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- NOVO
- SANOFI
- LILLY
- NOVARTIS
- ASTRA ZENECA
- MEDTRONIC
- MERCK
- TAKEDA
- BOEHRINGER

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e la denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

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IL CROSS-TALK
cuore-rene
FISIOPATOLOGIA
ED ASPETTI CLINICI

MILANO 15 OTTOBRE 2019

Cross-talk rene-cuore: effetti della CKD sull'apparato cardiovascolare

Roberto Trevisan

UOC Malattie Endocrine 1 – Diabetologia

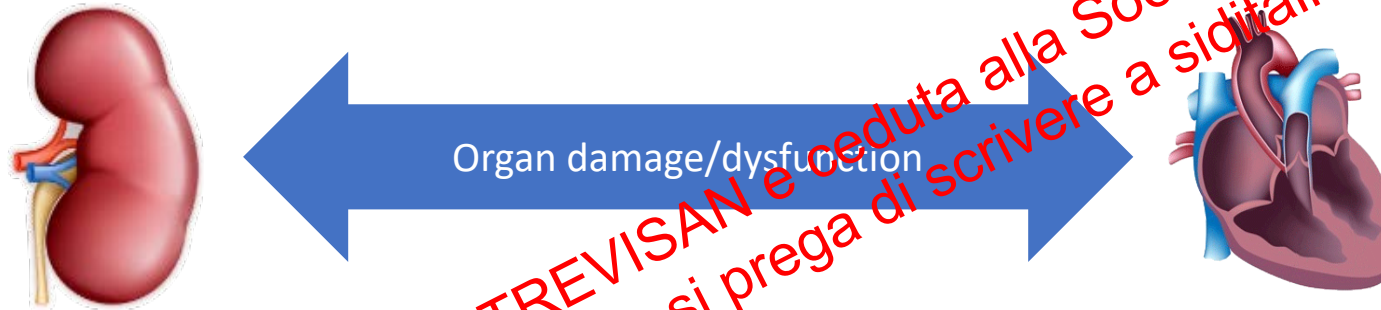
ASST Papa Giovanni XXIII, Bergamo

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Kidney disease is associated with significant impairment of cardiac function

CV events

Renal and cardiac systems are inextricably linked; acute or chronic disorder of one can induce dysfunction in the other¹



Elderly patients with CKD are more likely to die of heart disease than advance to ESRD and dialysis²

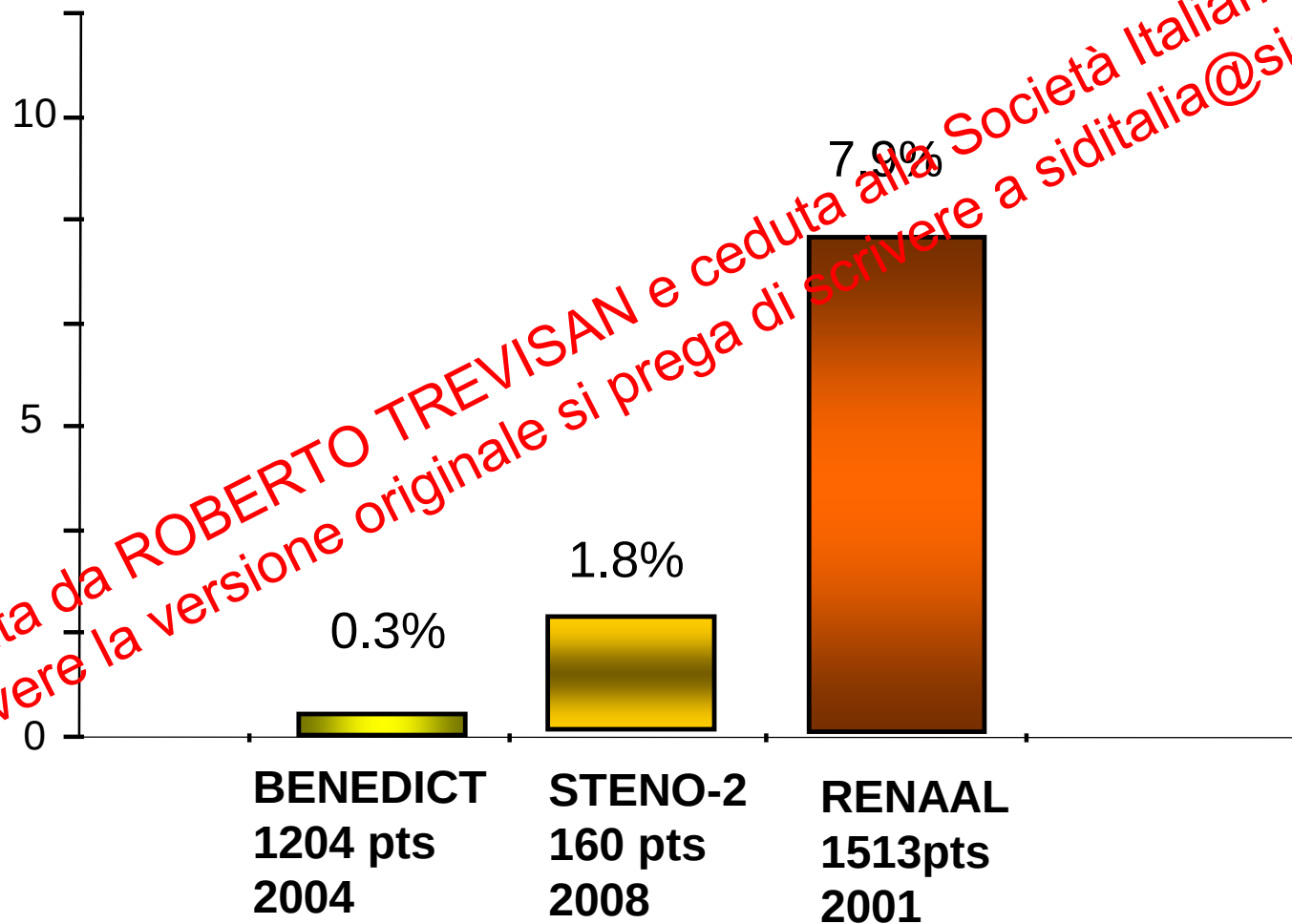
Renal and cardiac systems should be considered together

CKD, chronic kidney disease; CV, cardiovascular; ESRD, end-stage renal disease

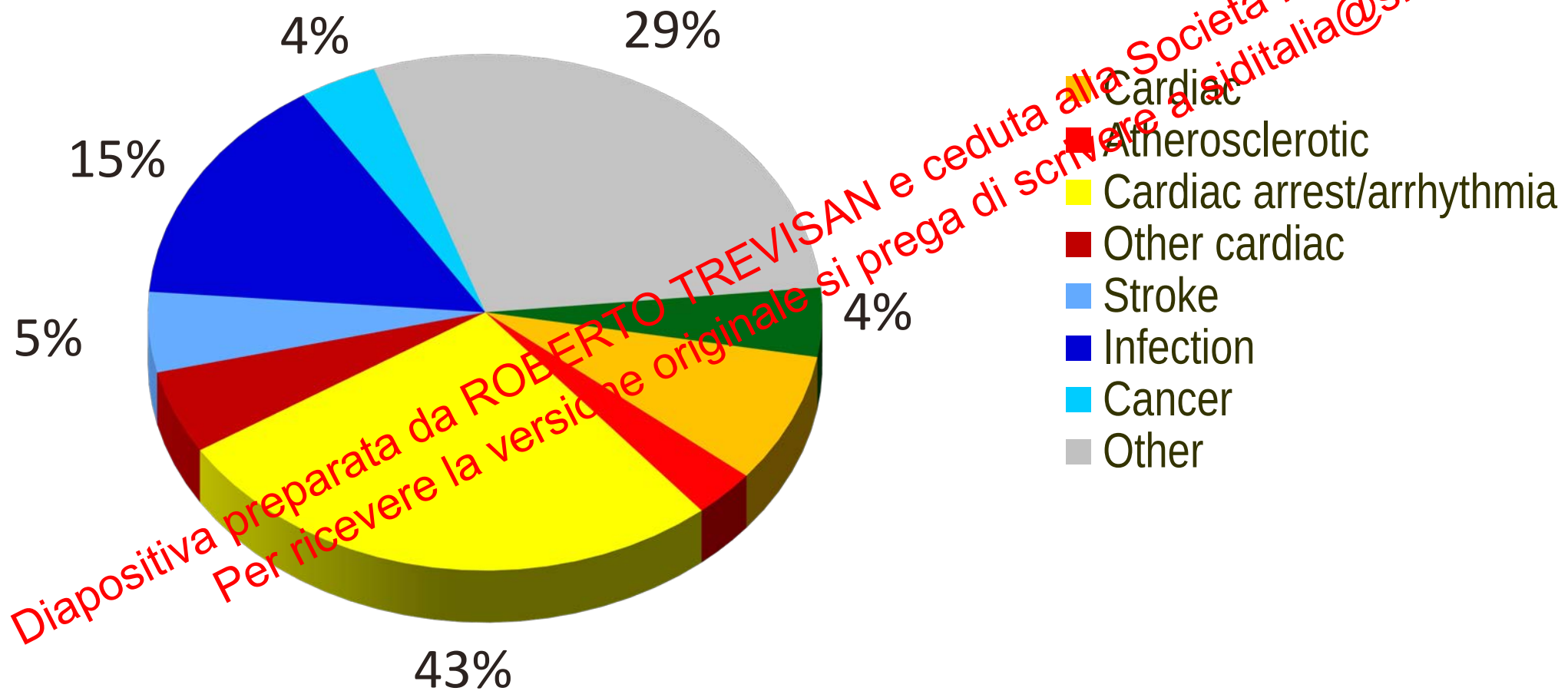
1. Ronco C et al. *J Am Coll Cardiol* 2008;52:1527; 2. Dalrymple L et al. *J Gen Intern Med* 2011;26:379

BENEDICT; Mortality for cardiovascular disease is low in Type 2 Diabetes with normoalbuminuria

CVD mortality rate per yr (%)



