



PROGRAMMA

1° CONVEGNO NAZIONALE CONGIUNTO SIN - SID

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

RIMINI, 2 OTTOBRE 2019

**DKD: vale ancora la visione
albuminocentrica nella
progressione del danno
renale?**

No

Diapositiva preparata da GIUSEPPE PENNO e ceduta alla Società Italiana di Diabetologia.
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Giuseppe Penno

Dipartimento di Medicina Clinica e Sperimentale



UNIVERSITÀ
DI PISA



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La Malattia Renale Diabetica (DKD):

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Integrato Nefro-Diabetologico

TEAM WORK FOR WORK SUCCESS

RIMINI, 2 OTTOBRE 2019

Dichiarazione esplicita di trasparenza delle fonti di finanziamento
e dei rapporti con soggetti portatori di interessi commerciali

Il sottoscritto Dr. Giuseppe Penno

in qualità di

Moderatore

Relatore

ai sensi dell'art. 5.3 sul Conflitto di Interessi, pag. 17 del Reg.
Applicativo dell'Accordo Stato-Regioni del 5 novembre 2009,
dichiara

che negli ultimi due anni ha avuto i seguenti rapporti anche di
finanziamento con soggetti portatori di interessi commerciali in
campo sanitario:

**Alfasigma, AstraZeneca, Boehringer
Ingelheim, Eli-Lilly, Merck Sharp & Dohme,
Mundipharma Pharmaceuticals,
Novo Nordisk, Takeda**

Rimini 2 ottobre, 2019

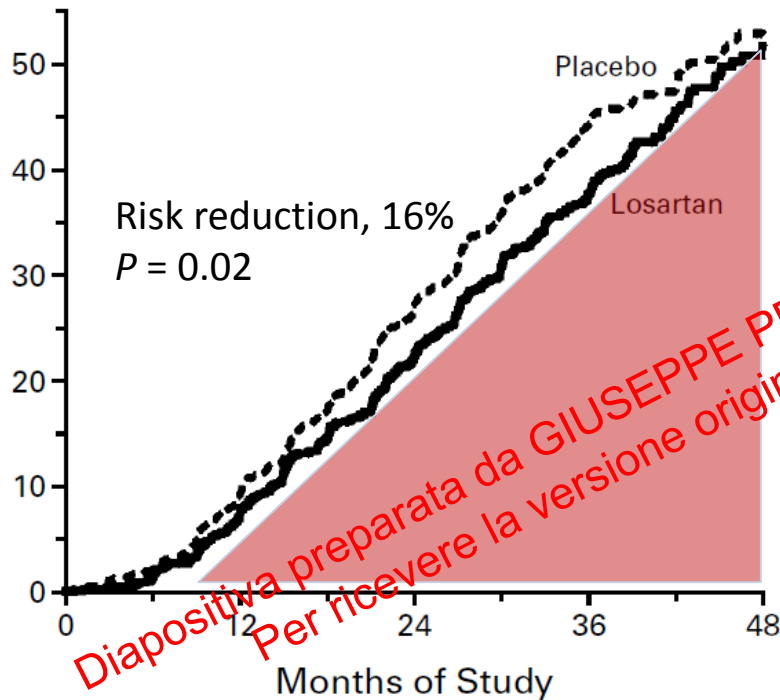
Why he is not here?



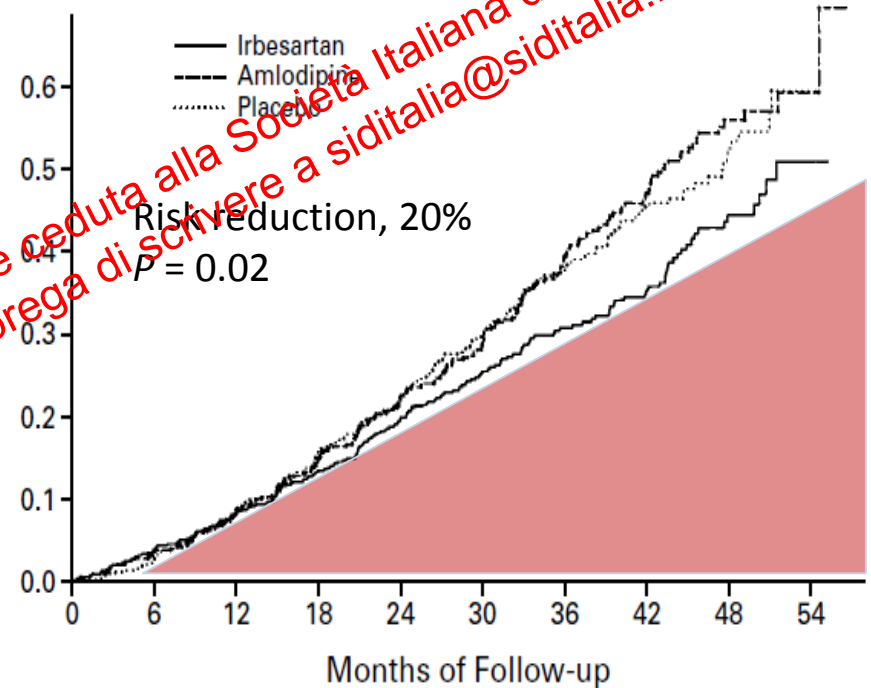
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Renal protection with blockers of the renin-angiotensin system (RAS)

The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study



The Irbesartan Diabetic Nephropathy Trial (IDNT)

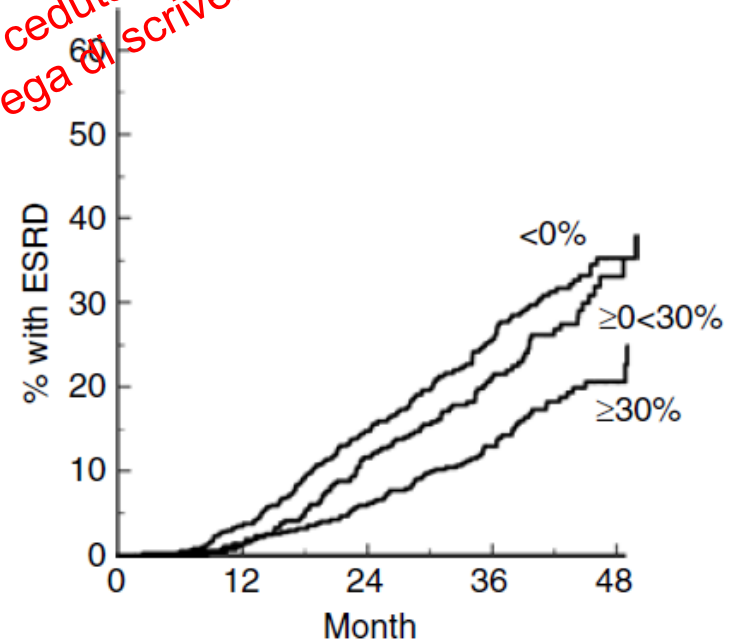
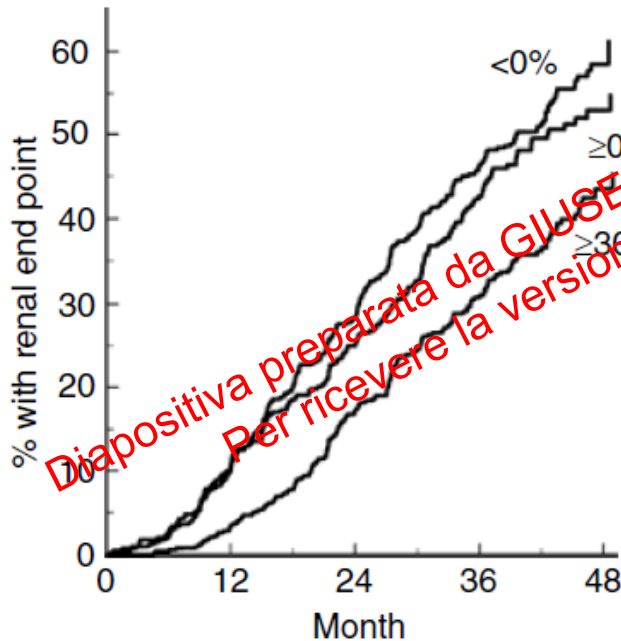


Renal composite
(doubling of serum
creatinine, ESKD, or death)

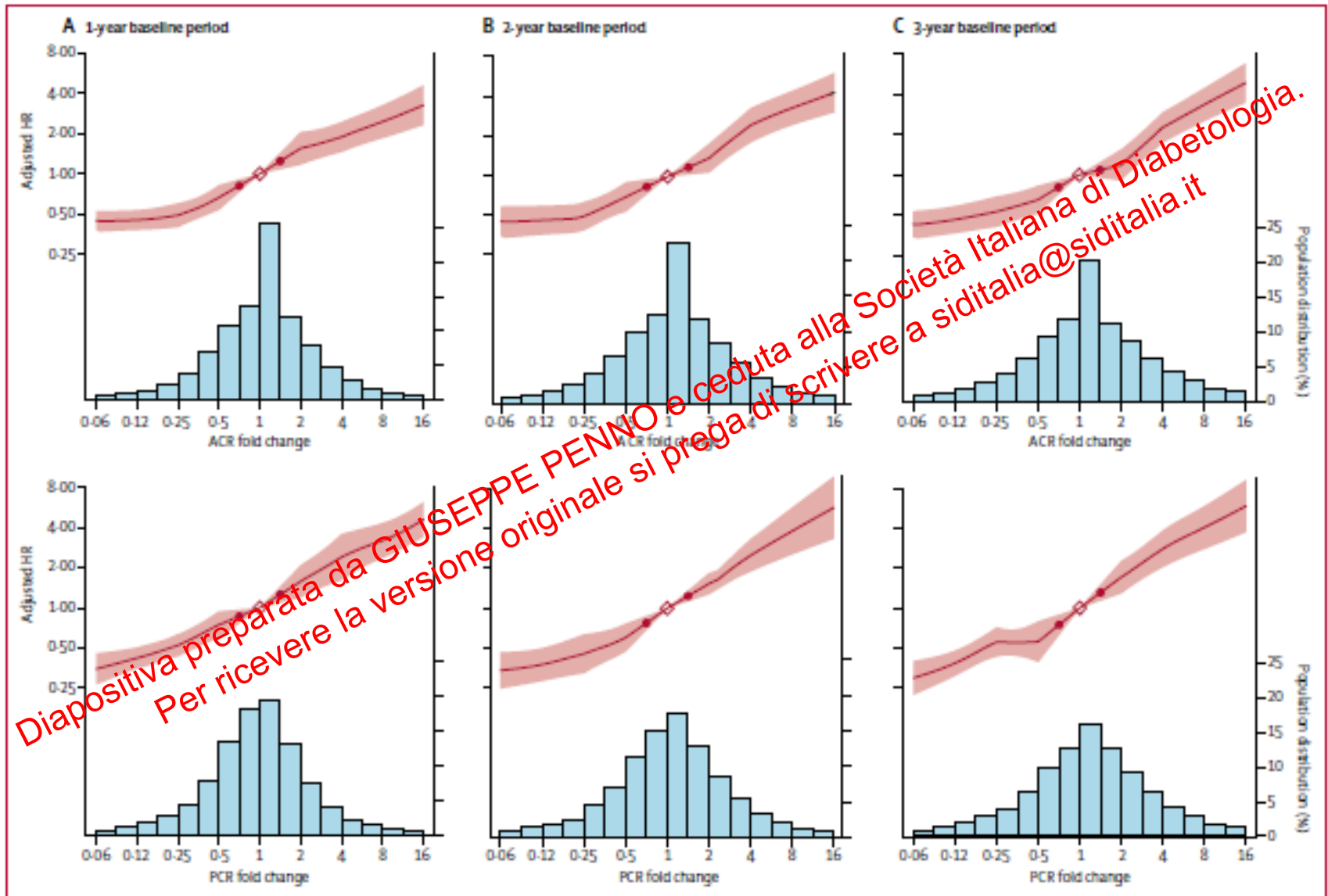
Reduction of proteinuria and renal protection with RAS blockers

