

DKD:

***Vale ancora la visione
albuminocentrica nella
progressione del danno
renale?***

SI

**Salvatore Di Paolo
Barletta**



MERCOLEDÌ 2 OTTOBRE

**I° CONVEGNO NAZIONALE
CONGIUNTO SIN - SID**

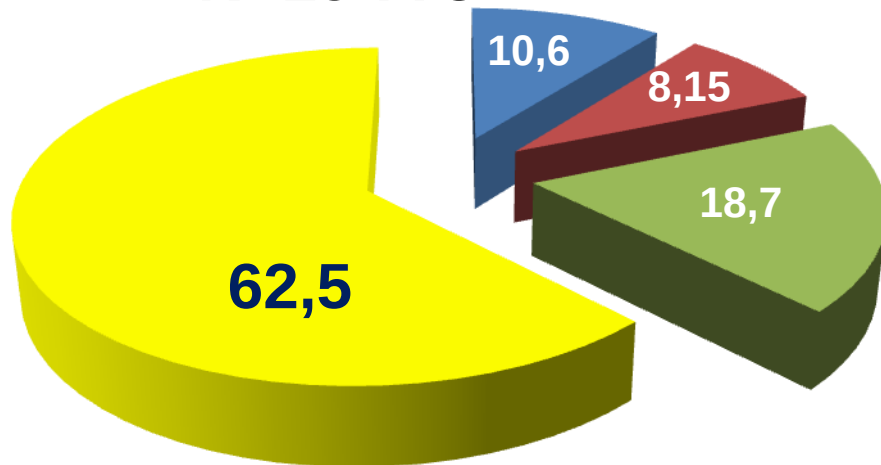
**La Malattia Renale Diabetica (DKD):
Presente e Futuro dell'Approccio
Integrato Nefro-Diabetologico**

TEAM WORK FOR WORK SUCCESS



DMT2 e FUNZIONE RENALE

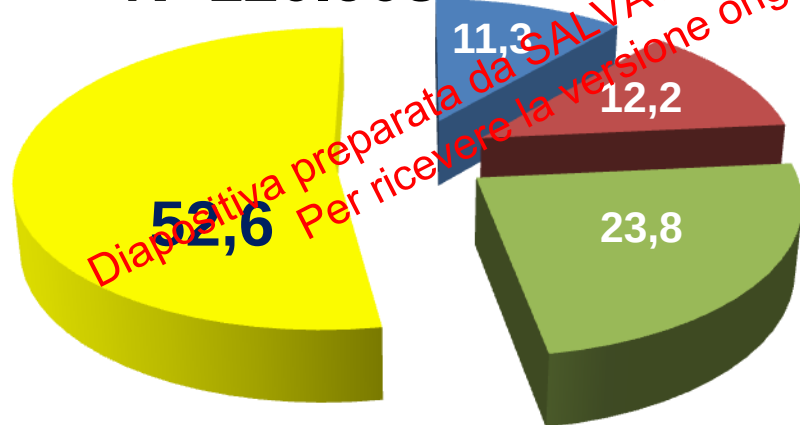
N=15.773



Studio RIACE

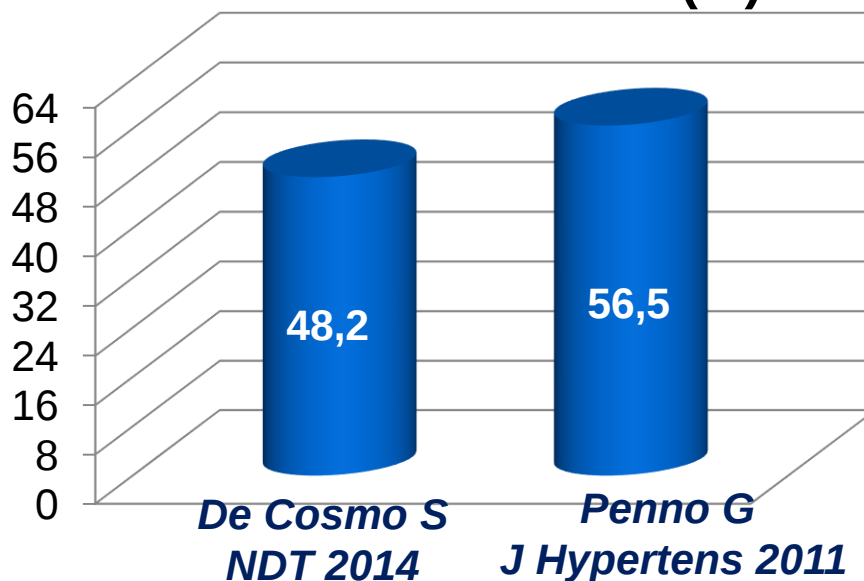
(Penno G, J Hypertens 2011)

N=120.903



De Cosmo S, NDT 2014

Pazienti con CKD Normoalbuminurica (%)

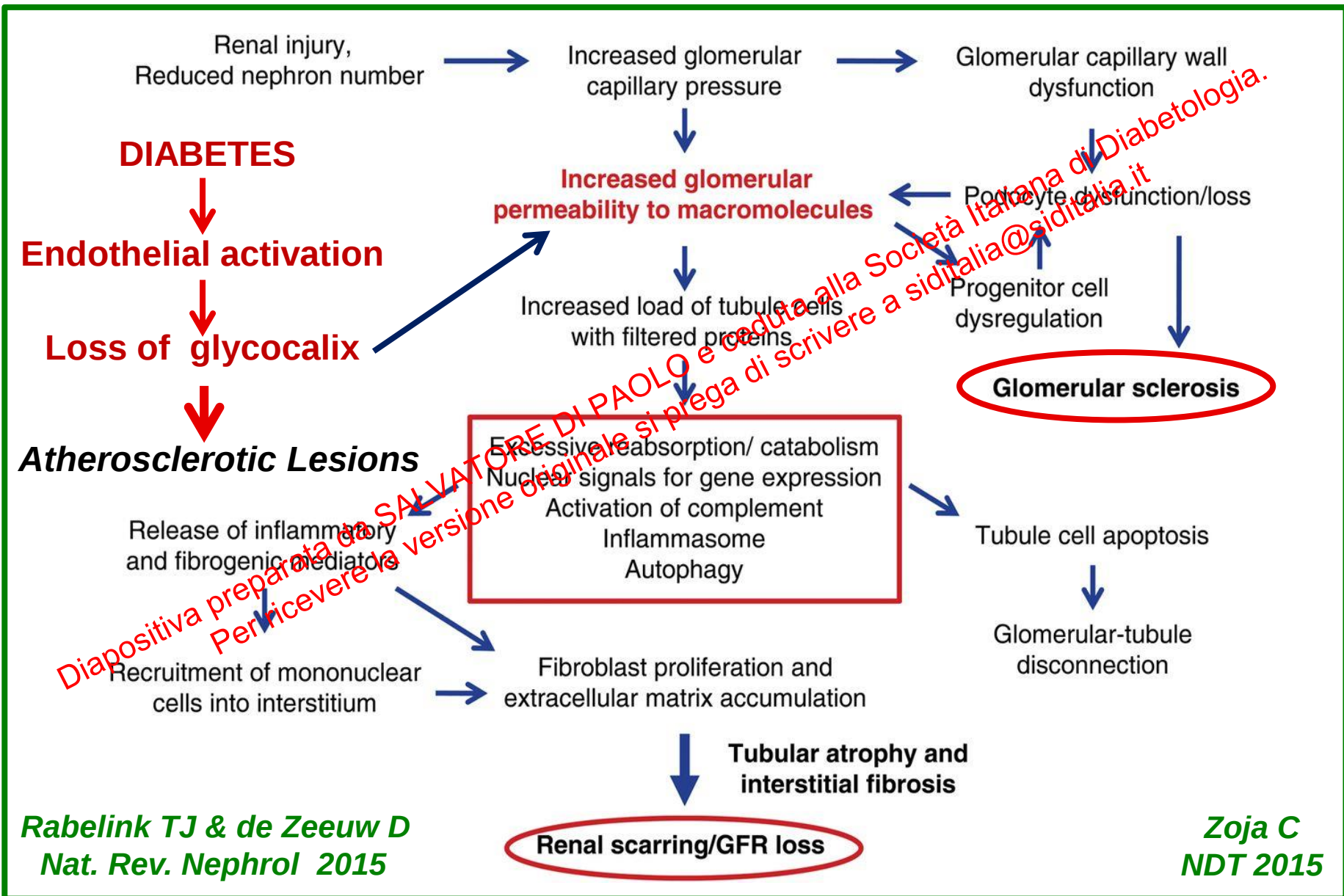


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Schematic representation of events underlying progressive glomerular and tubulointerstitial injury of proteinuric nephropathies.

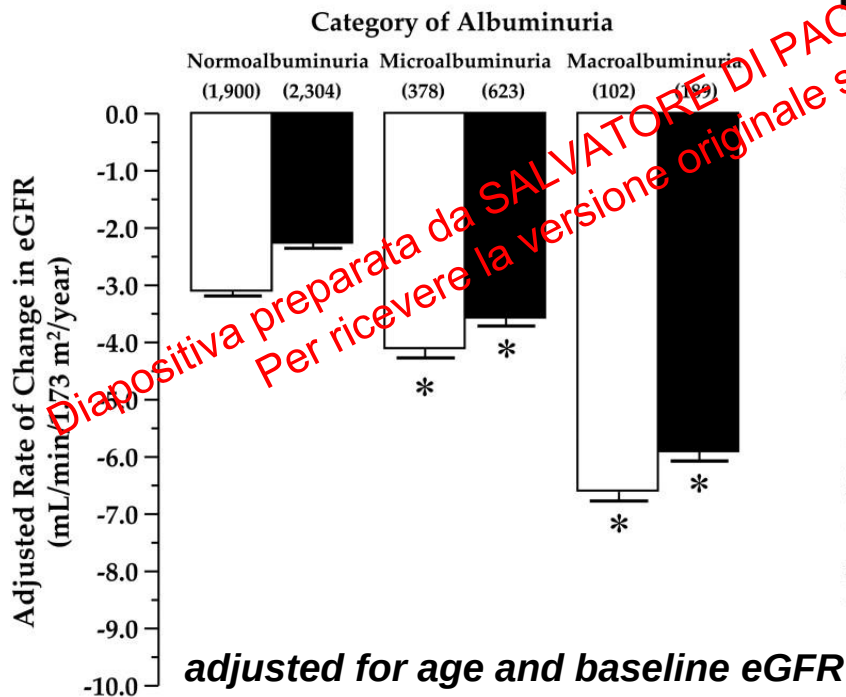


Higher Levels of Urinary Albumin Excretion Within the Normal Range Predict Faster Decline in Glomerular Filtration Rate in Diabetic Patients