Causes of death in dialysis patients



Riace Study: prevalence (%) of renal disease in Italian Type 2 diabetic patients

15773 T2DM patients randomly selected in Italian outpatient clinics

↑AER
26.9%

eGFR < 60 ml/min/1.73 m²
18.8%

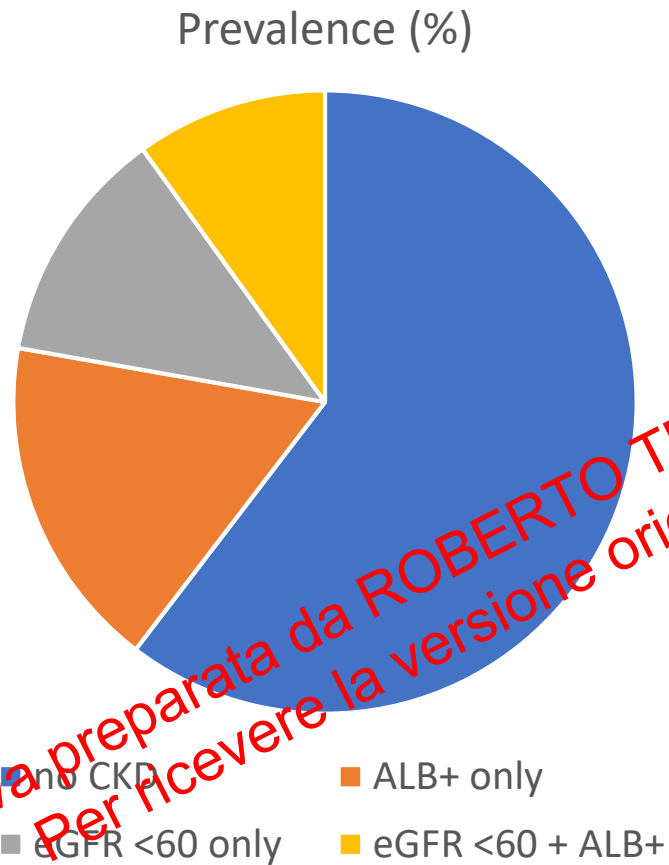
With CKD
37.5%



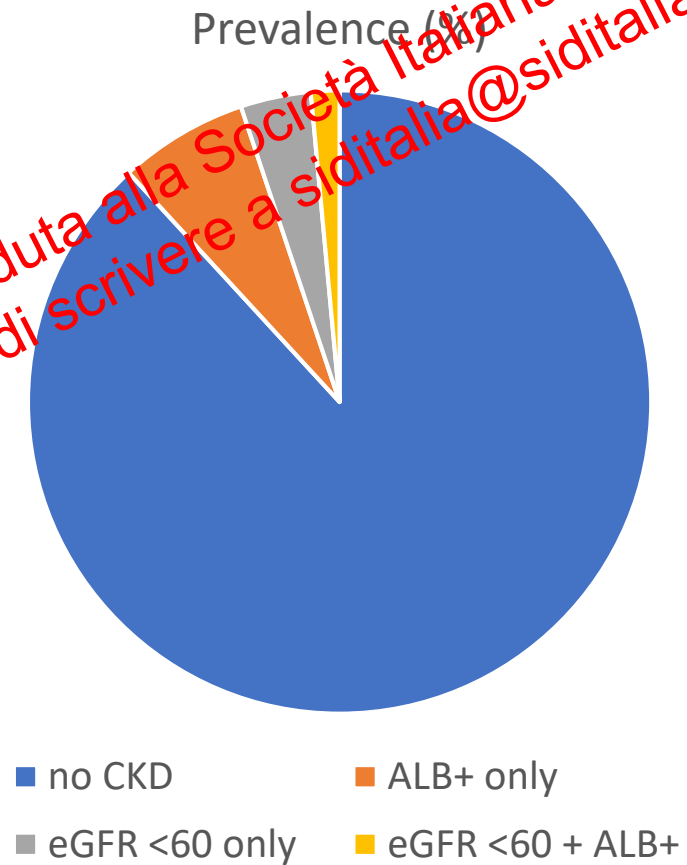
52%
With normal AER

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Distribution of DKD phenotypes in individuals with T1D



Thorn LM et al; Diabetes Care 2015; 38: 2128



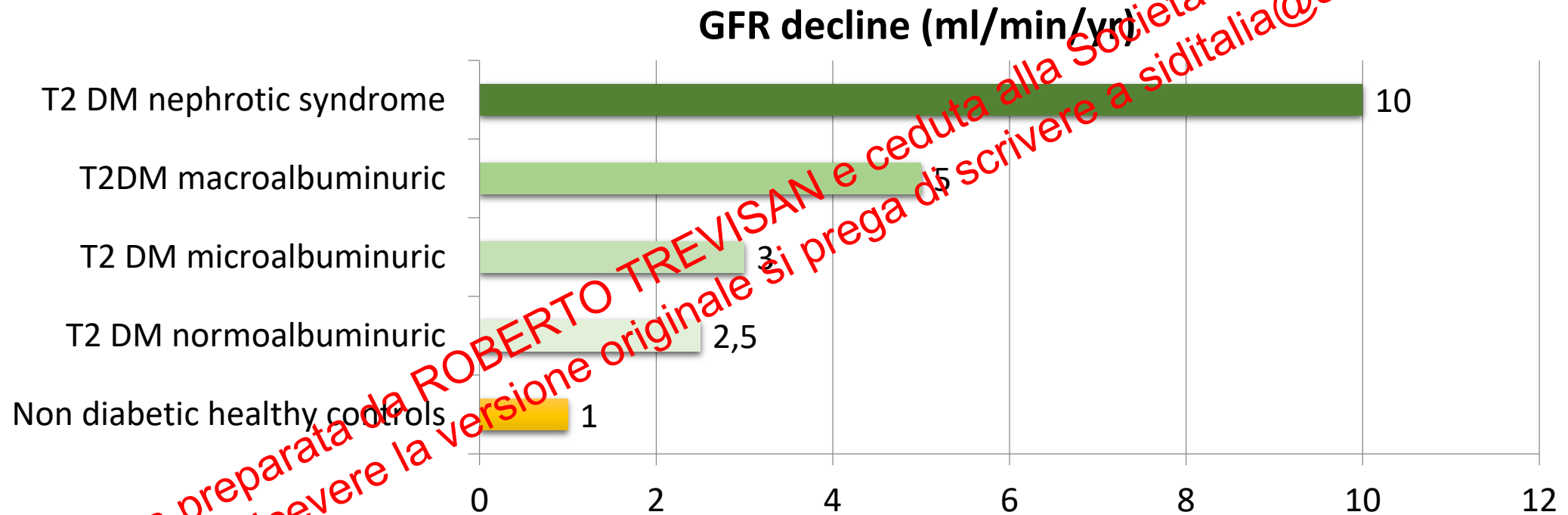
Penno G et al; Diabetologia 60: 1102

Perché i diabetici perdono funzione renale anche in assenza di nefropatia proteinurica?

- Nefroangiosclerosi
- Nefropatia ischemica
- Danno da farmaci
- Proteinuria prevenuta dal trattamento precoce con ACE/ARBs
- Insufficienza cardiaca
- Altre malattie renali

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Glomerular filtration rate (GFR) decline in healthy patients compared with patients with type 2 diabetes and normo-, micro-, macroalbuminuria, or severe proteinuria



Data from studies that did repeated measurements of GFR using gold standard procedures

Ci sono differenze nel rischio cardiovascolare tra il fenotipo di CKD con albuminuria e quello senza albuminuria?

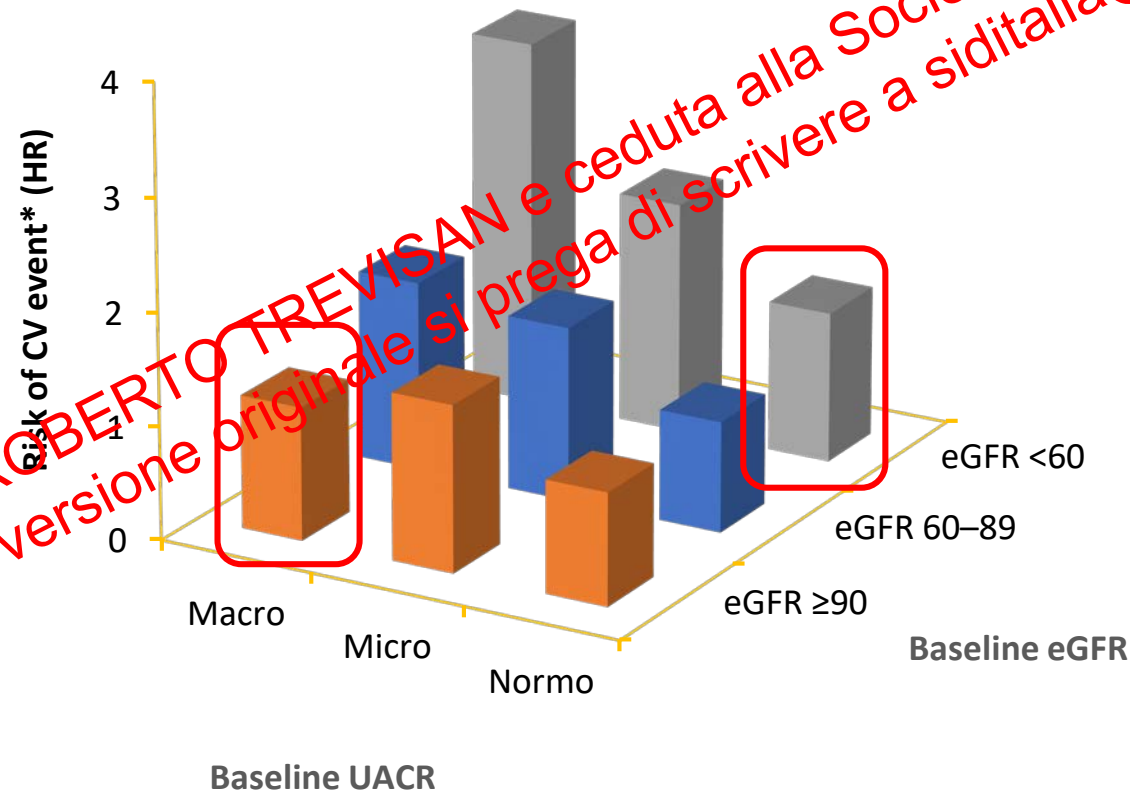
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Albuminuria and reduced eGFR are associated with increased risk of CV events

ADVANCE: observational analyses examining the association between albuminuria and eGFR at baseline and 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



*CV events defined as: CV death, non-fatal myocardial infarction or nonfatal stroke. eGFR in ml/min/1.73 m²
CV, cardiovascular; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio

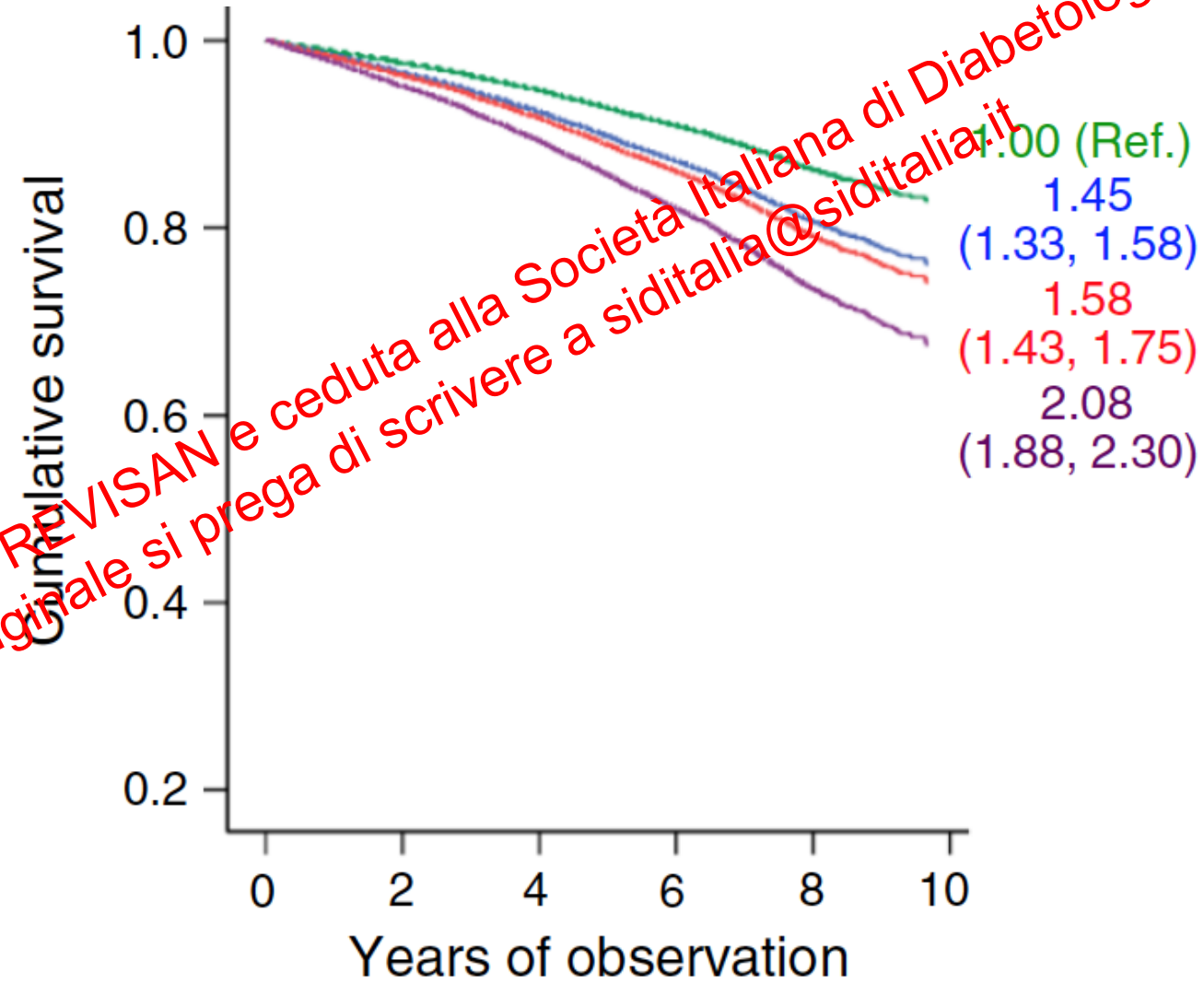
The RIACE Study

Cumulative survival by
Kaplan–Meier analysis
according to DKD phenotype

Diabetologia (2018) 61:2277–2289

- Green, Alb–/eGFR– (no DKD)
- Blue, Alb+/eGFR– (albuminuric DKD with preserved eGFR)
- Red, Alb–/eGFR+ (non-albuminuric DKD)
- Purple, Alb+/eGFR+ (albuminuric DKD with reduced eGFR)

Cox proportional hazards
regression, adjusted for multiple confounders

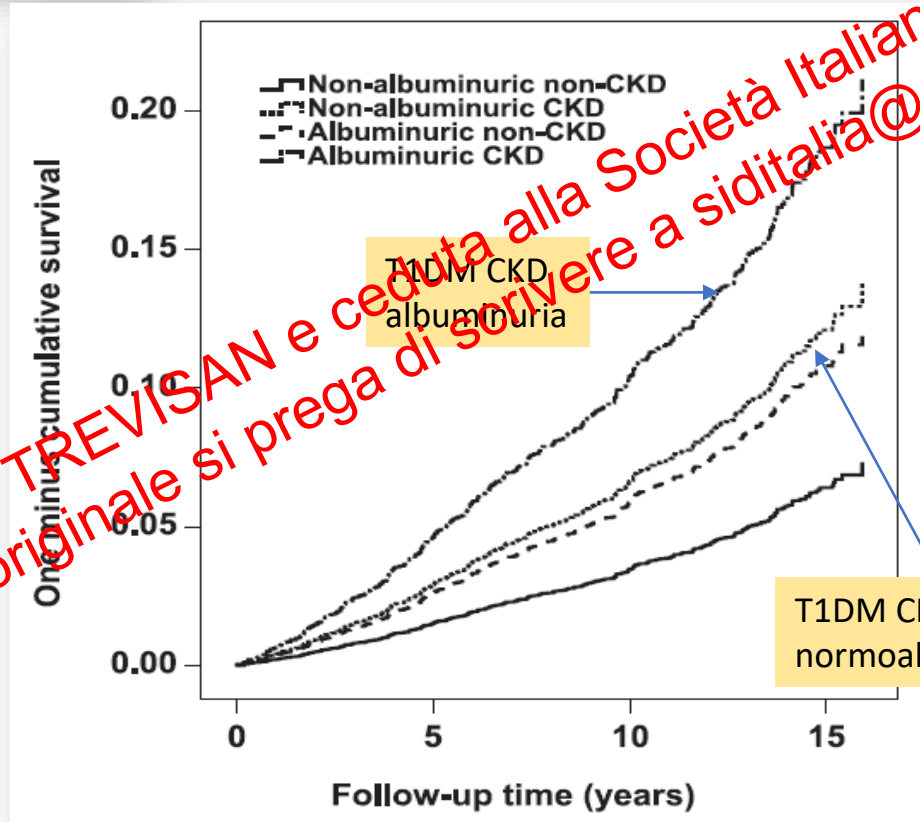


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The Presence and Consequence of Nonalbuminuric Chronic Kidney Disease in Patients With Type 1 Diabetes

Diabetes Care 2015;38:2128–2133 | DOI: 10.2337/dc15-0641

Lena M. Thorn,^{1–3} Daniel Gordin,^{1–3}
Valma Harjutsalo,^{1–3} Stefanie Hägg,^{1–3}
Robert Masar,^{1–3} Markku Saraheimo,^{1–3}
Nina Tolonen,^{1–3} Johan Wadén,^{1–3}
Per-Henrik Groop,^{1–4} and
Carol M. Forsblom,^{1–3} on behalf of the
FinnDiane Study Group



The adjusted- risk of suffering a CVD event by the four groups based on albuminuria and CKD.

