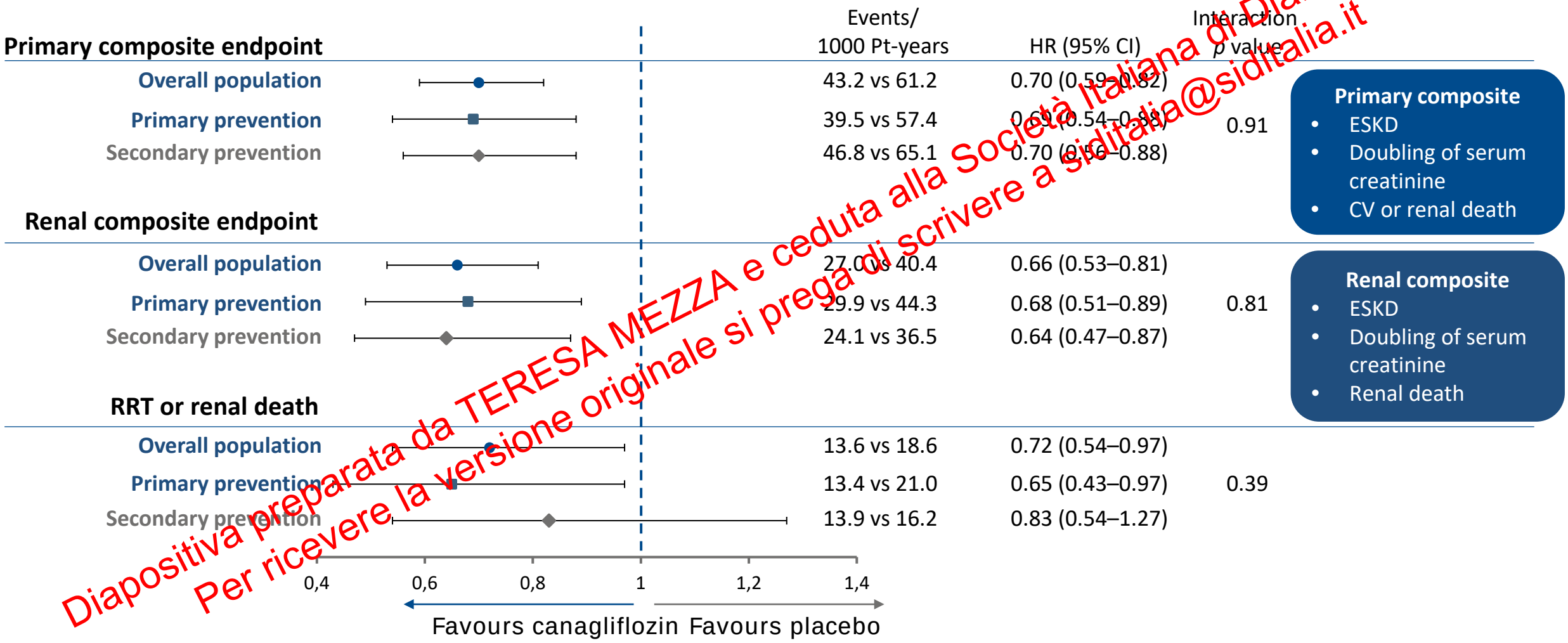
Effects on eGFR



No. of Participants									
Placebo	2178	2084	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2074	2005	1919	1782	1648	1116	652	241