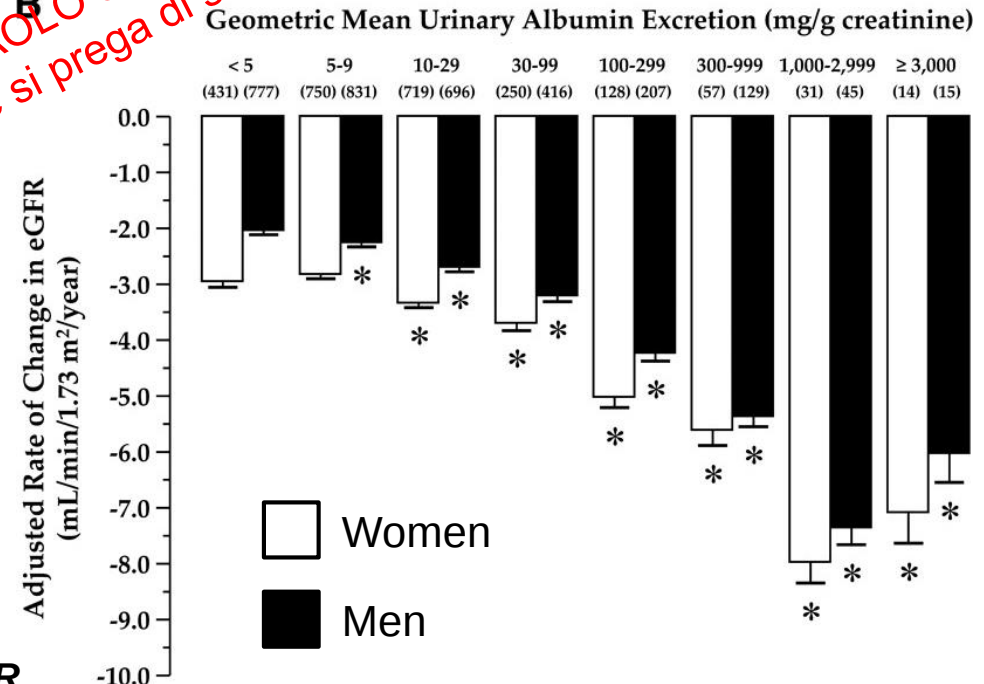
Comparison of the rate of change in eGFR, among traditional categories (A) and subcategories of the urinary ACR (B)

5449 T2DM. sCr: 0.65 ± 0.22 mg/dL F-U: 9.2 ± 2.4 yrs

A



B



Initial Angiotensin Receptor Blockade-Induced Decrease in Albuminuria Is Associated With Long-Term Renal Outcome in Type 2 Diabetic Patients With Microalbuminuria

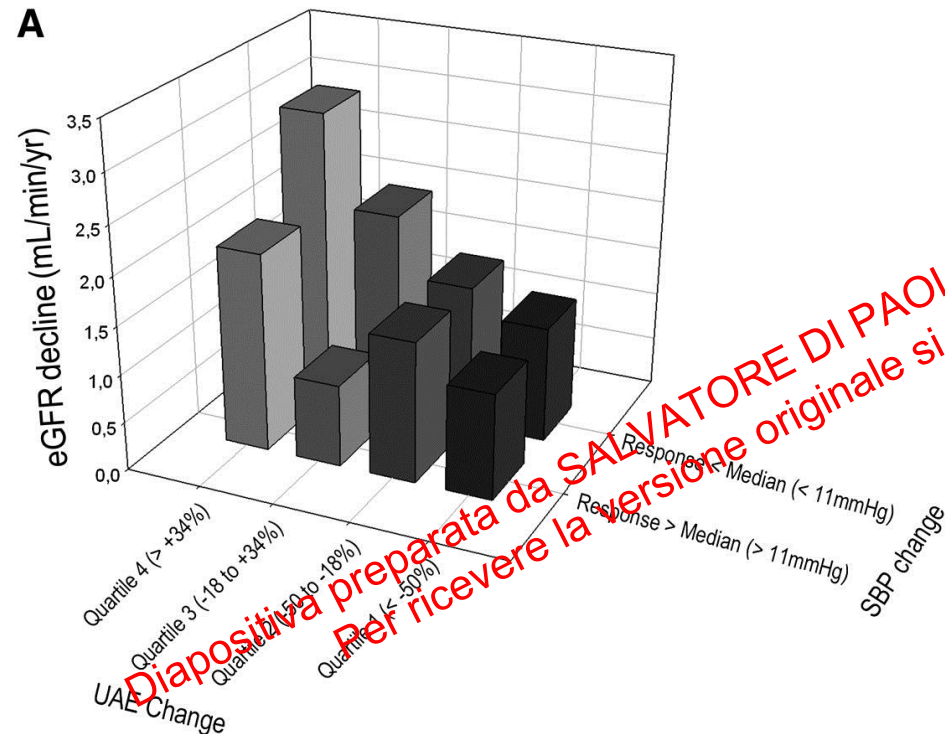
American Diabetes Association Diabetes Care

Hellemons ME, 2011

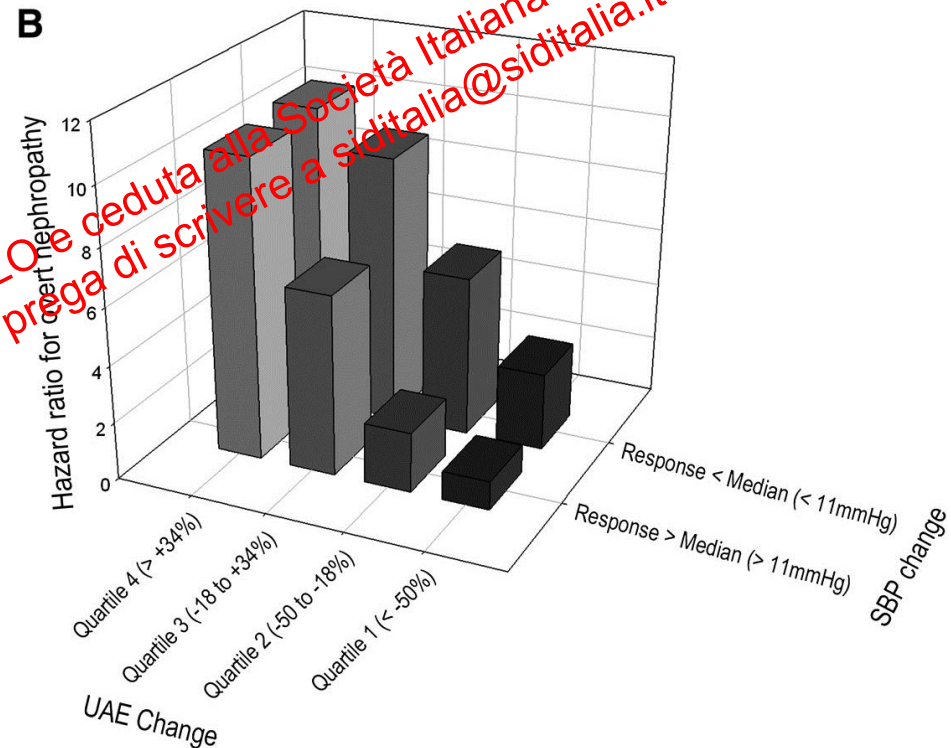
A post hoc analysis of the IRMA-2 trial

531 T2DM. sCr <1.5 mg/dL. All μ Alb. 6-mo change. FU 2 yrs

A



B



Within an individual, UAE response to ARB therapy may be discordant from SBP response. The initial change in UAE was independently associated with eGFR slope; the more UAE reduction the less eGFR decline, irrespective of the SBP change

LA MICROALBUMINURIA NON RAPPRESENTA UNO STADIO IRREVERSIBILE DELLA NEFROPATIA DIABETICA

La progressione a Macroalbuminuria rappresenta l'evenienza meno frequente

Progression to macroalbuminuria No change

The development of microalbuminuria can no longer be viewed as a committed and irreversible stage of DKD

Conclusions regarding the kidney health of individuals with diabetes will continue to be flawed if an inappropriate emphasis is placed on the presence or absence of microalbuminuria or **changes in albuminuria within the micro-albuminuric range.**

Author:	Tabaei ¹⁸	Perkins ²⁰	Hovind ²¹	Steinke ²²	de Boer ²³	Gaede ²⁴	Araki ²⁵	Yamada ²⁶
Year:	2001	2003	2004	2005	2011	2004	2005	2005
Number with microalbuminuria:	16	386	79	22	325	151	216	94

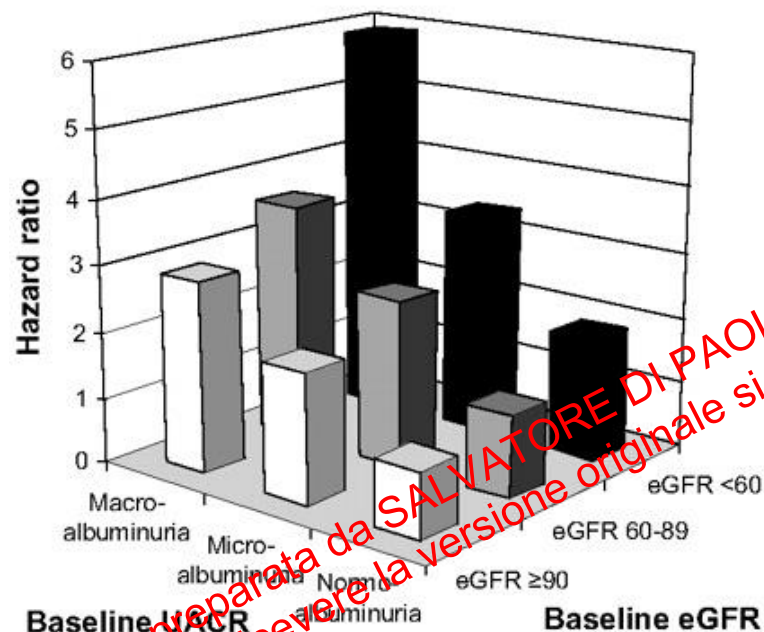
Albuminuria and Kidney Function Independently Predict Cardiovascular and Renal Outcomes in Diabetes

JASN

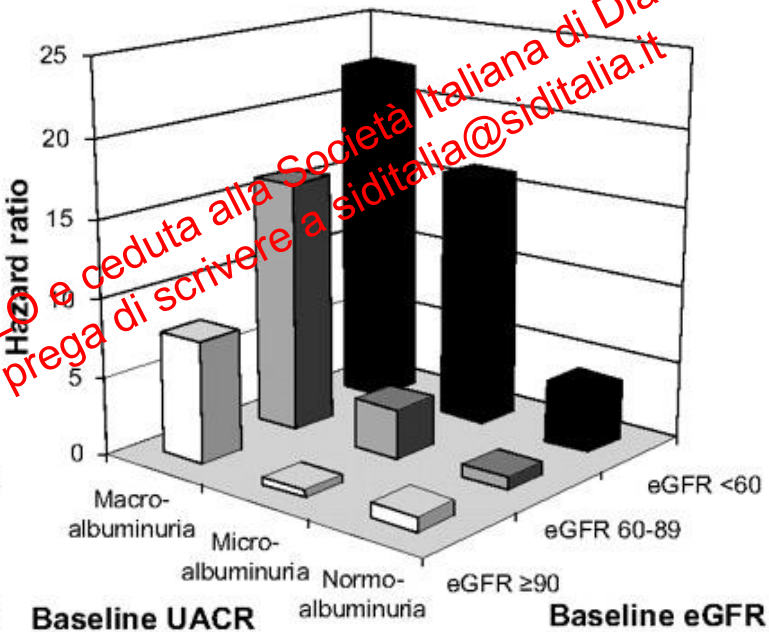
Ninomiya T, 2009 ADVANCE Collaborative Group

