



## ROBERTO TREVISAN

*Prof. Associato di Endocrinologia  
Dipartimento di Medicina e Chirurgia  
Università degli Studi di Milano Bicocca*



*Direttore UOC Malattie Endocrine 1 – Diabetologia  
ASST Papa Giovanni XXIII, Bergamo*



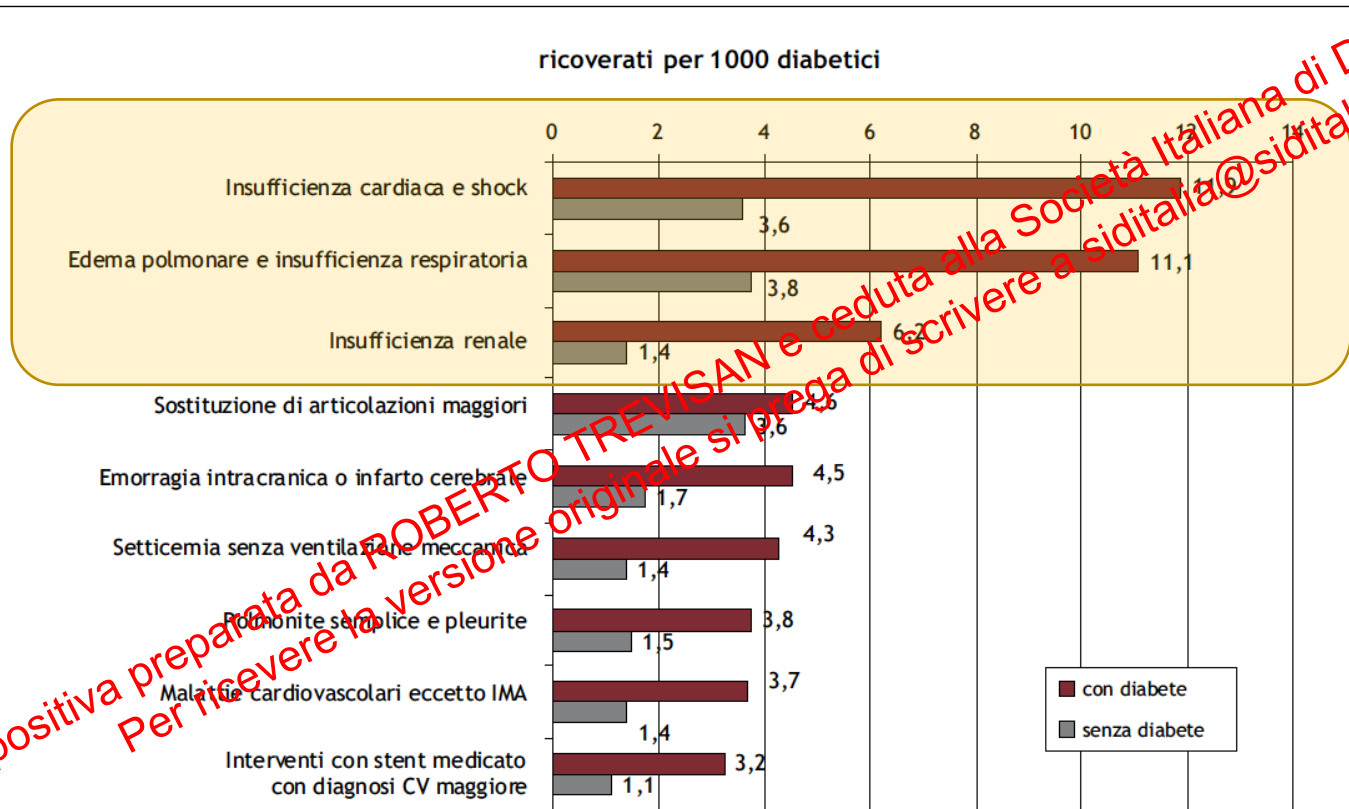
Sistema Socio Sanitario  
**Regione Lombardia**  
ASST Papa Giovanni XXIII

# SGLT2 inibitori e loro rilevanza nell'influenzare la prognosi del paziente con diabete di tipo 2

*Il Diabetologo*

Diapositiva preparata da ROBERTO TREVISAN e ceduta alla Società Italiana di Diabetologia.  
Per ricevere la versione originale si prega di scrivere a [siditalia@siditalia.it](mailto:siditalia@siditalia.it)

I 10 più frequenti DRG in caso di ricovero ordinario nei soggetti con e senza diabete  
(tassi per 1000 soggetti)



The RIACE Study

# Renal dysfunction is common in Italian T2DM Patients

*J Hypertens 2011, 29: 1802-1809*

15773 T2DM patients randomly selected in Italian out-patient clinics

↑ AER  
26.9%

eGFR  
≤ 60 ml/min/1.73<sup>2</sup>  
18.8%

52 % normoalbuminurici

With  
CKD  
37.5%

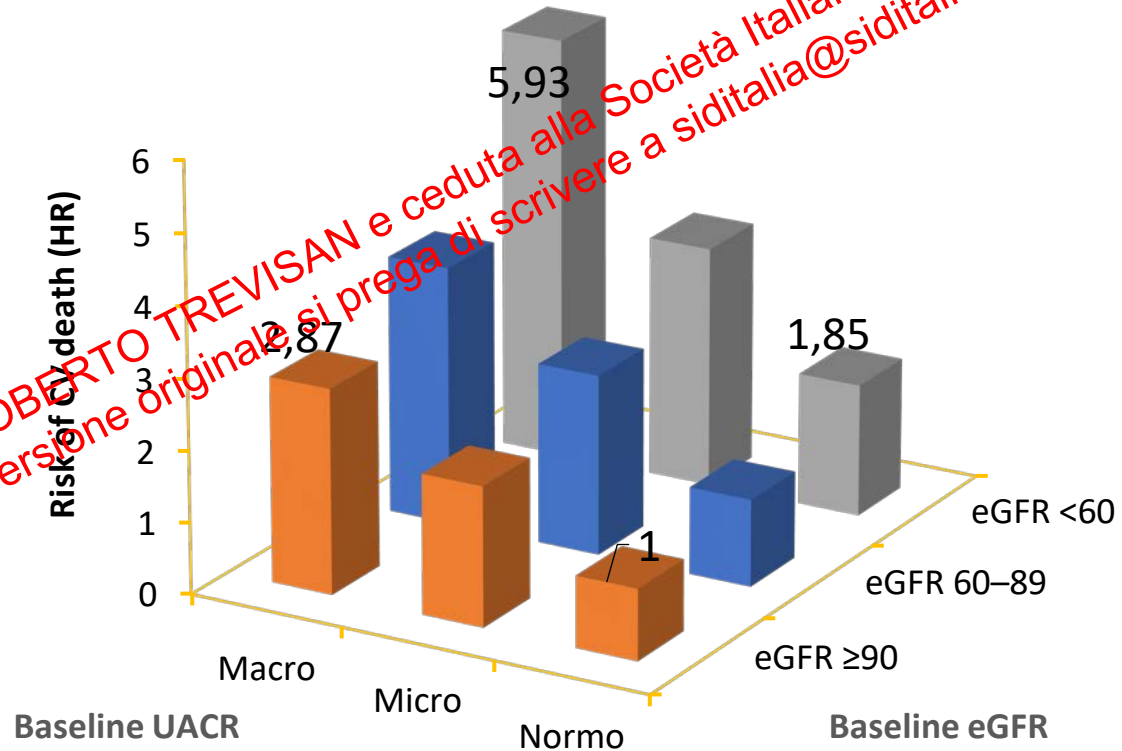
Diapositiva preparata da ROBERTO TREVISAN e ceduta alla Società Italiana di Diabetologia.  
Per ricevere la versione originale si prega di scrivere a [siditalia@siditalia.it](mailto:siditalia@siditalia.it)

# Albuminuria and reduced eGFR are associated with increased risk of CV death

ADVANCE: Observational analyses examining the association between albuminuria and eGFR at baseline or during follow-up and the risk for CV events and renal events in T2D

10,640 patients with available data

Average follow-up  
4.3 years



# The RIACE Study

Cumulative survival by  
Kaplan–Meier analysis according to  
DKD phenotype

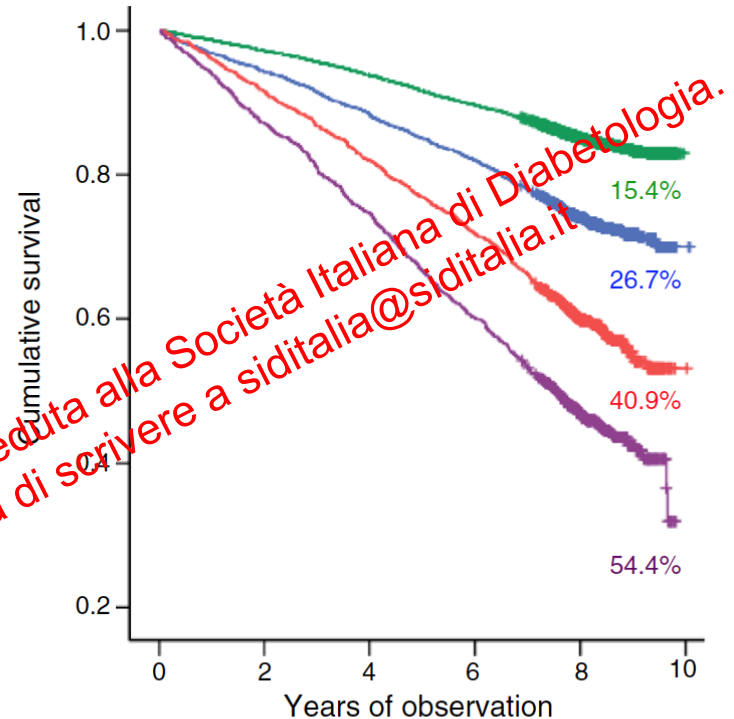
*Diabetologia* (2018) 61:2277–2289

Green, Alb<sup>-</sup>/eGFR<sup>-</sup> (no DKD)