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eGFR < 60
ml/min/1.73m²

Con
Albuminuria

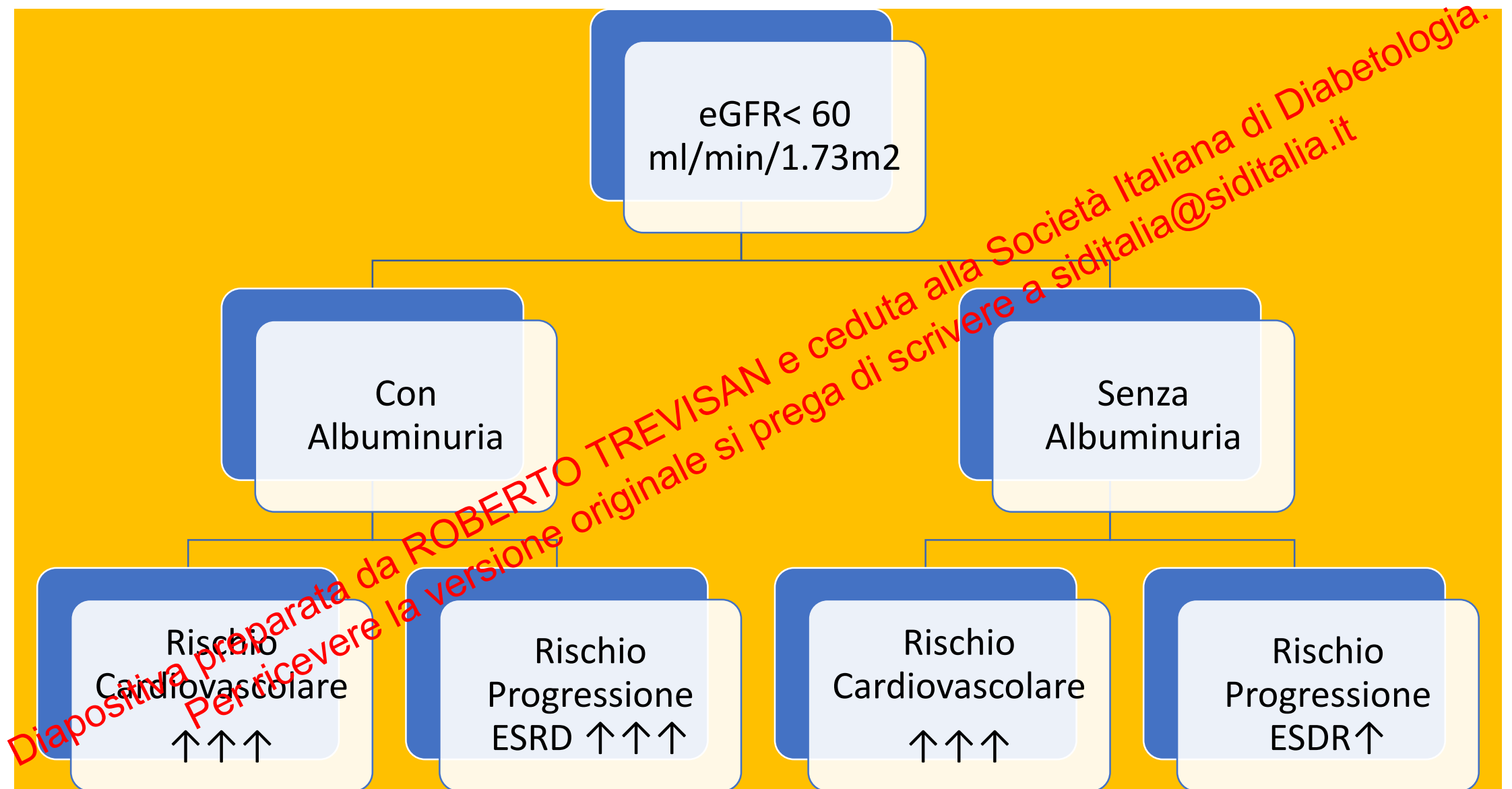
Senza
Albuminuria

Rischio
Cardiovascolare
↑↑↑

Rischio
Progressione
ESRD ↑↑↑

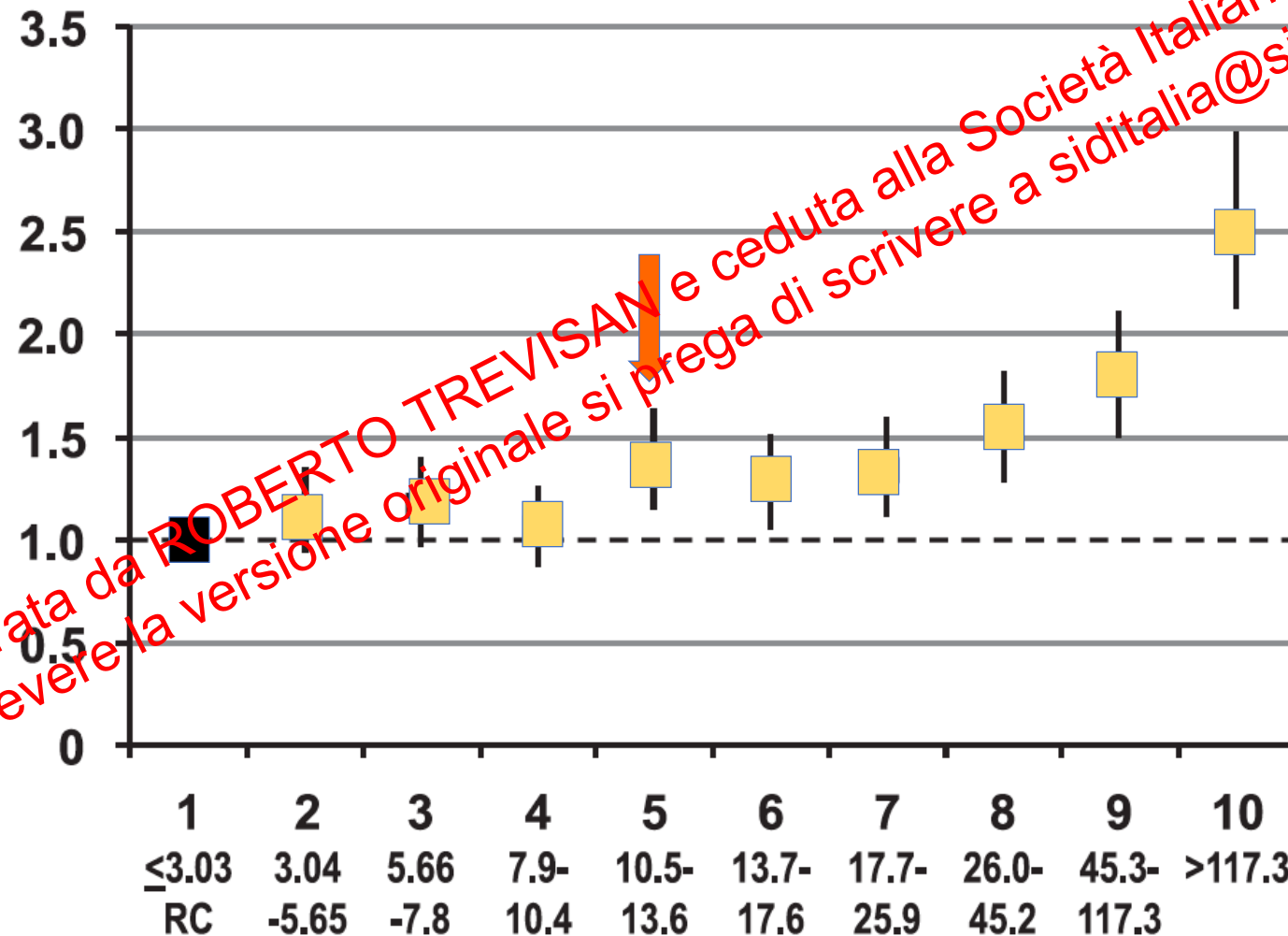
Rischio
Cardiovascolare
↑↑↑

Rischio
Progressione
ESDR ↑



RIACE STUDY: Age- and sex-adjusted risk of major acute CVD events (OR [95% CI]) according to albuminuria deciles (mg/24 ore)

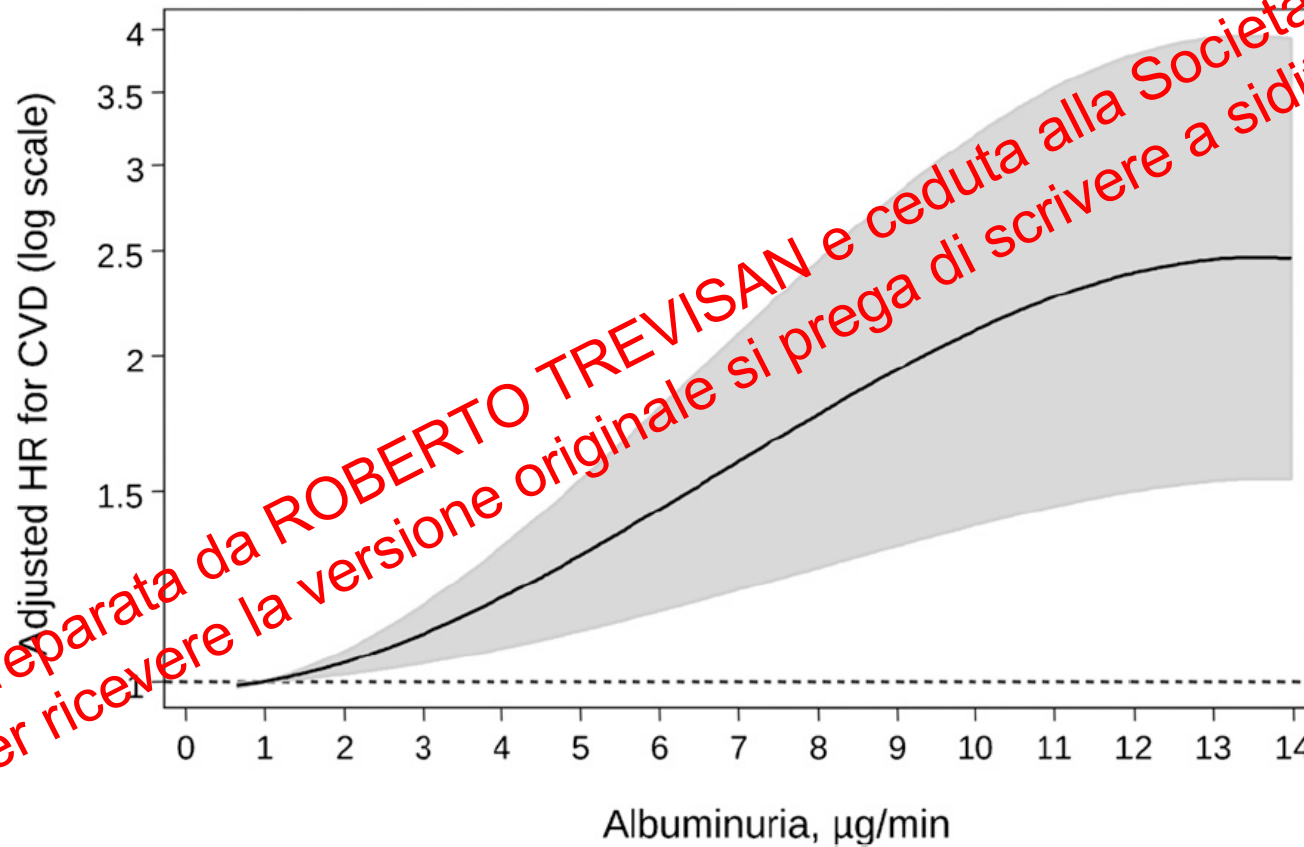
Solini A et al. Dia Care 2012;35:143-149



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Measurable urinary albumin predicts cardiovascular risk among 1208 normoalbuminuric patients with type 2 diabetes
Median follow-up 9.2 yrs

J Am Soc Nephrol. 2012; 23:1717-24



↑ Albuminuria



Disfunzione
endoteliale



Microangiopatia
diffusa



Danno renale



Danno
cardiovascolare

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Il rischio CARDIORENALE, perchè?

Fattori di rischio per la malattia renale = Fattori di rischio cardiovascolare

■ Modificabili:

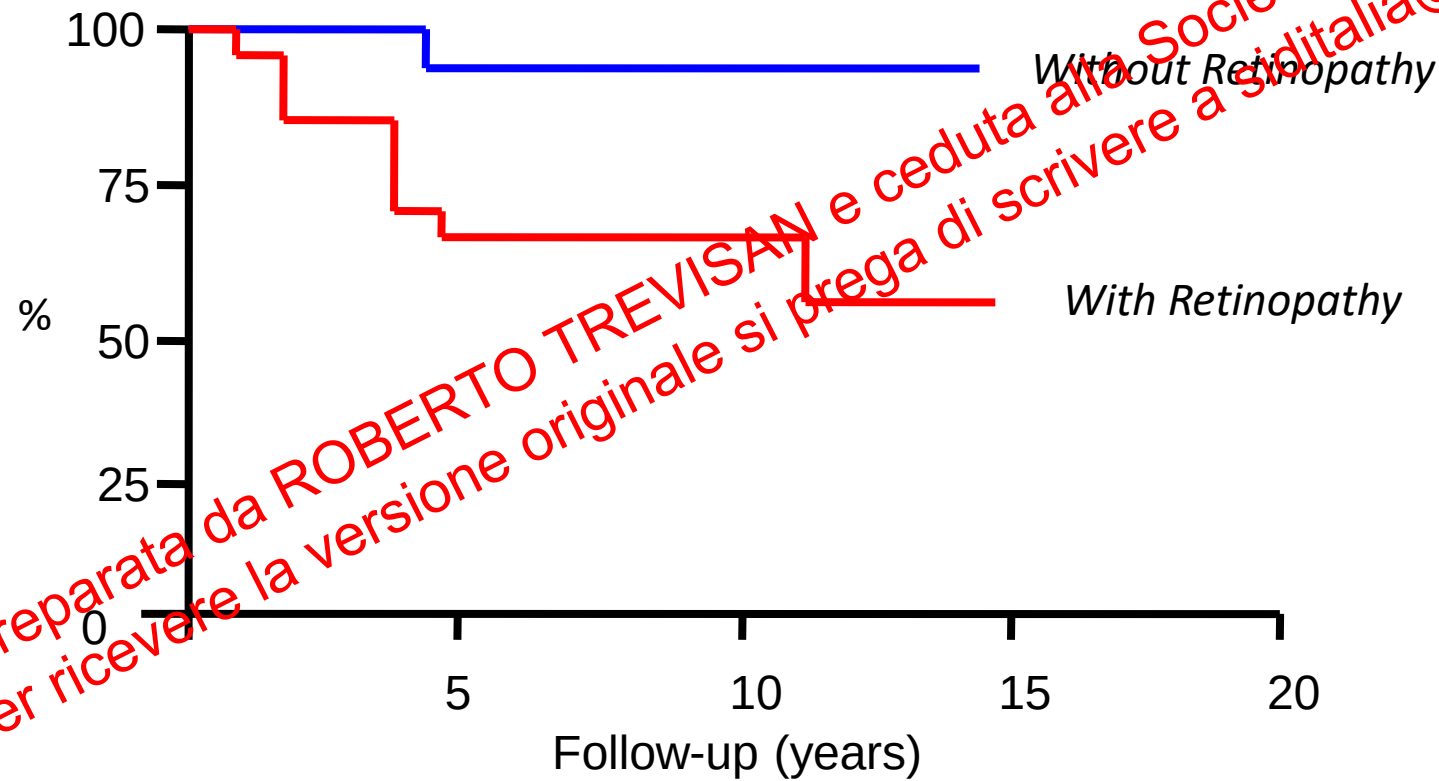
- Glicemia
- Pressione arteriosa
- Proteinuria
- Iperlipidemia
- Apporto proteico e di sale nella dieta
- Disfunzione endoteliale
- Insulino-resistenza
- Fumo

