



FERRARA 22 APRILE 2017 HOTEL IL DUCA D'ESTE

**IL CONCETTO DI RISCHIO GLOBALE NEL PAZIENTE
CON SINDROME METABOLICA/DMT2:
RISCHIO INFETTIVO, RISCHIO
CARDIOVASCOLARE, RISCHIO ONCOLOGICO**

con il Patrocinio di: **AMD EMILIA ROMAGNA** e **SBCO**

**MALATTIA RENALE, NUOVI IPOGLICEMIZZANTI E COMPLICANZE CARDIOVASCOLARI
NEL PAZIENTE CON DIABETE DI TIPO 2**

SINDROME CARDIORENALE E RISCHIO CARDIOMETABOLICO

Roberto Trevisan, Malattie Endocrine – Diabetologia,
ASST –Papa Giovanni XXIII, Bergamo

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

Penno G et al, J Hypertens 2011; 29:1802-1809

15773 T2DM patients randomly selected in Italian outpatient clinics

↑AER
26.9%

eGFR < 60 ml/min/1.73m²
18.8%

With CKD
37.5%

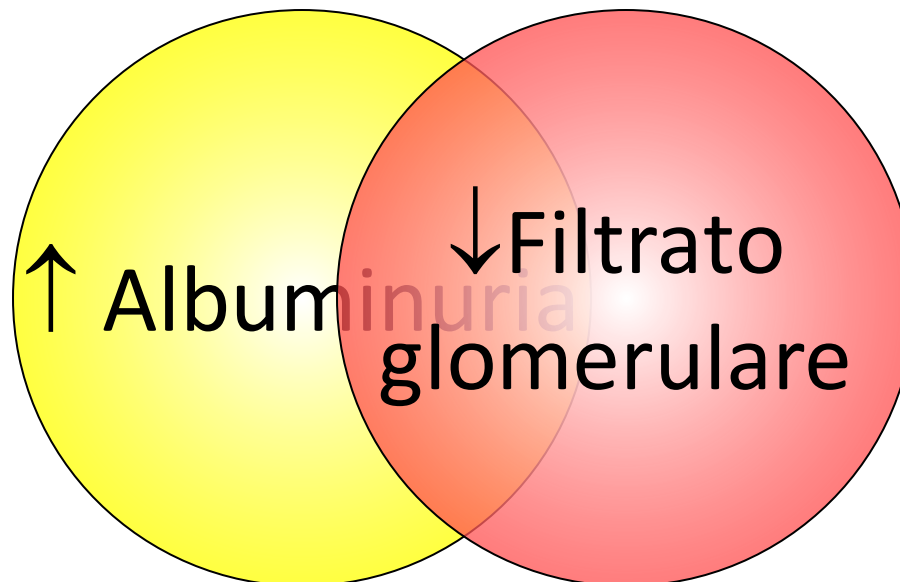


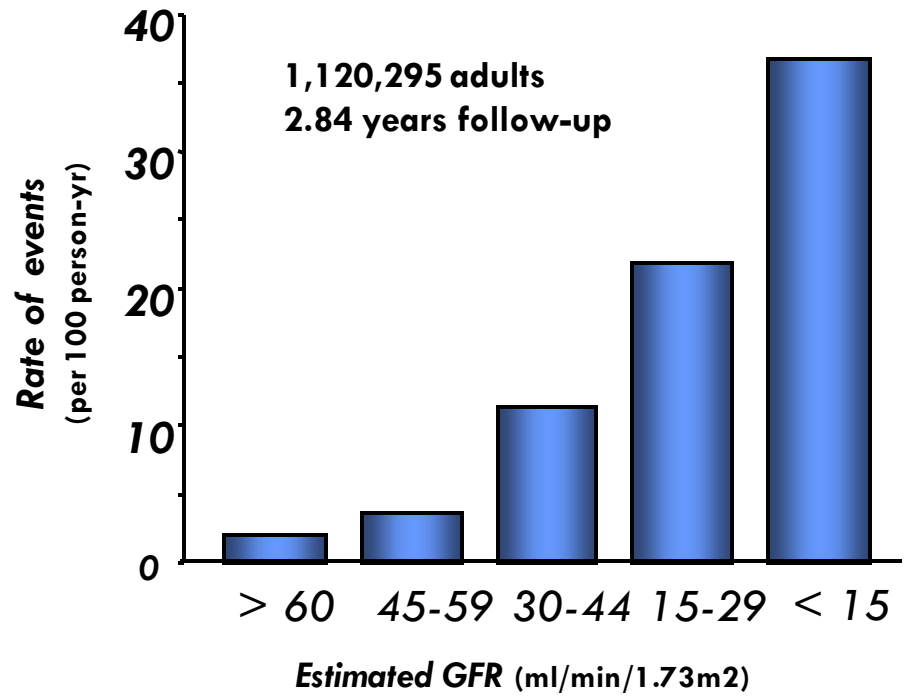
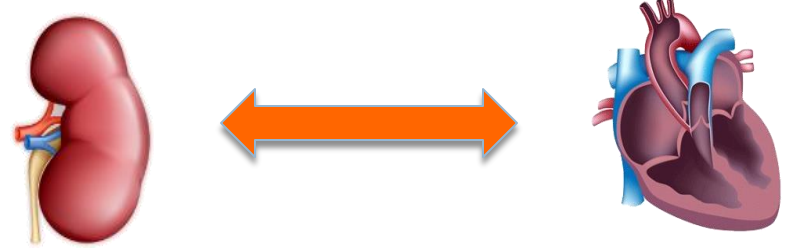
52%
With normal AER

NEFROPATIA CRONICA E DIABETE

de Boer IH & Steffes MW, J Am Soc Nephrol 2007; 18:1036-1037

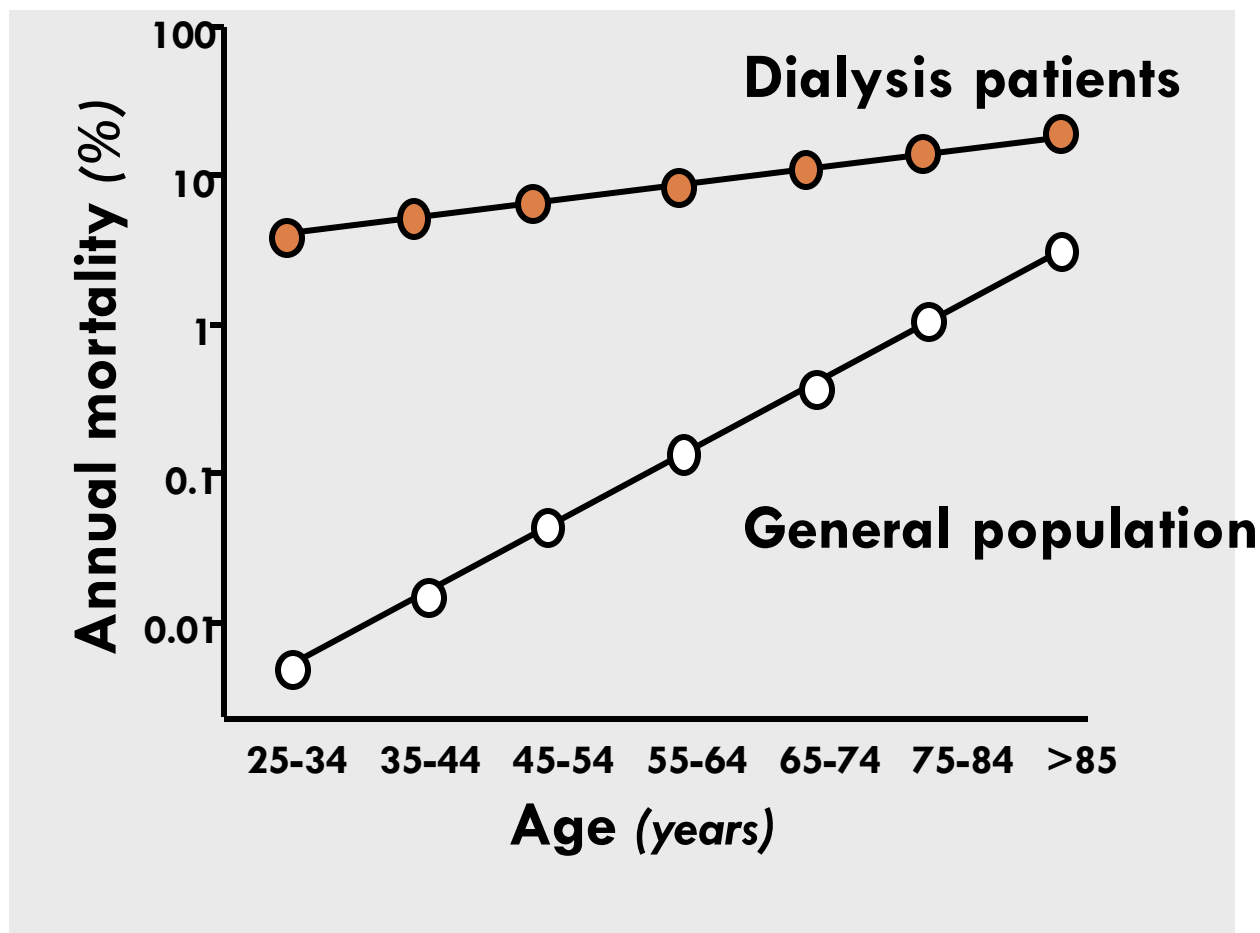
- Non solo nefropatia diabetica
- La malattia renale cronica nel diabetico di tipo 2 è elevata anche in assenza di nefropatia diabetica proteinurica





Go et al., N Engl J Med, 2004

CARDIOVASCULAR MORTALITY IN DIALYSIS PATIENTS AS COMPARED TO THE GENERAL POPULATION



In dialysis patients age adjusted cardiovascular mortality is 100 to 10 fold higher than in the general population