Blue, Alb<sup>+</sup>/eGFR<sup>-</sup> (albuminuric DKD with  
preserved eGFR)

Red, Alb<sup>-</sup>/eGFR<sup>+</sup> (non-albuminuric DKD)

Purple, Alb<sup>+</sup>/eGFR<sup>+</sup> (albuminuric  
DKD with reduced eGFR)



No. at risk

|                                     |        |        |        |        |      |   |
|-------------------------------------|--------|--------|--------|--------|------|---|
| All                                 | 15,656 | 14,926 | 14,110 | 13,179 | 8243 | 3 |
| Alb <sup>-</sup> /eGFR <sup>-</sup> | 9984   | 9707   | 9362   | 8949   | 5761 | 0 |
| Alb <sup>+</sup> /eGFR <sup>-</sup> | 2966   | 2795   | 2619   | 2430   | 1535 | 1 |
| Alb <sup>-</sup> /eGFR <sup>+</sup> | 1476   | 1352   | 1210   | 1060   | 558  | 2 |
| Alb <sup>+</sup> /eGFR <sup>+</sup> | 1230   | 1072   | 919    | 740    | 389  | 0 |

eGFR < 60  
ml/min/1.73m<sup>2</sup>

Con  
Albuminuria

Senza  
Albuminuria

Rischio  
Cardiovascolare  
↑↑↑

Rischio  
Progressione  
ESRD ↑↑↑

Rischio  
Cardiovascolare  
↑↑↑

Rischio  
Progressione  
ESDR ↑

Diapositiva preparata da ROBERTO TREVISAN e ceduta alla Società Italiana di Diabetologia.  
Per ricevere la versione originale si prega di scrivere a [siditalia@siditalia.it](mailto:siditalia@siditalia.it)

# Qual è il compito del diabetologo oggi?

- Non solo ridurre la glicemia
- **(il controllo glicemico precoce riduce il rischio di nefropatia)**
- **Ridurre il rischio cardio-renale nel paziente diabetico ad alto rischio**

Diapositiva preparata da ROBERTO TREVISAN e ceduta alla Società Italiana di Diabetologia.  
Per ricevere la versione originale si prega di scrivere a [siditalia@siditalia.it](mailto:siditalia@siditalia.it)

# Diabetes is a major CV risk factor

- ESC Guidelines on diabetes, pre-diabetes and CV diseases – 2019



| The classification of CV risk levels in patients with diabetes and pre-diabetes |                                                                                                                                                                                                                                           |
|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Very high risk</b>                                                           | Patients with diabetes <b>and</b> established CV disease<br><b>Or</b> other target organ damage <sup>†</sup><br><b>Or</b> three or more major risk factors <sup>‡</sup><br><b>Or</b> early-onset T1DM of long duration ( $\geq 20$ years) |
| <b>High risk</b>                                                                | <b>Patients with diabetes duration of <math>\geq 10</math> years without target organ damage plus any other additional risk factor</b>                                                                                                    |
| <b>Moderate risk</b>                                                            | Young patients (T1DM aged $< 35$ years or T2DM aged $< 50$ years) with diabetes duration $< 10$ years, without other risk factors                                                                                                         |

Macroalbuminuria  
eGFR:  
 $< 30$  ml/min/1.73m<sup>2</sup>

Microalbuminuria  
eGFR:  
30-60 ml/min/1.73m<sup>2</sup>

\*Table modified from the 2016 European Guidelines on CV disease prevention in clinical practice;

<sup>†</sup>Proteinuria, kidney impairment defined as

eGFR  $< 30$  ml/min/1.73 m<sup>2</sup>, left ventricular hypertrophy or retinopathy; <sup>‡</sup>Age, hypertension, dyslipidaemia, smoking, obesity

Cosentino F et al. Eur Heart J 2020;41:255

## EVIDENZE PER UN RUOLO SPECIFICO DI SGLT2 nel DANNO RENALE

SGLT2 i: risultati su ESRD, Raddoppio Creatinina e  
Mortalità Renale

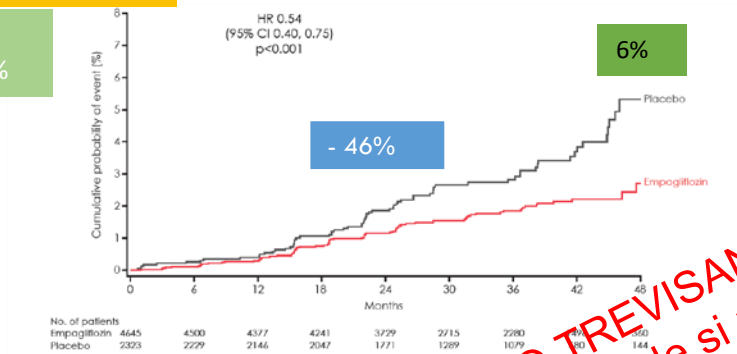
Diapositiva preparata da ROBERTO TREVISAN e ceduta alla Società Italiana di Diabetologia.  
Per ricevere la versione originale si prega di scrivere a [siditalia@siditalia.it](mailto:siditalia@siditalia.it)