10,640 T2DM eGFR < 60 ml/min: 19% Macroalbuminuria: 4% F-U: 4,3 yrs

Cardiovascular death



Renal events

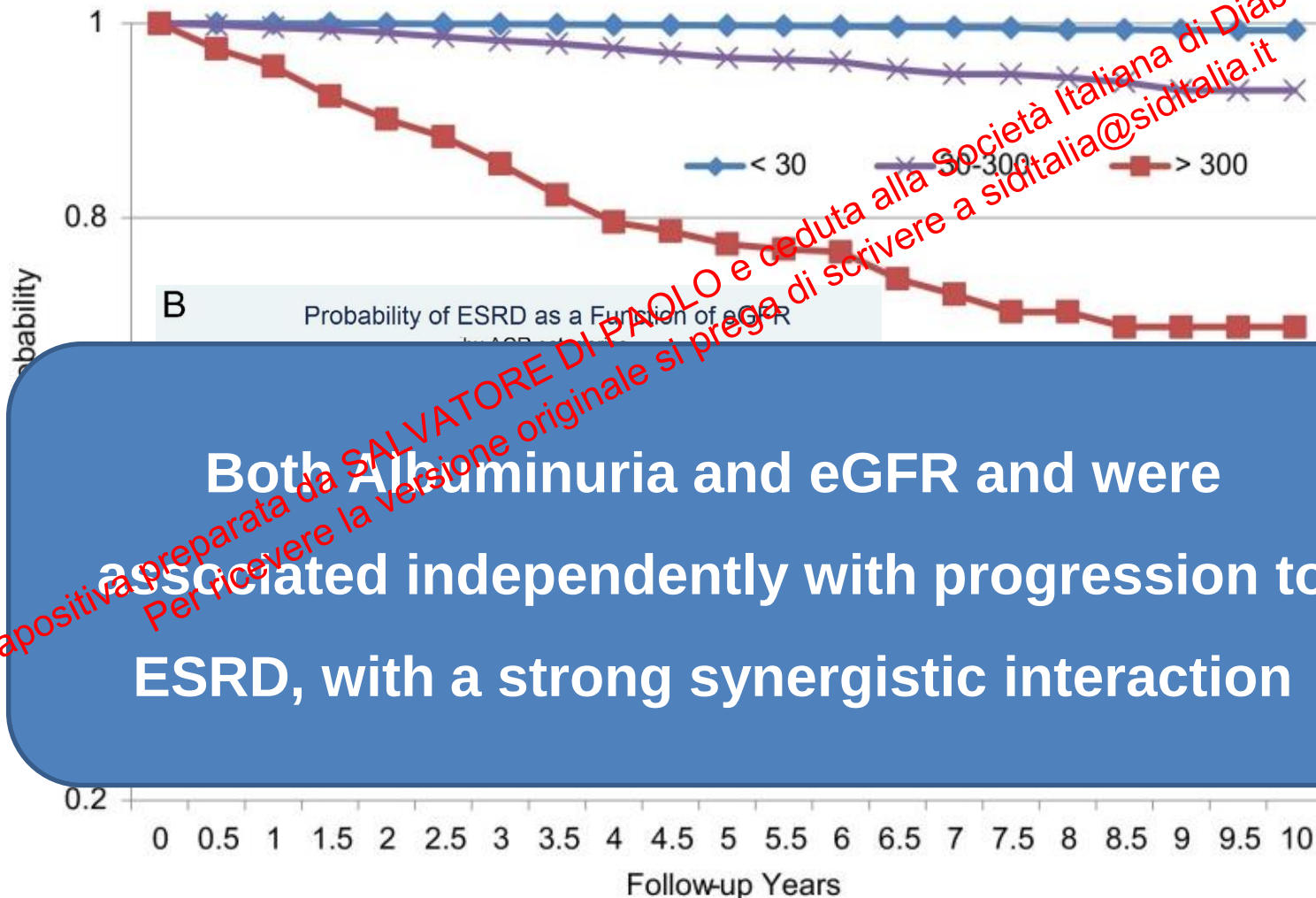


Patients with both UACR > 300 mg/g and eGFR < 60 ml/min at baseline had a 3.2-fold higher risk for CV events and a 22.2-fold higher risk for renal events, compared with patients with neither of these risk factors.

In conclusion, high albuminuria and low eGFR are independent risk factors for cardiovascular and renal events among patients with type 2 diabetes.

The Synergistic Relationship Between Estimated GFR and Microalbuminuria in Predicting Long-term Progression to ESRD or Death in Patients With Diabetes: Results From the Kidney Early Evaluation Program (KEEP)

42,671 T2DM, 8,618 (20,2%) with eGFR < 60 mL/min/1.73 m²



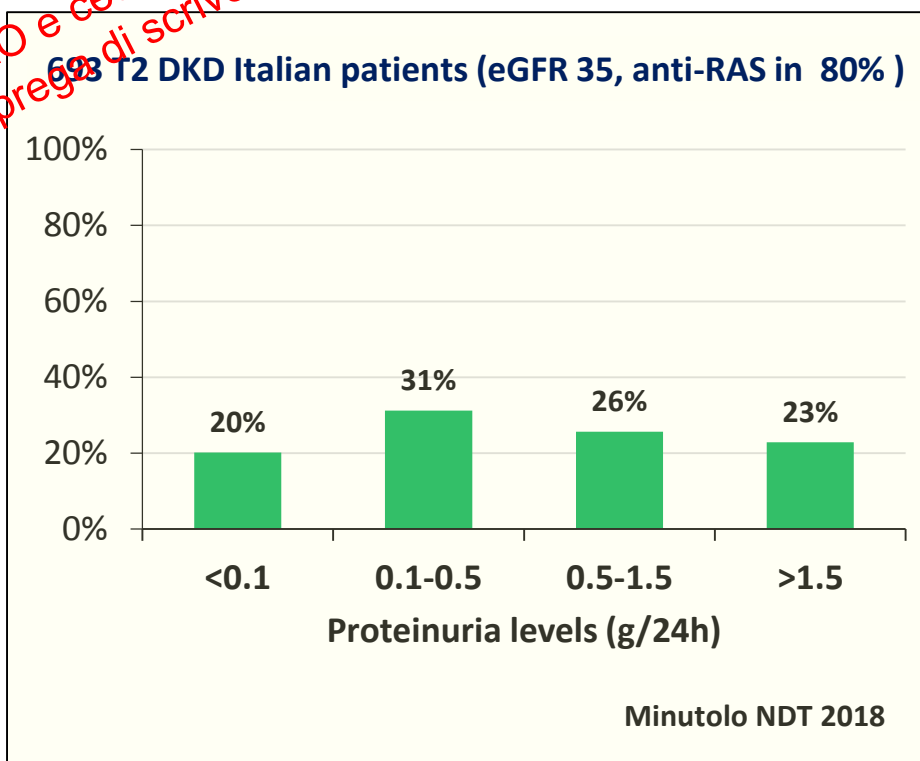
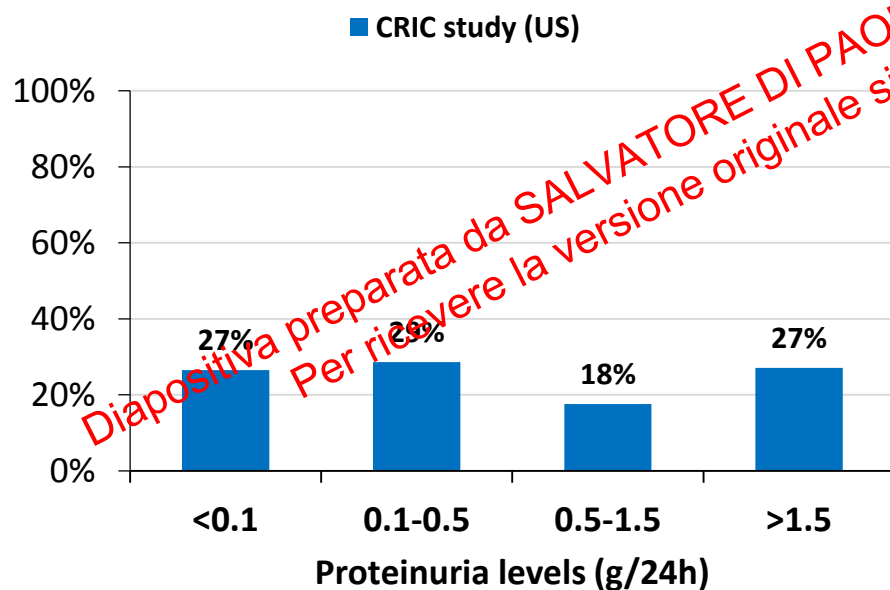
Both Albuminuria and eGFR were associated independently with progression to ESRD, with a strong synergistic interaction

Risk of Progression of Nonalbuminuric CKD to End-Stage Kidney Disease in People With Diabetes: The CRIC (Chronic Renal Insufficiency Cohort) Study

Digsu N. Koye, Dianna J. Magliano, Christopher M. Reid, Christopher Jepson, Harold I. Feldman, William H. Herman, and Jonathan E. Shaw

AJKD Vol XX | Iss XX | Month 2018

1,831 T2 DKD with reduced eGFR (41 mL/min) and under anti-RAS in 80% stratified by proteinuria