■ Non modificabili:

- Fattori genetici
- Sesso
- Retinopatia diabetica

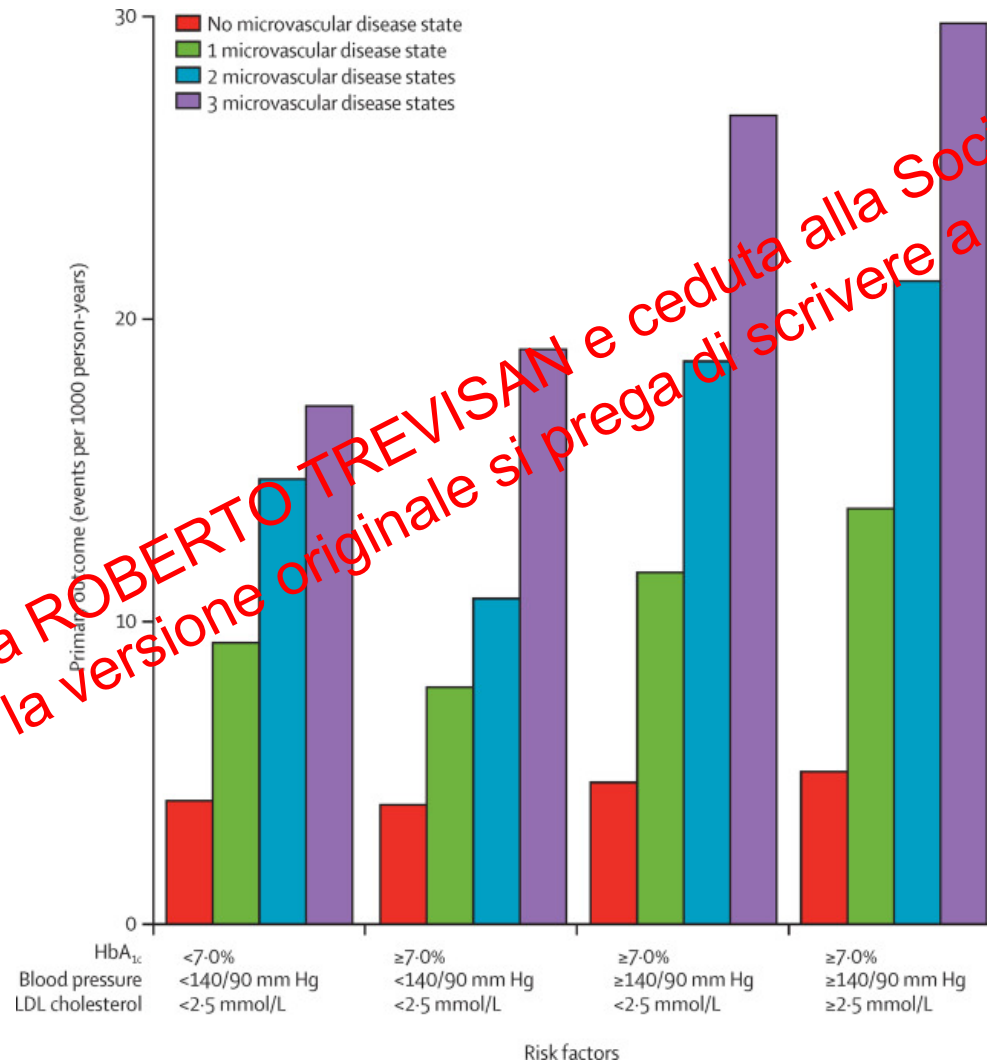
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Survival curves of Type 2 diabetic patients with overt proteinuria In relation to retinopathy status



Adjusted event rates for the primary outcome by cumulative burden of microvascular disease and established risk factor goals

The Lancet Diabetes & Endocrinology, Volume 4, Issue 7, 2016, 588–597



The RIACE Study

Clinical features by eGFR

	>90	89-60	50-30	<30	P<
Waist (cm)	103±12	103±13	106±13	112±17	0.0001
SBP (mmHg)	136±18	139±18	140±19	142±21	0.0001
Ch (mg/dl)	184±38	184±37	186±40	189±45	ns
TG (mg/dl)	112(81-160)	116(84-162)	133(97-189)	156(117-214)	0.0001
HDL (mg/dl)	50±13	50±13	48±14	46±16	0.0001

The RIACE Study

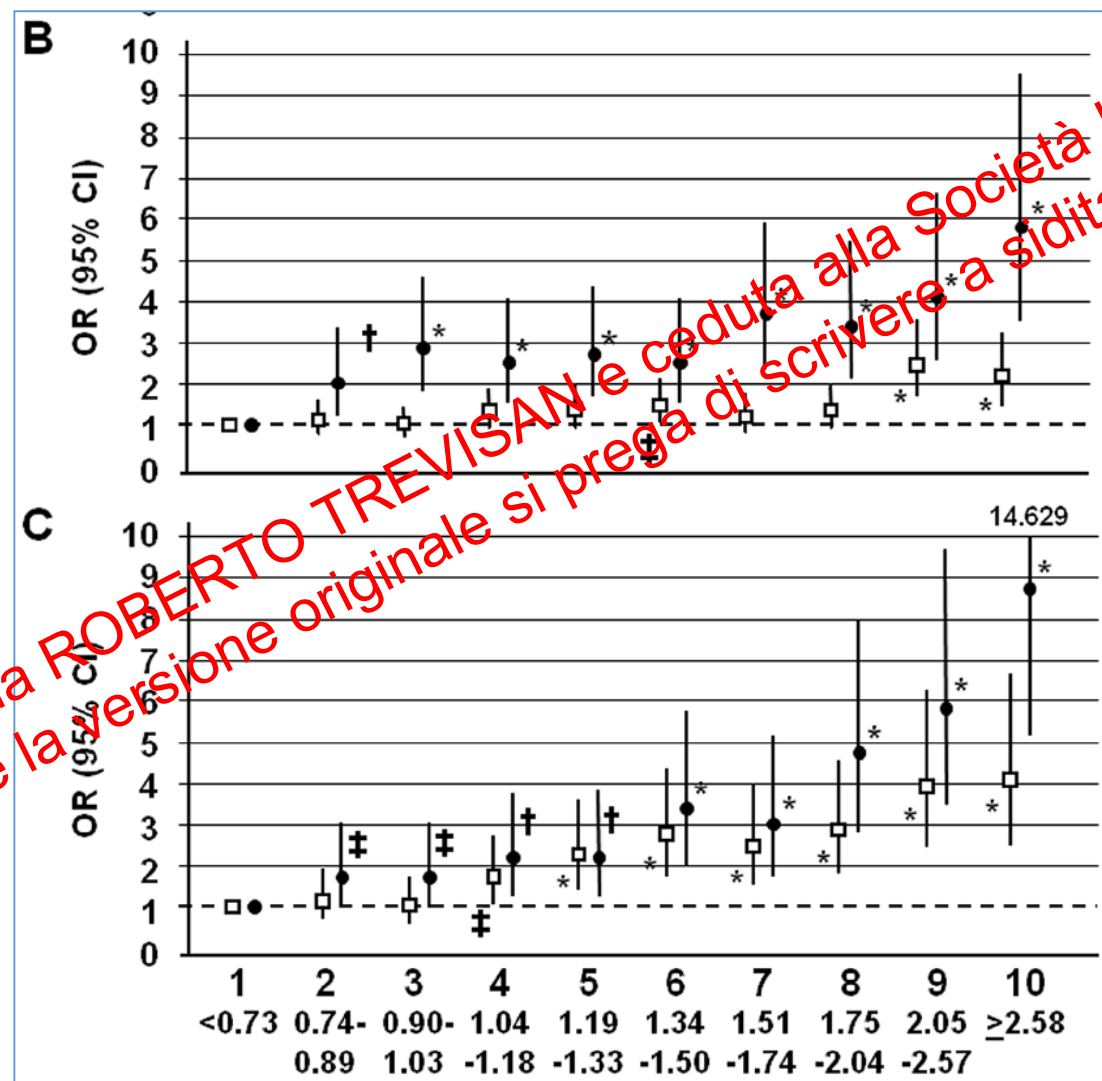
Clinical features by UAE

	Normo	Micro	Macro	P<
Waist (cm)	103±12	105±13	110±13	0.0001
SBP (mmHg)	137±18	139±19	144±20	0.0001
Ch (mg/dl)	185±33	183±40	189±43	0.0045
TG (mg/dl)	115(84-161)	127(92-180)	154(104-210)	0.0001
HDL (mg/dl)	51±13	48±13	46±13	0.0001

Adjusted risk of CKD (OR [95% CI]) according to deciles of TG levels
in subjects without (□) and with (●) statin treatment