On treatment

Renal endpoints stratified by CV risk status



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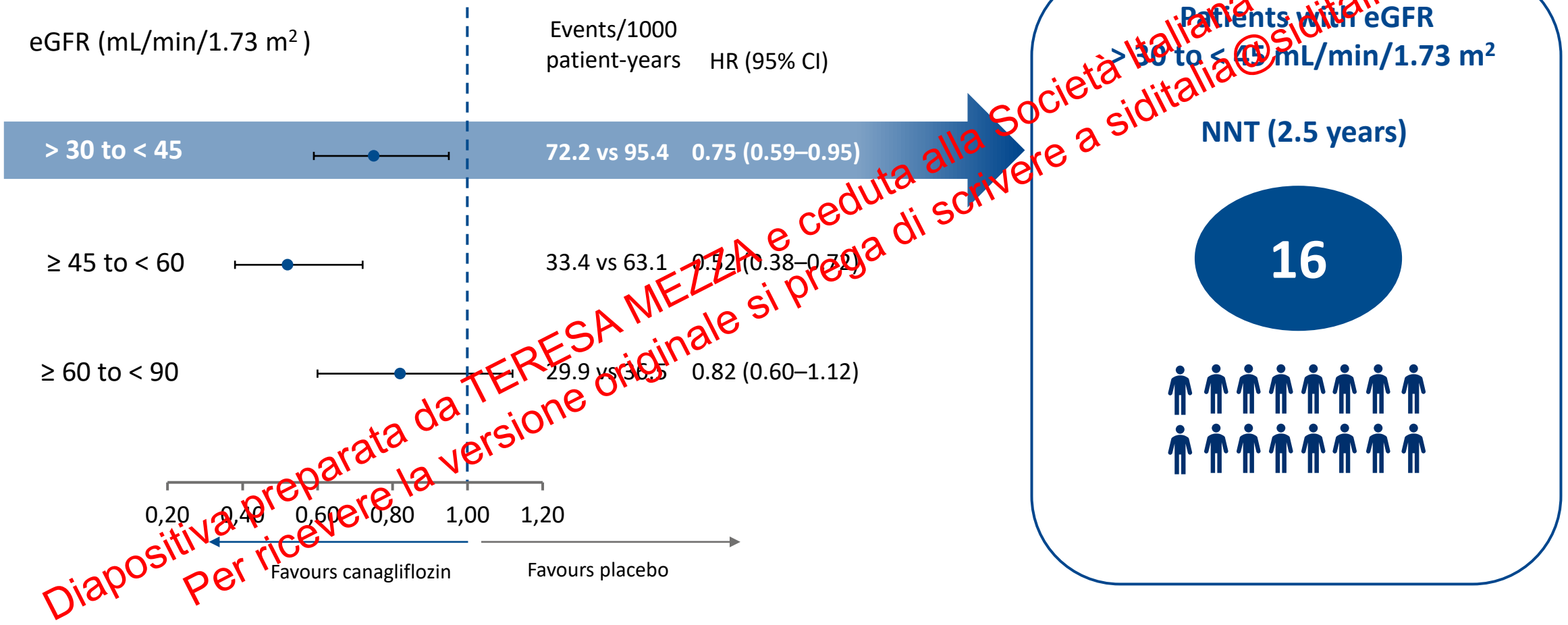
1. Mahaffey KW et al. Circulation 2019;140:739–50; 2. Mahaffey KW. Presented at the 79th Scientific sessions of the American Diabetes Association; June 7–11 2019 San Francisco, USA.

CREDENCE primary endpoint stratified by eGFR



1. Perkovic V *et al. N Engl J Med* 2019;380:2295–306; 2. Zinman B. Presented at the 79th Scientific sessions of the American Diabetes Association; June 7–11 2018 San Francisco, USA.

QNOW: Fino a quale valore di filtrato renale può essere utilizzato un SGLT2i?

A. Esclusivamente in pazienti con eGFR >60 ml/min
B. Tutti i farmaci della classe possono essere utilizzati sino ad un valore di eGFR di 30 ml/min, anche se perdono l'efficacia ipoglicemizzante
C. Il canagliflozin può essere iniziato sino a valori di eGFR di 30 ml/min, al dosaggio di 100 mg, se presente albuminuria >300 mg/g
D. Sino ad un valore di eGFR di 45 ml/min.

ADA Standards of Medical Care have been updated with renal guidance based on CREDENCE[1]

"The CREDENCE trial was the first SGLT2 inhibitor trial to assess renal-specific primary outcomes and ended early due to efficacy. Incorporating these findings into the Standards of Care now gives providers the latest evidence-based recommendations to treat people with T2D and diabetes-related CKD"

William T. Cefalu, MD, Chief Scientific, Medical and Mission Officer of the ADA[1]

Based on the Grade A evidence from the CREDENCE trial, the ADA *living guidelines* (updated on June 3, 2019) propose the following:[2]

"For patients with T2D and diabetic kidney disease, consider use of an SGLT2 inhibitor in patients with an eGFR ≥ 30 mL/min/1.73 m^2 and particularly in those with > 300 mg/g albuminuria to reduce risk of CKD progression, cardiovascular events, or both."