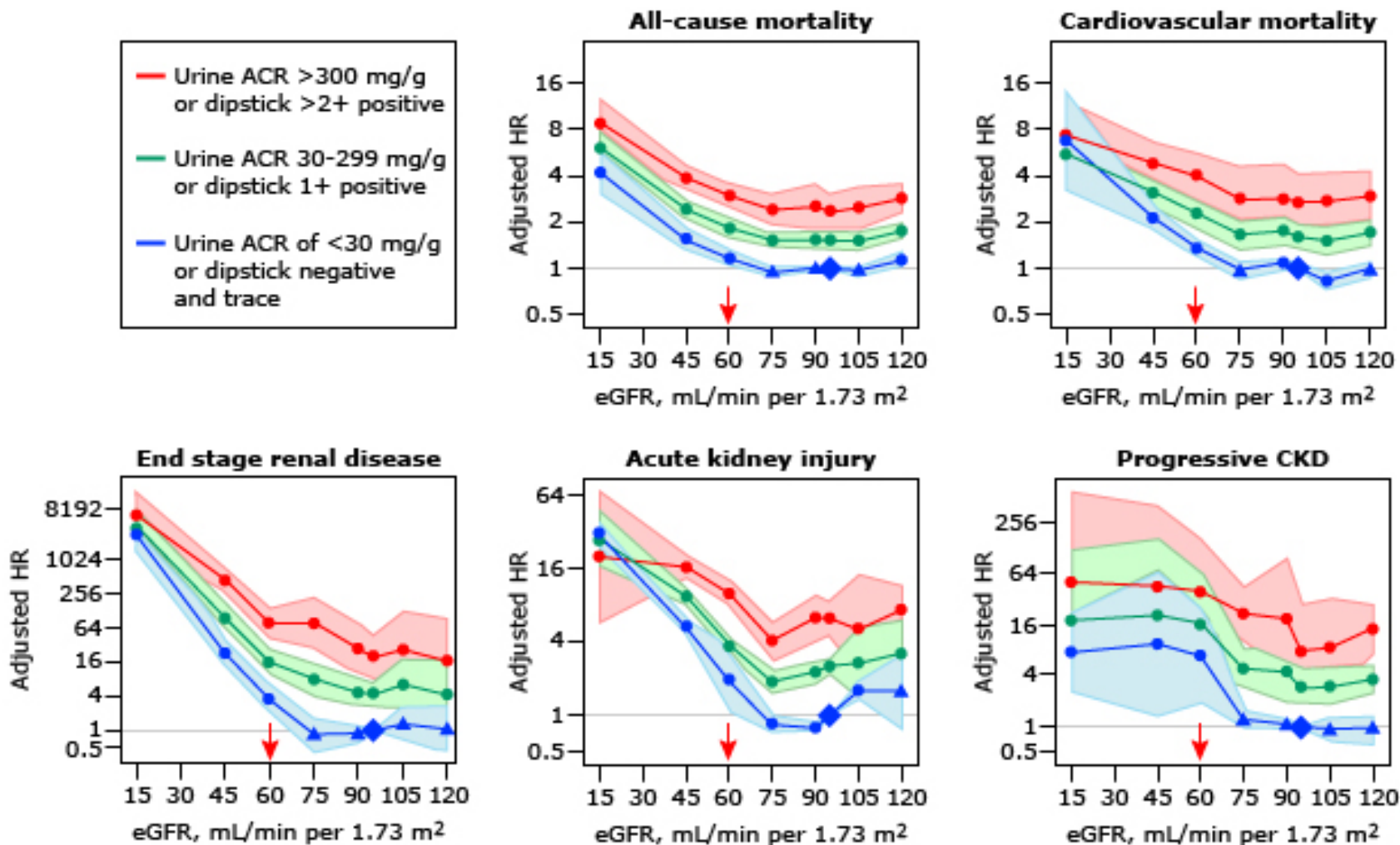
UKPDS Progression

Bilous R, DM 2008; 25 Suppl 2: 25-29

	Proportion alive at 10 yrs	Years spent in stage (IQR)
No nephropathy	87.1 %	18.9 (7.8 – 37.8)
MAU	70.8 %	10.9 (4.5 – 21.8)
CP	65.1 %	9.7 (4.0 – 19.4)
PCr > 175 μ M or RRT	8.5 %	2.5 (1.0 – 5.0)

Relative risks of major complications of chronic kidney disease based upon a continuous meta-analysis

Levey AS, de Jong PE, Coresh J, et al. *Kidney Int* 2010; 80:17.

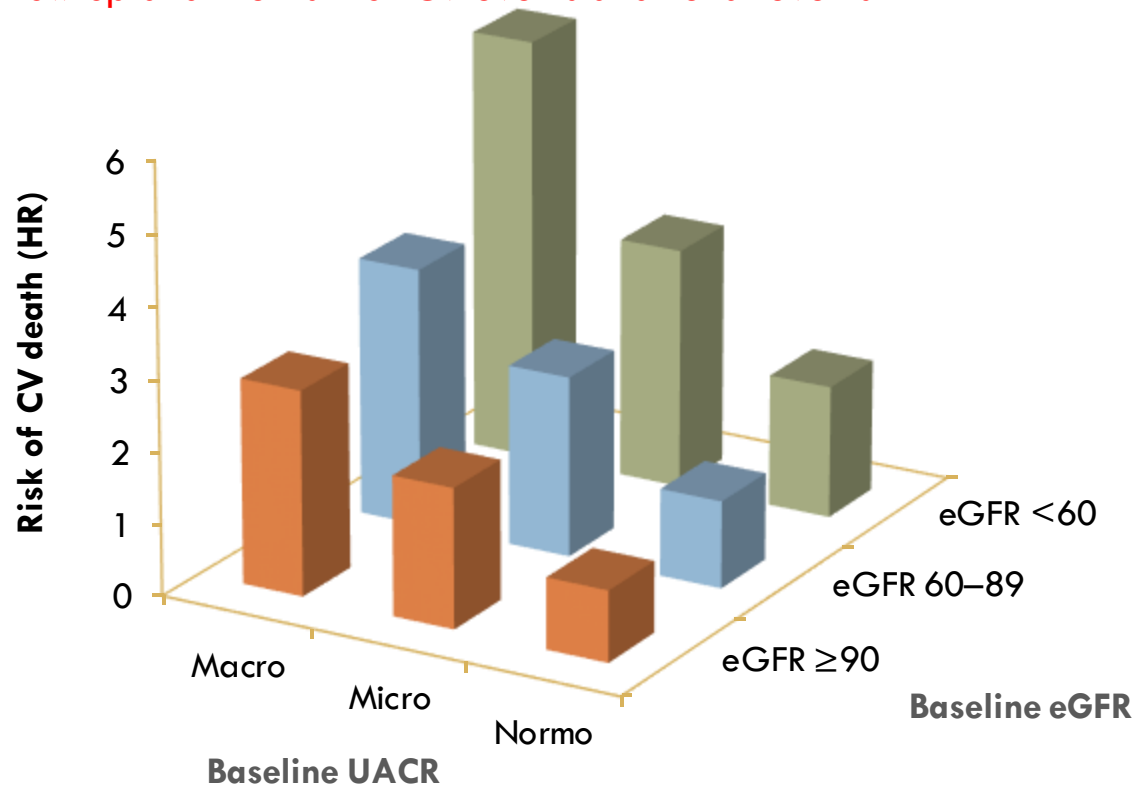


Albuminuria and reduced eGFR are associated with increased risk of CV death

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



eGFR in ml/min/1.73 m²

CV, cardiovascular; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio

Ninomiya T et al. *J Am Soc Nephrol* 2009;20:1813

Summary of categorical meta-analysis (adjusted RRs) for general population cohorts with ACR

Kidney International Supplements (2013) 3, 19–62



All-cause mortality

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR > 105	1.1	1.5	2.2	5.0
eGFR 90-105	Ref	1.4	1.5	3.1
eGFR 75-90	1.0	1.3	1.7	2.3
eGFR 60-75	1.0	1.4	1.8	2.7
eGFR 45-60	1.3	1.7	2.2	3.6
eGFR 30-45	1.9	2.3	3.3	4.9
eGFR 15-30	5.3	3.6	4.7	6.6

Cardiovascular mortality

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR > 105	0.9	1.3	2.3	2.1
eGFR 90-105	Ref	1.5	1.7	3.7
eGFR 75-90	1.0	1.3	1.6	3.7
eGFR 60-75	1.1	1.4	2.0	4.1
eGFR 45-60	1.5	2.2	2.8	4.3
eGFR 30-45	2.2	2.7	3.4	5.2
eGFR 15-30	14	7.9	4.8	8.1

Kidney failure (ESRD)

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR > 105	Ref	Ref	7.8	18
eGFR 90-105	Ref	Ref	11	20
eGFR 75-90	Ref	Ref	3.8	48
eGFR 60-75	Ref	Ref	7.4	67
eGFR 45-60	5.2	22	40	147
eGFR 30-45	56	74	294	763
eGFR 15-30	433	1044	1056	2286

Acute kidney injury (AKI)