CKD Stages 3–5
non-albuminuric

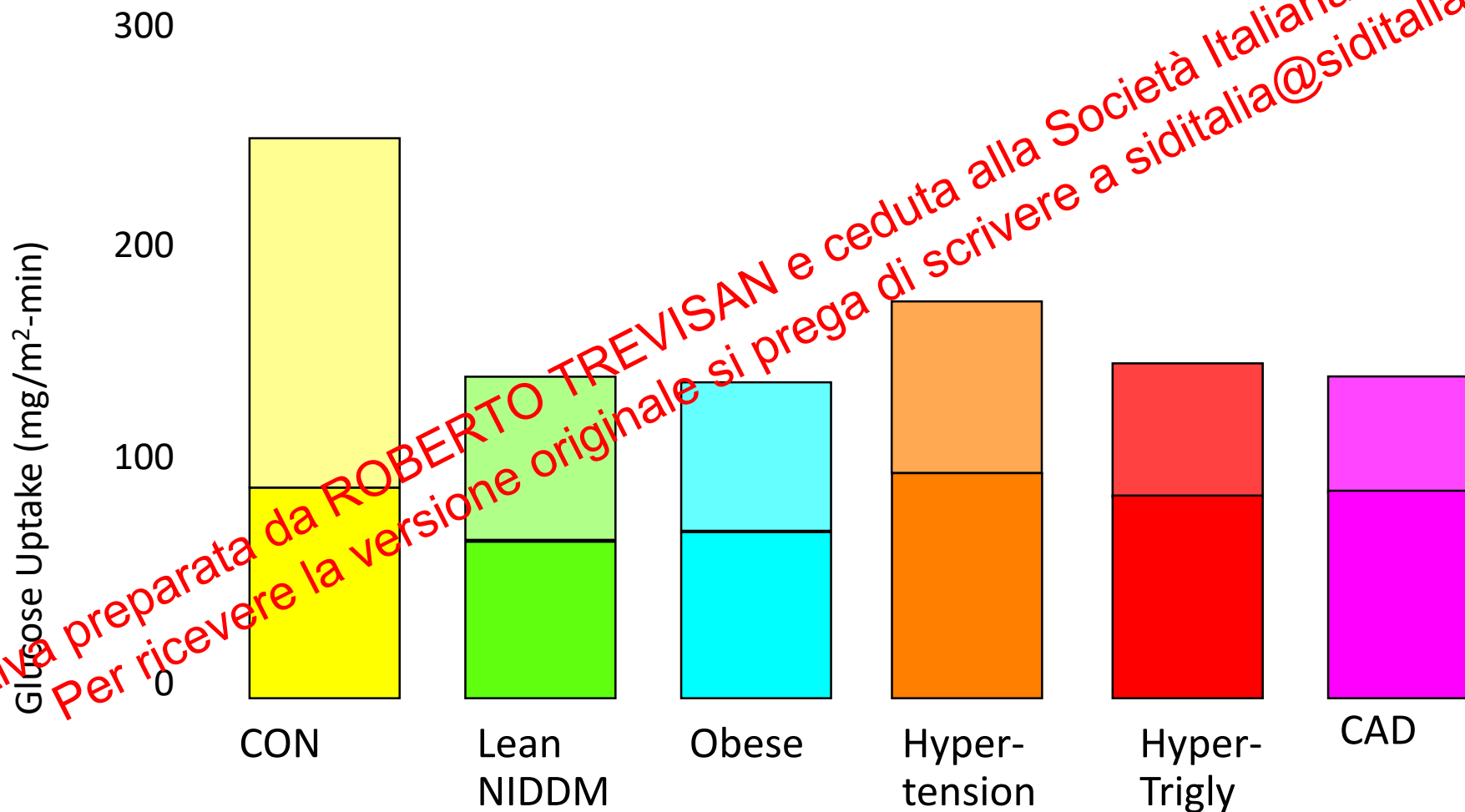
CKD Stages 3–5
albuminuric



WHAT DOES **CARDIOVASCULAR**
DISEASE HAVE IN COMMON WITH
T2DM, OBESITY, DYSLIPIDEMIA,
HYPERTENSION AND
RENAL DISEASE?

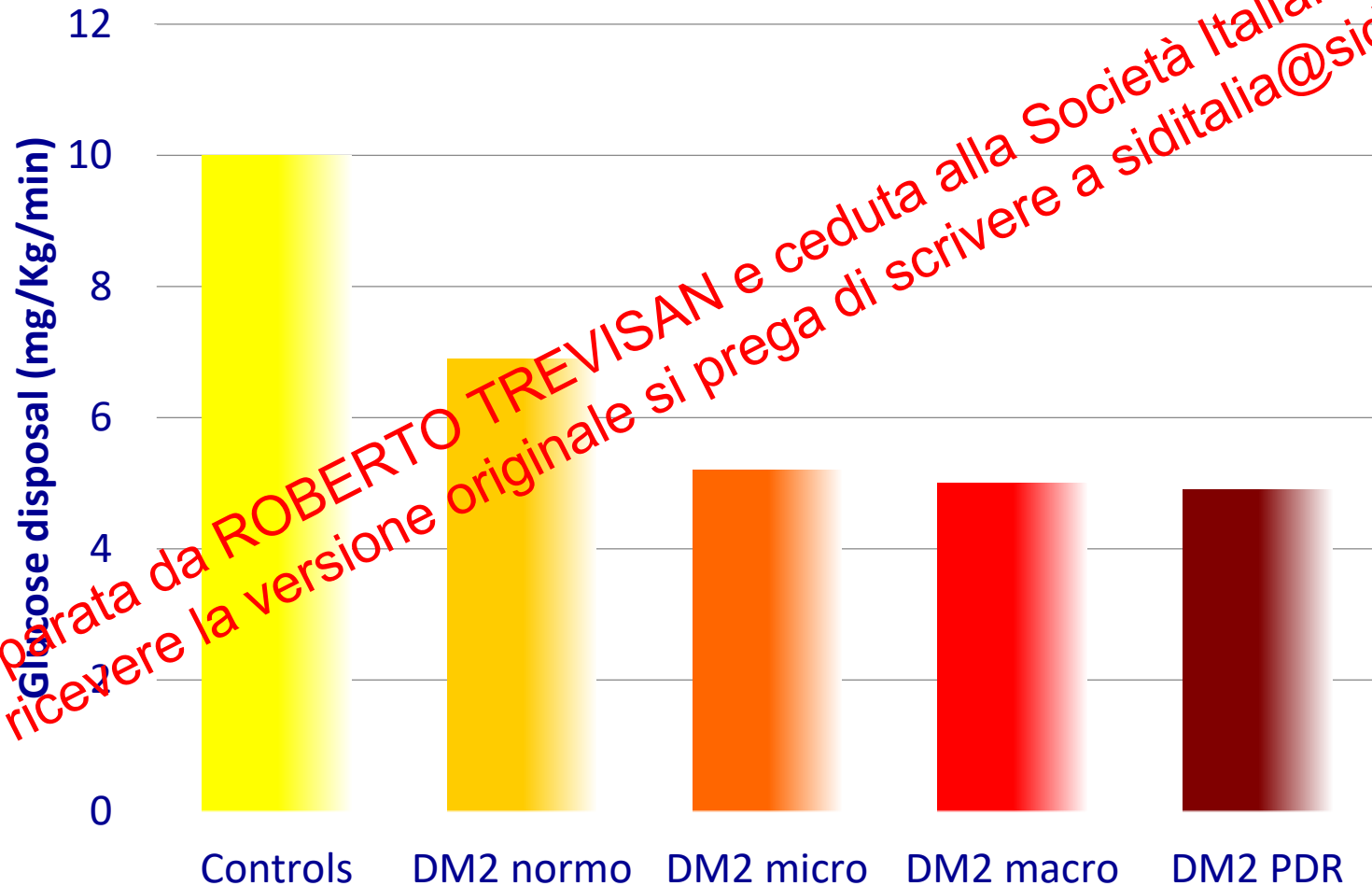
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INSULIN SENSITIVITY IN THE IRS

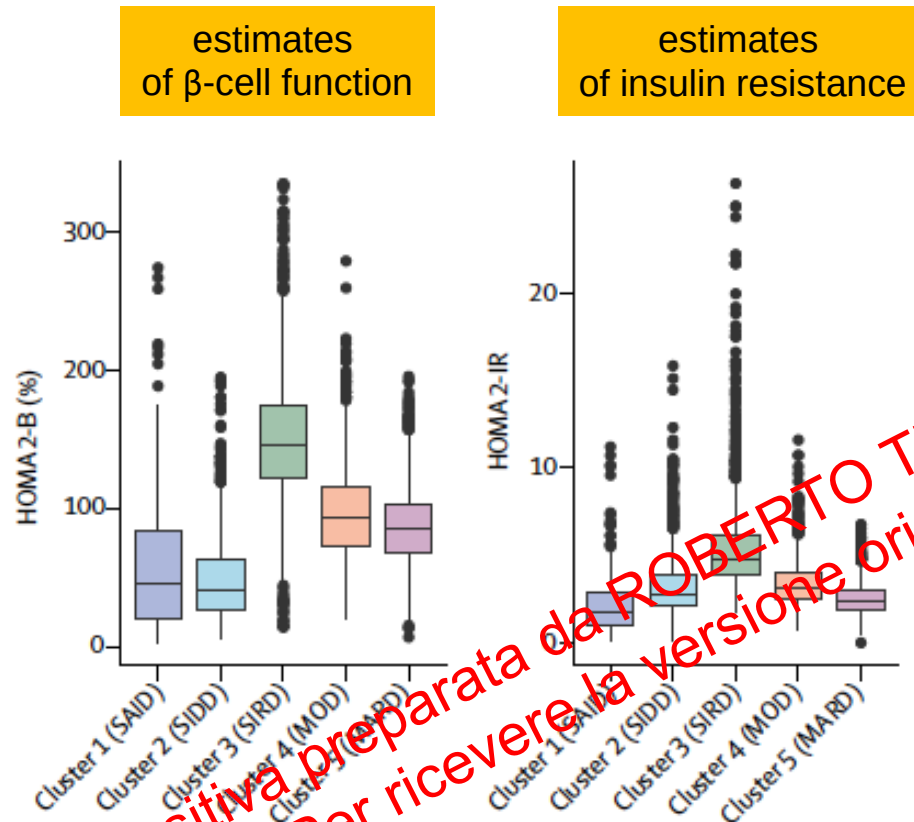


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Type 2 diabetic patients with increased AER and PDR have a greater insulin resistance

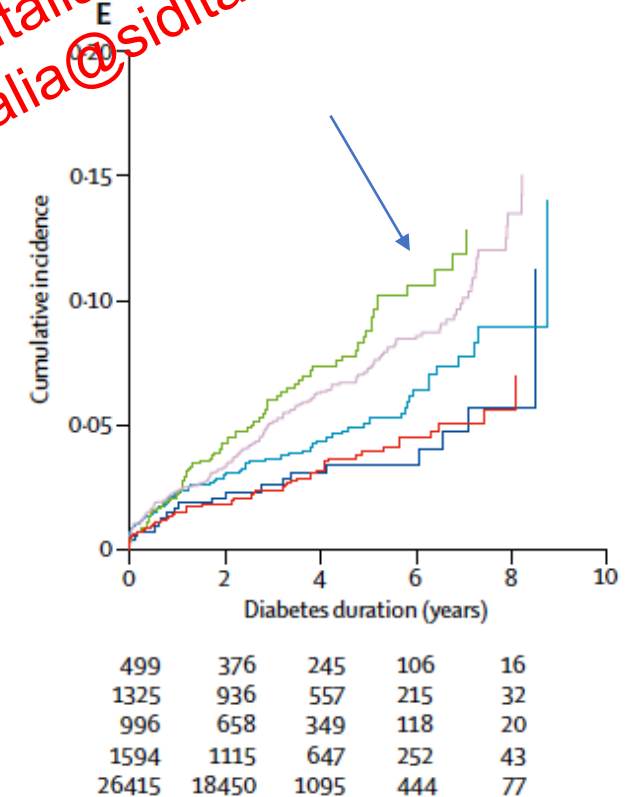
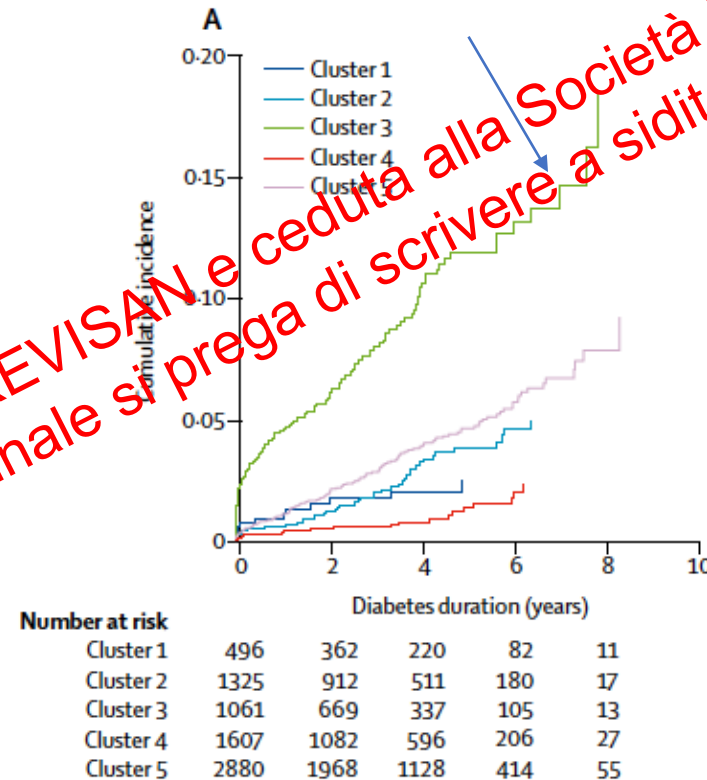


Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables



Time to chronic kidney disease
(eGFR > 45/ml/1.73 m²)

Time to coronary events



SAID=severe autoimmune diabetes. SIDD=severe insulin-deficient diabetes. SIRD=severe insulin-resistant diabetes. MOD=mild obesity-related diabetes. MARD=mild age-related diabetes.