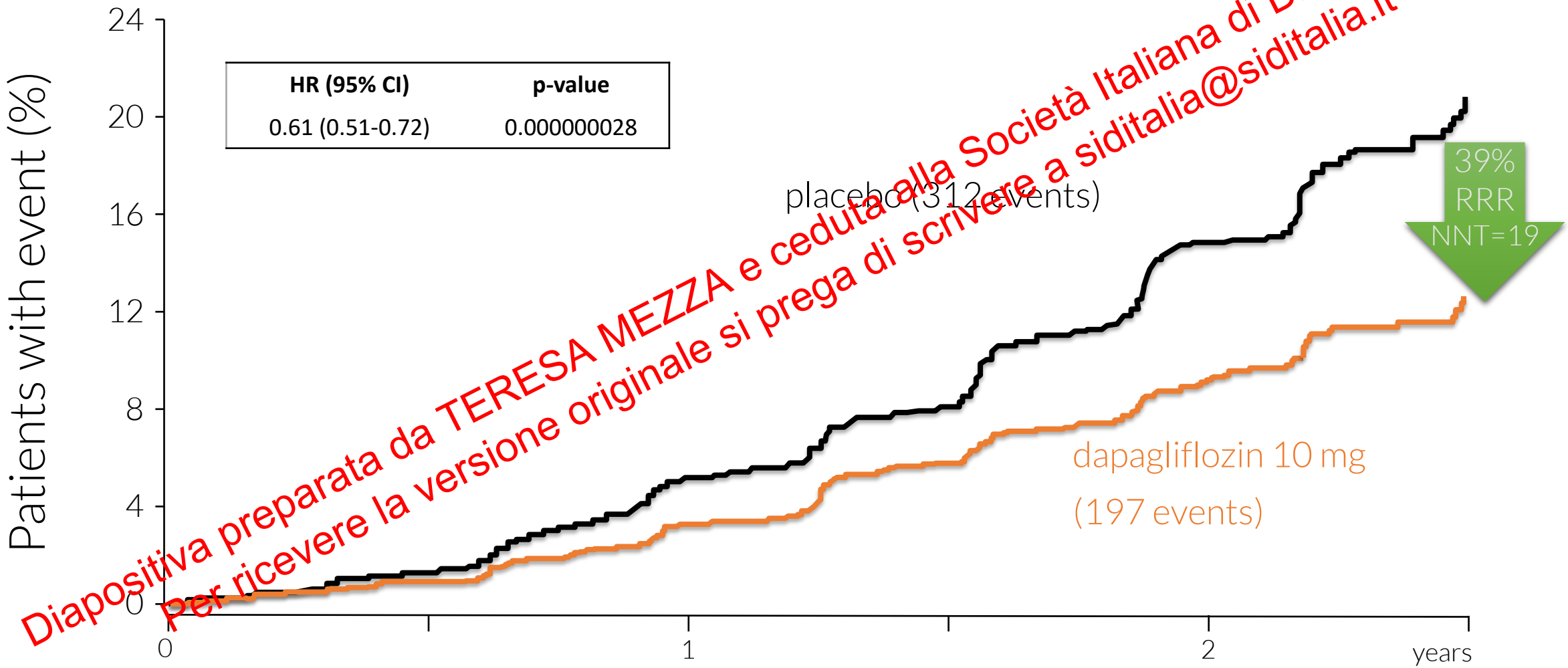
La Commissione Europea ha approvato l'estensione di indicazione per canagliflozin in seguito ai risultati osservati nello studio CREDENCE per i pazienti con malattia renale diabetica e diabete di tipo 2