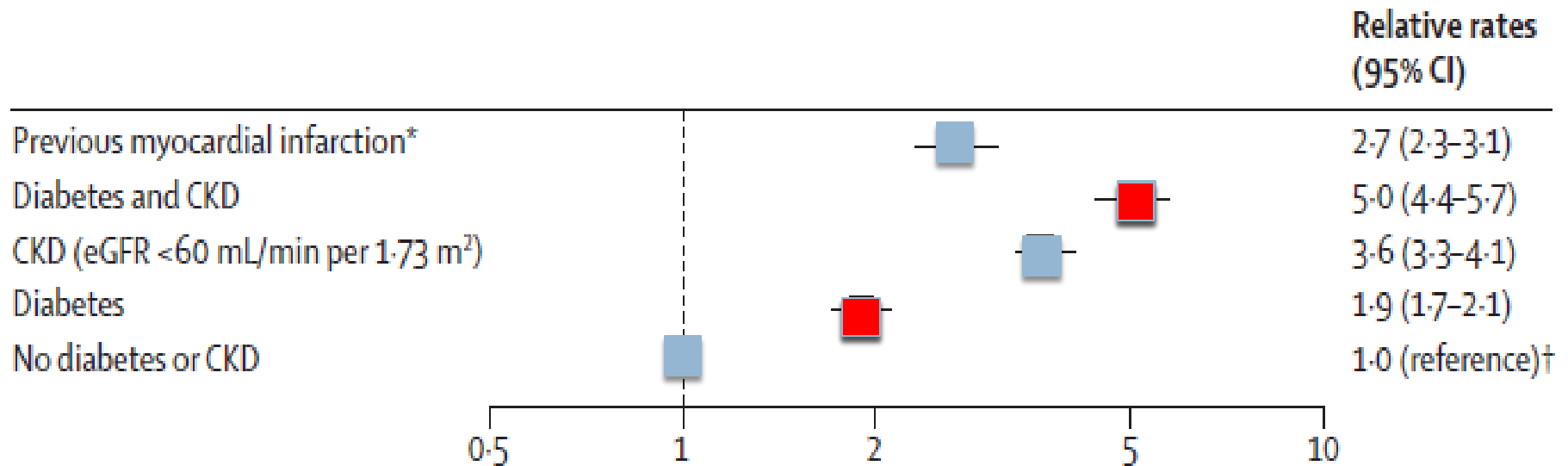
	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR > 105	Ref	Ref	2.7	8.4
eGFR 90-105	Ref	Ref	2.4	5.8
eGFR 75-90	Ref	Ref	2.5	4.1
eGFR 60-75	Ref	Ref	3.3	6.4
eGFR 45-60	2.2	4.9	6.4	5.9
eGFR 30-45	7.3	10	12	20
eGFR 15-30	17	17	21	29

Progressive CKD

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR > 105	Ref	Ref	0.4	3.0
eGFR 90-105	Ref	Ref	0.9	3.3
eGFR 75-90	Ref	Ref	1.9	5.0
eGFR 60-75	Ref	Ref	3.2	8.1
eGFR 45-60	3.1	4.0	9.4	57
eGFR 30-45	3.0	19	15	22
eGFR 15-30	4.0	12	21	7.7

L'Insufficienza Renale Cronica (CKD) rappresenta un importante fattore di rischio indipendente dal diabete per mortalità e malattia cardiovascolare

Relative rates of all-cause mortality after myocardial infarction in each risk group



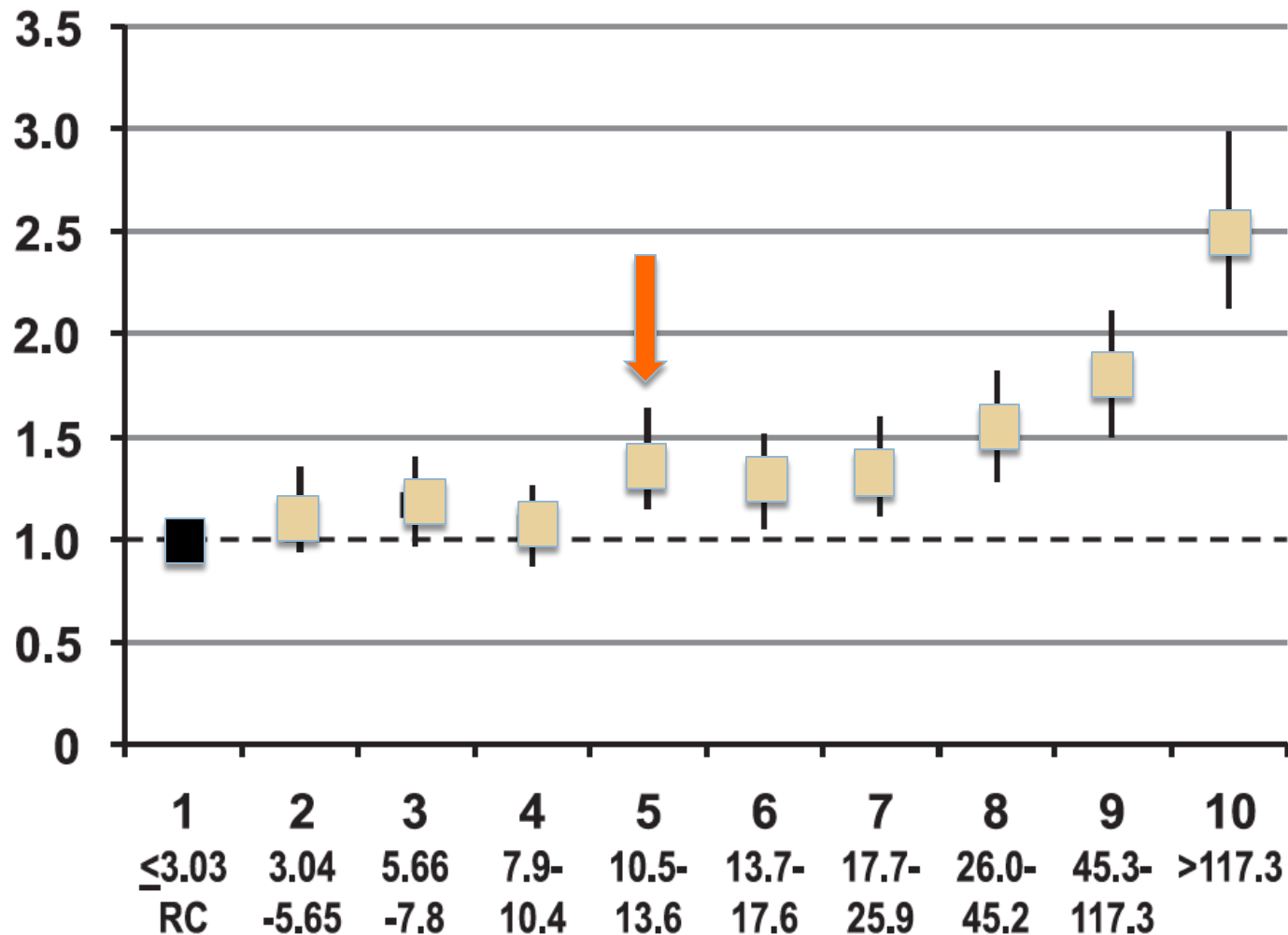
Population-based cohort analysis, median follow-up 48 months, 1 268 029 participants

CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate. *with or without diabetes and CKD. † based on the absence of diabetes and CKD (defined by eGFR <60 mL/min per 1.73m² with or without proteinuria).

Tonelli M, et al. *Lancet* 380(1): 807-14, 2012.

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

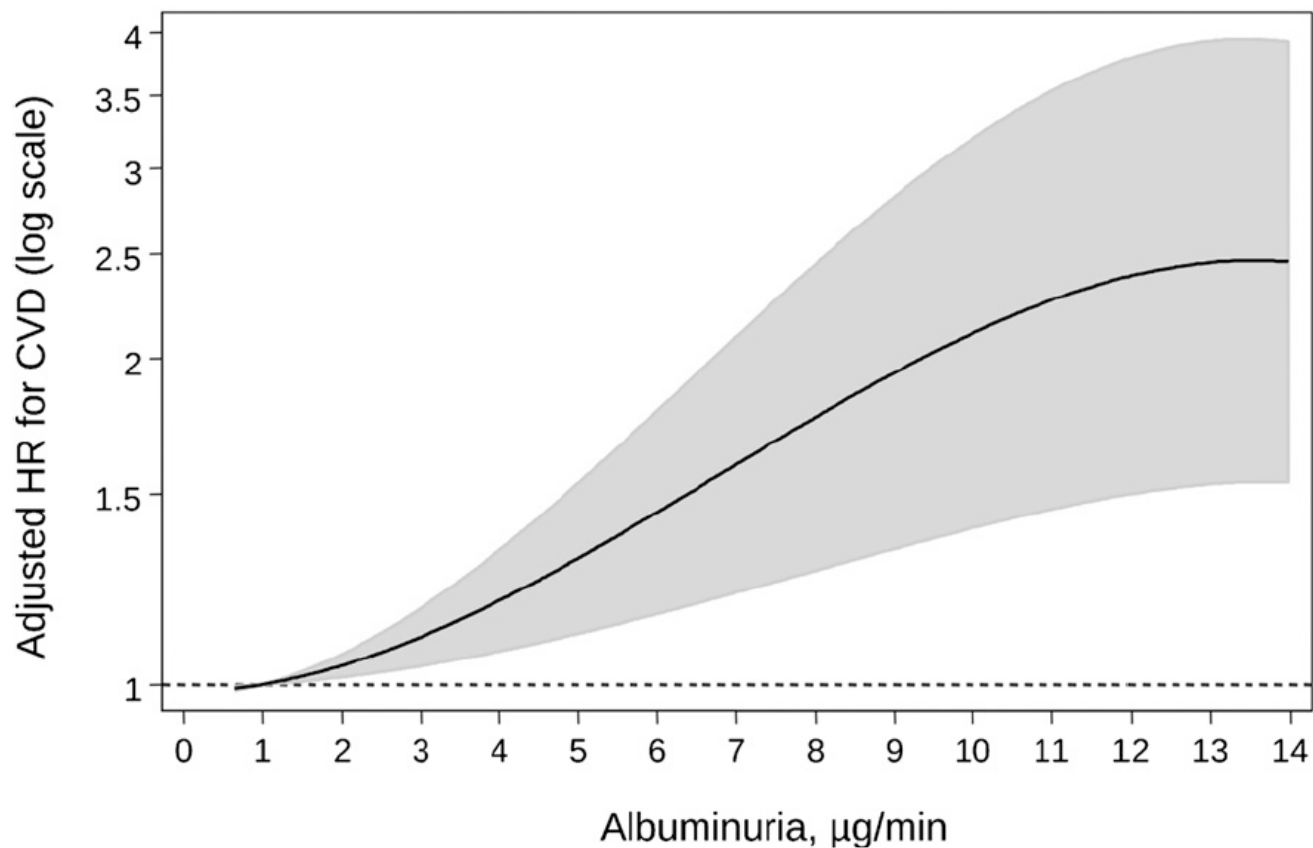
Solini A et al. *Diabetes Care* 2012;35:143-149