The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study

	Renal end point					ESRD			
	Unadjusted		Adjusted			Unadjusted		Adjusted	
	HR	P values	HR	P values		HR	P values	HR	P values
Δ Alb: ≥0<30 vs. <0%	0.88	0.1570	0.76	0.0028	Δ Alb: ≥0<30 vs. <0%	0.86	0.1242	0.62	<.0003
Δ Alb: ≥30 vs. <0%	0.60	<.0001	0.46	<.0001	Δ Alb: ≥30 vs. <0%	0.51	<.0001	0.37	<.0001
Δ Alb: ≥30 vs. ≥0<30%	0.68	0.0003	0.61	<.0001	Δ Alb: ≥30 vs. ≥0<30%	0.62	0.0019	0.60	0.0010



Reduction of albuminuria and DKD progression



DKD IN THE ABSENCE OF ALBUMINURIA

I° CONVEGNO

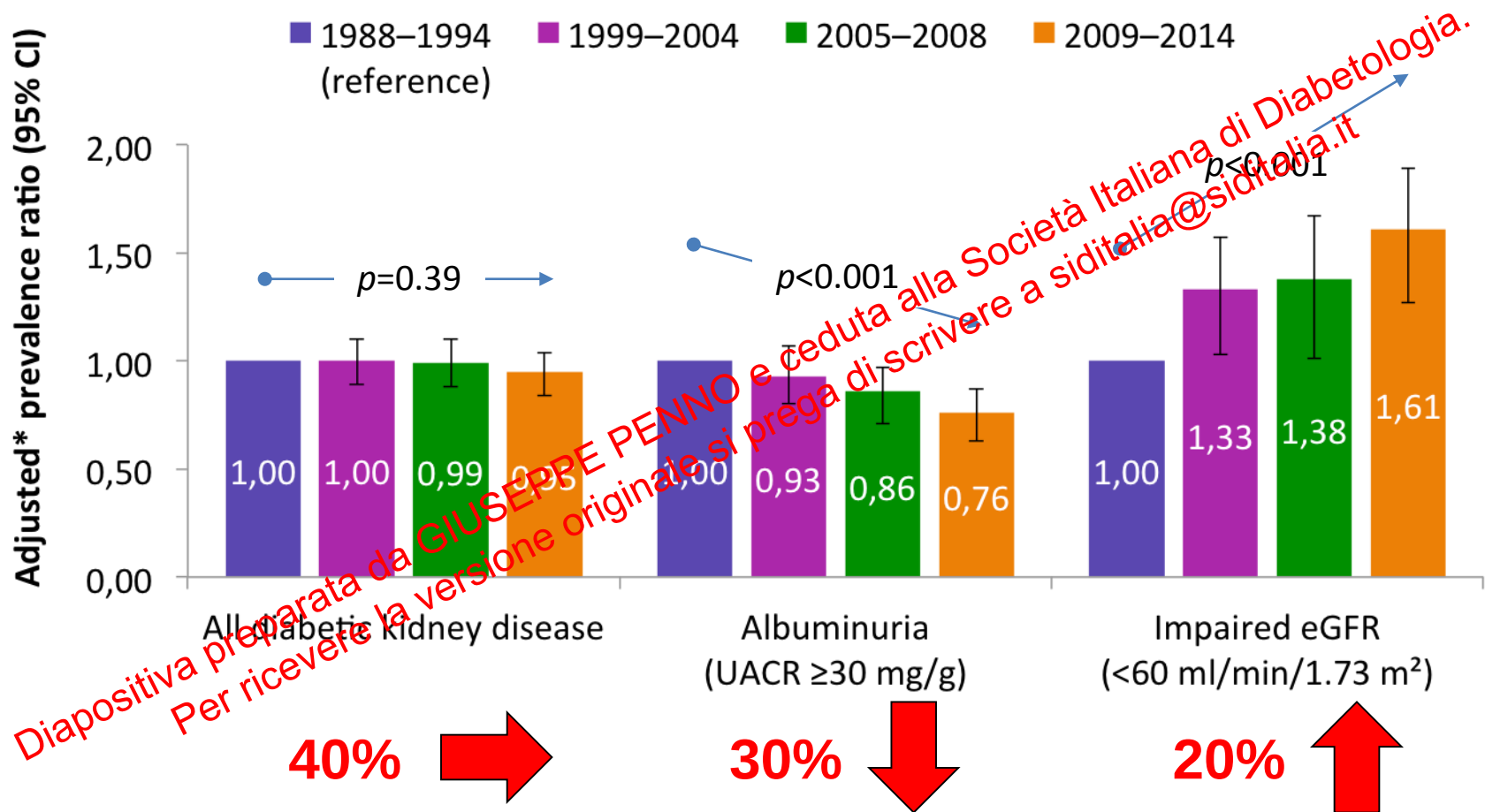
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Clinical manifestations of Kidney Disease among US Adults with Diabetes, 1988-2014

Prevalent cases of diabetic kidney disease in the United States accounting for persistence

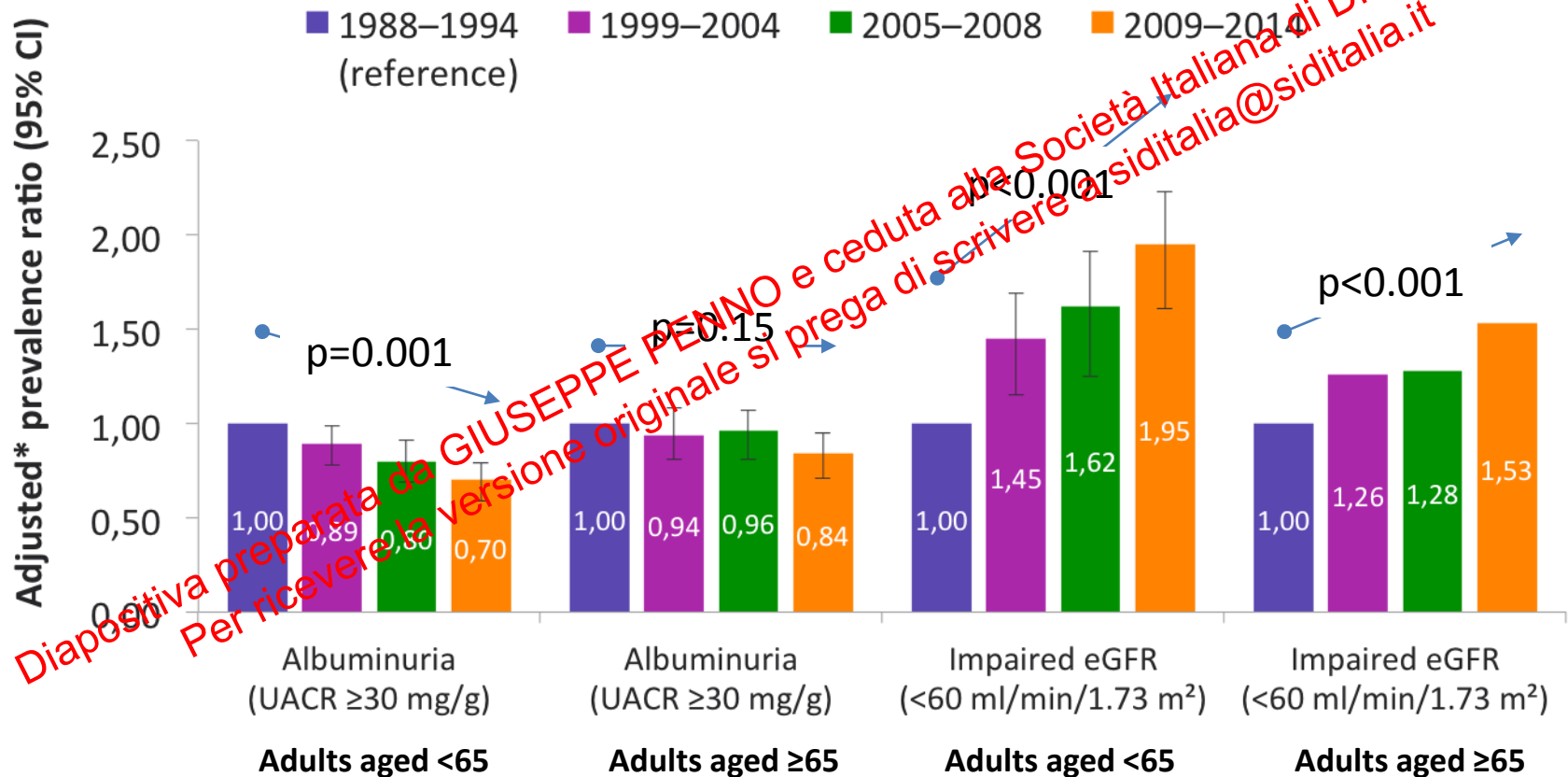


2009-2014: eGFR <30;
PR 2.86, p<0.004

*Adjusted for age, sex, and race/ethnicity. p-values are for trend
UACR, urine albumin-to-creatinine ratio