- *L'approvazione della Commissione Europea (CE) si basa sullo studio di fase III, degli esiti renali, Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), che è stato interrotto precocemente dopo l'analisi ad interim pianificata, basata sul raggiungimento di un criterio di efficacia pre-specificato.*
- *Canagliflozin è la prima terapia approvata negli ultimi 20 anni in Europa, dopo l'approvazione degli inibitori dell'enzima di conversione dell'angiotensina (ACE) e dei bloccanti del recettore dell'angiotensina II (ARB) **per rallentare la progressione della malattia renale diabetica** (DKD) nei pazienti con diabete mellito di tipo 2 (DMT2), compresi i pazienti con insufficienza renale moderata e grave e albuminuria (rapporto albumina: creatinina urinarie ≥300 mg/g).*
- *Circa 59 milioni di adulti in Europa hanno il diabete, il 90% dei quali ha DMT2[2]. Circa il 40% delle persone con DMT2 svilupperà una malattia renale[3].*
- *Per la prima volta in Europa, i pazienti con DMT2 con una velocità di filtrazione glomerulare stimata (eGFR) tra 60 e 45 ml/min/1,73 m² possono ora iniziare il trattamento con canagliflozin 100 mg. Inoltre, i pazienti con DMT2 con albuminuria e eGFR ≥30 mL/min/1,73 m² possono ora iniziare il trattamento con canagliflozin 100 mg e continuare fino alla dialisi o al trapianto renale[4].*
- *Trattandosi di una procedura centralizzata, AIFA recepisce le indicazioni da EMA.*

European Commission. 26th June 2020 Decision C(2013)8171(final) for canagliflozin. Available at: https://ec.europa.eu/health/documents/community-register/html/h884.htm. Last accessed July 2020.

DAPA-CKD: primary composite renal

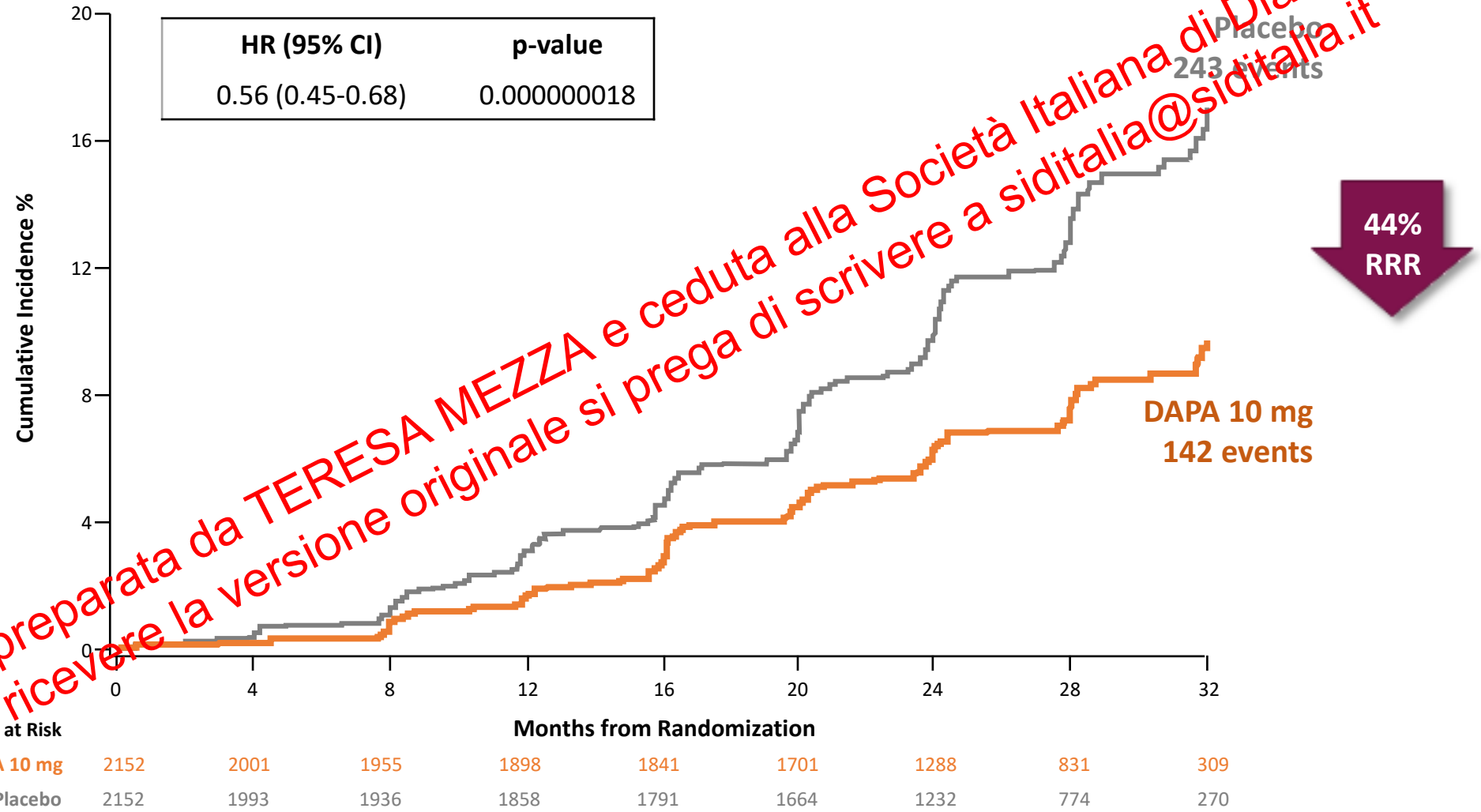
Sustained ≥50% eGFR Decline, ESKD, Renal or CV Death*



*ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld

Heerspink HJL et al.: Nephrol Dial Transplant. 35:274, 2020

Secondary Composite Outcome: Sustained ≥50% eGFR Decline, ESKD, or Renal Death[a]

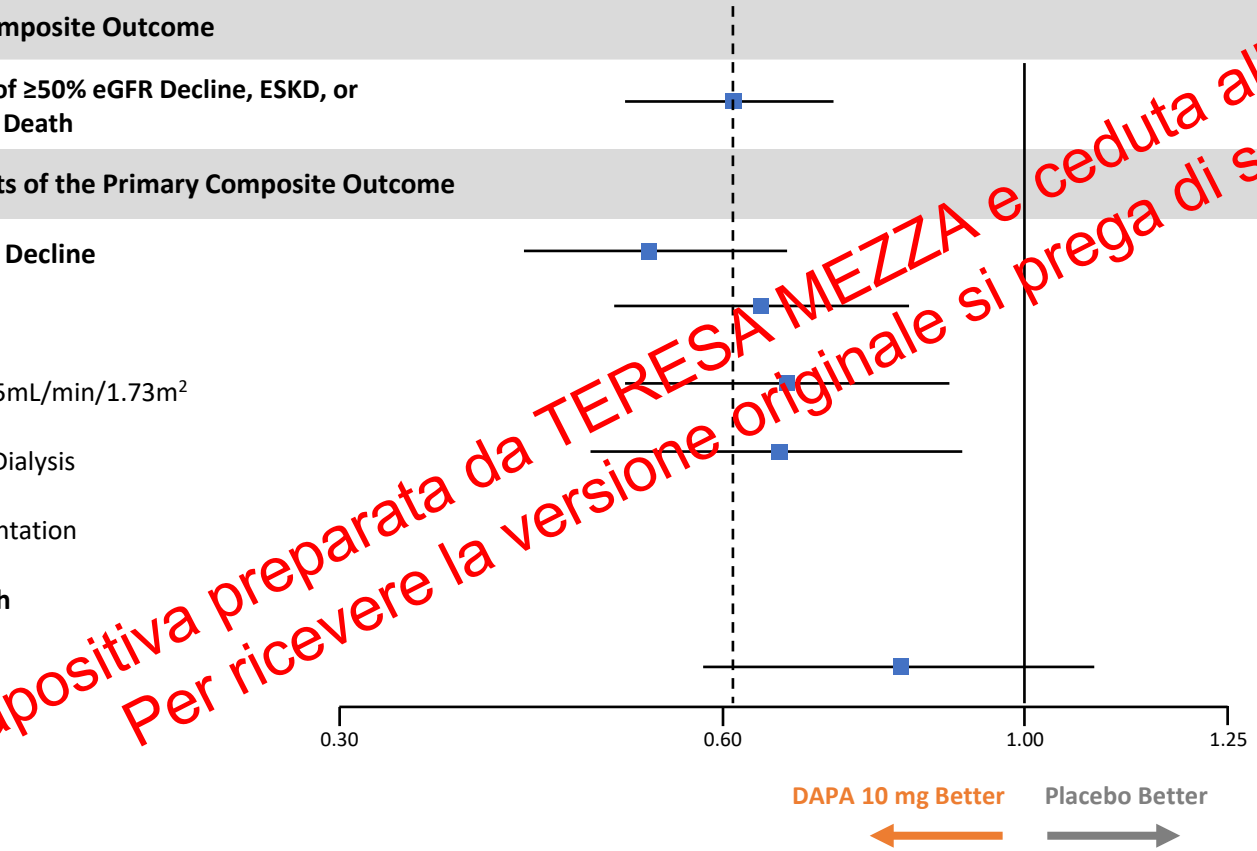


[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.[2] DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; RRR = relative risk reduction.

1. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020. 2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282.

Primary Composite Outcome: All Components Contributed to the Observed Treatment Effect

	Number of Events				
HR (95% CI)	DAPA 10 mg (N=2152)	Placebo (N=2152)	HR	95% CI	p-value