# EMPA-REG, CANVAS, DECLARE and CREDENCE: Renal Outcomes

## ESKD, Doubling of Serum Creatinine, or Renal Death

### EMPA-REG

CVD  
100%



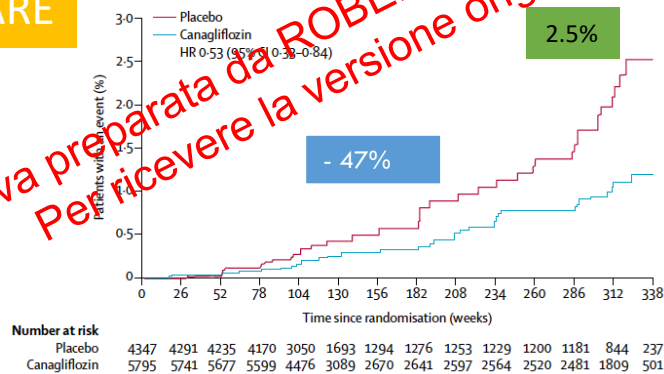
### CANVAS

CVD 66%



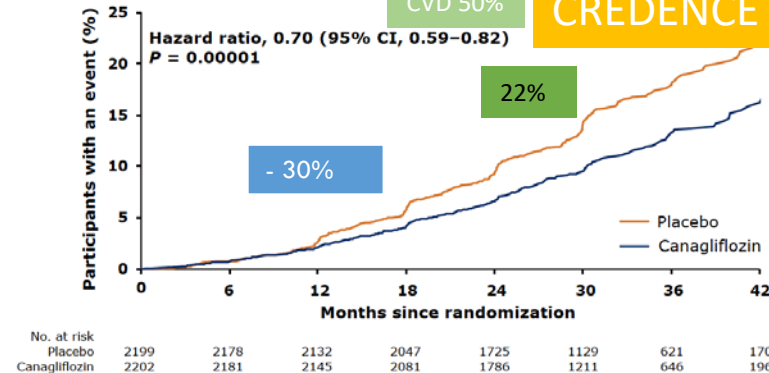
### DECLARE

CVD 41%



CVD 50%

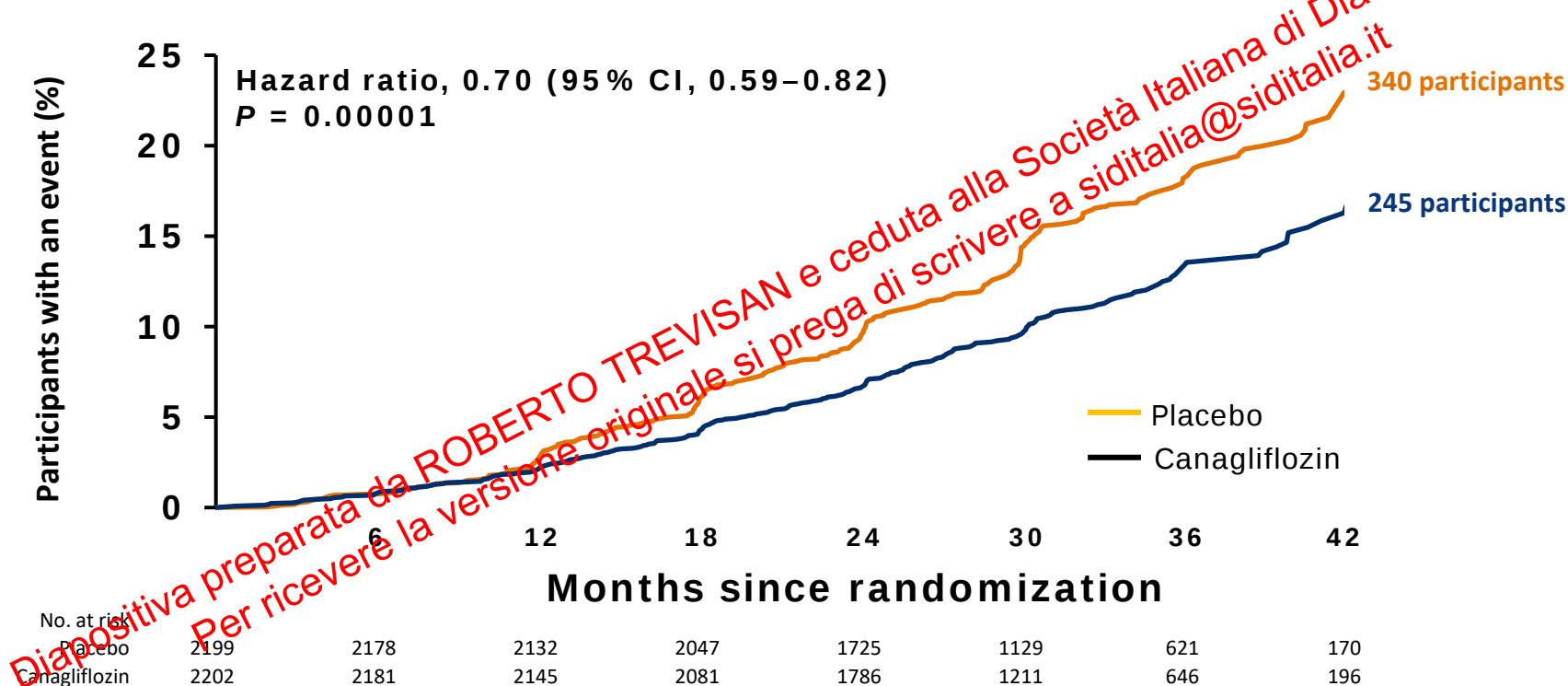
### CREDENCE



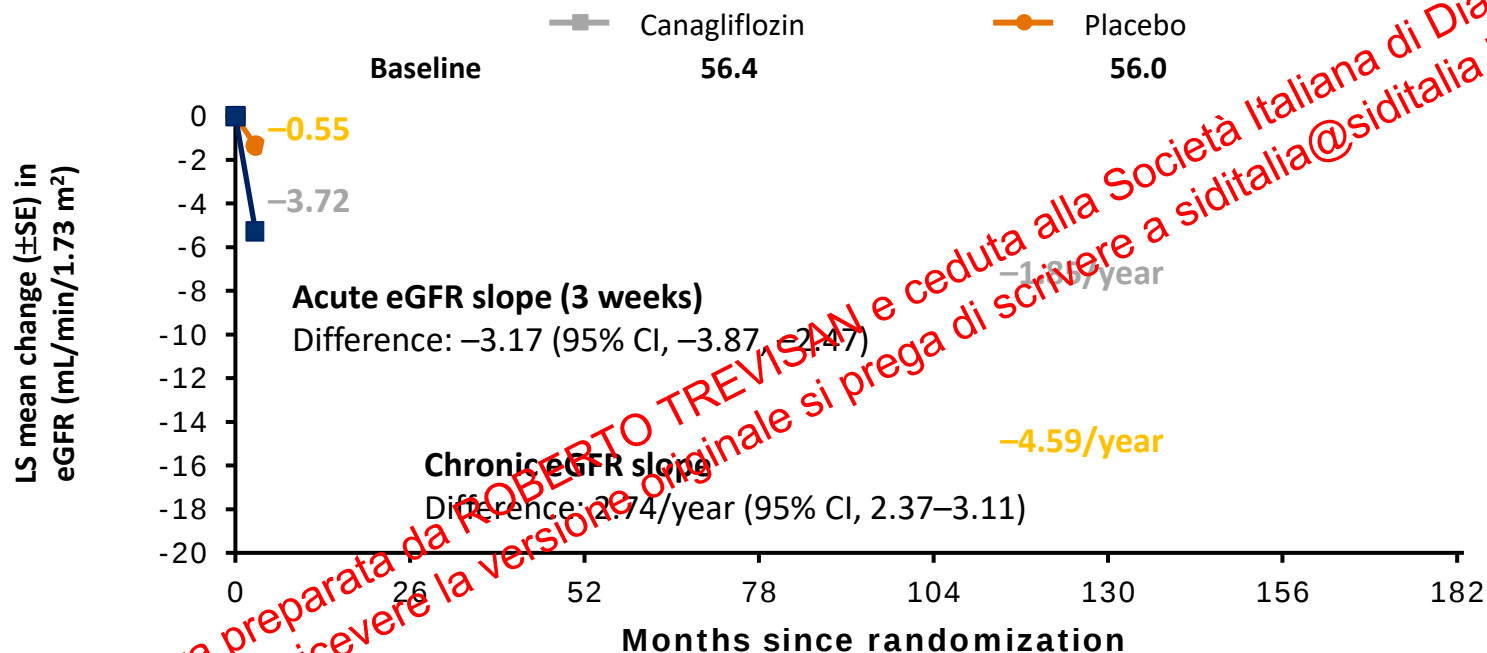
Diapositiva preparata da ROBERTO TREVISAN e ceduta alla Società Italiana di Diabetologia.  
Per ricevere la versione originale si prega di scrivere a [siditalia@siditalia.it](mailto:siditalia@siditalia.it)