Measurable urinary albumin predicts cardiovascular risk among 1208 normoalbuminuric patients with type 2 diabetes

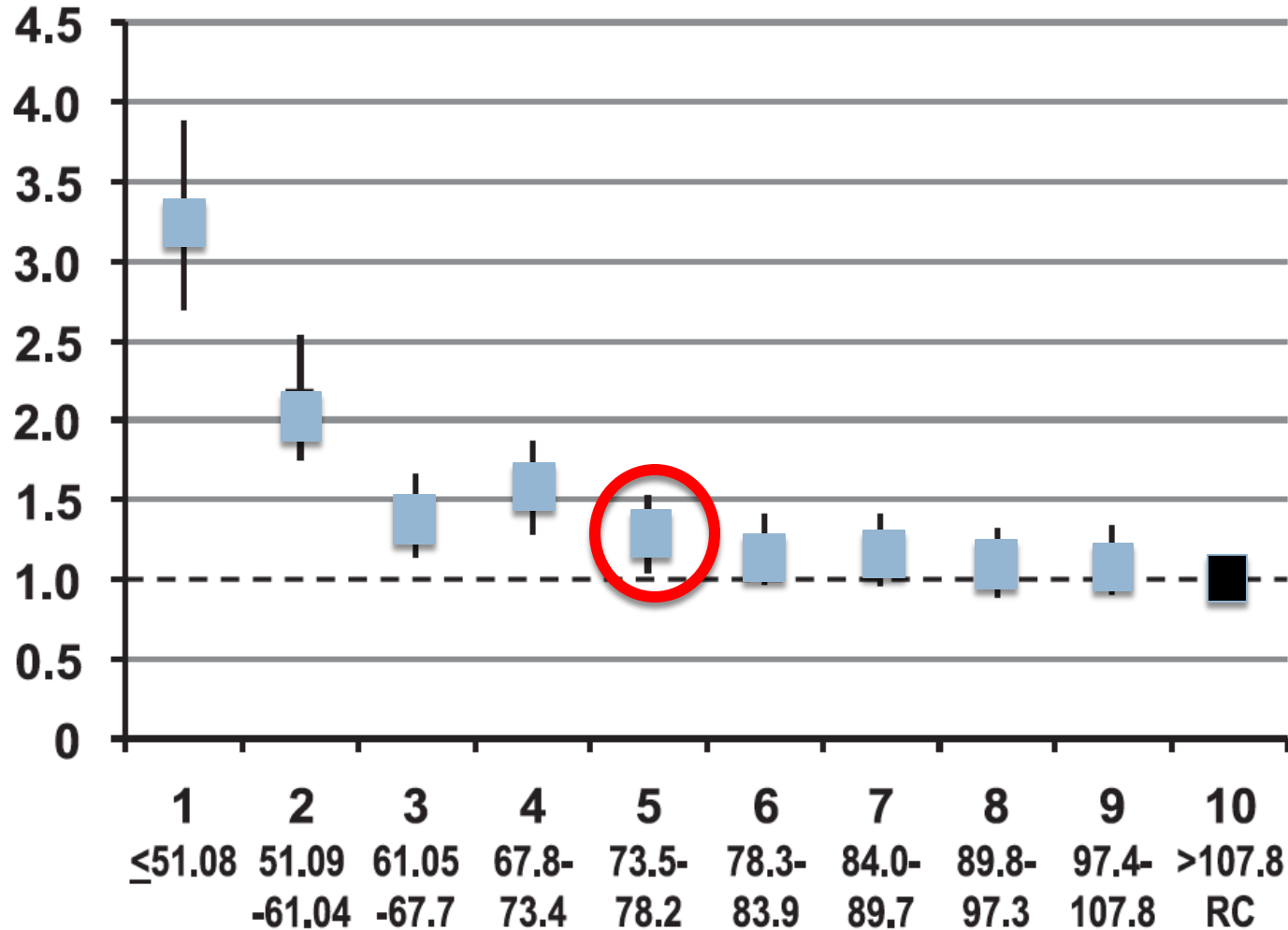
Median follow-up 9.2 yrs

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



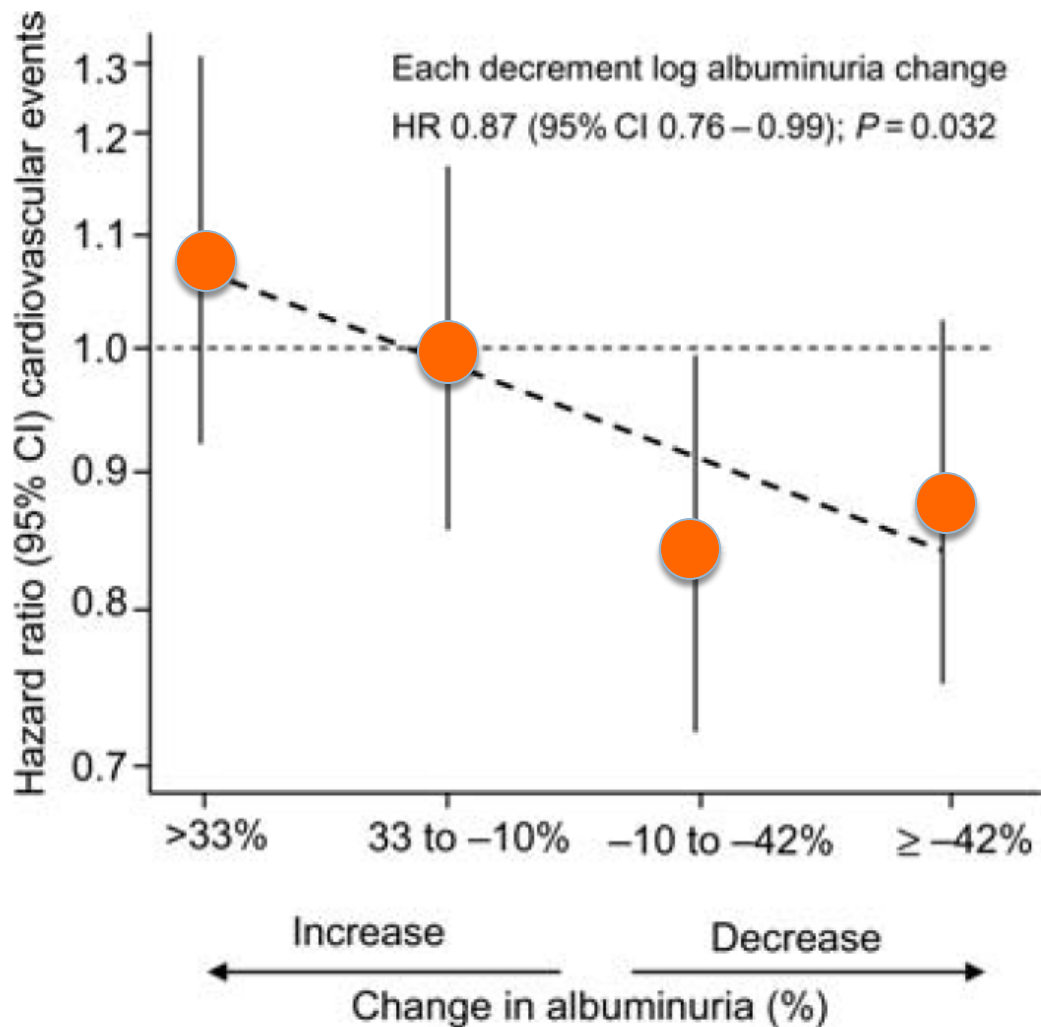
RIACE STUDY: Age- and sex-adjusted risk of major acute CVD events (OR [95% CI]) according to eGFR deciles (mL/min/1.73 m²)

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



Relationship between Month 6 change in albuminuria and cardiovascular outcome in the RENAAL and IDNT studies