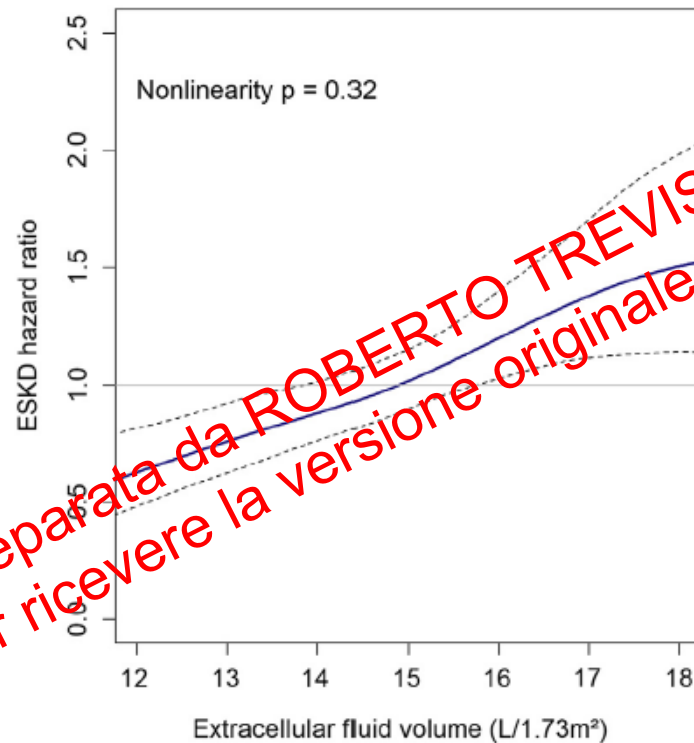
Insulin-resistance: Mechanisms of renal and cardiovascular damage

- Abdominal adiposity
- ↓ Ch-HDL
- ↑ Triglyceride
- ↑ Blood Pressure
- Higher nocturnal BP
- Sodium sensitivity, ↑ ECV
- Endothelial dysfunction
- Arterial stiffness
- Renal dysfunction
- High uric acid

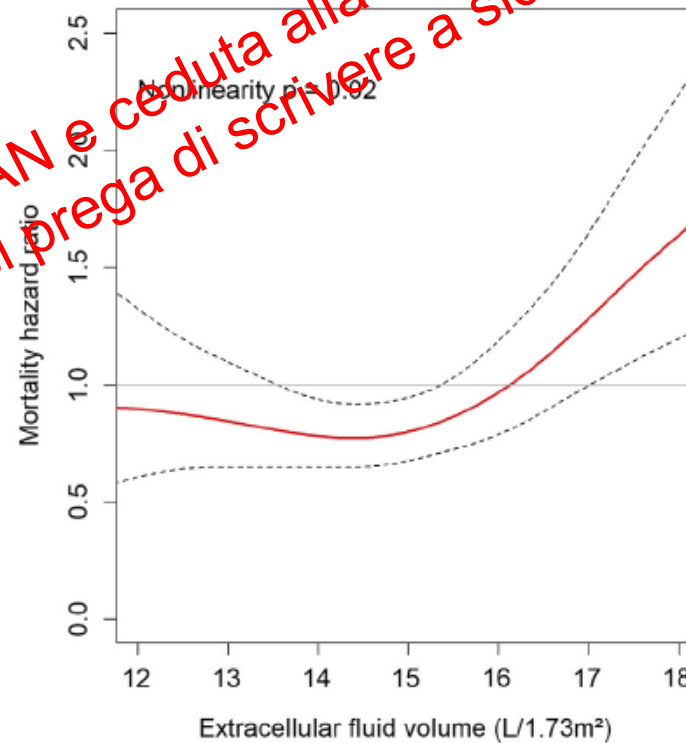
Extracellular fluid volume is associated with incident end-stage kidney disease and mortality in patients with chronic kidney disease

Prospective cohort of 1593 pts with CKD stage 1-4 (NephroTest Study)

Estimated adjusted hazard ratio for the association of ECF with ESKD

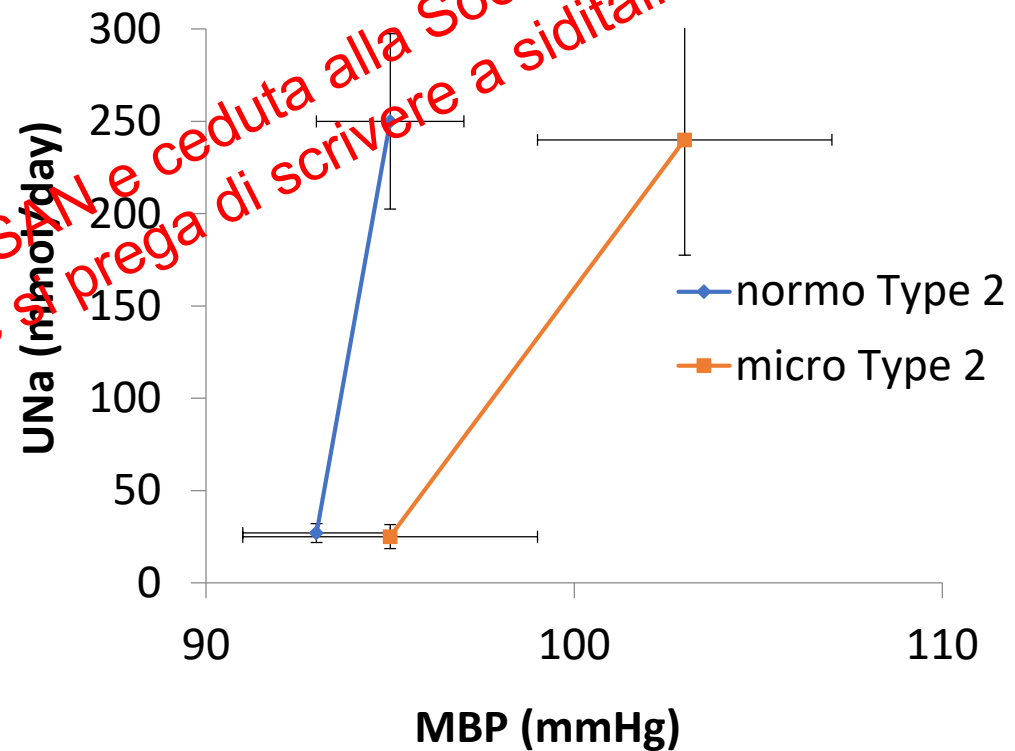
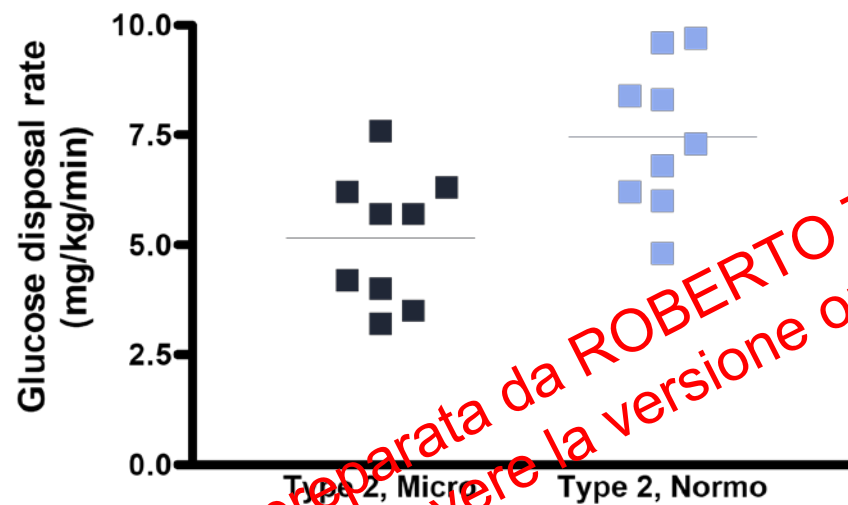