# CREDENCE: Primary Outcome

ESKD, Doubling of Serum Creatinine, or Renal or CV Death



# CREDENCE: Effects on eGFR

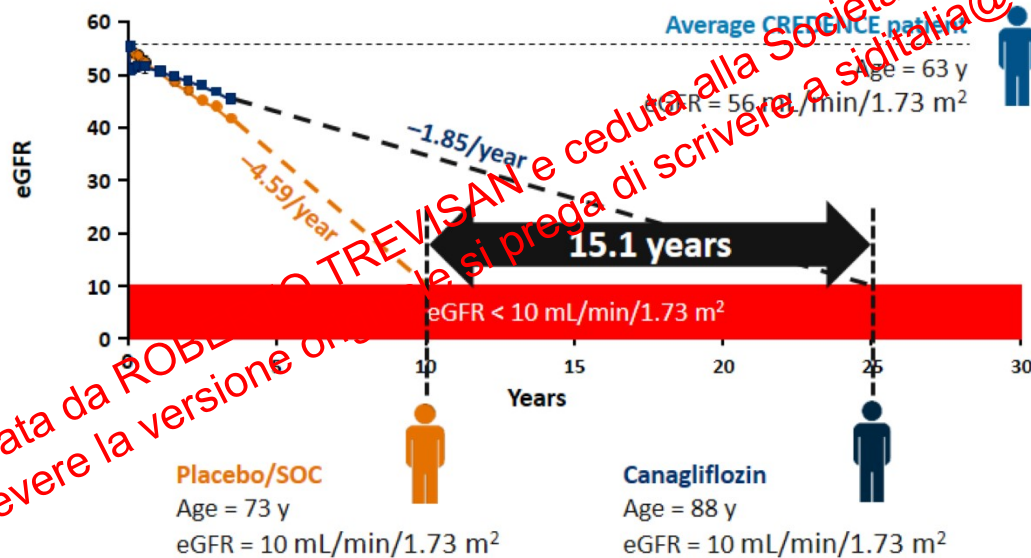


No. of Participants

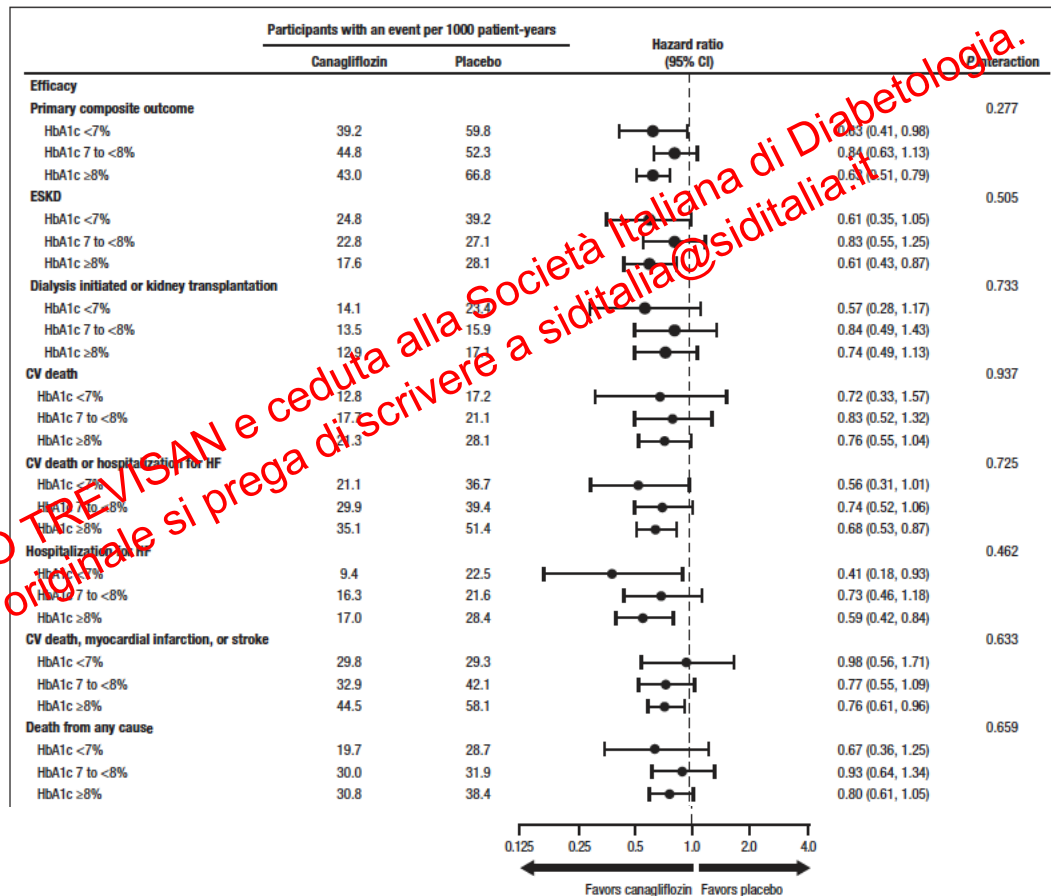
|               |      |      |      |      |      |      |      |     |     |
|---------------|------|------|------|------|------|------|------|-----|-----|
| Placebo       | 2178 | 2084 | 1985 | 1882 | 1720 | 1536 | 1006 | 583 | 210 |
| Canagliflozin | 2179 | 2074 | 2005 | 1919 | 1782 | 1648 | 1116 | 652 | 241 |

On treatment

# Projected Effects of Canagliflozin on eGFR

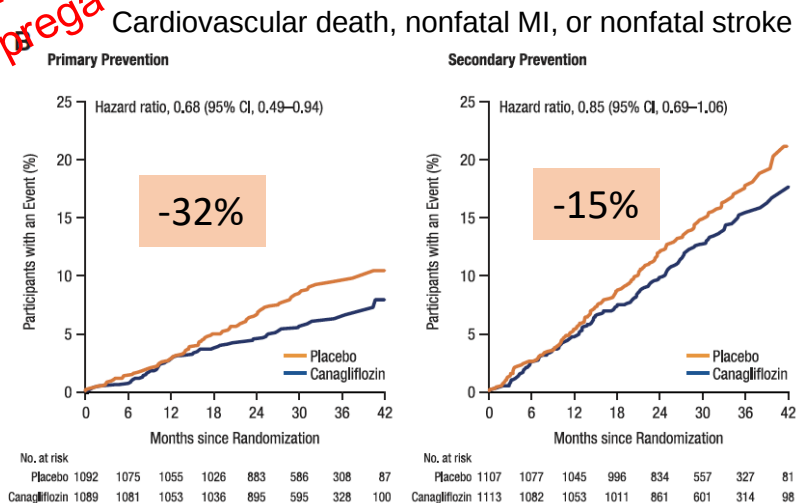
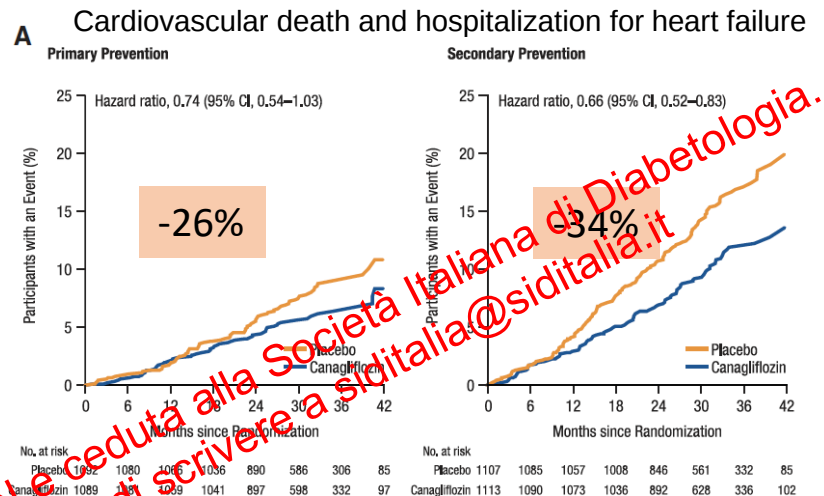


# CREDENCE: Efficacy and safety outcomes by baseline HbA1c



## CREDENCE

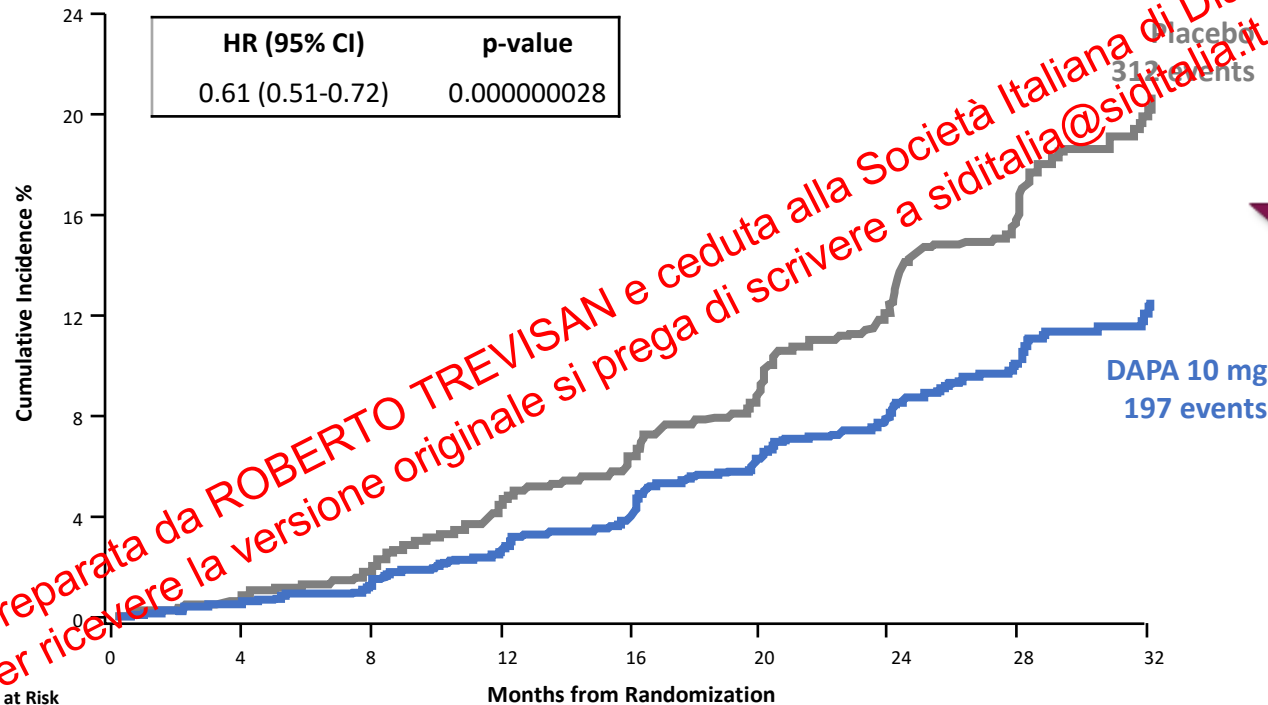
Effects of canagliflozin on cardiovascular outcomes in the primary and secondary prevention cohorts



Circulation. 2019;140:739–750.