European Heart Journal (2011) 32, 1493–1499



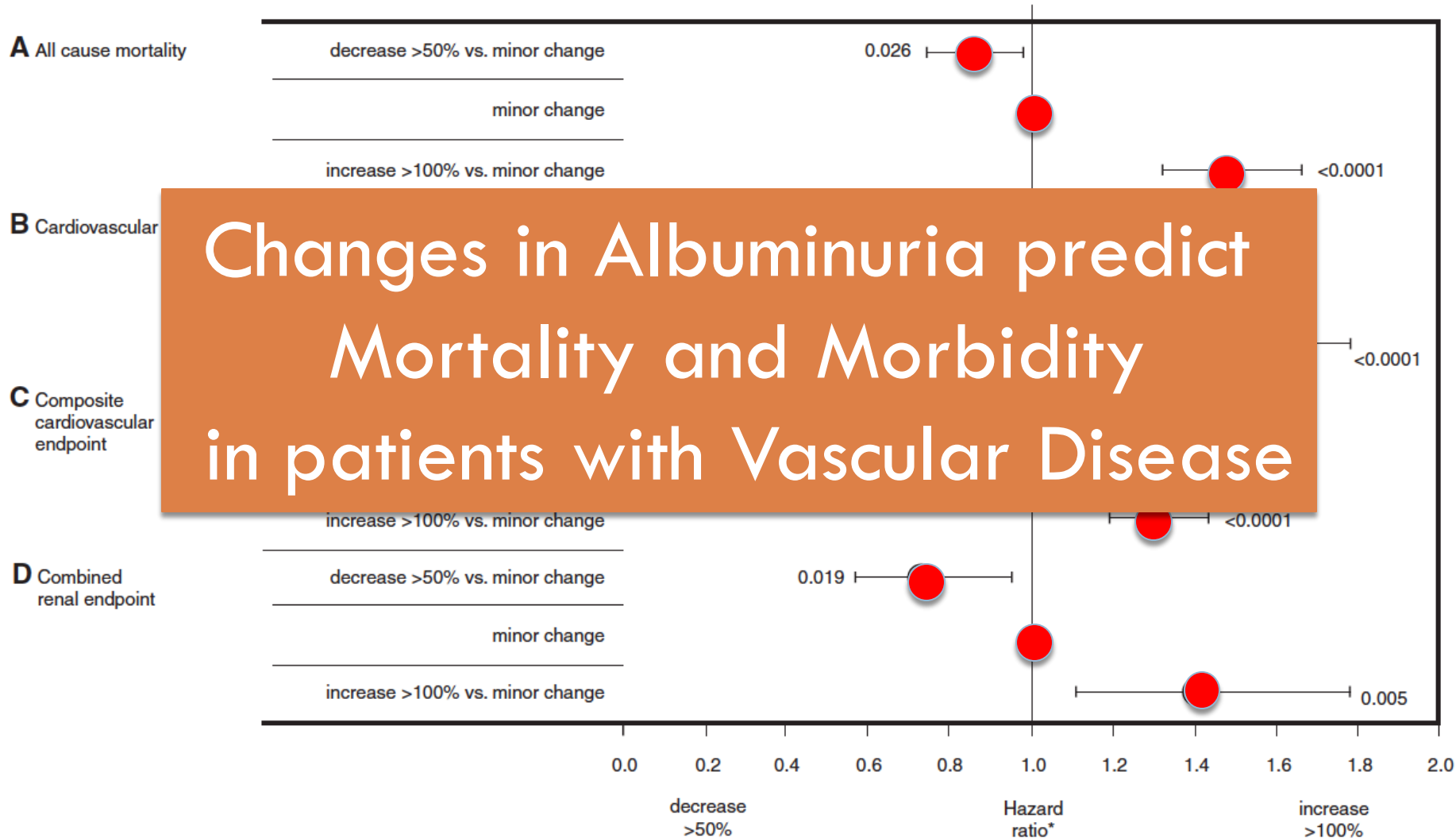
3228 type 2 diabetic patients with overt nephropathy participating in the RENAAL and IDNT trials

S-creatinine 1.8 mg/dl
AER 1334 mg/24hrs

ONTARGET: Adjusted HR (95 CI %) of changes in UACR from baseline to 2-year visit for all-cause mortality, cardiovascular events and renal outcome after the 2-year visit with mean follow-up of 32 months in the whole study group (23480 pts)

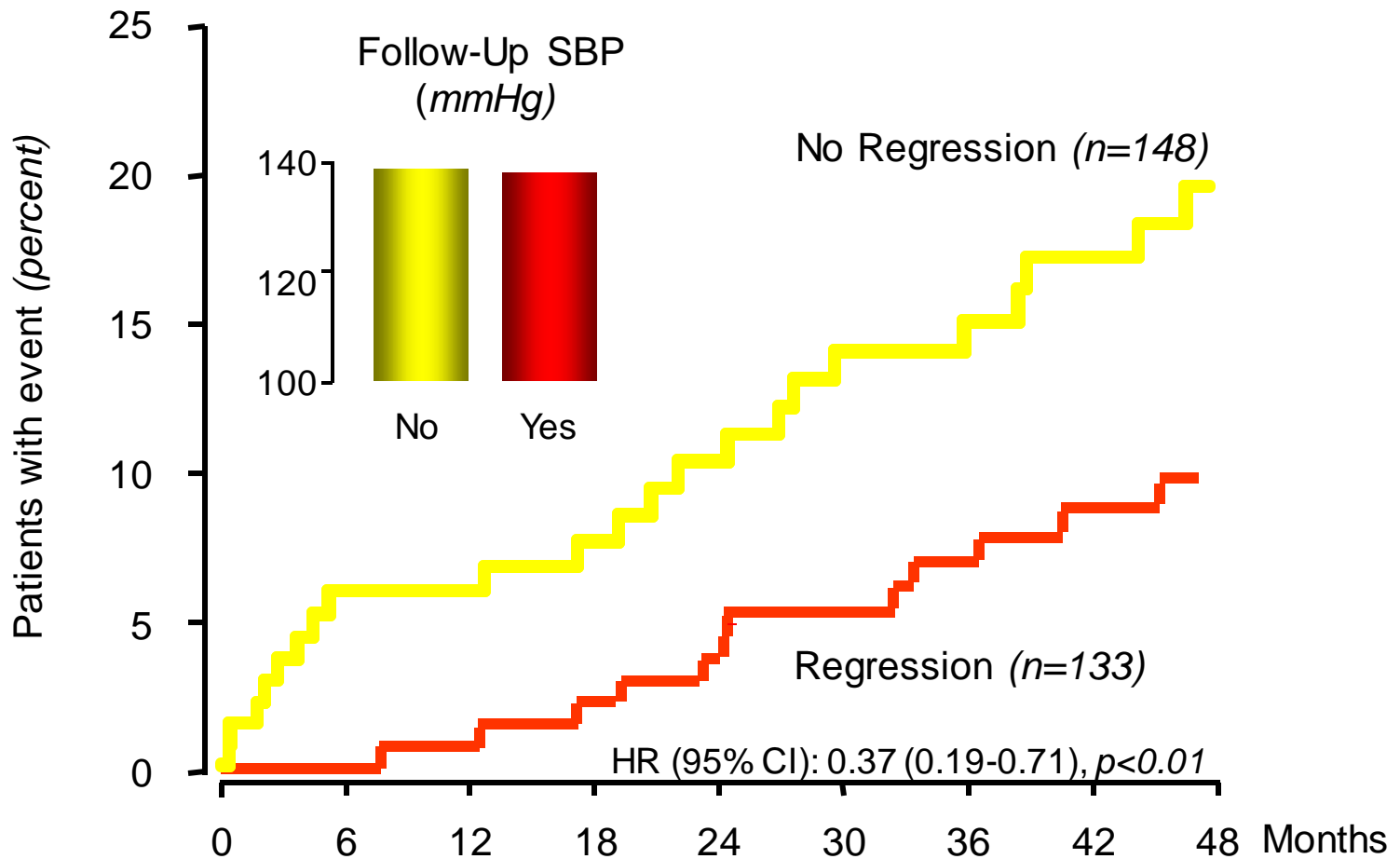
J Am Soc Nephrol 22: 1353–1364, 2011

Changes in Albuminuria predict Mortality and Morbidity in patients with Vascular Disease



BENEDICT 2: Patients with fatal or non fatal major cardiovascular events according to regression to Normoalbuminuria

Ruggenenti et al, *J Hypertension*, 2010



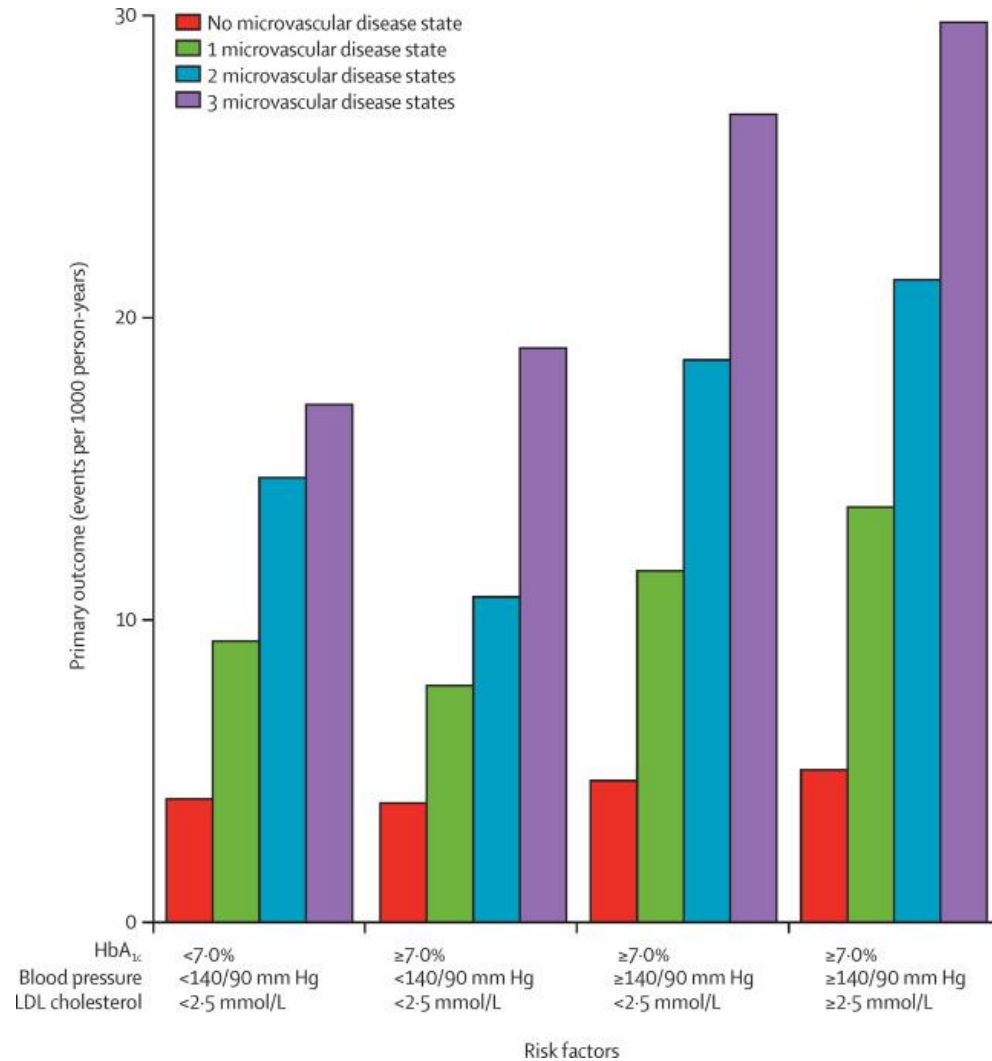
Il rischio CARDIORENALE, perchè?