Primary Composite Outcome					
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death	197	312	0.61	(0.51, 0.72)	0.000000028
Components of the Primary Composite Outcome					
≥50% eGFR Decline	112	201	0.53	(0.42, 0.67)	<0.0001
ESKD	109	161	0.64	(0.50, 0.82)	0.0004
eGFR <15mL/min/1.73m^2	84	120	0.67	(0.51, 0.88)	0.0045
Chronic Dialysis	68	99	0.66	(0.48, 0.90)	0.0080
Transplantation	3	8	NC		
Renal Death	2	6	NC		
CV Death	65	80	0.81	(0.58, 1.12)	0.2029

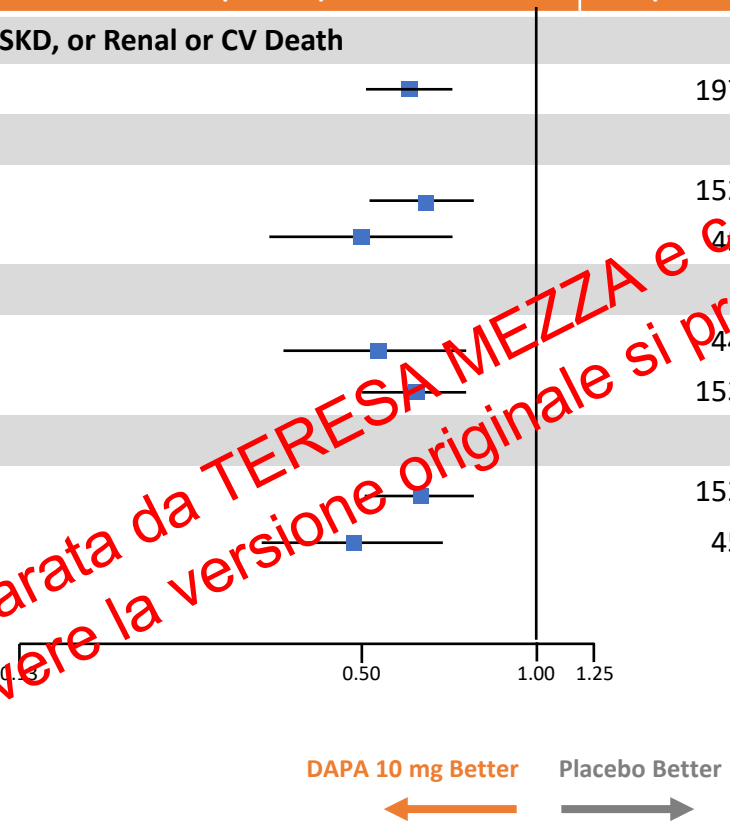


CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; NC = not calculable

Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.