# DAPA-CKD: Primary Composite Outcome: Sustained $\geq 50\%$ eGFR Decline, ESKD, Renal or CV Death<sup>a</sup>

68% T2D  
32% without T2D



N at Risk

DAPA 10 mg

2152

2001

1955

1898

1841

1701

1288

831

309

Placebo

2152

1993

1936

1858

1791

1664

1232

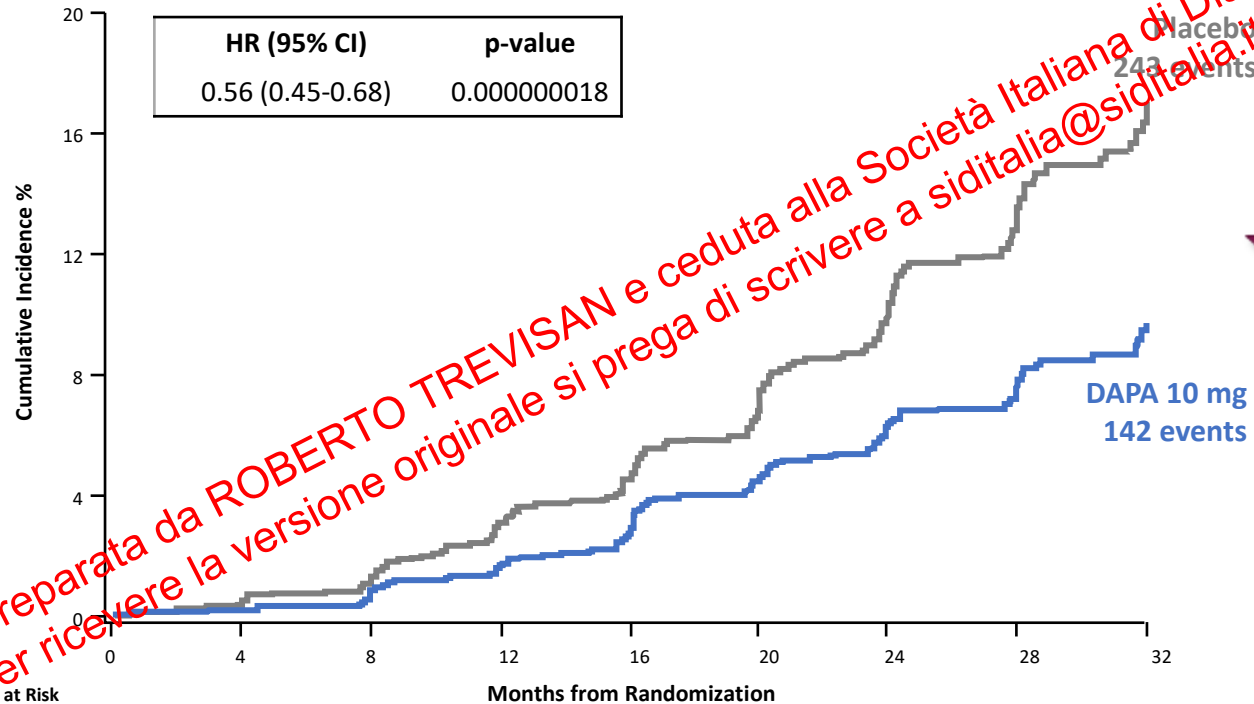
774

270

<sup>a</sup>ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR  $<15\text{mL/min/1.73m}^2$  for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.<sup>2</sup> CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; ; NNT = number needed to treat; 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.

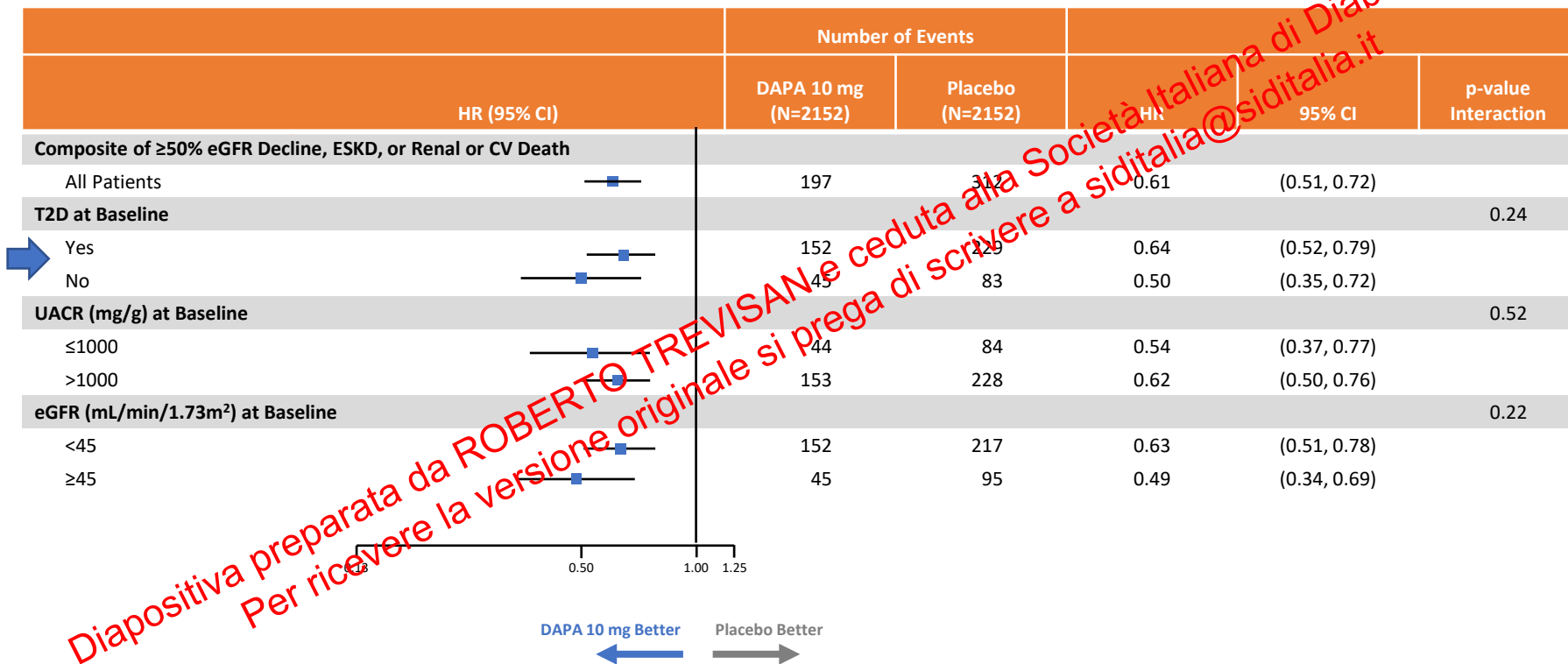
# DAPA-CKD: Secondary Composite Outcome: Sustained $\geq 50\%$ eGFR Decline, ESKD, or Renal Death<sup>a</sup>



<sup>a</sup>ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR  $<15\text{mL}/\text{min}/1.73\text{m}^2$  for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.<sup>2</sup> 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: Treatment Benefit Consistent Across Prespecified Subgroups

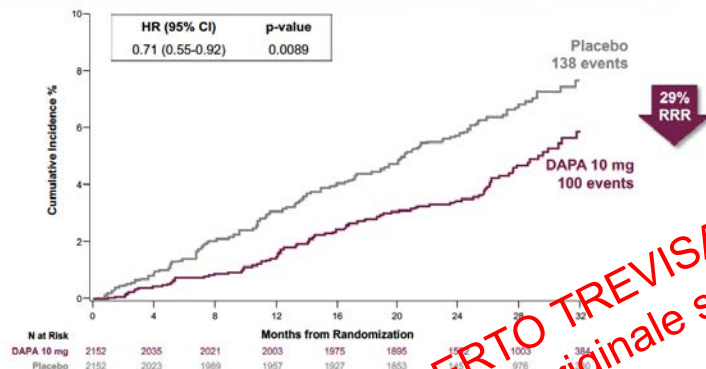


CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

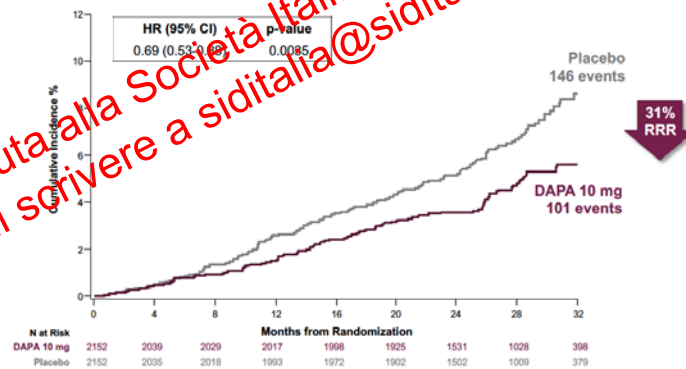
Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.

# DAPA-CKD

## Secondary Composite Outcome: CV Death or Hospitalization for Heart Failure



## Secondary Outcome: All-cause Mortality



**39%** RRR

for the primary composite endpoint (≥50% sustained decline in eGFR, ESKD, renal or CV death)

**44%** RRR

for the renal composite (≥50% sustained decline in eGFR, ESKD, or renal death)