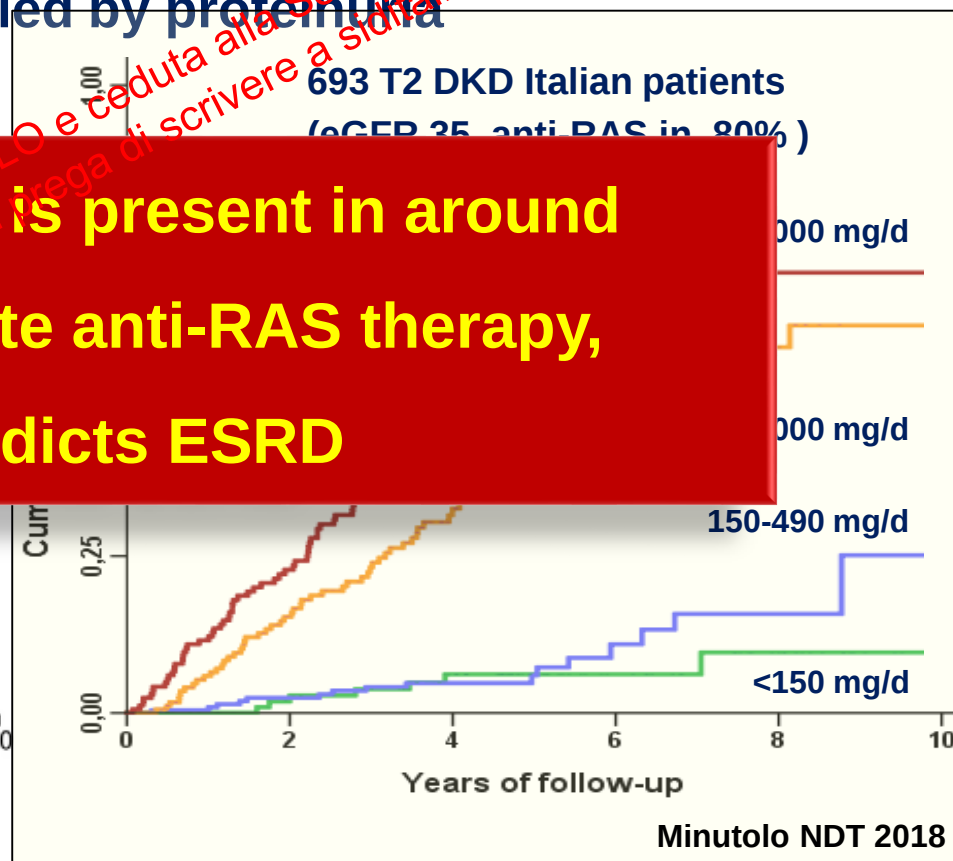
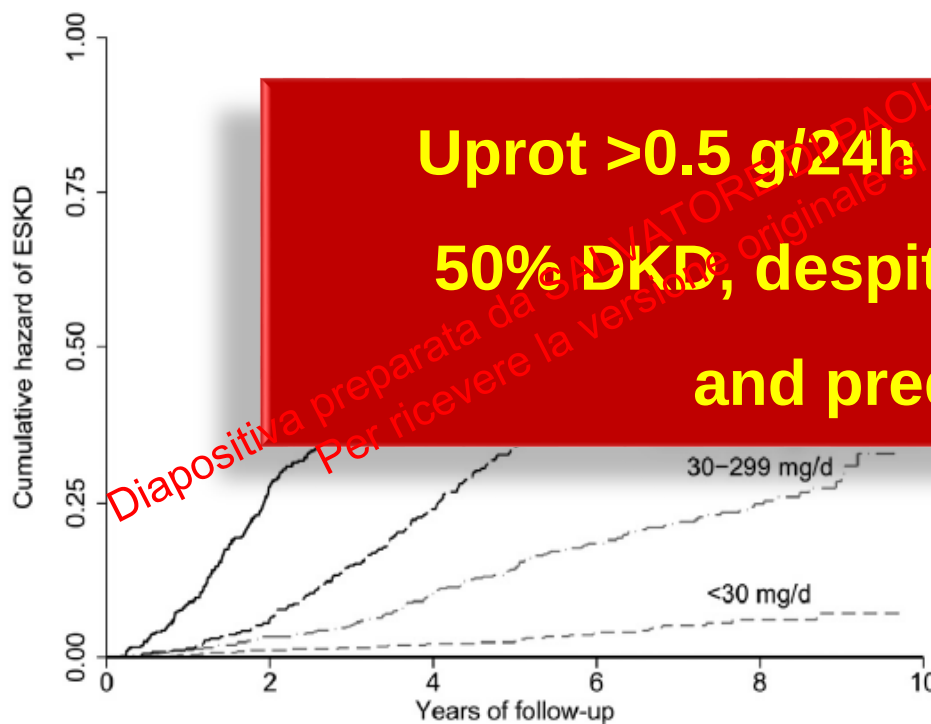


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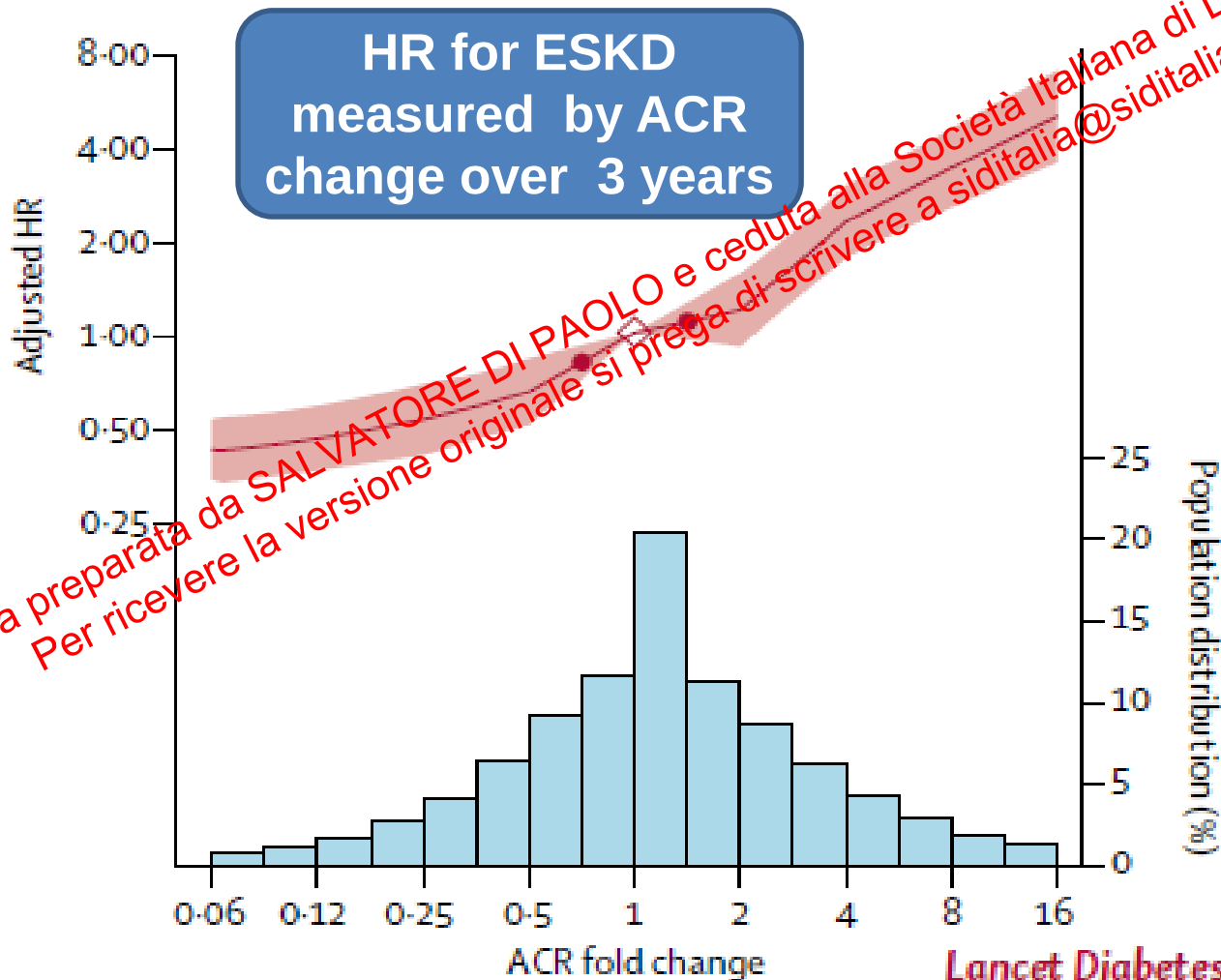
CRIC participants with diabetes and reduced GFR (n=1,813) stratified by proteinuria



Uprot >0.5 g/24h is present in around 50% DKD, despite anti-RAS therapy, and predicts ESRD

Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies

693816 individuals 80% T2DM Baseline eGFR 78.2 ± 21 mL/min/1.73 m²

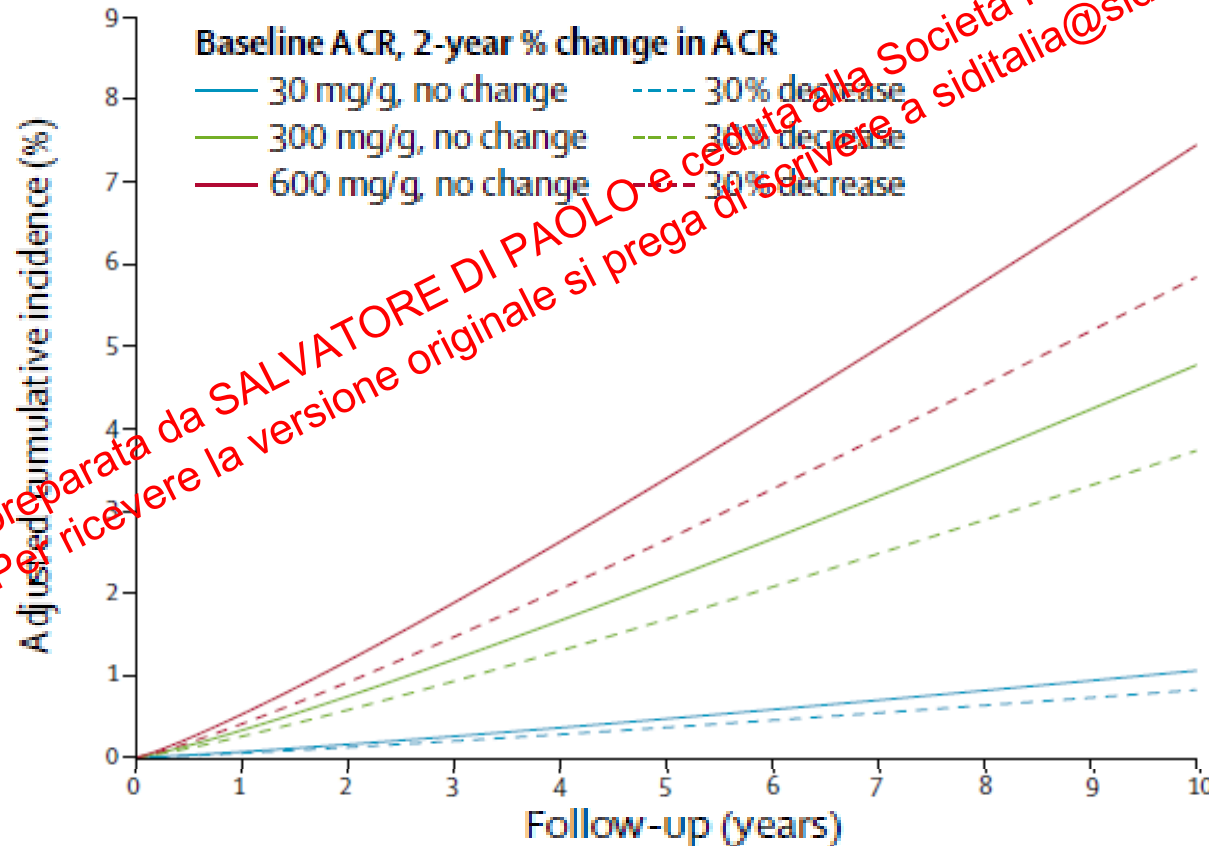


Josef Coresh,

Lancet Diabetes Endocrinol 2019

Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies

Adjusted cumulative incidence of ESKD for 3 levels of baseline Albuminuria and a 30% decline in Albuminuria for each level