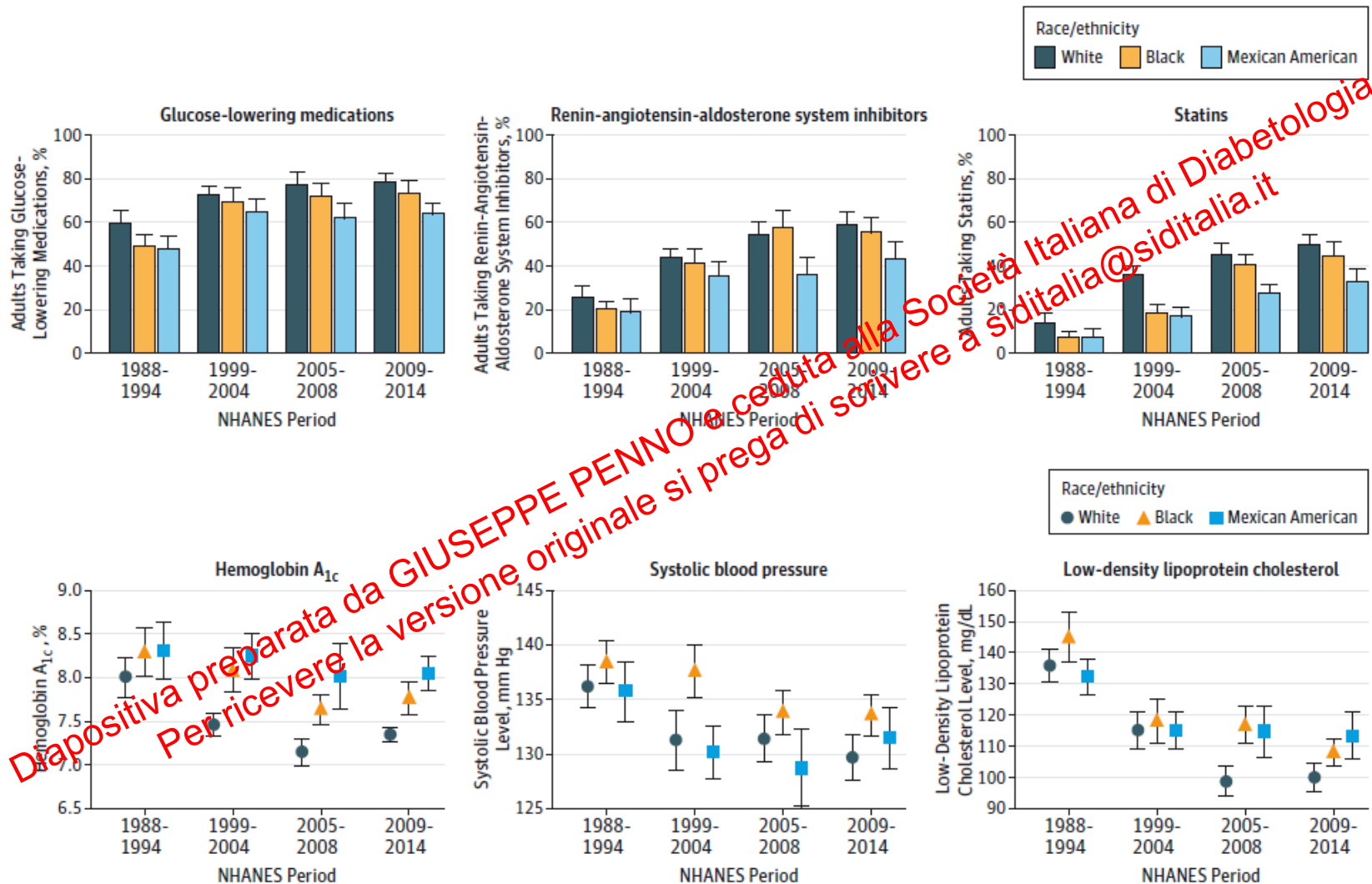
Clinical manifestations of Kidney Disease among US Adults with Diabetes, 1988-2014

Prevalent cases of albuminuria and reduced eGFR in the United States by age accounting for persistence



*Adjusted for age, sex, and race/ethnicity. p-values are for trend
UACR, urine albumin-to-creatinine ratio

Clinical manifestations of Kidney Disease among US Adults with Diabetes, 1988-2014

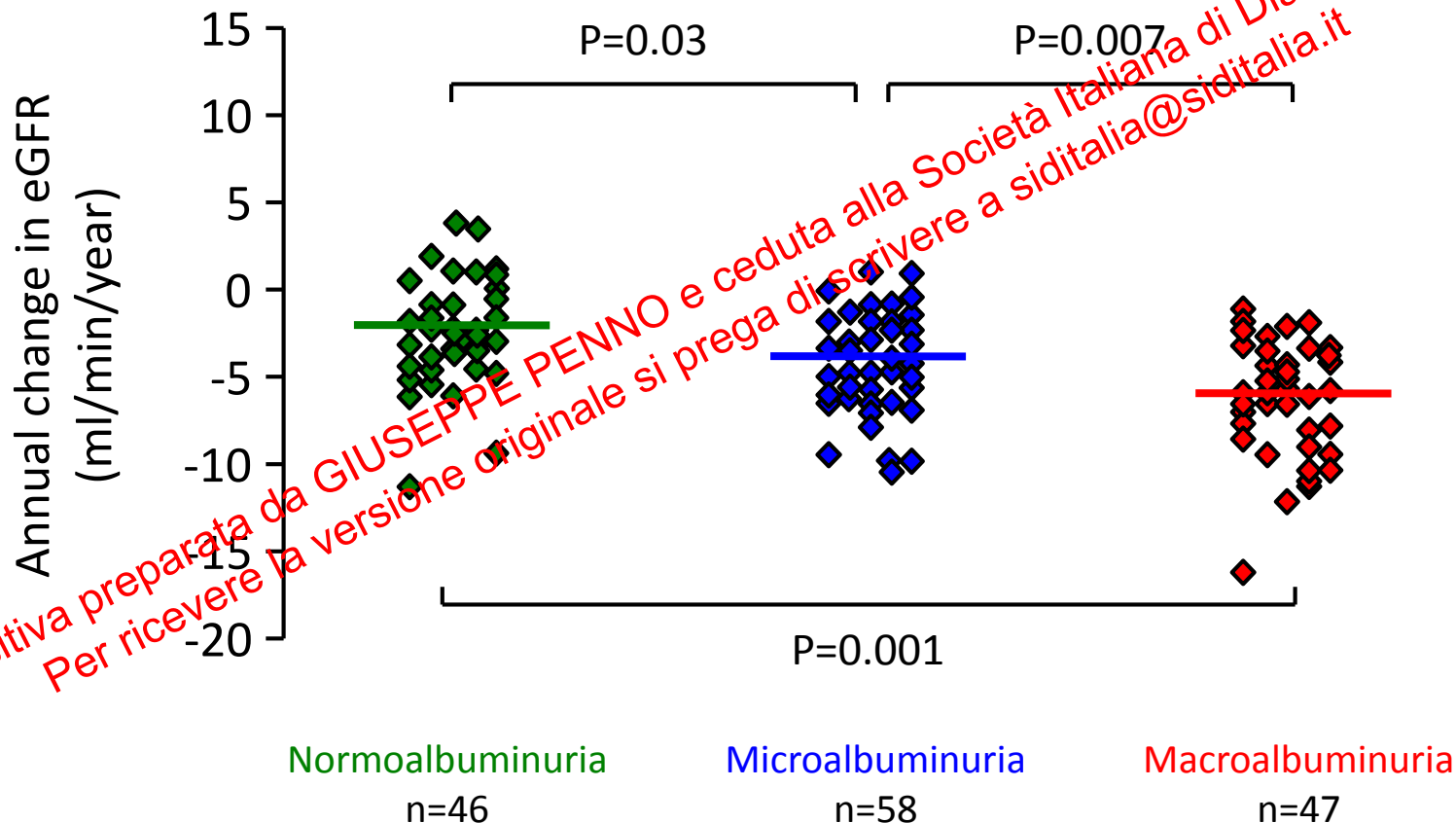


Data Source: National Health and Nutrition Examination Survey (NHANES), 2007–2012 participants aged 20 & older. Single-sample estimates of eGFR & ACR; eGFR calculated using the CKD-EPI equation.

Remission/regression of albuminuria

The Steno-2 Study

151 patients with type 2 diabetes and persistent microalbuminuria.