Estimated adjusted hazard ratio for the association of ECF with mortality



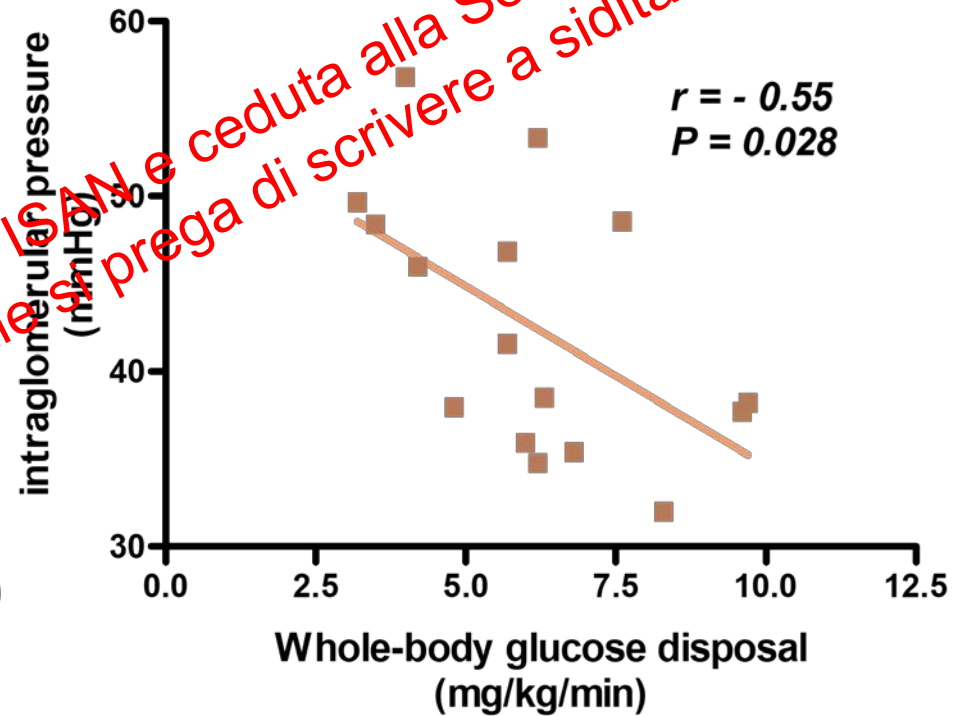
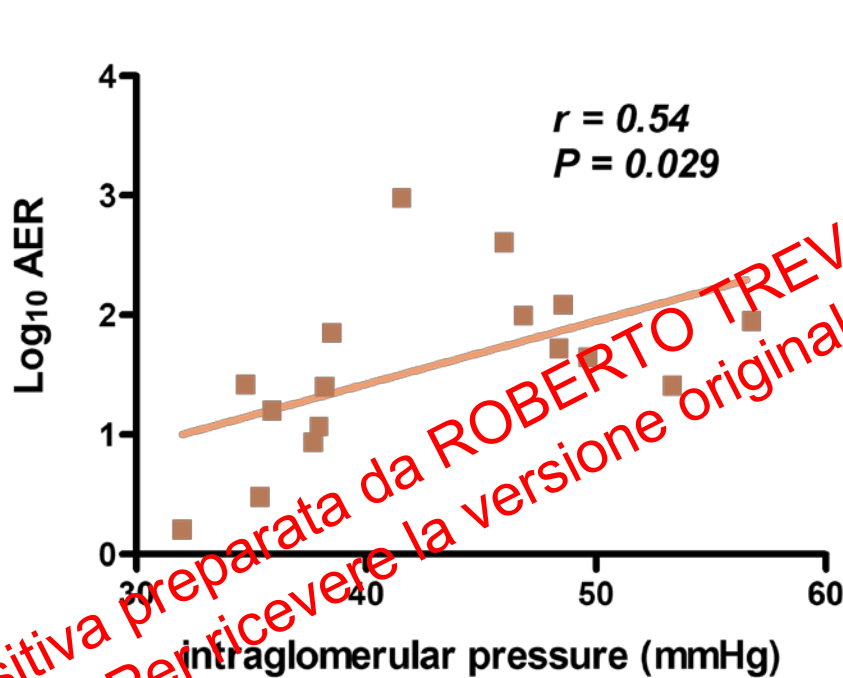
The pressure-natriuresis curve in type 2 diabetic patients with and without microalbuminuria

La microalbuminuria si associa alla Sodio-sensibilità

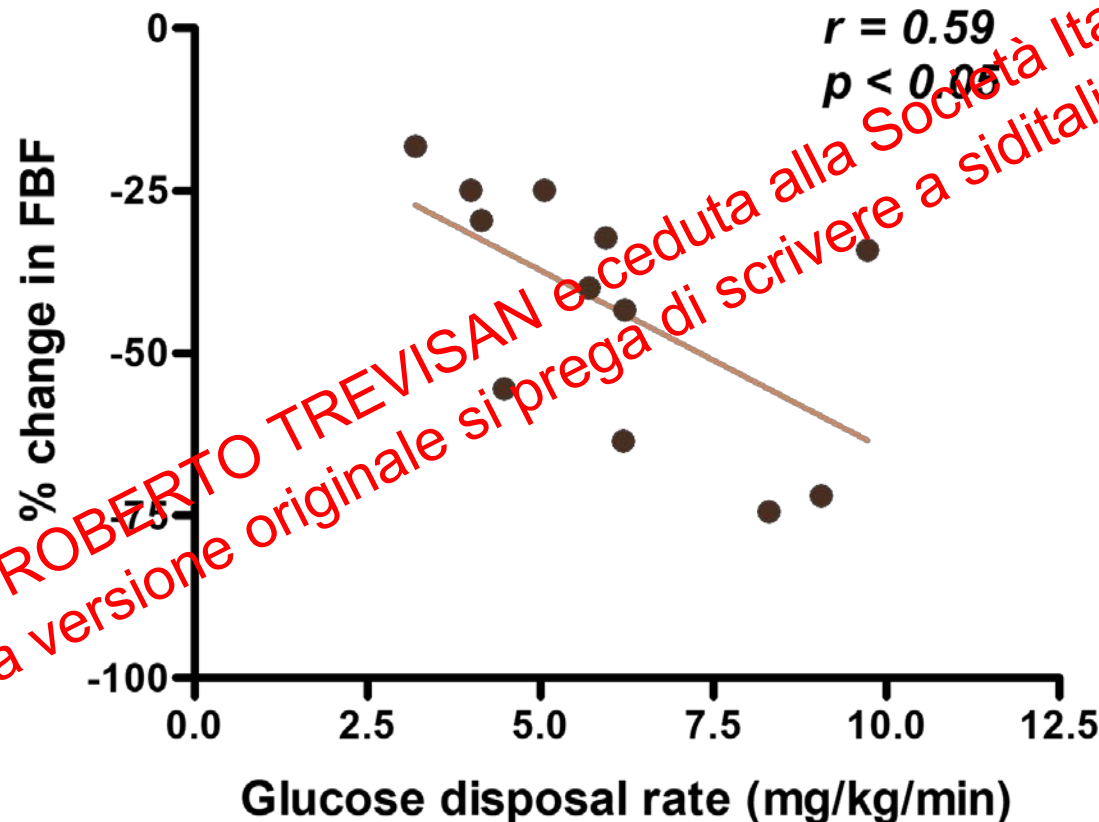


L'ALBUMINURIA E'
CORRELATA ALLA PRESSIONE
INTRAGLOMERULARE

LA PRESSIONE
INTRAGLOMERULARE È
CORRELATA ALL'INSULINO-
RESISTENZA



RELATIONSHIP BETWEEN TOTAL GLUCOSE DISPOSAL RATE AND PERCENT CHANGE IN FOREARM BLOOD FLOW AFTER L-NMMA INFUSION IN TYPE 2 DIABETIC PATIENTS



Insulin resistance is associated with a reduced NO availability

A specific role for Insulin Resistance in the pathogenesis of target organ damage

Insulin Resistance



Loss of
Autoregulation
Endothelial
dysfunction

Systemic hypertension



**Increased
perfusion pressure**



MICROANGIOPATHY, SCARRING
(nephropathy, retinopathy, cardiomyopathy)

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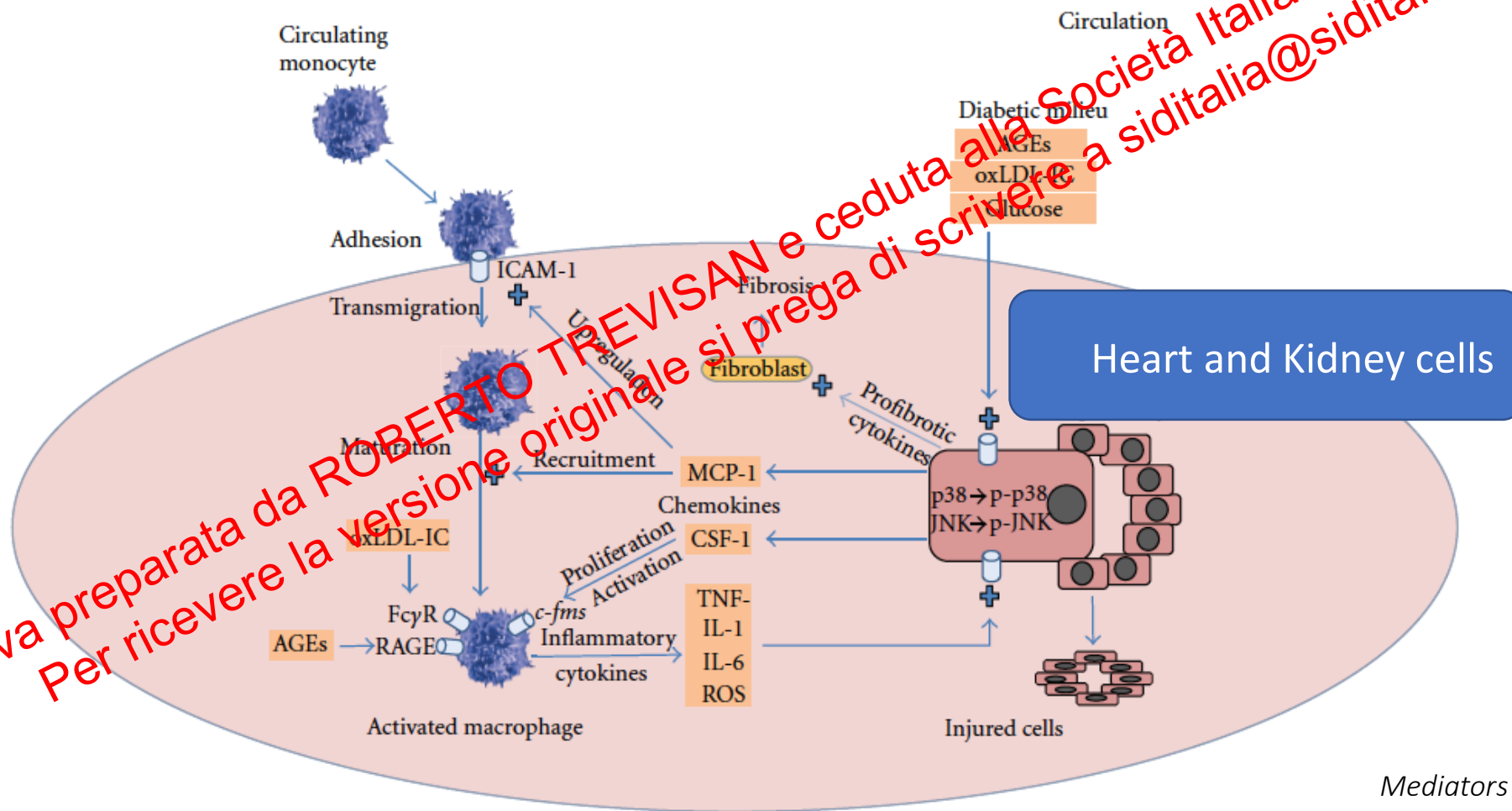
SUMMARY: METABOLIC ETIOLOGY OF ATHEROSCLEROSIS IN T2DM with CKD

- **Insulin Resistance (IR) Syndrome**
 - Individual components
- **Molecular Etiology of IR** → **MAPK** activity
- **Lipotoxicity – activation of inflammatory pathways (I κ B / NF κ B, p38 MAPK, JNK)**

• **Sick Fat Cell Syndrome** →
↑ **adipocytokines**

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The inflammatory amplification loop in the diabetic kidney and heart



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CONCLUSIONI

- I diabetici con malattia renale cronica dimostrano un maggiore rischio di eventi cardiovascolari indipendentemente dalla presenza di albuminuria.
- Fattori di rischio cardiometabolici agiscono sinergicamente nel determinare il rischio cardio-renale.
- Una maggiore insulina-resistenza è strettamente associata alla malattia renale cronica e sicuramente, attraverso molteplici meccanismi metabolici, infiammatori, endoteliali ed emodinamici, contribuisce all'aumentato rischio cardiovascolare.