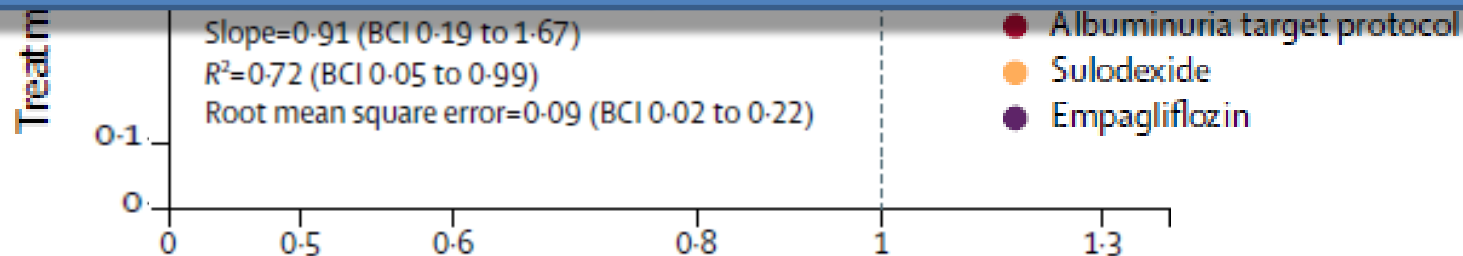
Josef Coresh, Lancet Diabetes Endocrinol 2019

Change in albuminuria as a surrogate endpoint for progression of kidney disease: a meta-analysis of treatment effects in randomised clinical trials

Lancet Diabetes Endocrinol 2019



Each 30% decrease in 6-month Albuminuria by the treatment relative to the control was associated with an average 27% lower HR for the clinical endpoint: ESRD, doubling of sCr, eGFR<15 ml/min



Heerspink HIL, 2019

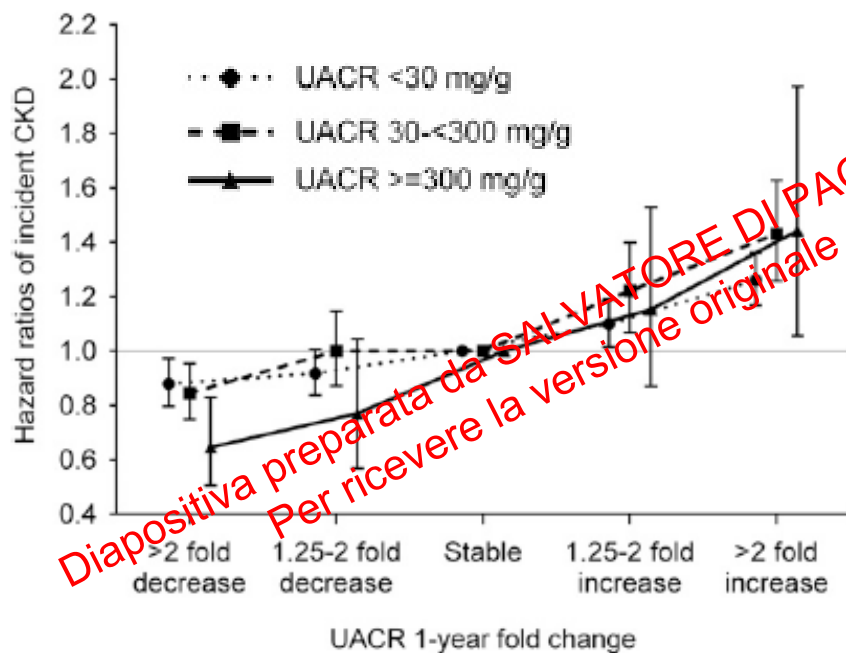
Changes in Albuminuria and Subsequent Risk of Incident Kidney Disease

CJASN
Clinical Journal of the American Society of Nephrology

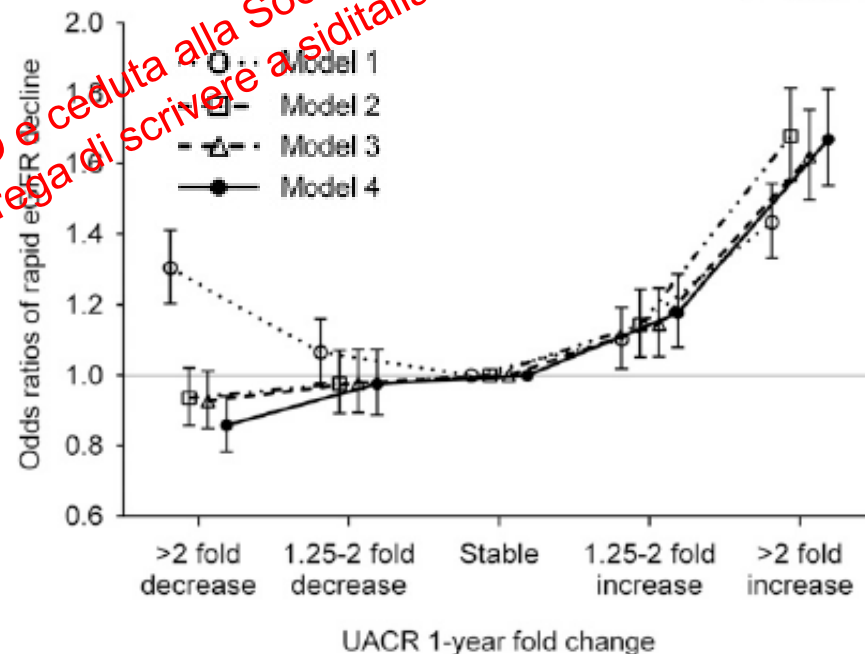
Sumida K, 2017

56,946 pts, 91% diabetics eGFR > 60 ml/min

1-yr fold changes of UACR
and incident CKD



1-yr fold change of UACR and
rapid (<-5 ml/min/yr) eGFR decline



Relative changes in Albuminuria over a 1-yr interval were linearly associated with subsequent risk of kidney outcomes

Mortality risk by Albuminuria and eGFR in DM2

435,369 pts from Swedish National Diabetes Register . Mean F-UP 4.6 yrs

Variable	Death from Cardiovascular Causes			
	<55 Yr	55–64 Yr	65–74 Yr	≥75 Yr
Reference	1.00	1.00	1.00	1.00
Normoalbuminuria	2.19 (1.82–2.62)	1.43 (1.33–1.55)	0.95 (0.91–1.00)	0.79 (0.73–0.81)
Microalbuminuria	4.26 (3.19–5.70)	2.38 (2.11–2.69)	1.55 (1.44–1.66)	1.01 (0.97–1.04)
Macroalbuminuria	5.58 (3.79–8.20)	3.81 (3.33–4.35)	2.62 (2.44–2.81)	1.37 (1.32–1.42)
Stage 5 chronic kidney disease	30.03 (16.08–56.10)	9.22 (6.40–13.29)	5.49 (4.43–6.70)	2.45 (2.11–2.86)

Reference	1.00	1.00	1.00	1.00
>90 ml/min	2.47 (2.08–2.94)	1.56 (1.43–1.69)	1.02 (0.96–1.09)	0.72 (0.69–0.76)
>60–90 ml/min	1.59 (1.39–1.82)	1.60 (1.47–1.74)	1.04 (1.00–1.10)	0.77 (0.75–0.78)
>45–60 ml/min	6.56 (2.98–10.38)	3.83 (3.29–4.45)	1.75 (1.63–1.89)	1.02 (1.00–1.05)
>30–45 ml/min	8.59 (3.21–22.97)	4.72 (3.69–6.04)	2.94 (2.68–3.24)	1.39 (1.35–1.44)
15–30 ml/min	35.03 (16.63–73.79)	8.96 (6.59–12.19)	4.58 (3.97–5.28)	2.13 (2.01–2.25)
Stage 5 chronic kidney disease	30.26 (16.20–56.52)	9.30 (6.45–13.40)	5.57 (4.53–6.86)	2.48 (2.13–2.89)

Tancredi M



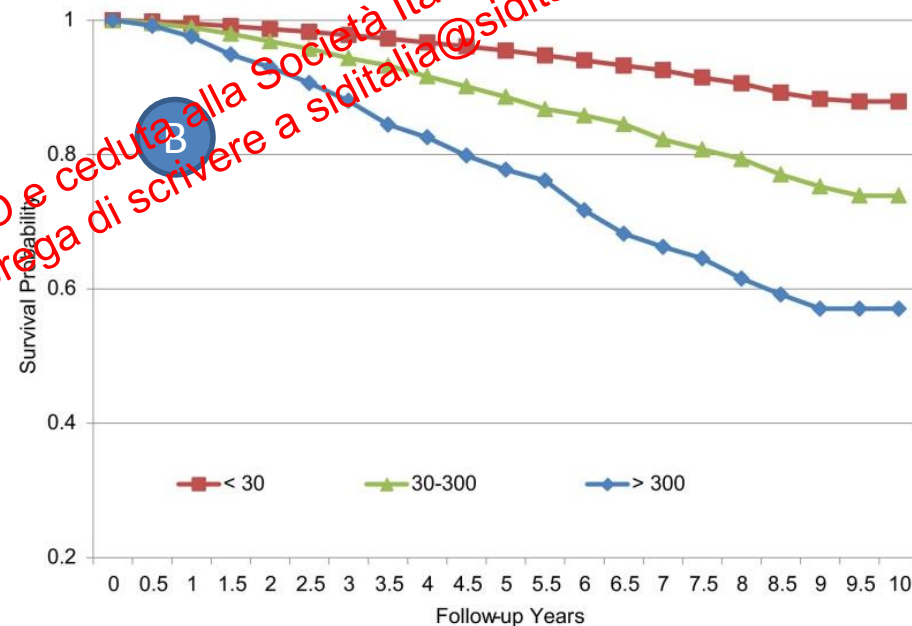
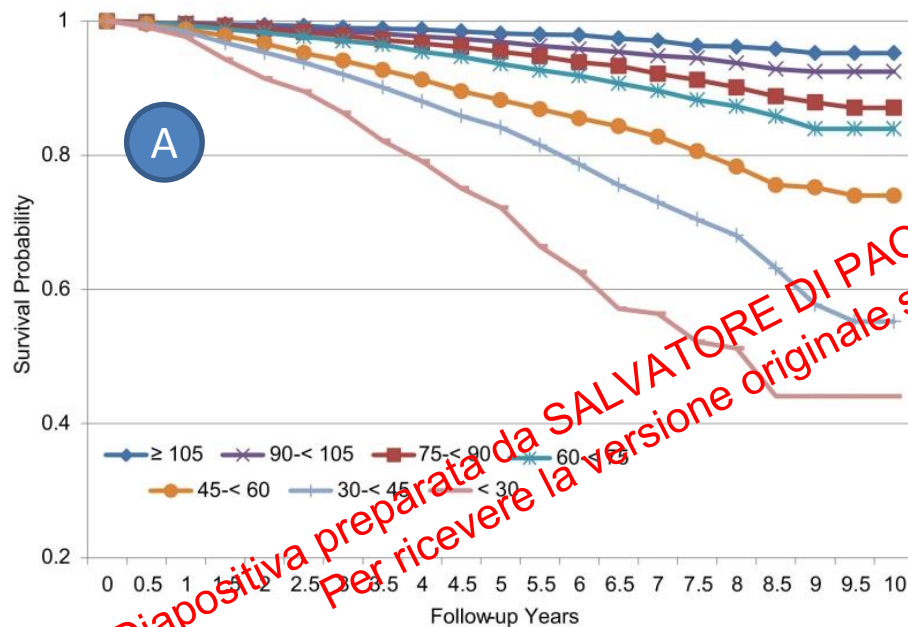
NEJM 2015

The **excess risks** of CV death **increased** with younger age, worse glycemic control, and **greater severity of renal complications**