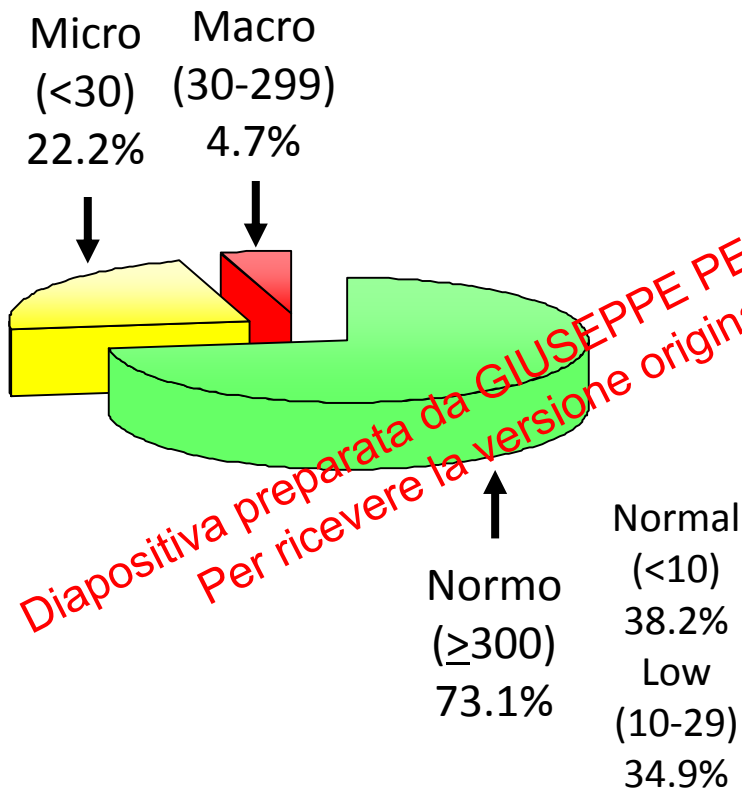


Diabetic Kidney Disease (DKD)

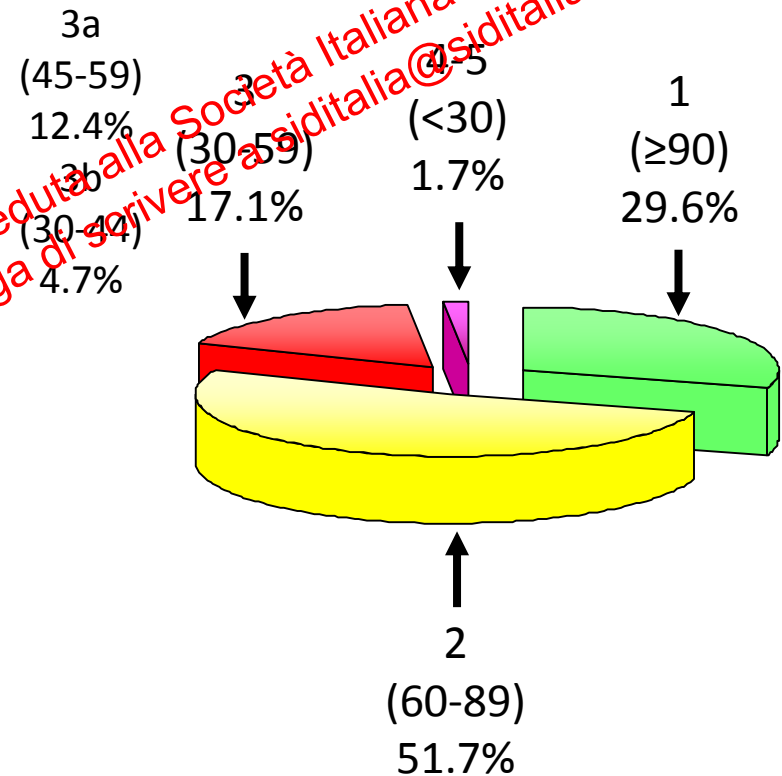
The Renal Insufficiency And Cardiovascular Events (RIACE) Study

15,773 patients with type 2 diabetes

Albuminuria (mg/24 h)

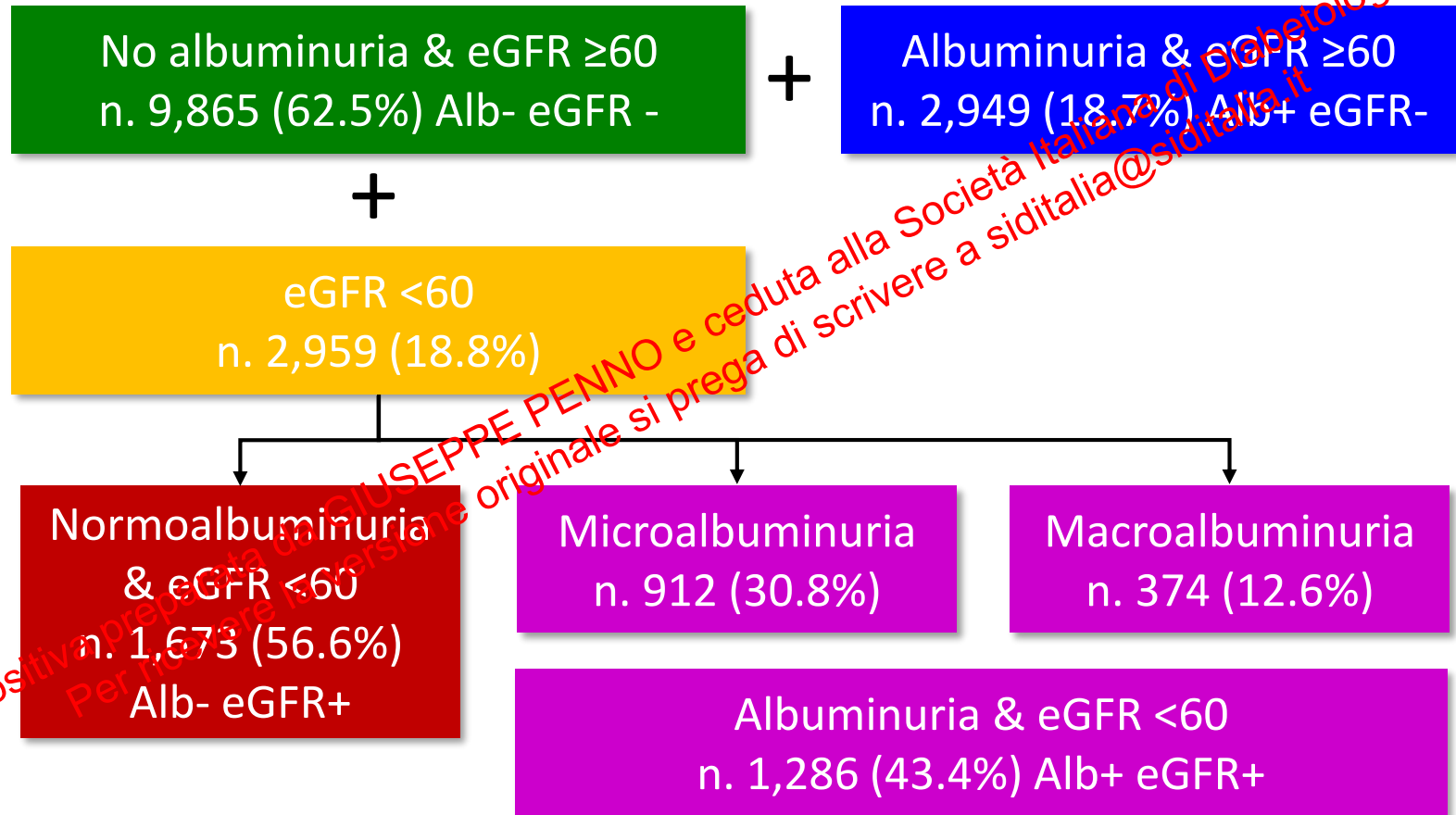


eGFR (ml/min/1.73 m²)



Diabetic Kidney Disease (DKD)

The Renal Insufficiency And Cardiovascular Events (RIACE) Study



Diabetic Kidney Disease (DKD)

The prevalence of DKD phenotypes in different populations with type 1 and type 2 DM is increasing

- **T2DM (Alb-DKD of all eGFR↓)**

- NHANES 1988-1994 = 35.1%; ➔ NHANES 2001-2008 = 51.8%
- Cross-sectional studies from several countries:

DEMAND	GLOBAL	2003	40.1%
JDDM	Japan	2004-2005	54.2%
NEFRON	Australia	2005	54.1%
RIACE	Italy	2006-2008	56.6%
Swedish National Diabetes Register	Sweden	2007	61.9%
UK National Diabetes Audit	UK	2007-2008	63.7%
AMO Annals	Italy	2009	48.2%
Gao B. et al.	China	2008-2009	69.9%
PERCEDIMED2	Spain	2011	69.4%
DPV/DIVE Registry	Germany	2010-2017	68.3%

Diabetic Kidney Disease (DKD)

The prevalence of DKD phenotypes in different populations with type 1 and type 2 DM is increasing

- **T1DM (Alb-DKD of all eGFR↓)**

- Cross-sectional studies from several countries:

FinnDiane	FINLAND	1998-2005	15.5%
Penno G. et al.	ITALY	2001-2009	58.6%
Pacilli A. et al.	ITALY	2004-2011	48.9%
Lamacchia O. et al.	ITALY	2004-2011	51.5%
UK National Diabetes Audit	UK	2007-2008	54.4%
Colombo M. et al.	Scotland	2010-2013	61.4%

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Diabetic Kidney Disease (DKD)

The Renal Insufficiency And Cardiovascular Events (RIACE) Study

10.6%

18.7%

8.2%

	Stage ≥ 3 CKD nonalbuminuric		Stages 1–2 CKD		Stage ≥ 3 CKD albuminuric	
	OR	95% CI	OR	95% CI	OR	95% CI
Age (year)	1.101	1.093–1.109	1.019	1.014–1.024	1.092	1.083–1.101
Male sex	0.444	0.392–0.503	2.089	1.891–2.308	1.365	1.182–1.576
Smoking						
Ex	–	–	0.075	0.969–1.193	–	–
Current	–	–	1.409	1.247–1.592	–	–
Diabetes duration	1.006	1.000–1.012	1.026	1.020–1.032	1.019	1.012–1.026
HbA _{1c}	–	–	1.179	1.144–1.214	1.061	1.014–1.110
BMI (unit)	1.027	1.015–1.039	1.035	1.026–1.034	1.034	1.020–1.049
Triglycerides ($\times 10$ mg/dl)	1.046	1.036–1.056	1.027	1.020–1.034	1.070	1.059–1.081
HDL-cholesterol ($\times 5$ mg/dl)	0.942	0.919–.965	–	–	0.936	0.910–.963
Lipid-lowering treatment	1.216	1.082–1.367	–	–	–	–
Hypertension	1.612	1.317–1.974	1.804	1.576–2.065	2.534	1.922–3.340
Retinopathy						
Nonadvanced	1.086	0.910–1.297	1.400	1.229–1.594	1.944	1.624–2.327
Advanced	1.447	1.184–1.769	2.252	1.953–2.597	3.927	3.261–4.730
Previous CVD	1.661	1.454–1.898	1.211	1.090–1.345	2.274	1.982–2.610