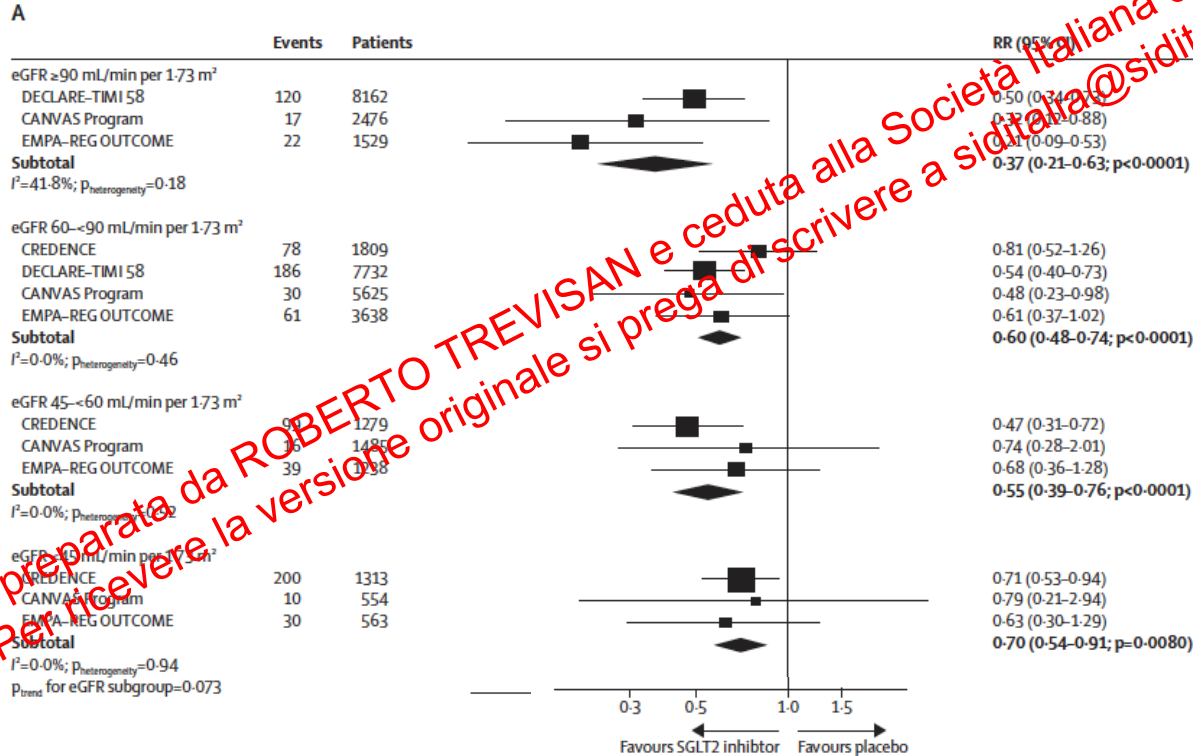
**29%** RRR

for the composite of CV death or hospitalization for heart failure

**31%** RRR

all-cause mortality

# Effect of SGLT2 inhibitors on substantial loss of kidney function, ESKD, or death due to kidney disease, stratified by baseline eGFR



- 63%

- 40%

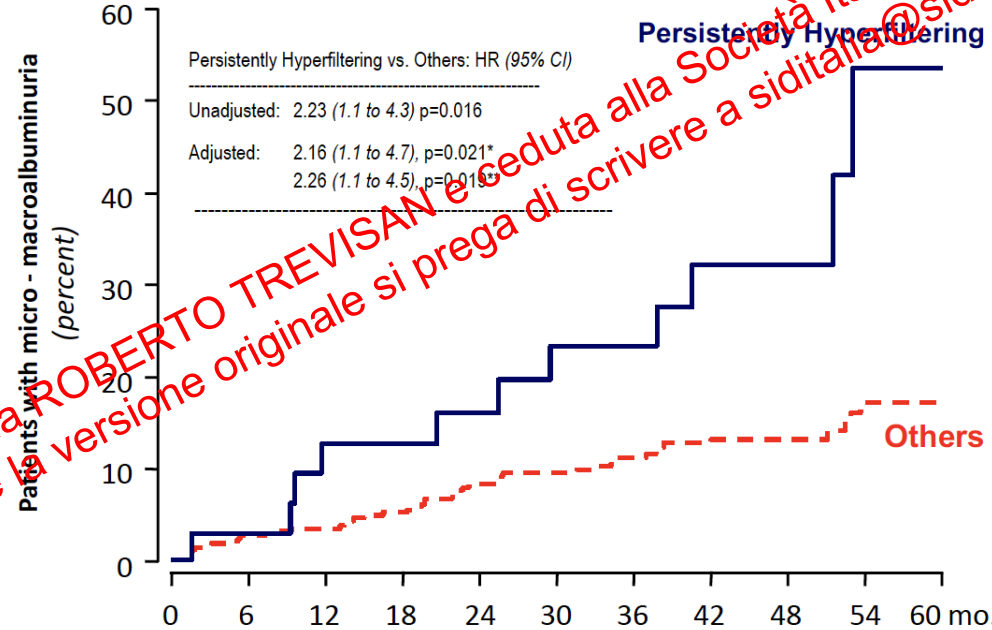
- 45%

- 30%

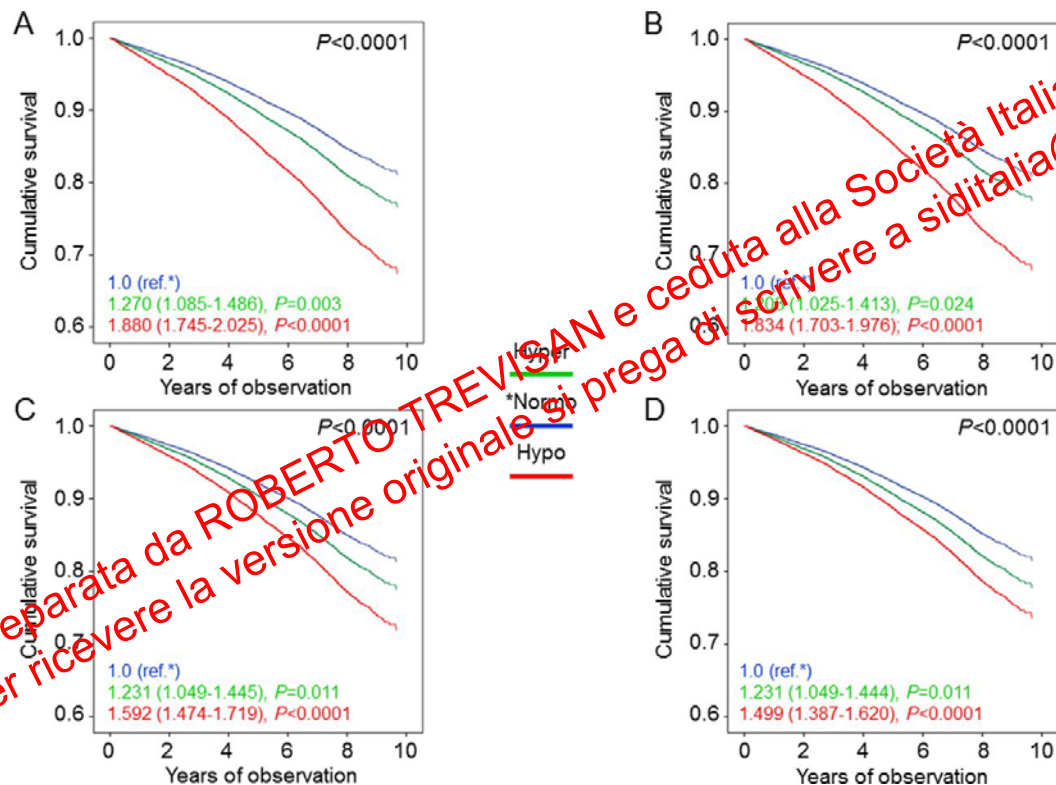
Diapositiva preparata da ROBERTO TREVISAN e ceduta alla Societa Italiana di Diabetologia. Per ricevere la versione originale si prega di scrivere a [siditalia@siditalia.it](mailto:siditalia@siditalia.it)

# Glomerular Hyperfiltration and Renal Disease Progression in Type 2 Diabetes

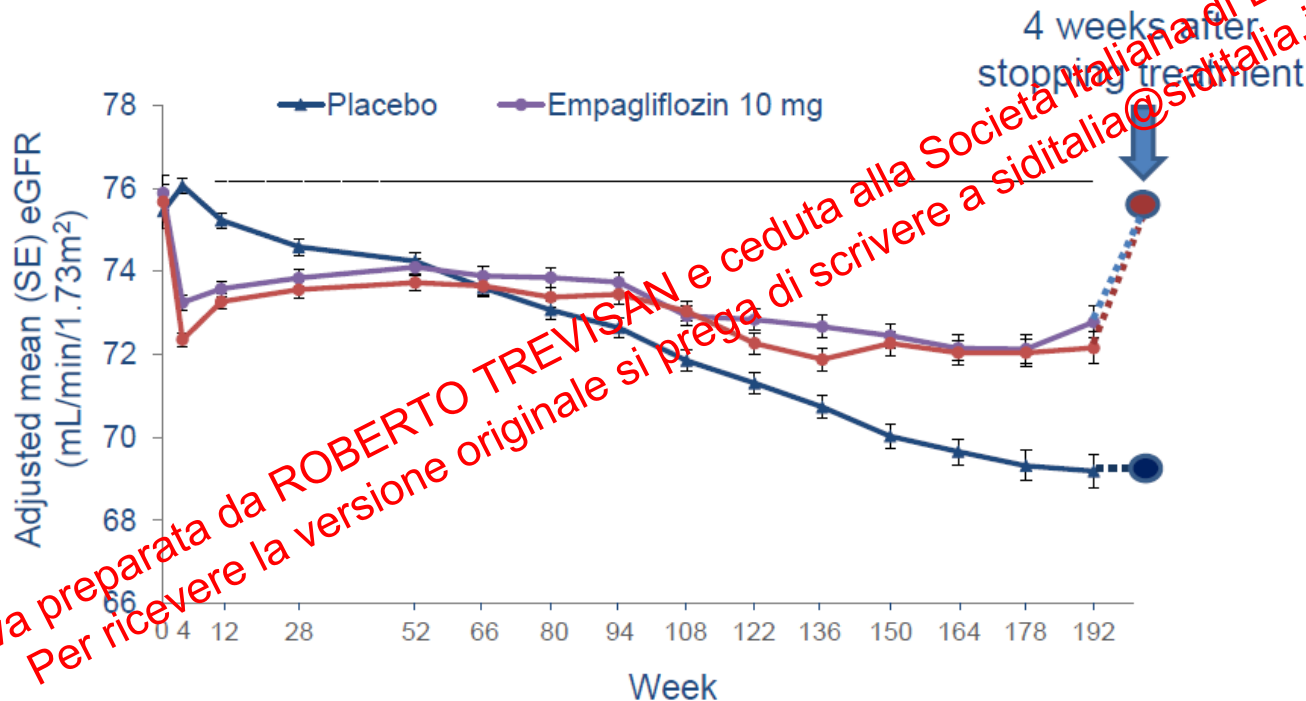
- 600 normo or microalbuminuric T2DM from BENEDICT B and DEMAND trials
- GFR by *Iohexol Plasma clearance*
- Hyperfiltration: GFR>120 ml/min/1.73m<sup>2</sup>