The Synergistic Relationship Between Estimated GFR and Microalbuminuria in Predicting Long-term Progression to ESRD or Death in Patients With Diabetes: Results From the Kidney Early Evaluation Program (KEEP)

Kaplan-Meier estimates of long-term survival by (A) eGFR and (B) albumin-creatinine ratio (ACR)

42,671 T2DM 20,2% with eGFR<60 mL/min/1.73 m²

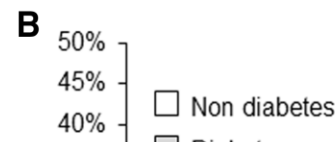
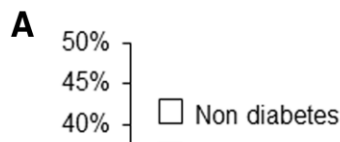


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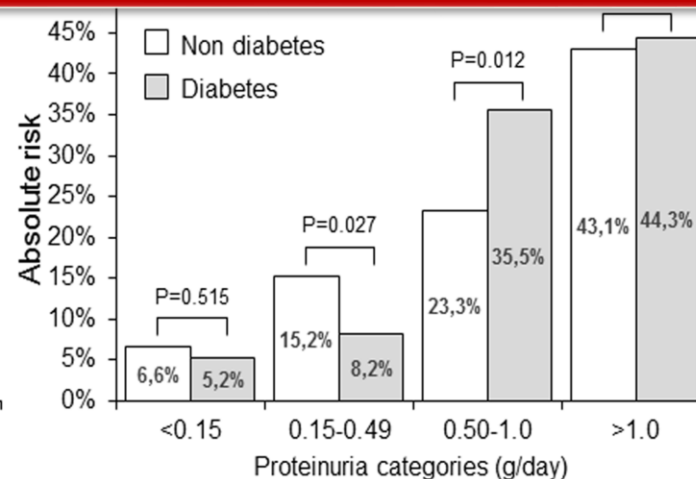
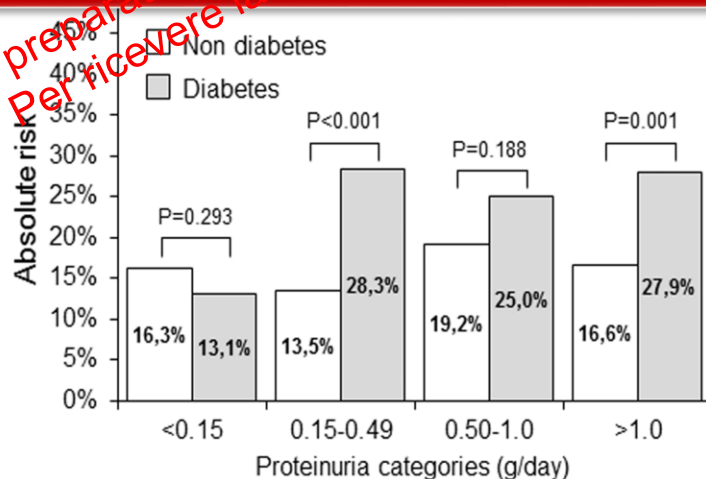
Both Albuminuria and eGFR and were associated independently with mortality and progression to ESRD, with a strong synergistic interaction.

Cardiorenal prognosis by residual proteinuria level in diabetic chronic kidney disease: pooled analysis of four cohort studies

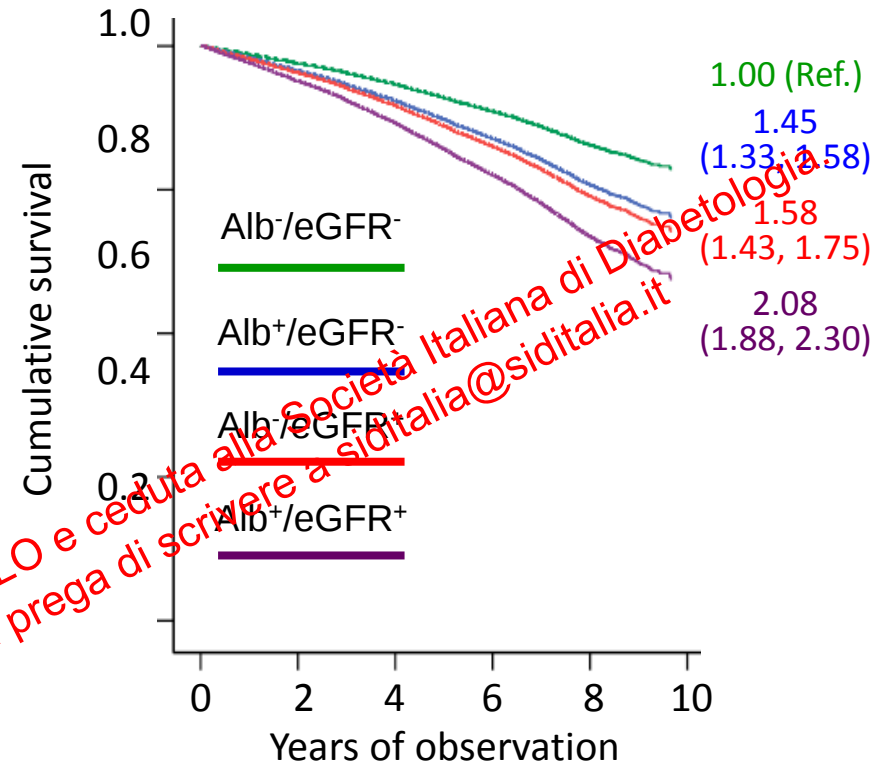
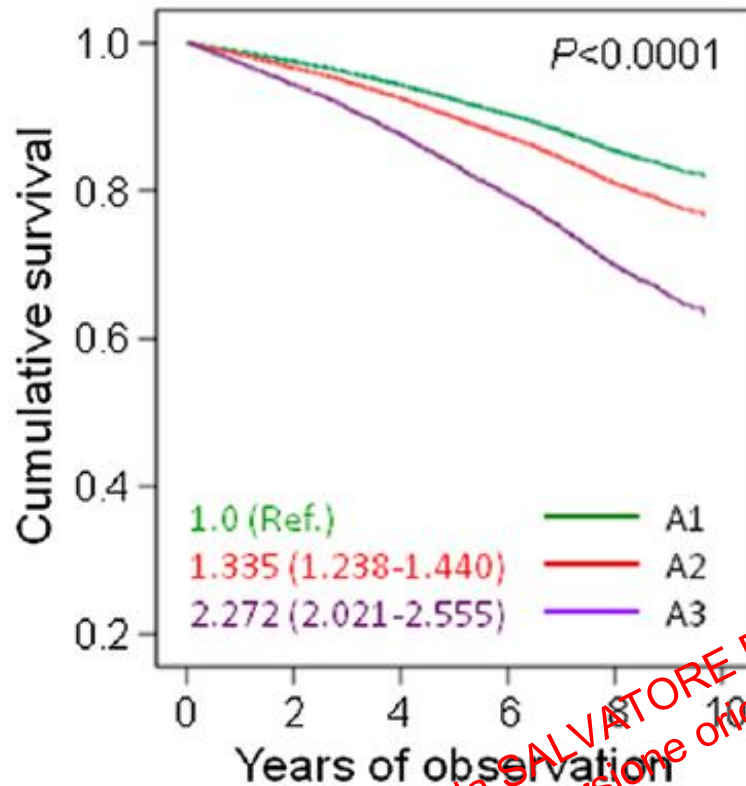
Roberto Minutolo¹, Francis B. Gabbai², Michele Provenzano¹, Paolo Chiodini³, Silvio Borrelli¹, Carlo Garofalo¹, Ferdinando C. Sasso⁴, Domenico Santoro⁵, Vincenzo Bellizzi⁶, Giuseppe Conte¹ and Luca De Nicola¹



- In the subgroup with urine protein <0.15 g/day the risks of ESRD, CV events and mortality were similar in diabetic and non-diabetic.
- Uprot >0.15 g/24h higher mortality risk only in DM



Mortality in T2DM: the RIACE Study



Categories

Age categories

< 55 years

Albuminuria

Reference	1.00
A1a (< 10 mg day ⁻¹)	1.90 (1.39–2.60)
A1b (10–29 mg day ⁻¹)	2.88 (2.15–3.86)
A2 (30–299 mg day ⁻¹)	5.14 (3.85–6.86)
A3 (≥ 300 mg day ⁻¹)	10.69 (7.02–16.29)

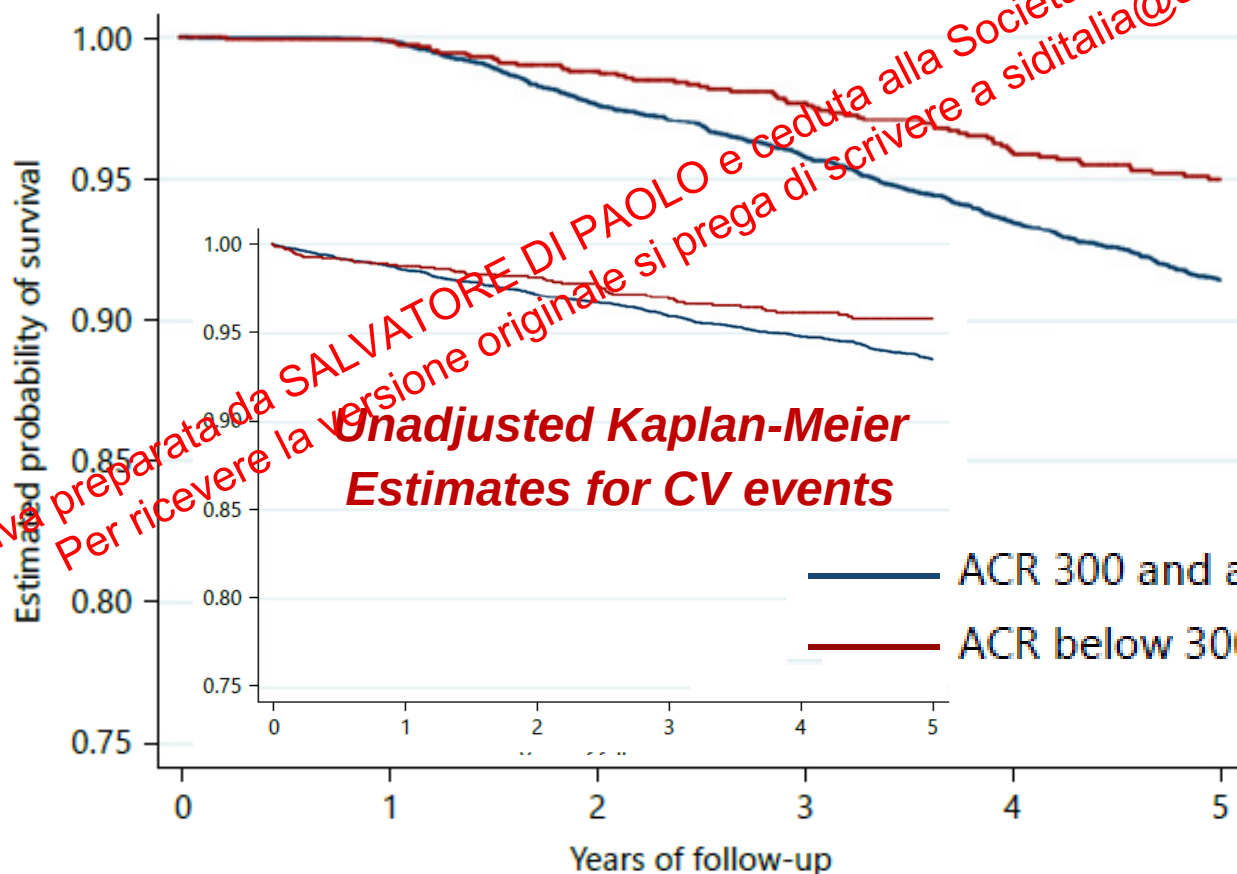
Penno G, Acta Diabetol 2018

Penno G, Diabetologia 2018

Albuminuria Regression and All-Cause Mortality among Insulin-Treated Patients with Type 2 Diabetes: Analysis of a Large UK Primary Care Cohort