Logistic regression analysis with stepwise variable selection. Variable exclusion using the MDRD Study formula. Cholesterol. Classes of eGFR were: independent correlates of nonalbuminuric and albuminuric renal impairment (eGFR < 60 ml/min per 1.73m^2 , stage ≥ 3 CKD) and albuminuria with nonreduced eGFR (eGFR ≥ 60 ml/min per 1.73m^2 , stages 1–2 CKD) vs. no CKD (eGFR ≥ 60 ml/min per 1.73m^2 without albuminuria)

Diabetic Kidney Disease (DKD)

The Renal Insufficiency And Cardiovascular Events (RIACE) Study

18.7%

10.6%

8.2%

Variables	Stages 1–2 CKD		Stages 3–5 nonalbuminuric CKD		Stages 3–5 albuminuric CKD	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Model 1						
HbA _{1c} -MEAN, 1% increment	1.196 (1.132–1.264)	0.0001				
Model 2						
HbA _{1c} -MEAN, 1% increment	1.156 (1.089–1.228)	0.0001				
HbA _{1c} -SD, 1% increment	1.221 (1.069–1.395)	0.003			1.331 (1.097–1.613)	0.004
Model 3						
HbA _{1c} -MEAN quartiles		0.0001				
Quartile 1	1.0					
Quartile 2	1.119 (0.933–1.341)	0.227				
Quartile 3	1.140 (0.944–1.377)	0.175				
Quartile 4	1.523 (1.244–1.864)	0.0001				
HbA _{1c} -SD quartiles		0.043				0.006
Quartile 1	1.0				1.0	
Quartile 2	1.082 (0.905–1.294)	0.387			0.934 (0.711–1.228)	0.626
Quartile 3	1.139 (0.949–1.368)	0.162			1.268 (0.968–1.661)	0.084
Quartile 4	1.305 (1.080–1.578)	0.0006			1.469 (1.100–1.962)	0.009

8,260 patients with type 2 diabetes from Italy

Diabetic Kidney Disease (DKD)

Clinical features of 120,903 patients with type 2 diabetes: whole sample and divided according to the presence/absence of albuminuria or low eGFR.

RIACE



62.5%

10.6%

18.7%

8.2%

	Whole sample	Alb- and low eGFR-	Alb- and low eGFR+	Alb+ and low eGFR-	Alb+ and low eGFR+
n (%)	120 903	63 639 (52.6%)	13 660 (11.3%)	26 866 (23.8%)	14 684 (12.2%)
Male gender n (%)	70 247 (58.1)	35 822 (56.3)	5 776 (42.2)	19 874 (69.0)	8741 (59.5)
Age (years)	66.6 ± 11.0	64.1 ± 10.7	74.0 ± 8.0	65.0 ± 10.8	73.4 ± 8.5
BMI (kg/m ²)	29.7 ± 5.2	29.4 ± 5.2	29.7 ± 5.1	30.2 ± 5.3	30.0 ± 5.2
Serum creatinine (mg/dL)	1.0 ± 0.5	0.8 ± 0.2	1.3 ± 0.5	0.9 ± 0.2	1.6 ± 0.8
eGFR	75.5 ± 1.5	85.1 ± 13.2	28.0 ± 9.8	84.1 ± 14.4	42.8 ± 12.7
Known duration of diabetes (years)	11.1 ± 9.4	9.7 ± 8.6	13.3 ± 10.4	11.0 ± 9.0	15.3 ± 10.5
HbA1c (%)	7.5 ± 1.5	7.4 ± 1.5	7.4 ± 1.4	7.8 ± 1.6	7.7 ± 1.5
Total cholesterol (mg/dL)	186.6 ± 41.0	187.9 ± 40.0	185.7 ± 40.7	185.6 ± 42.3	183.4 ± 42.7
Triglycerides (mg/dL)	148.1 ± 108.2	139.4 ± 99.7	151.1 ± 87.4	157.2 ± 131.0	166.6 ± 108.1
HDL cholesterol (mg/dL)	49.2 ± 13.5	50.4 ± 13.7	49.6 ± 13.8	47.7 ± 13.2	46.5 ± 13.4
LDL cholesterol (mg/dL)	108.1 ± 34.2	110.0 ± 33.8	106.4 ± 34.1	107.1 ± 34.9	103.9 ± 34.4
SBP (mmHg)	139.6 ± 19.1	137.7 ± 18.3	139.5 ± 18.9	141.5 ± 19.5	143.8 ± 20.5
DBP (mmHg)	79.2 ± 9.8	79.1 ± 9.5	77.3 ± 9.8	80.5 ± 10.0	78.5 ± 10.3
Pulse pressure (mmHg)	60.5 ± 16.5	58.7 ± 15.7	62.3 ± 16.6	61.1 ± 16.6	65.4 ± 18.0
Retinopathy	18.6	14.2	18.5	22.4	30.5
Smokers (%)	17.6	17.5	8.8	23.8	13.4

Alb-, normoalbuminuria; Alb+, albuminuria; eGFR, estimated glomerular filtration rate; BMI, body mass index; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure All the between-group differences are statistically significant with P < 0.0001.

De Cosmo S, et al., The AMD-Annals Study Group. **Nephrol Dial Transplant**, 29: 657-662, 2014

52.6%

11.3%

23.8%

12.2%

DKD IN THE ABSENCE OF ALBUMINURIA

ALB- DKD, MORTALITY & CVD (Type 2 DM; *shortly*)

I° CONVEGNO

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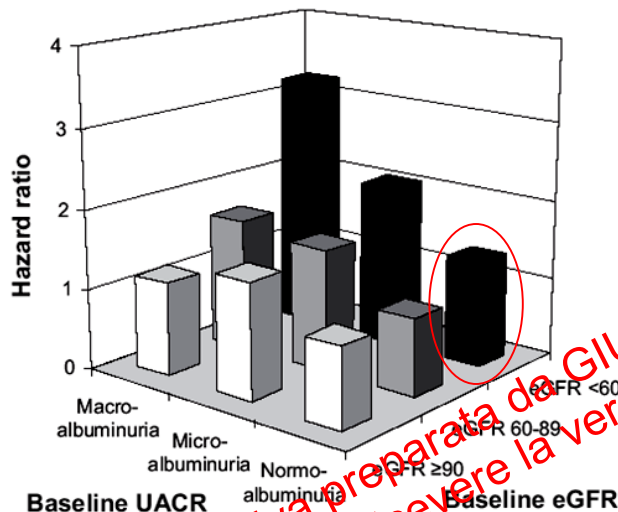
RIMINI, 2 OTTOBRE 2019

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Albuminuria and eGFR independently predict cardiovascular and renal outcomes in type 2 diabetes

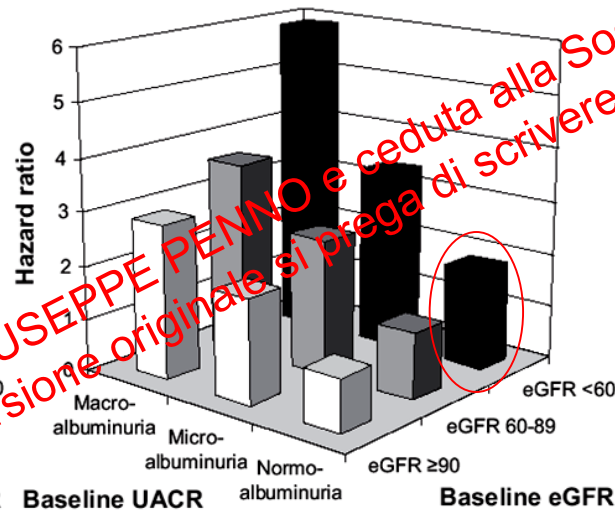
10,640 patients with type 2 diabetes, aged ≥ 55 yr, and with at least one additional risk factor for CVD enrolled in the ADVANCE study

Cardiovascular events



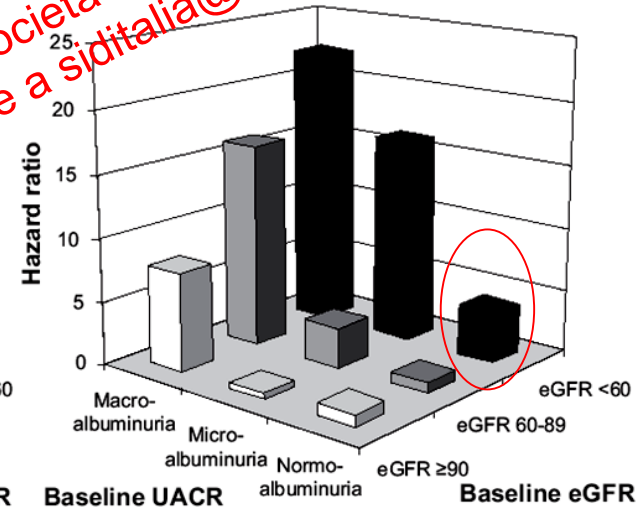
	Baseline eGFR (ml/min/1.73 m ²)		
	GFR ≥ 90	GFR 60-89	GFR <60
Baseline UACR			
Normoalbuminuria	1.00 (Reference)	0.98 (0.78-1.22)	1.33 (1.02-1.75)
Microalbuminuria	1.48 (1.09-2.01)	1.54 (1.20-1.98)	2.04 (1.54-2.69)
Macroalbuminuria	1.18 (0.52-2.69)	1.67 (1.09-2.57)	3.23 (2.20-4.73)

Cardiovascular death



	Baseline eGFR (ml/min/1.73 m ²)		
	GFR ≥ 90	GFR 60-89	GFR <60
Baseline UACR			
Normoalbuminuria	1.00 (Reference)	1.22 (0.81-1.84)	1.85 (1.17-2.92)
Microalbuminuria	1.96 (1.16-3.32)	2.52 (1.65-3.84)	3.37 (2.15-5.30)
Macroalbuminuria	2.87 (1.01-8.18)	3.61 (2.02-6.43)	5.93 (3.45-10.20)