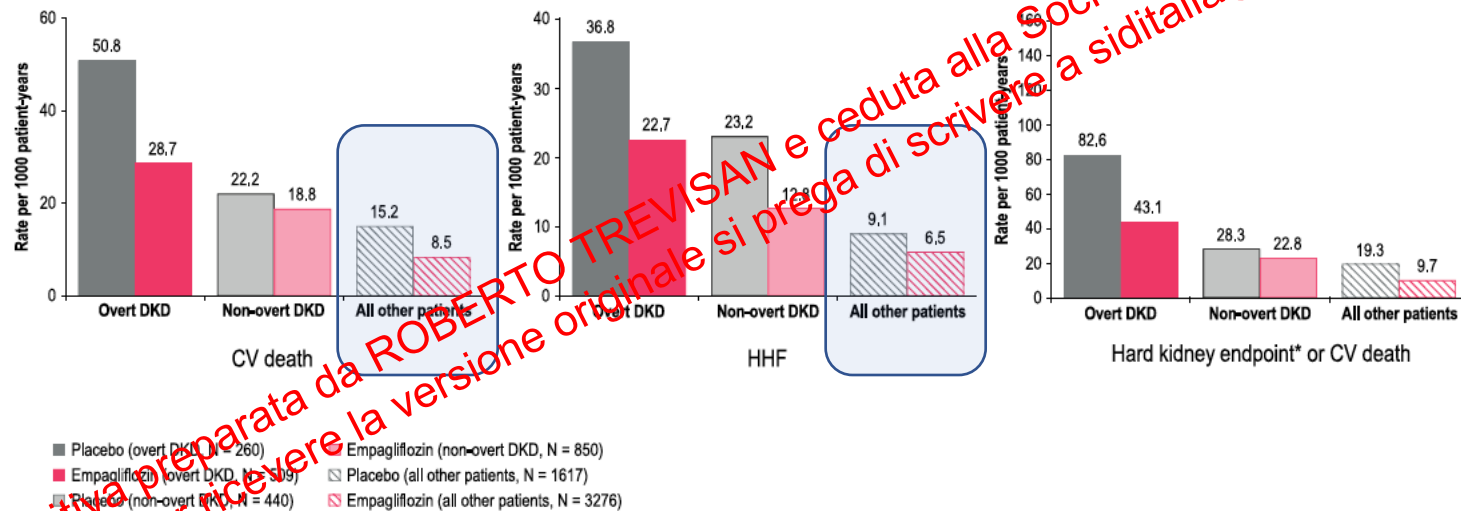
Cox proportional hazards regression adjusted for age and gender (A), plus albuminuria (B), plus CVD risk factors (C), plus complications/comorbidities (D), according to age-adjusted filtration status.



## Reversal of acute effect on eGFR

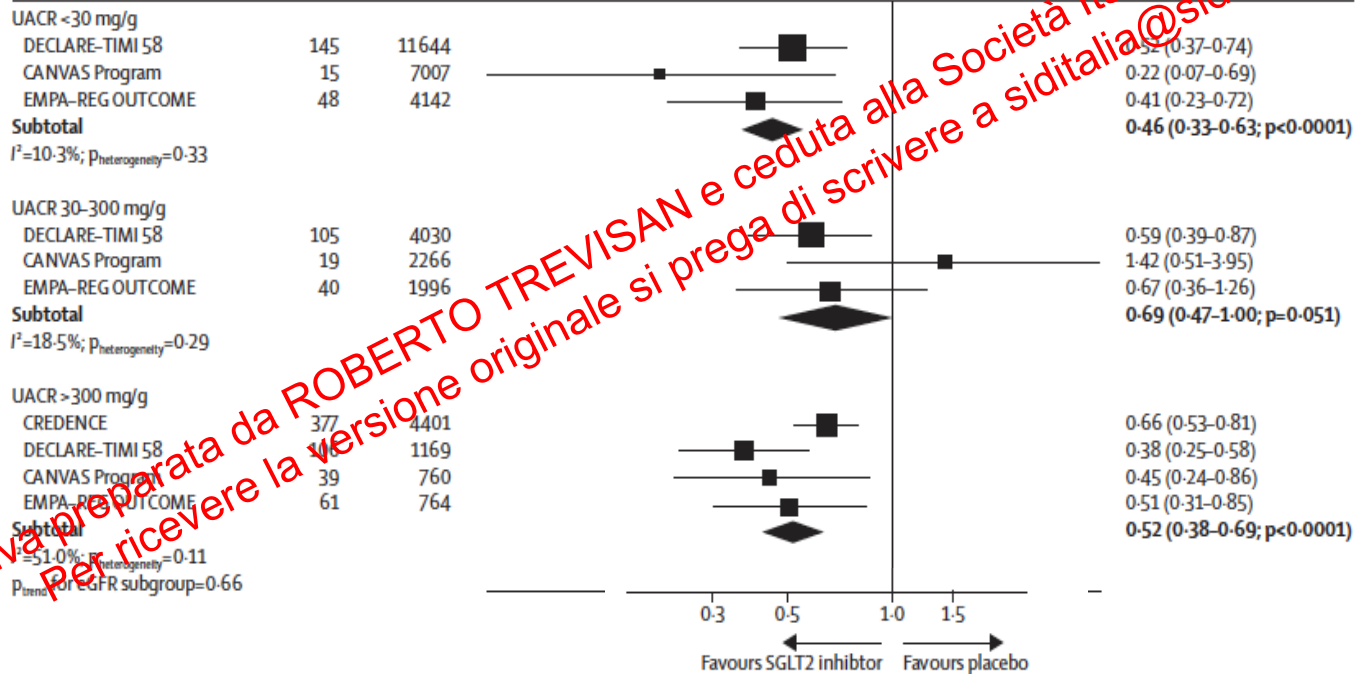


Incidence rates of cardiovascular, kidney and cardio/kidney endpoints with empagliflozin and placebo in EMPA-REG OUTCOME among subgroups of patients with overt diabetic kidney disease (DKD), patients with non-overt DKD and 'all others' at baseline



# Effect of SGLT2 inhibitors on substantial loss of kidney function, ESKD, or death due to kidney disease, stratified by baseline UACR