11,074 insulin-treated T2D Baseline ACR ≥ 300 mg/g eGFR 59.9 ± 21.2

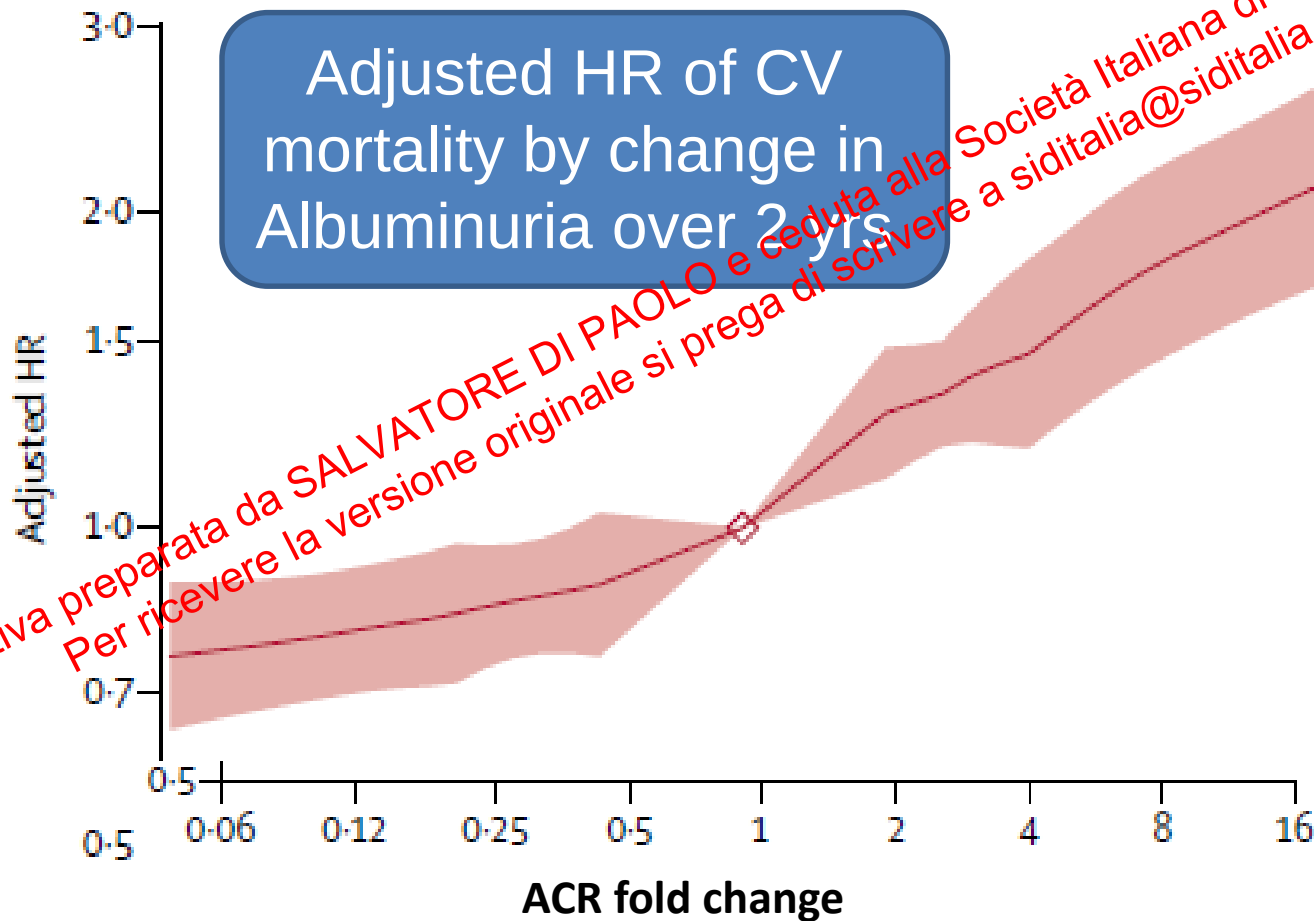
Unadjusted Kaplan-Meier Estimates for all-cause Mortality



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Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies

693816 individuals 80% T2DM Baseline eGFR 78.2 ± 21 mL/min/1.73 m²



Class effects of SGLT2 inhibitors on cardiorenal outcomes



Kluger AY, 2019

The population of CREDENCE had much higher baseline renal risk, and thus experienced more CV and renal outcomes. Specifically, CREDENCE had the lowest mean baseline eGFR and, most importantly, the highest degree of albuminuria. Together, these trials establish the UACR as a risk predictor not only for renal events but also CV outcomes.

In conclusion, **Baseline GFR** and **degree of albuminuria** are the most significant indicators of risk for **both CV and renal events**.

Thus, these two factors also anticipate the greatest clinical benefit for SGLT2i

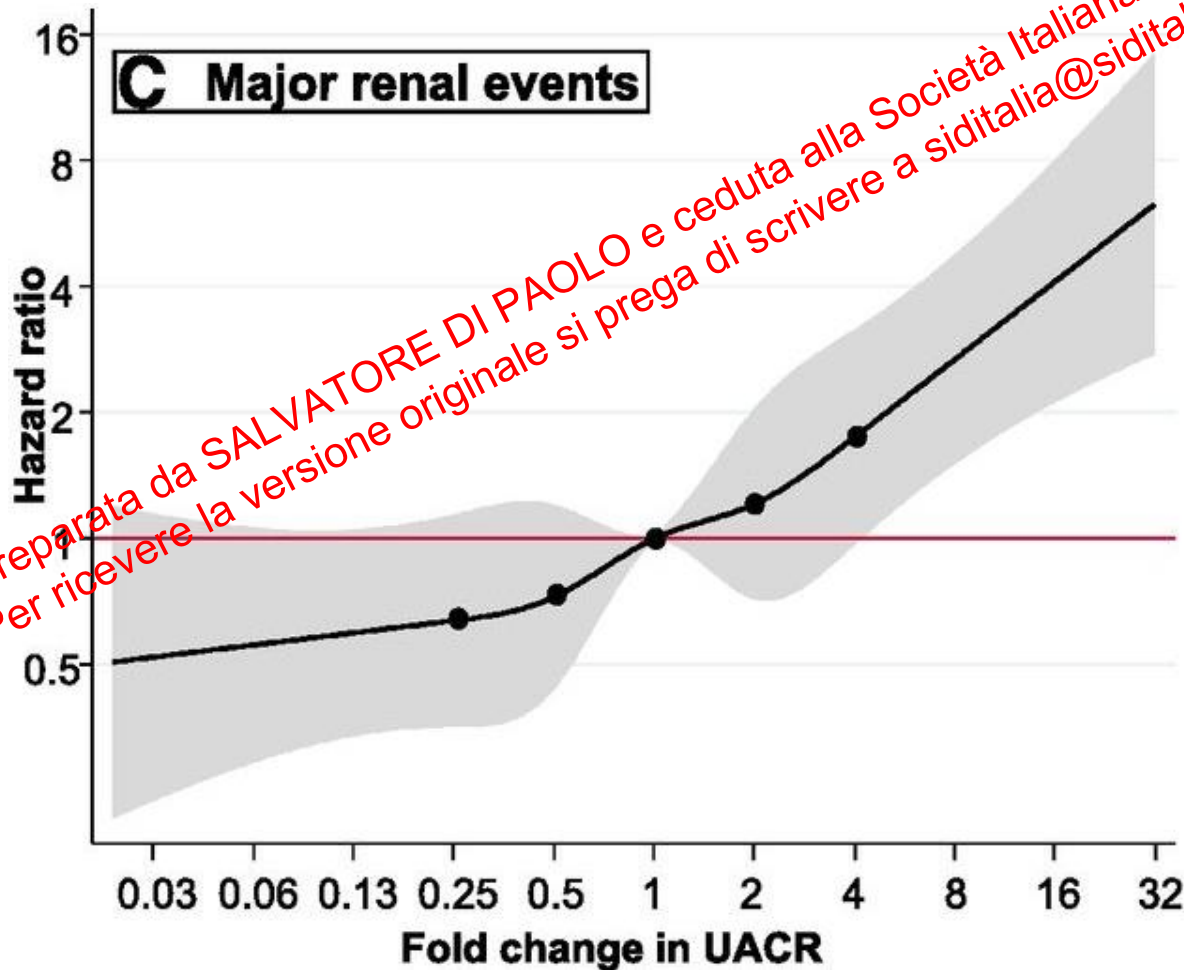
Increasing risk

CONCLUSIONI

- ❖ L'Albuminuria rappresenta un cruciale fattore patogenetico di progressione del danno renale, nel diabetico al pari del paziente non diabetico.
- ❖ Livelli elevati si associano ad un netto incremento di rischio per ESRD e per eventi CV fatali e non fatali e di converso la sua riduzione si associa ad un significativo decremento di entrambi i rischi
- ❖ La specificità della Albuminuria come biomarker prognostico è posta in discussione allo stadio di microalbuminuria (<300 mg/24 h) e la sua sensibilità è limitata dal crescente riscontro di DKD normoalbuminurica
- ❖ Infine, la validità della Albuminuria come end point surrogato negli Studi di Intervento può risultare limitata dalla frequente evenienza, misconosciuta, di Nefropatie non diabetiche

Changes in Albuminuria and the Risk of Major Clinical Outcomes in Diabetes: Results From ADVANCE-ON