Renal events

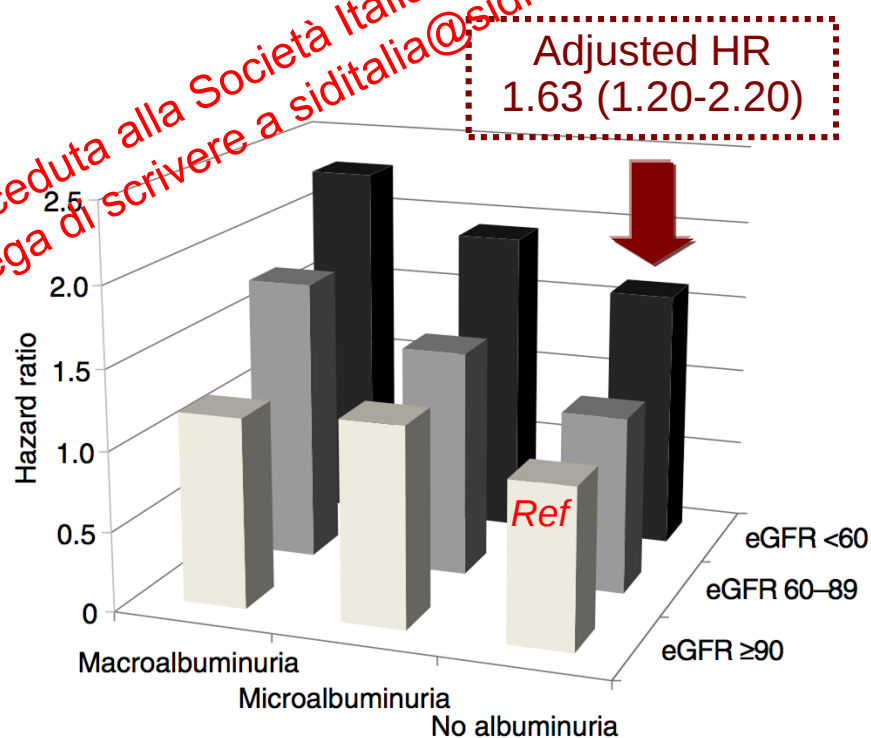
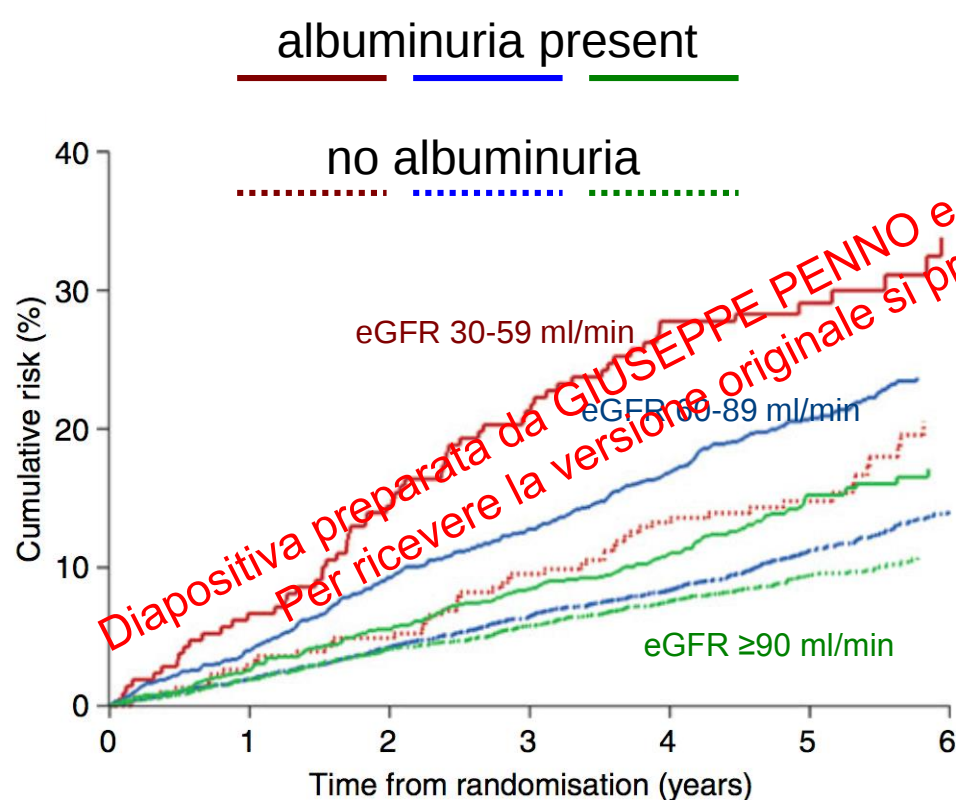


	Baseline eGFR (ml/min/1.73 m ²)		
	GFR ≥ 90	GFR 60-89	GFR <60
Baseline UACR			
Normoalbuminuria	1.00 (Reference)	0.89 (0.31-2.58)	3.95 (1.38-11.34)
Microalbuminuria	0.45 (0.05-3.83)	3.17 (1.15-8.74)	16.19 (6.16-42.54)
Macroalbuminuria	7.82 (1.51-40.53)	16.13 (5.49-47.42)	22.20 (7.62-64.72)

Albuminuria and eGFR independently predict cardiovascular events and death in type 2 diabetes

9,795 low-risk patients with type 2 diabetes enrolled in the FIELD Study

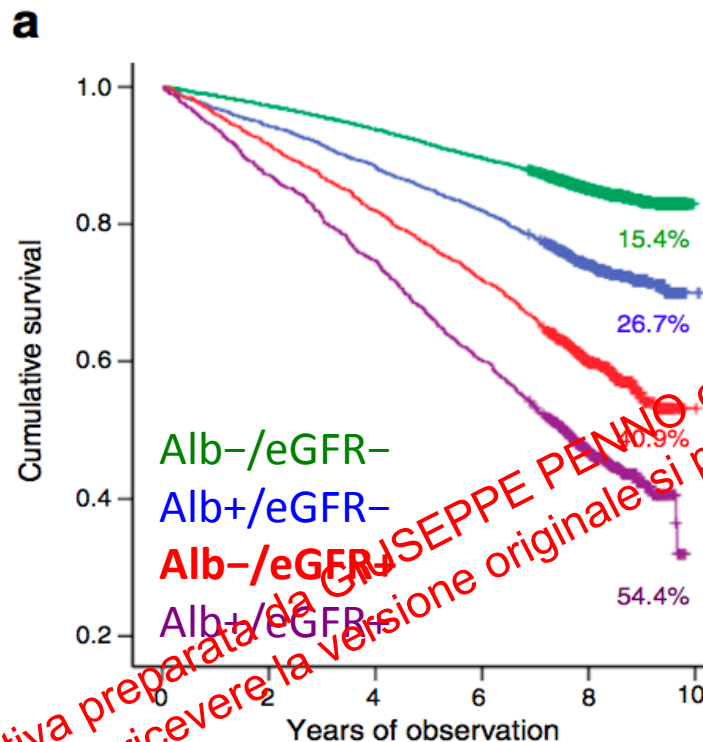
CV events (n. 1290; 13.2%, during an average follow-up of 5 yrs)



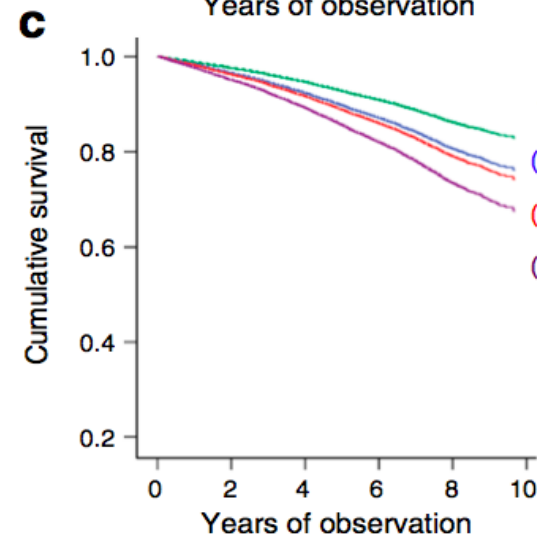
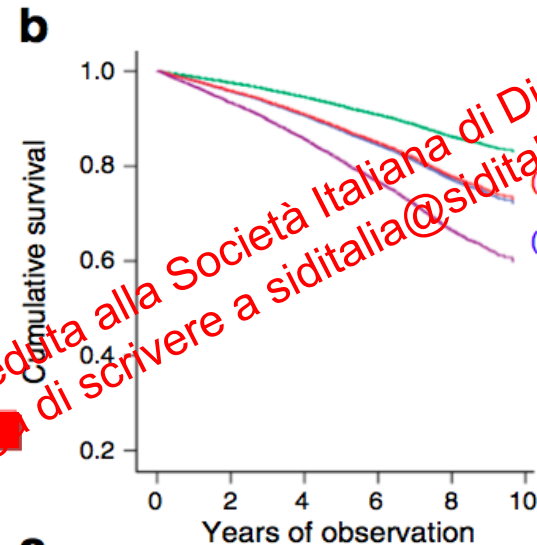
DKD phenotypes predict death in type 2 diabetes

15,656 individuals with type 2 diabetes enrolled in the RIACE Study

Deaths (n. 3602; 23.0%, during an average follow-up of 7.4 yrs)



No. at risk						
All	15,656	14,926	14,110	13,179	8243	3
Alb-/eGFR-	9984	9707	9362	8949	5761	0
Alb+/eGFR-	2966	2795	2619	2430	1535	1
Alb-/eGFR+	1476	1352	1210	1060	558	2
Alb+/eGFR+	1230	1072	919	740	389	0