Primary Composite Outcome: Treatment Benefit Consistent Across Prespecified Subgroups

	Number of Events				
HR (95% CI)	DAPA 10 mg (N=2152)	Placebo (N=2152)	HR	95% CI	p-value Interaction
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death					
All Patients	197	312	0.61	(0.51, 0.72)	
T2D at Baseline					0.24
Yes	152	229	0.64	(0.52, 0.79)	
No	45	83	0.50	(0.35, 0.72)	
UACR (mg/g) at Baseline					0.52
≤1000	44	84	0.54	(0.37, 0.77)	
>1000	153	228	0.62	(0.50, 0.76)	
eGFR (mL/min/1.73m²) at Baseline					0.22
<45	152	217	0.63	(0.51, 0.78)	
≥45	45	95	0.49	(0.34, 0.69)	



CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.

Key Renal Outcome Trials

	SGLT-2i			MRA
	DAPA-CKD[1,2] N = 4304	CREDENCE[3] N = 4401	EMPA-KIDNEY[4] N ~ 6000	FIDELIO-DKD[5,6] N = 5734
Status	**Completed**	**Completed**	**Ongoing** Est. Completion Date June 2022	**Completed**
Intervention	Dapagliflozin vs Placebo ≥4 weeks stable on ACEi or ARB	Canagliflozin vs Placebo ≥4 weeks stable on ACEi or ARB	Empagliflozin vs Placebo On ACEi or ARB	Finerenone vs Placebo ≥4 weeks on ACEi or ARB
Patient Population	• T2D and non-DM • eGFR ≥25 to ≤75 mL/min/1.73m^2 • UACR ≥200 to ≤5000 mg/g	• T2D • eGFR ≥30 to <90 mL/min/1.73m^2 • UACR >300 to ≤5000 mg/g	• T2D and non-DM • eGFR ≥20 to <45 mL/min/1.73m^2 **or** ≥45 to <90 mL/min/1.73m^2 and UACR ≥200 mg/g	• T2D • eGFR ≥25 to <60 mL/min/1.73m^2 and UACR ≥ 30 to <300 mg/g and presence of diabetic retinopathy **or** eGFR ≥25 to <75 mL/min/1.73m^2 and UACR ≥300 mg/g
Primary Endpoint	**Composite** • ≥50% sustained eGFR decline • ESKD • Renal or CV death	**Composite** • Doubling of serum creatinine • ESKD • Renal or CV death	**Composite** • Kidney disease progression • CV death	**Composite** • Kidney failure • ≥40% sustained eGFR decline • Renal death
Secondary Endpoints	• Renal composite • CV death or hHF • All-cause death	• CV death or hHF • CV death, MI, or stroke • hHF • Renal composite • CV death • All-cause death • Composite of CV death, MI, stroke, hHF or hospitalization for UA	• CV death or hHF • All-cause hospitalizations • All-cause death • Kidney disease progression • CV death • CV death or ESKD	• Stroke or hHF • All-cause death • All-cause hospitalizations • ≥57% sustained eGFR decline, kidney failure or renal death • UACR change from baseline

1. Study NCT03036150. ClinicalTrials.gov website. 2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282. 3. Perkovic V et al. *N Engl J Med*. 2019;380:2295-2306.
4. Study NCT03594110. ClinicalTrials.gov website. 5. Study NCT02540993. ClinicalTrials.gov website. 6. Bakris GL et al. *Am J Nephrol*. 2019;50:333-344.

Prima del CREDENCE

- SGLT2 inibitori erano:
- terapia per DM2 con un nuono meccanismo d'azione
- per persone con conservata funzionalità renale
- EMPA-REG OUTCOME è stato il primo di una serie di trials che ha cambiato le linee guida di diabetologi e cardiologi

Dopo il CREDENCE

- SGLT2 inibitori sono diventati:
- efficaci e sicuri anche in persone con eGFR 30-60 $ml \cdot min^{-1} \cdot 1.73m^{-2}$

e con albuminuria

- capaci di prevenire e ritardare la CKD (anche in non diabetici)