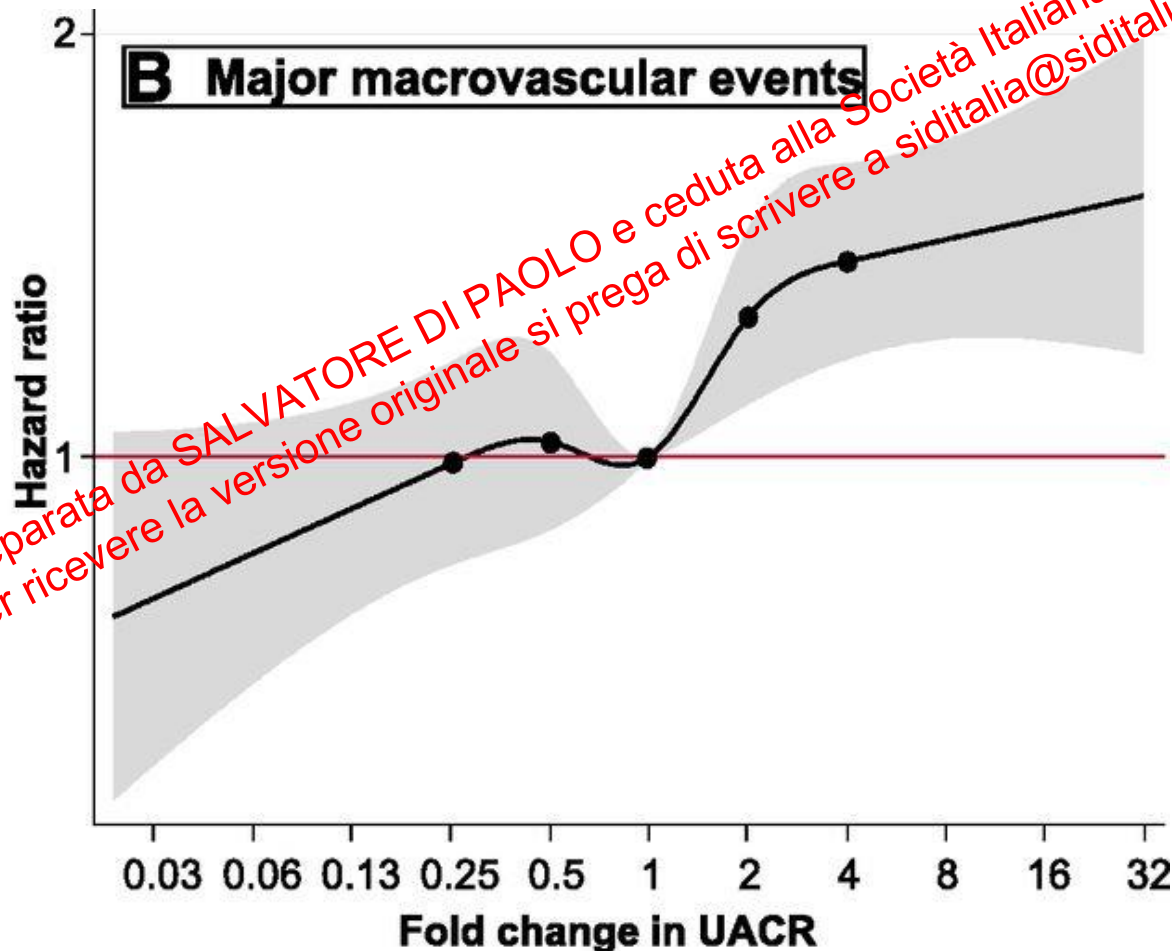
- ❖ 8766 T2DM patients. eGFR 75 ± 17 ml/min /1.73 m² Median UACR 14 μ g/mg
- ❖ Changes in eGFR and UACR at 2 years Follow-up 7.7 yrs



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Changes in Albuminuria and the Risk of Major Clinical Outcomes in Diabetes: Results From ADVANCE-ON

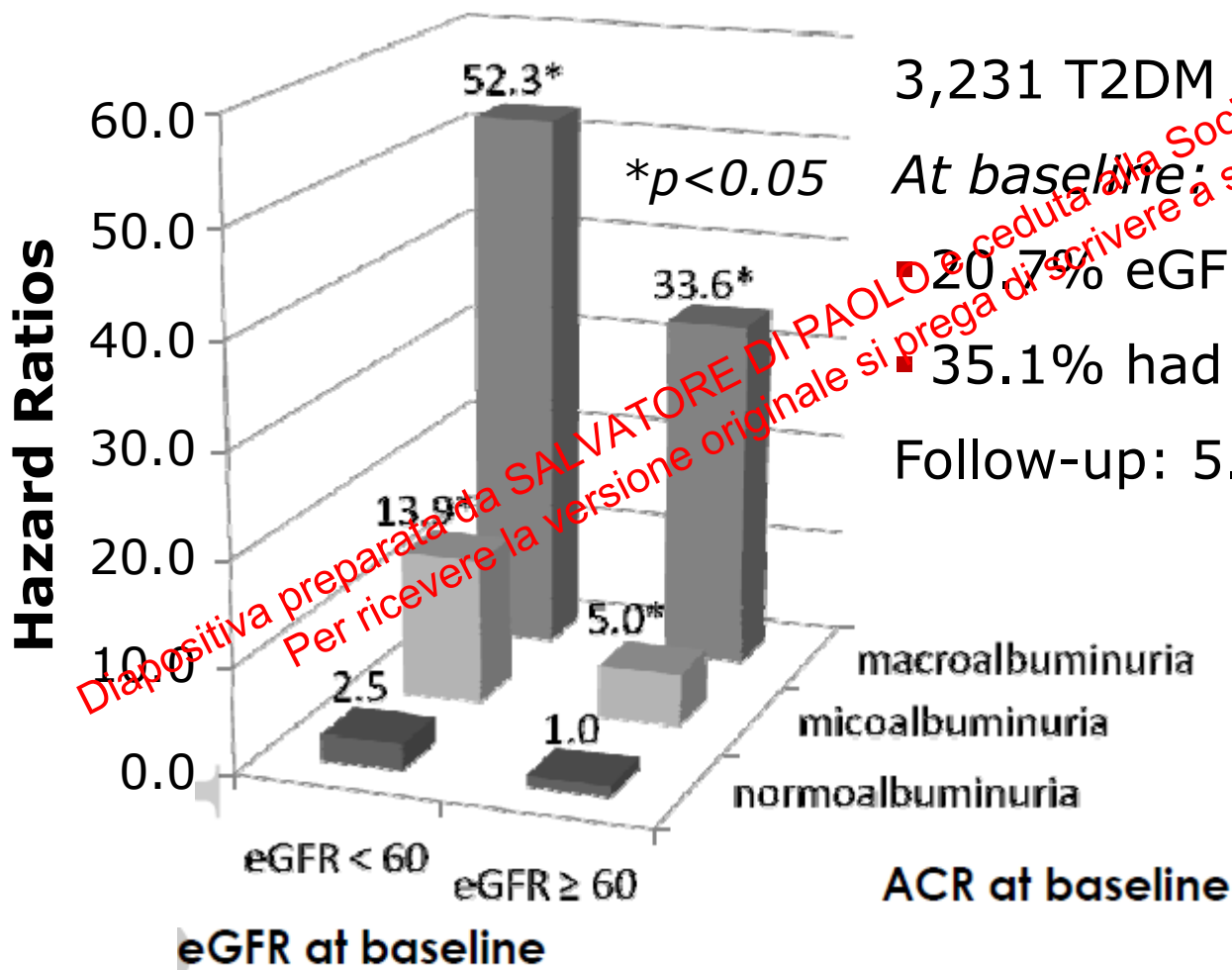
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Albuminuria and reduced glomerular filtration rate for predicting the renal outcomes in type 2 diabetic patients

Adjusted hazard ratio for renal endpoints: initiation of RRT and 50% decline in eGFR from the baseline



3,231 T2DM

At baseline:

20.7% eGFR < 60 mL/min/1.73m²

35.1% had albuminuria

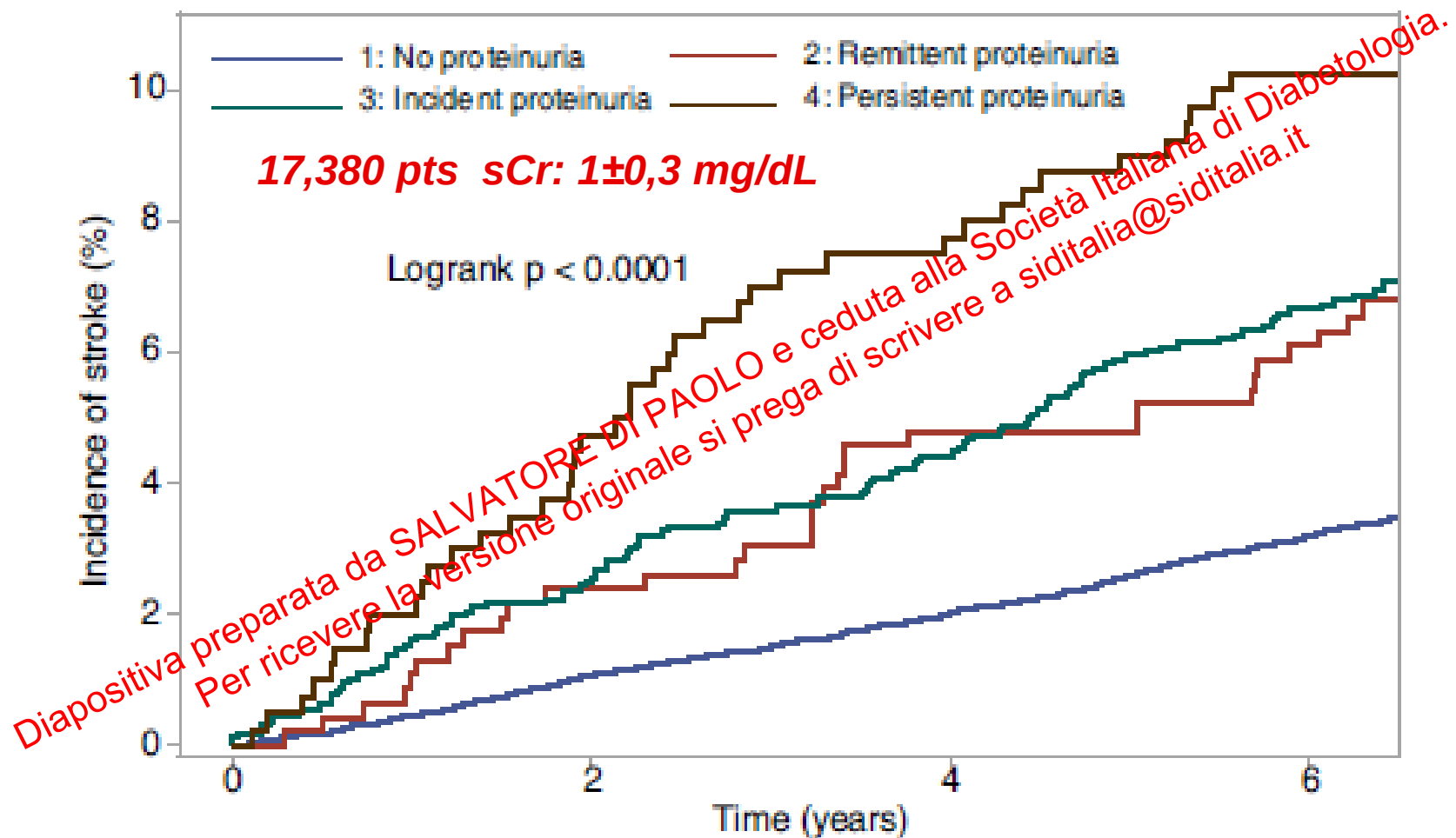
Follow-up: 5.9 ± 1.6 yrs

Tanaka N, 2015

NEPHROLOGY

Association of Persistent, Incident, and Remittent Proteinuria With Stroke Risk in Patients With Diabetes Mellitus or Prediabetes Mellitus

All-Type Stroke Incidence Rate



Reduction of Proteinuria=12% Reduction of Risk

Wang A, J Am Heart Assoc 2017