Fattori di rischio per la malattia renale

- **Modificabili:**
 - Glicemia
 - Pressione arteriosa
 - Proteinuria
 - Iperlipidemia
 - Apporto proteico e di sale nella dieta
 - Insulino-resistenza
 - Fumo
- **Non modificabili:**
 - Fattori genetici
 - Sesso
 - Retinopatia diabetica

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

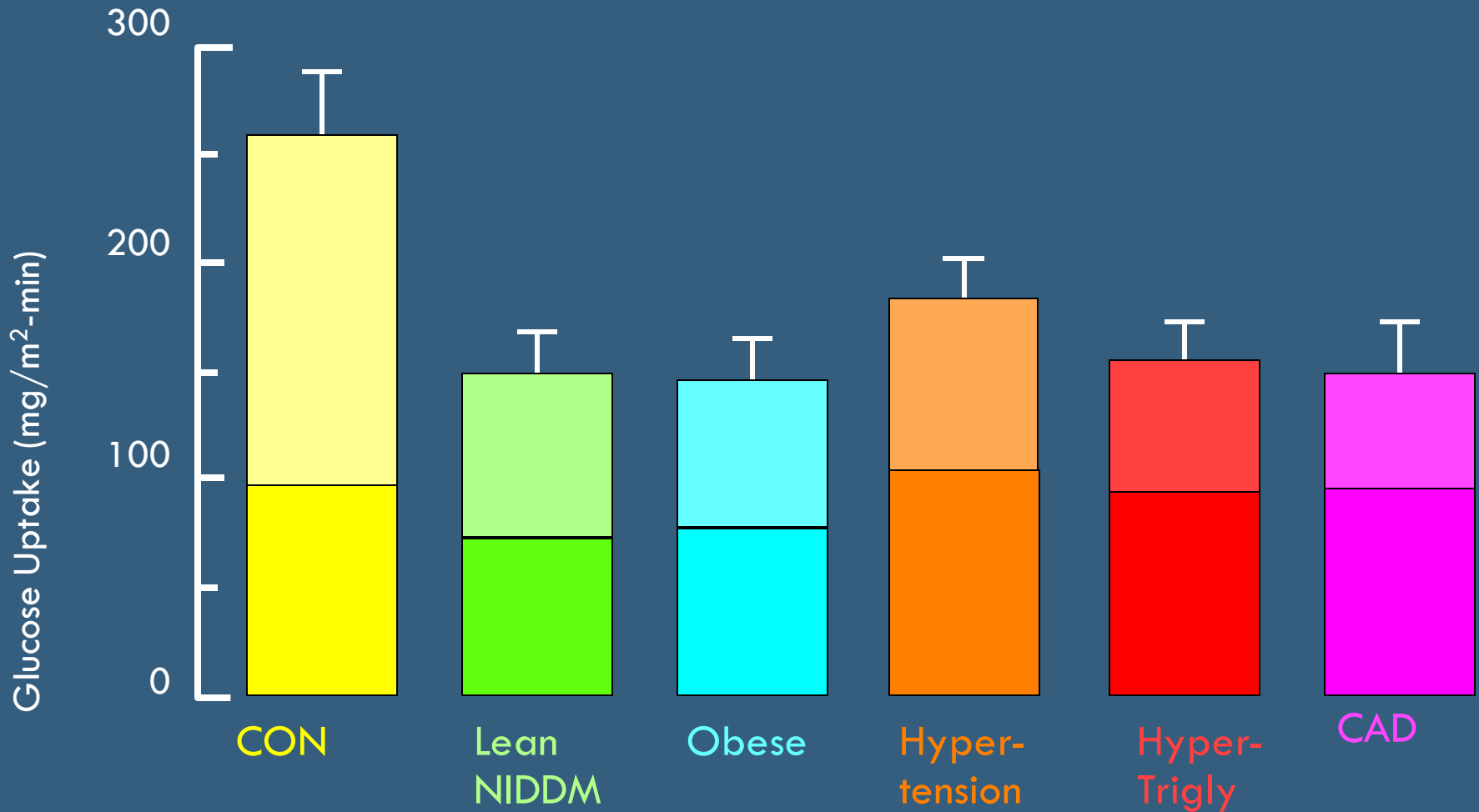
Clinical features by UAE

	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±38	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



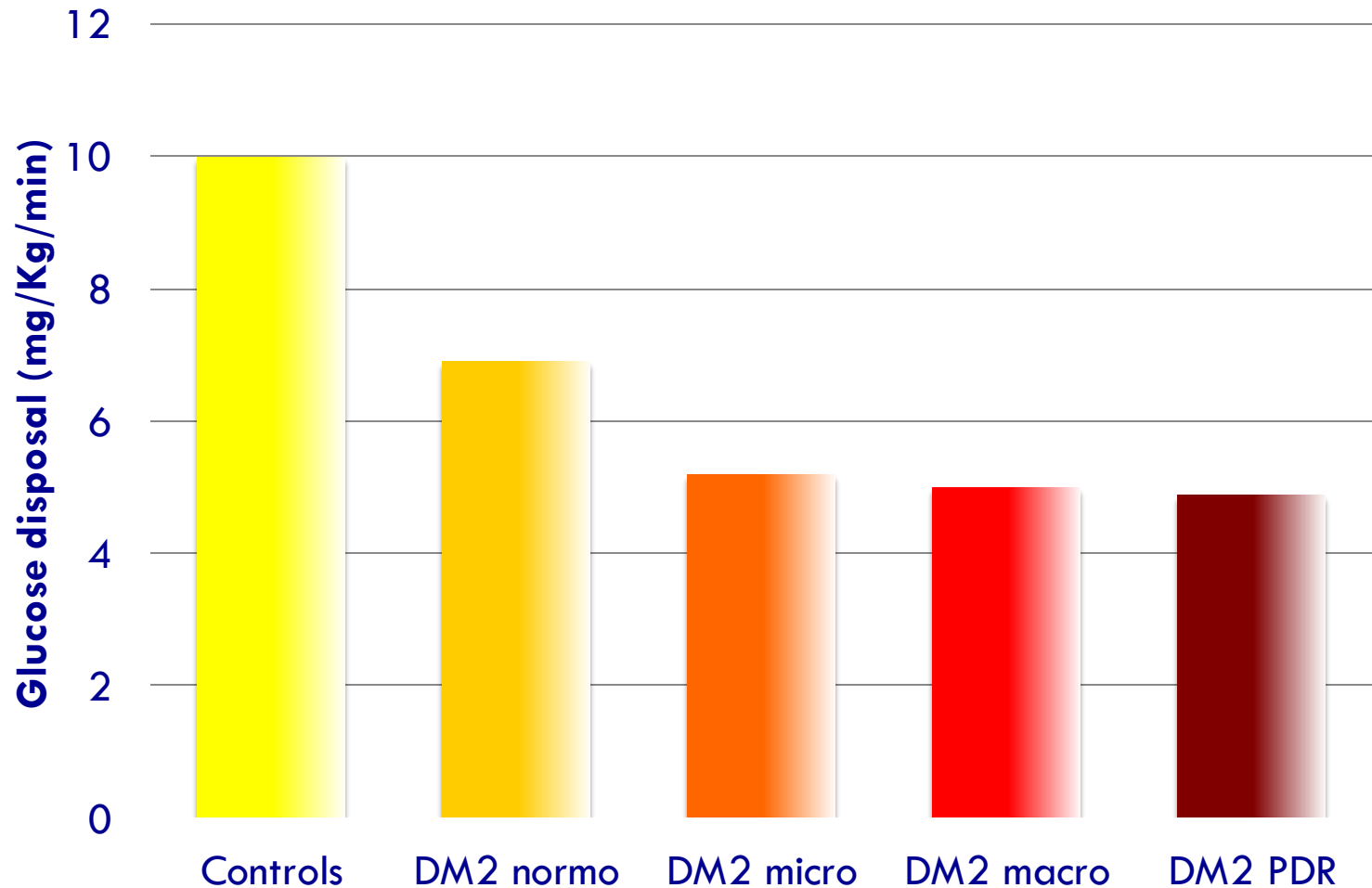
**WHAT DOES CORONARY
ARTERY DISEASE HAVE
IN COMMON WITH T2DM,
OBESITY, DYSLIPIDEMIA,
RETINOPATHY AND
HYPERTERTENSION?**