Albuminuria and eGFR independently predict death in type 2 diabetes

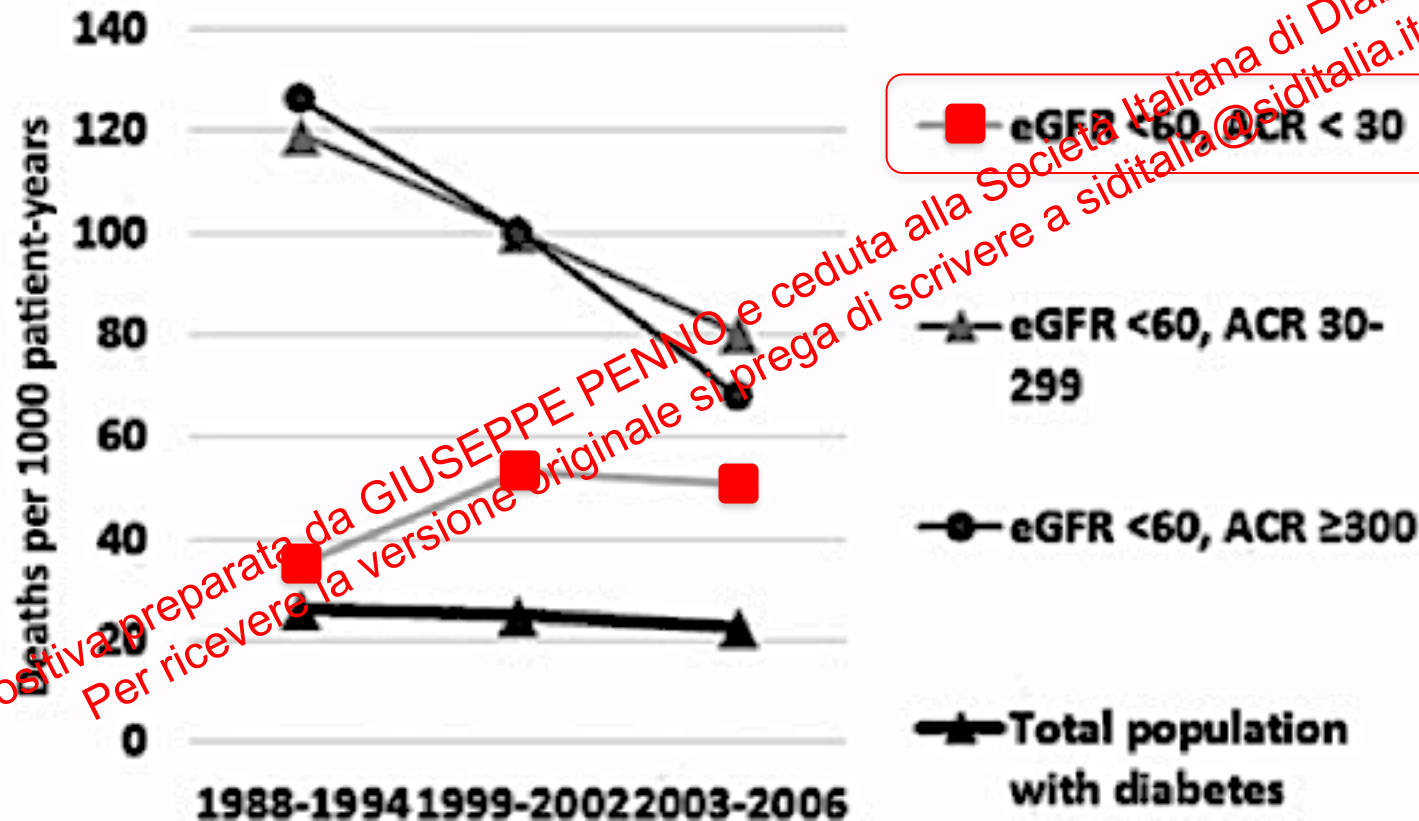
15,656 individuals with type 2 diabetes enrolled in the RIACE Study

Deaths (n. 3602; 23.0%, during an average follow-up of 7.4 yrs)

KDIGO category	A1a	A1b	A2	A3
G1	1 (Ref.)	0.94 (0.78, 1.12)	1.21 (1.08, 1.36)	2.19 (1.55, 3.11)
G2a	0.80 (0.67, 0.96)	1.05 (0.89, 1.25)	1.31 (1.09, 1.58)	2.48 (1.82, 3.38)
G2b	1.10 (0.83, 1.42)	1.06 (0.88, 1.27)	1.39 (1.15, 1.68)	1.71 (1.23, 2.36)
G3a	1.32 (1.07, 1.62)	1.39 (1.14, 1.69)	1.48 (1.22, 1.80)	2.26 (1.71, 3.00)
G3b	1.85 (1.40, 2.44)	2.25 (1.79, 2.82)	2.09 (1.69, 2.59)	2.78 (2.14, 3.63)
G4-5	1.61 (0.88, 2.97)	2.25 (1.49, 3.37)	2.79 (2.09, 3.70)	4.66 (3.59, 6.05)

Increasing mortality in adults with diabetes and eGFR in the absence of albuminuria

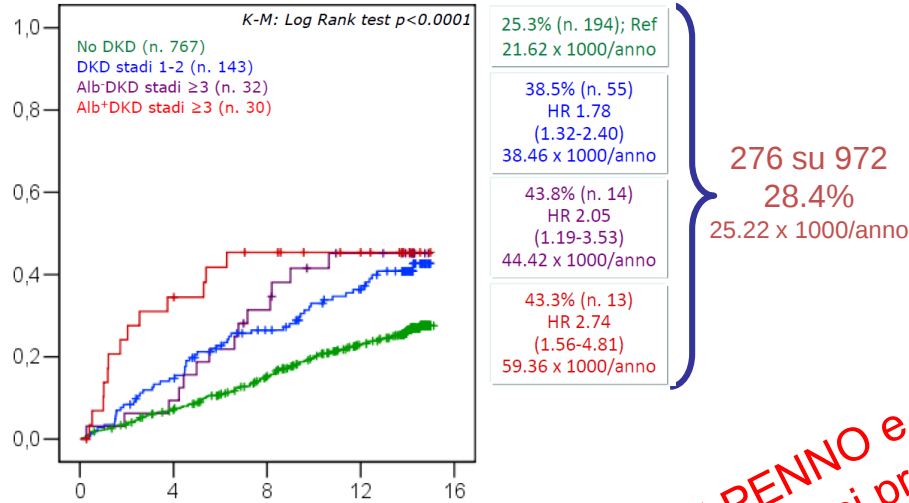
Adults with an eGFR <60 mL/min/1.73 m² and an ACR <30 mg/g increased from 6.6% of the total population with diabetes during years 1988–1994 to 10.1% of the total population with diabetes during years 2007–2010.



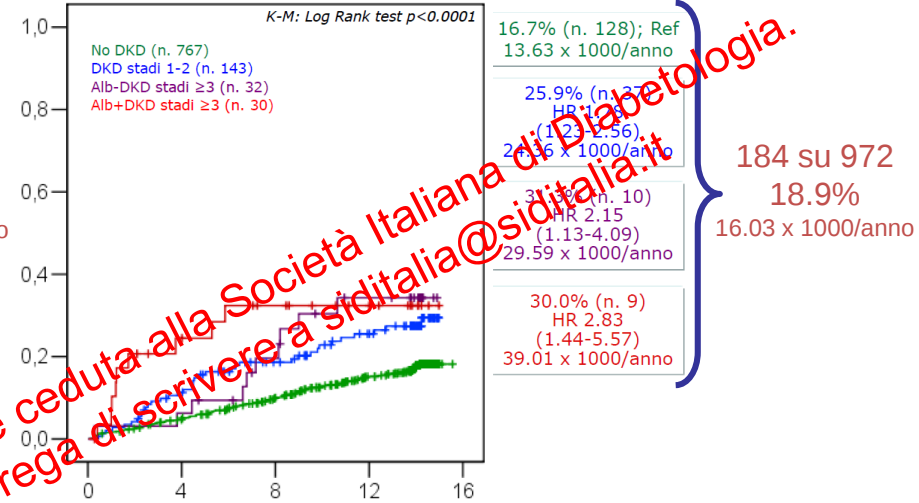
Optimal management strategies are needed to reduce mortality in those with a low eGFR and an ACR <30 mg/g.

Kaplan-Meier curves showing incidence of vascular outcomes by DKD phenotypes: 972 T2DM subjects, follow-up 11.3 ± 4.4 years

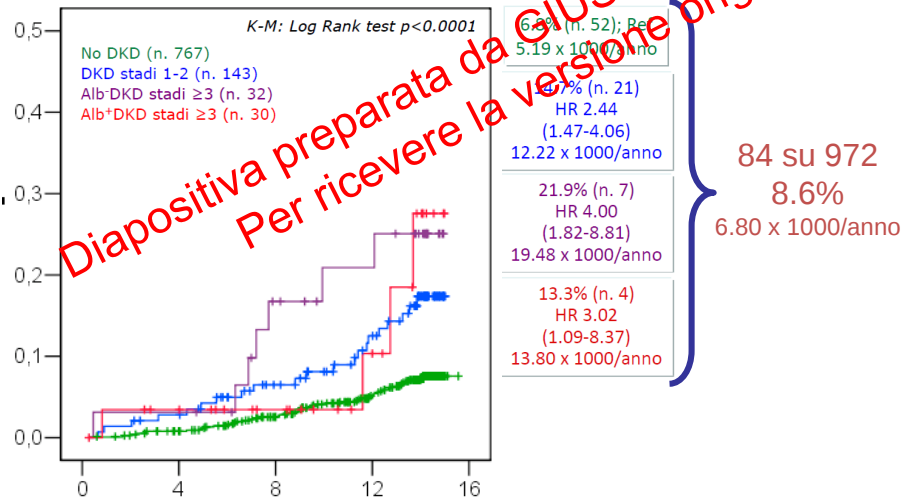
Major CV events



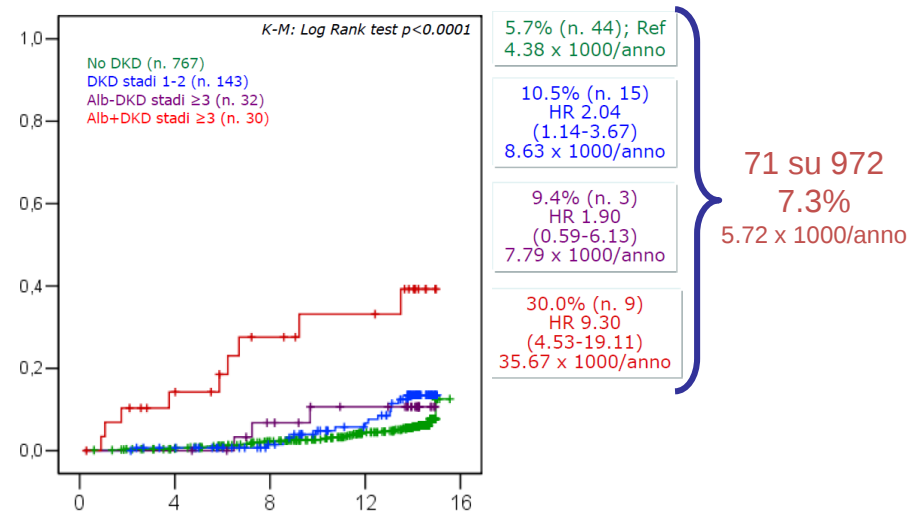
Coronary events



Heart failure



ESRD



Follow-up, years

Garofolo M. et al, unpublished data

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The RIACE (Renal Insufficiency and Cardiovascular Events) Italian Multicenter Study