B

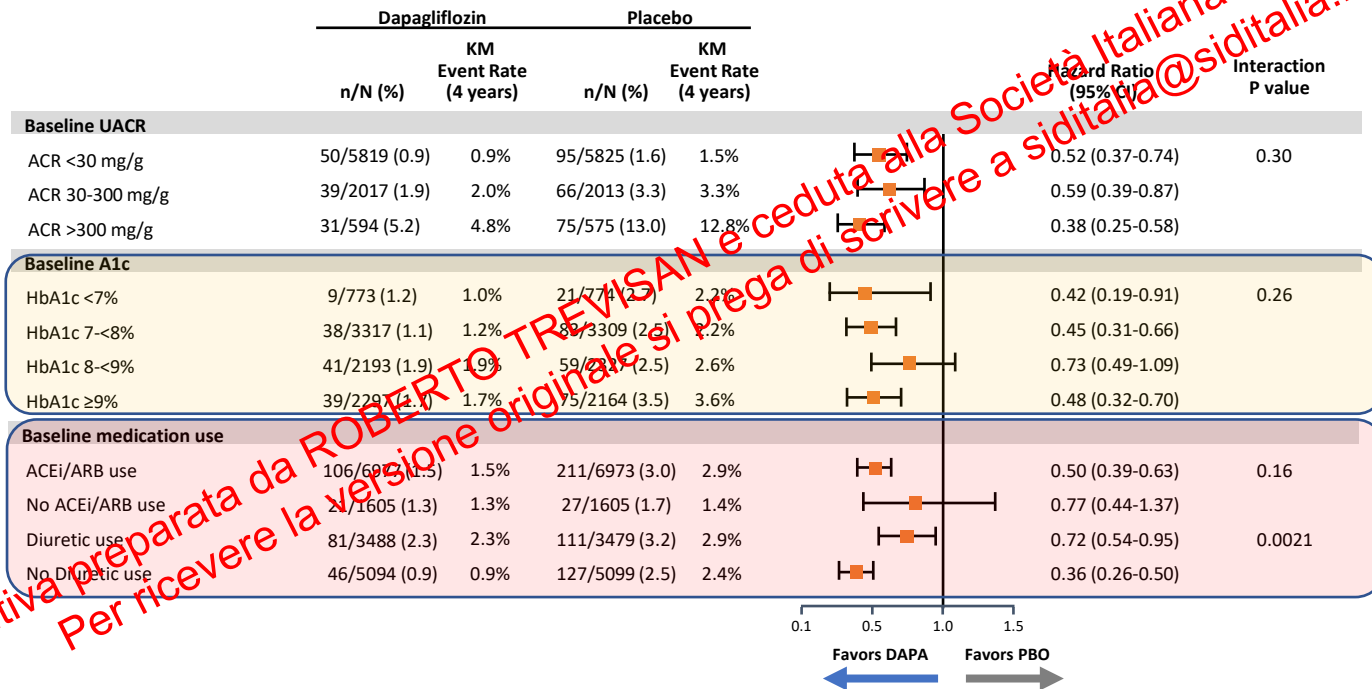


- 54%

- 31%

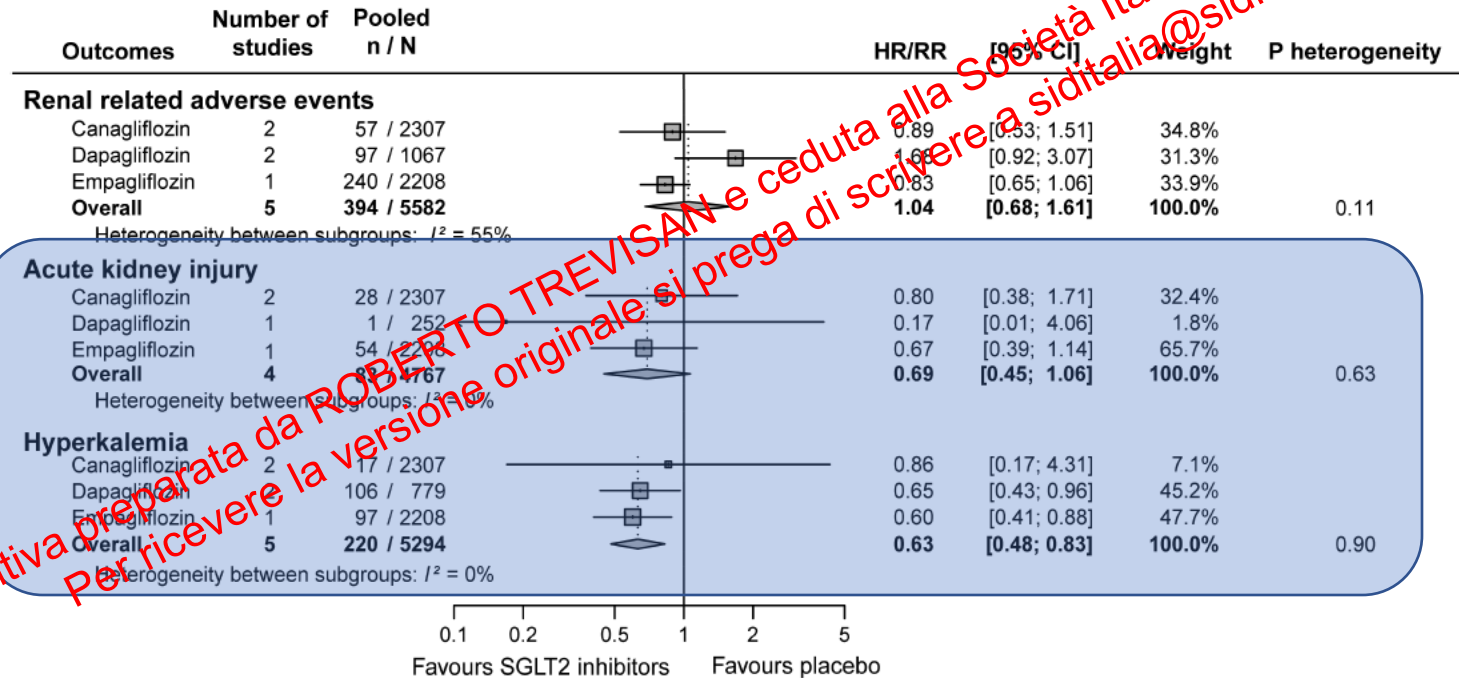
- 48%

# DECLARE: Renal-specific Outcome\* by Subgroup: Decrease eGFR $\geq 40\%$ , ESRD or Renal Death



- \*Prespecified exploratory outcome. ACEi = angiotensin converting enzyme inhibitor; ACR = albumin:creatinine ratio; ARB = angiotensin receptor blocker;
- CVD = cardiovascular disease; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; KM = Kaplan-Meier; PBO = placebo;
- UACR = urinary albumin: creatinine ratio
- Mosenzon O et al. Online ahead of print. *Lancet Diabetes Endocrinol.* 2019.

# Effects of SGLT2 inhibitors on renal adverse events in individuals with type 2 diabetes and chronic kidney disease (eGFR < 60 mL/min/1.73 m<sup>2</sup>)



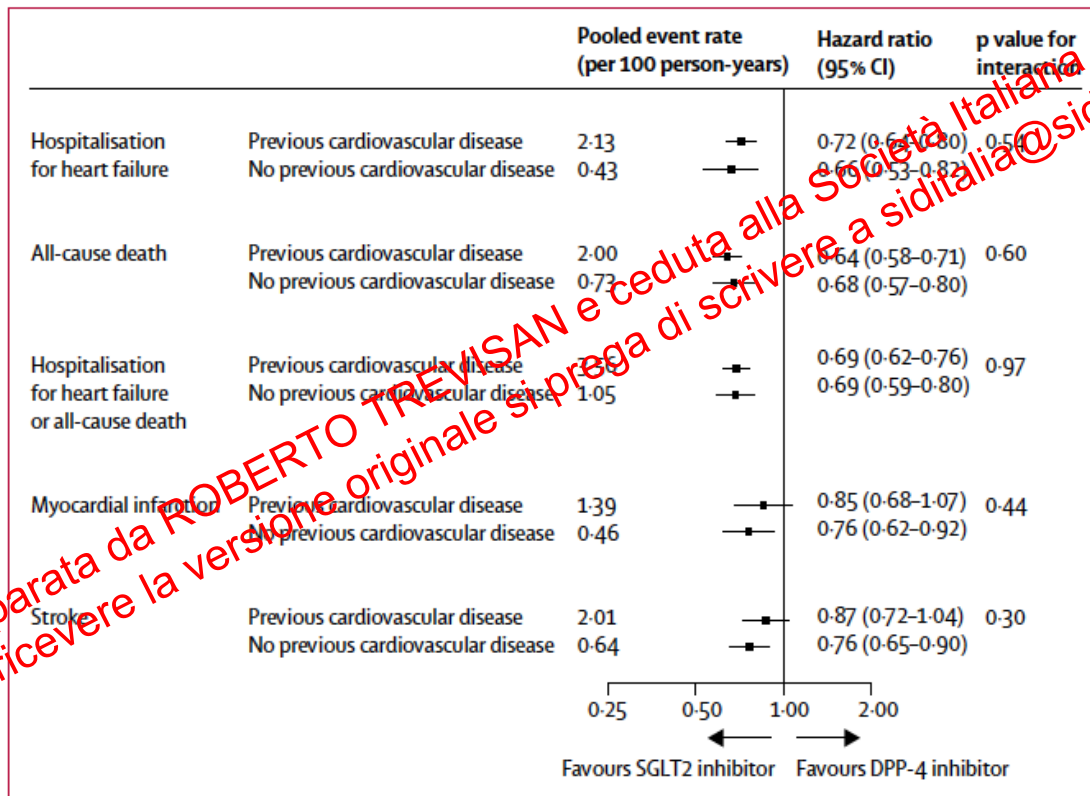
E nel real world?

Diapositiva preparata da ROBERTO TREVISAN e ceduta alla Società Italiana di Diabetologia.  
Per ricevere la versione originale si prega di scrivere a [siditalia@siditalia.it](mailto:siditalia@siditalia.it)

## CVD-REAL 2 multinational cohort study

Cardiovascular and mortality outcomes in patients with and without cardiovascular disease at baseline. SGLT2i vs DPP4i

193 124 new users of  
SGLT2 inhibitors  
Vs  
193 124 new users of  
DPP-4 inhibitors.



# CONCLUSIONI

- I diabetici con malattia renale cronica dimostrano un maggiore rischio di eventi cardiovascolari indipendentemente dalla presenza di albuminuria.
- I SGLT2i riducono non solo la progressione della malattia renale indipendentemente dall'albuminuria, ma anche il rischio cardiovascolare nel diabetico ad alto rischio, anche con ridotta funzione renale e con nefropatia diabetica conclamata.
- In caso di A1c non controllata, non vanno sospesi, ma vanno aggiunti altri farmaci.
- La prevenzione del danno cardio-renale è prioritaria nel diabetico e il beneficio degli SGLT2-i è in gran parte glucosio-indipendente.
- **Tutti i diabetici di Tipo 2 (salvo controindicazioni specifiche), ma soprattutto ad alto rischio, dovrebbero essere trattati con SGLT2-inibitori.**



Diapositiva preparata da ROBERTO TREVISAN e ceduta alla Società Italiana di Diabetologia.  
per ricevere la versione originale si prega di scrivere a [siditalia@siditalia.it](mailto:siditalia@siditalia.it)

*Grazie per la vostra attenzione*