INSULIN SENSITIVITY IN THE IRS



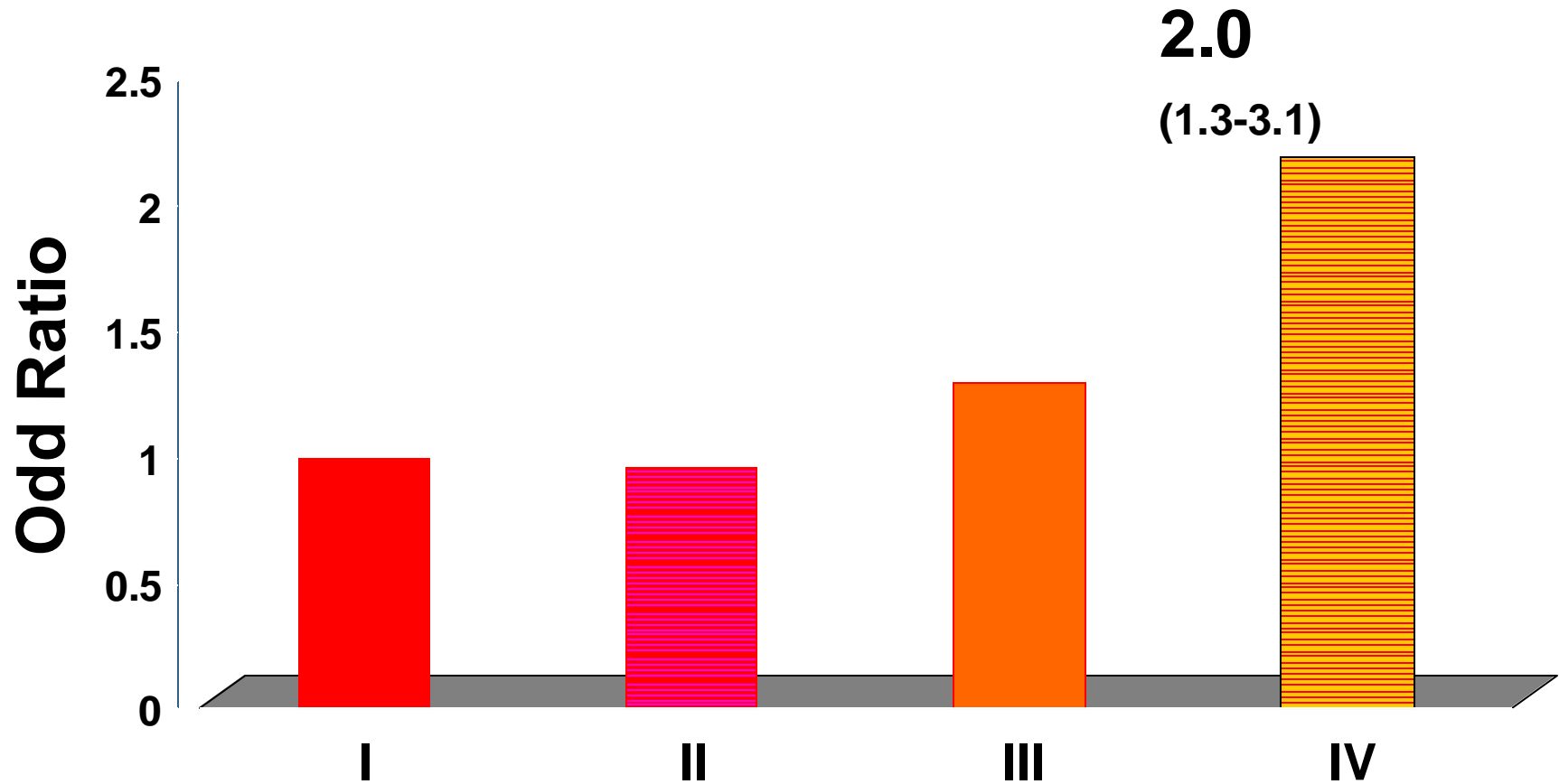
Type 2 diabetic patients with increased AER and PDR have a greater insulin resistance

R Trevisan, Diabetes 2006



Risk to develop micro-macroalbuminuria according to quartiles of HOMA_{IR}

De Cosmo et al. Diabetes Care 2005

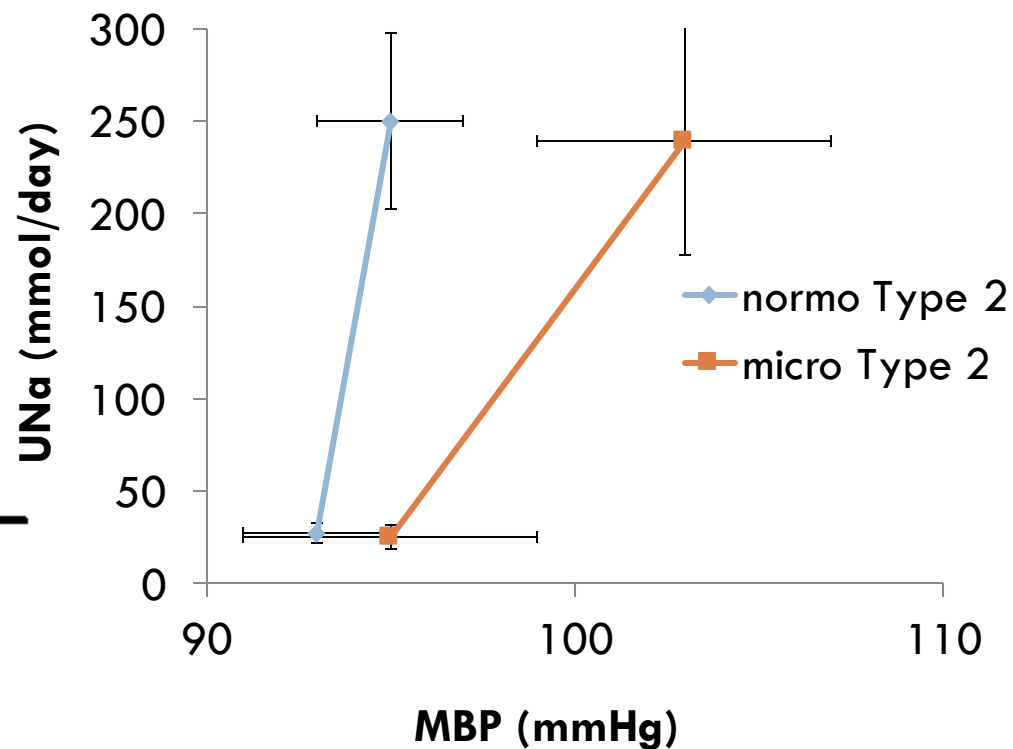
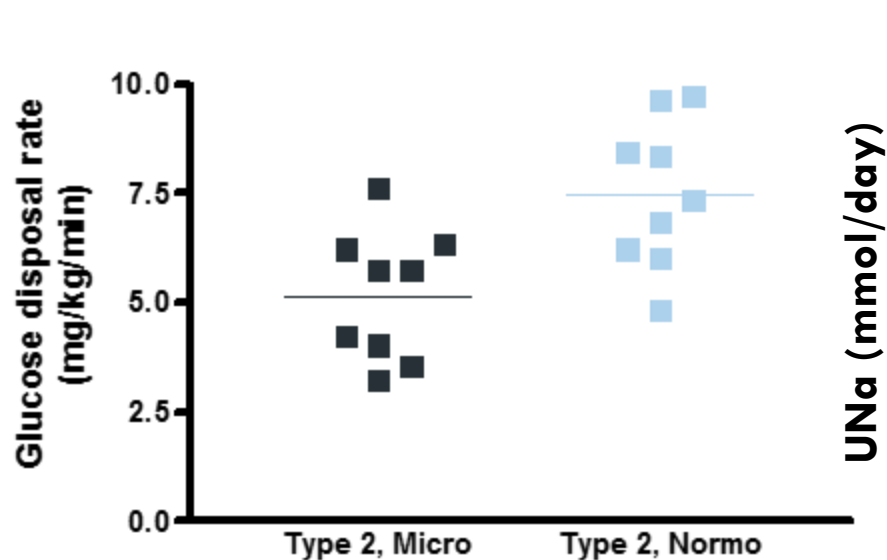


Insulin-resistance: Mechanisms of renal and cardiovascular damage

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

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

R. Trevisan, Diabetologia 2004

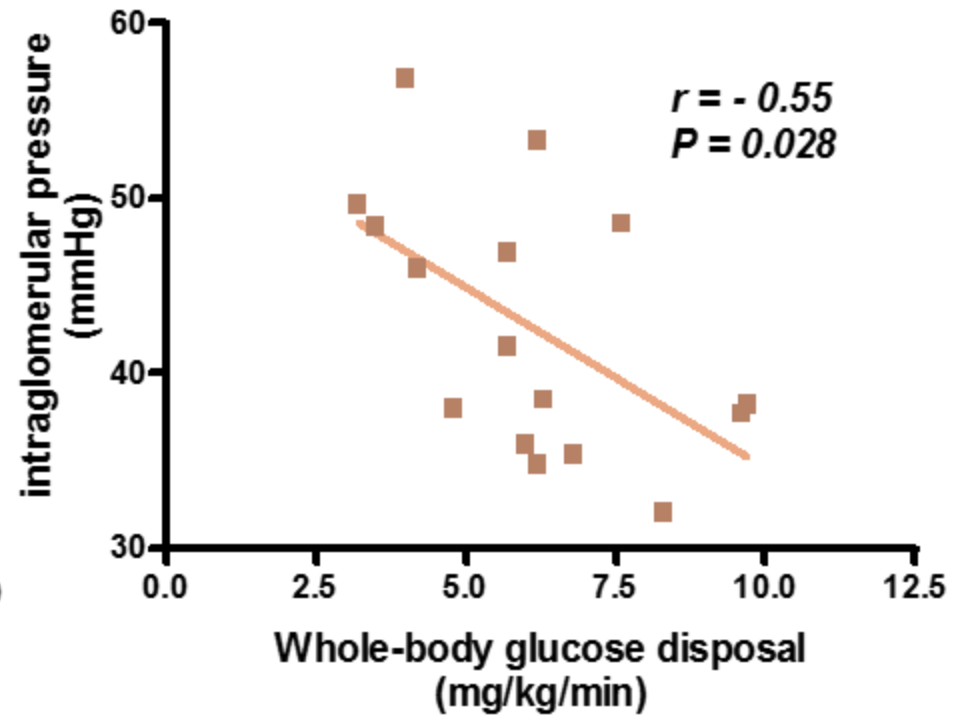
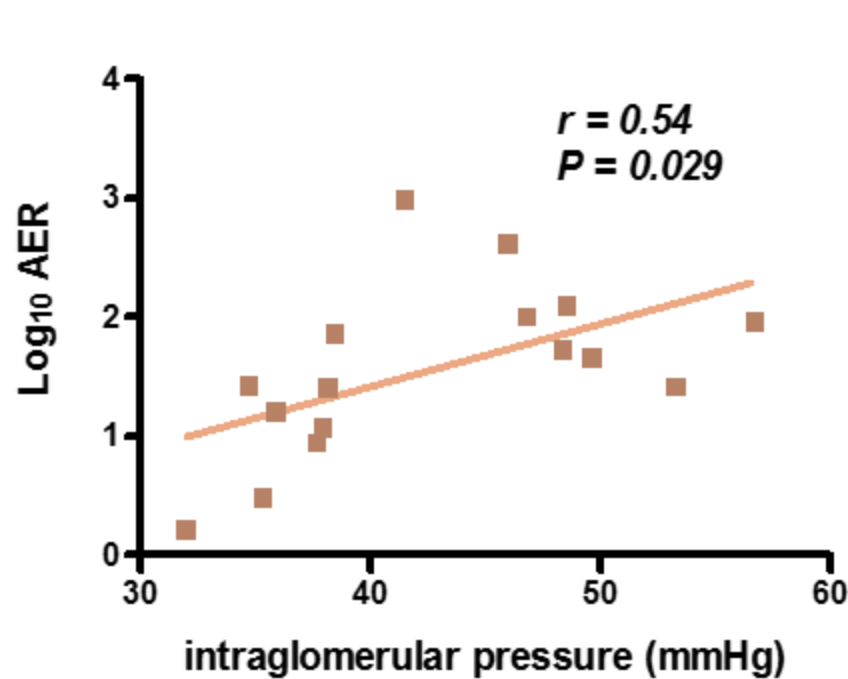


La microalbuminuria si associa alla Sodio-sensibilità

L'ALBUMINURIA E'
CORRELATA ALLA PRESSIONE
INTRAGLOMERULARE

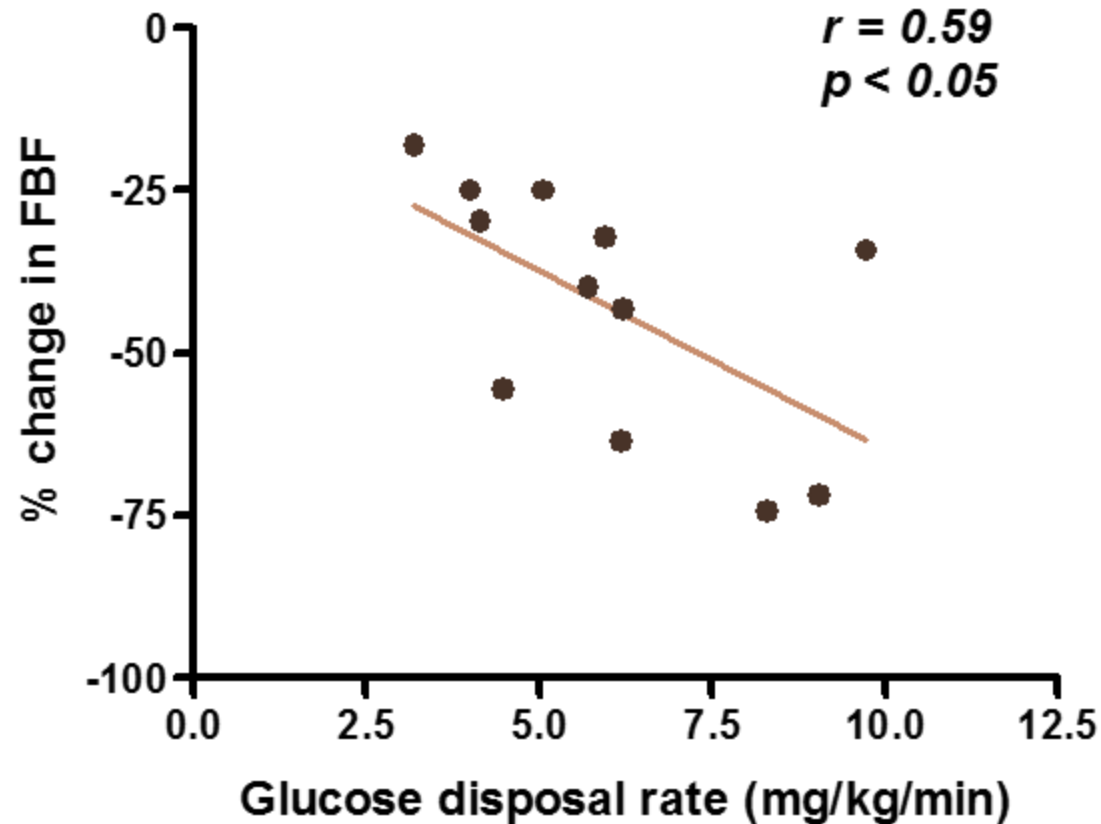
LA PRESSIONE
INTRAGLOMERULARE È
CORRELATA ALL'INSULINO-
RESISTENZA

R. Trevisan, Diabetes 2001



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

R. Trevisan, 2002



Insulin resistance is associated with a reduced NO availability

Insulin resistance contributes to increased arterial stiffness independently of blood pressure in type 2 diabetic patients

40

Arterial stiffness is increased in type 2 diabetes and in insulin resistant states

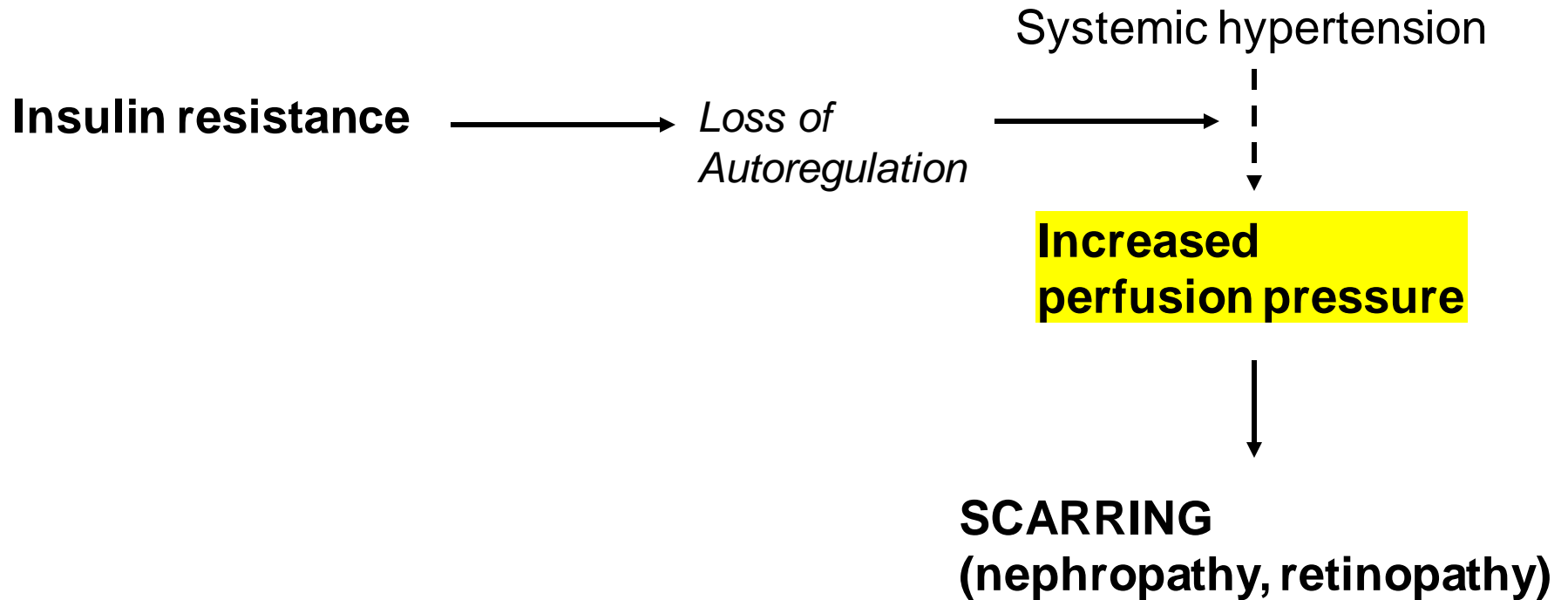
- It is an early phenomenon
- The presence of micro- and macro-vascular complications is associated with a further increase in arterial stiffness
- The consequence is a steeper increase in pulse pressure with age

Stehouwer, Diabetologia 2008, 51: 527

(mg/Kg/min)

Diabetes Care 21: 1178, 1998

A specific role for insulin resistance in the pathogenesis of target organ damage



SUMMARY: METABOLIC ETIOLOGY OF ATHEROSCLEROSIS IN T2DM

- **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**

CONCLUSIONI

- La sindrome cardio-metabolica è la principale responsabile dell'aumentato rischio cardiovascolare non solo nel paziente diabetico.
- L'insulino-resistenza è alla base della patogenesi della sindrome cardio-metabolica.