Logistic regression analysis of CVD events by vascular bed with CKD phenotypes as covariates

Variable	Coronary events	Cerebrovascular events	Peripheral events
Retinopathy			
Absent	—	1.0	1.0
Nonadvanced	—	1.37 (1.17–1.62)	1.71 (1.41–2.06)
Advanced	—	0.88 (0.72–1.08)	2.52 (2.07–3.07)
CKD phenotype			
No CKD	1.0	1.0	1.0
Stages 1–2 CKD	0.901 (0.794–1.022)	1.41 (1.20–1.65)	1.51 (1.25–1.82)
Nonalbuminuric stage ≥ 3 CKD	1.514 (1.304–1.757)	1.22 (1.01–1.48)	1.40 (1.11–1.76)
Albuminuric stage ≥ 3 CKD	1.270 (1.083–1.490)	1.69 (1.40–2.00)	1.88 (1.52–2.34)

Results are presented as OR (95% CI). Variables excluded: HbA_{1c}, BMI, OHA, oral hypoglycemic agent.

DKD IN THE ABSENCE OF ALBUMINURIA

ALB- DKD, MORTALITY & CVD (Type 2 DM; *shortly*)

ALB- DKD, MORTALITY & CVD (Type 1 DM; *shortly*)

I° CONVEGNO

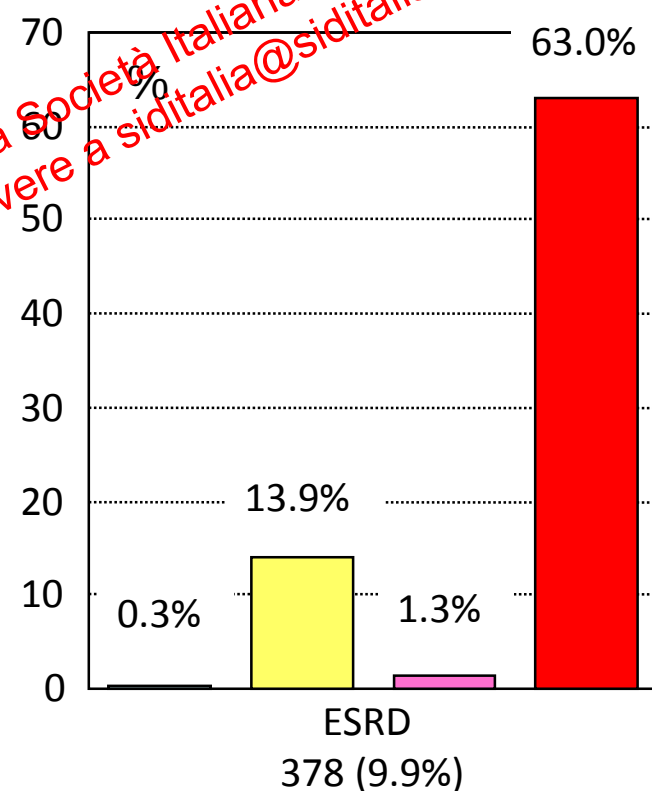
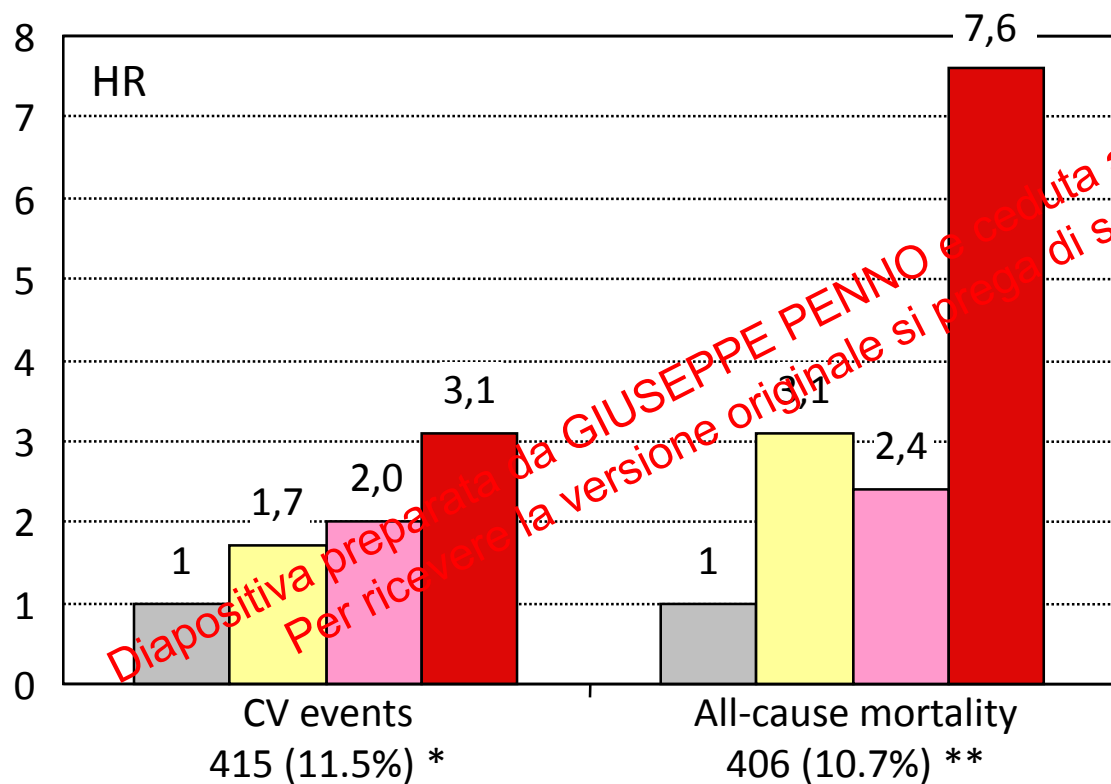
La Malattia Renale Diabetica (DKD):
Presente e Futuro dell'Approccio
Integrato Nefro-Diabetologico
TEAM WORK FOR WORK SUCCESS

RIMINI, 2 OTTOBRE 2019

Diapositiva preparata da GIUSEPPE PENNO e ceduta alla Società Italiana di Diabetologia.
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The presence and consequence of nonalbuminuric chronic kidney disease in patients with type 1 diabetes

Development of ESRD, CV events and all-cause mortality during 13 years of median follow-up

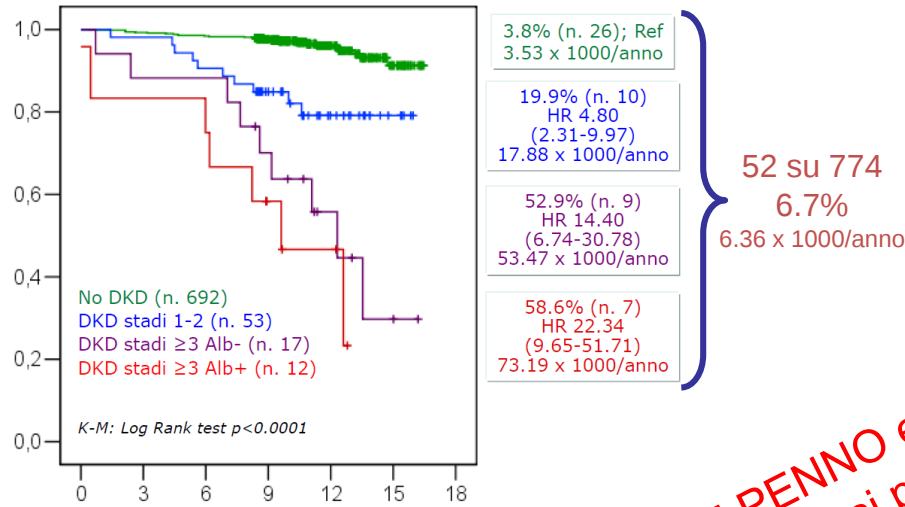


* Adjusted for sex, age, BMI, sBP, HbA1c, non-HDL cholesterol, history of retinal laser tx, and current smoking;

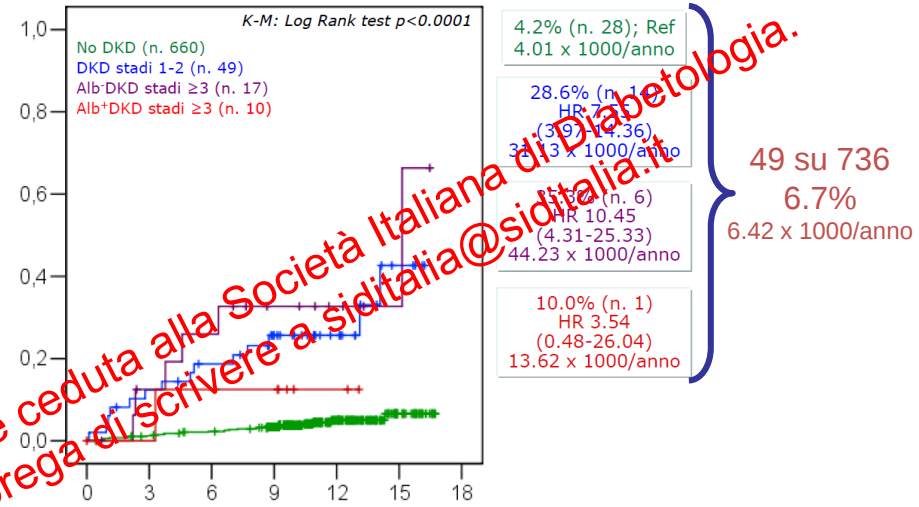
** Adjusted for age

Kaplan-Meier curves showing incidence of vascular outcomes by DKD phenotypes: 736 T1DM subjects, follow-up 10.4 ± 2.9 years

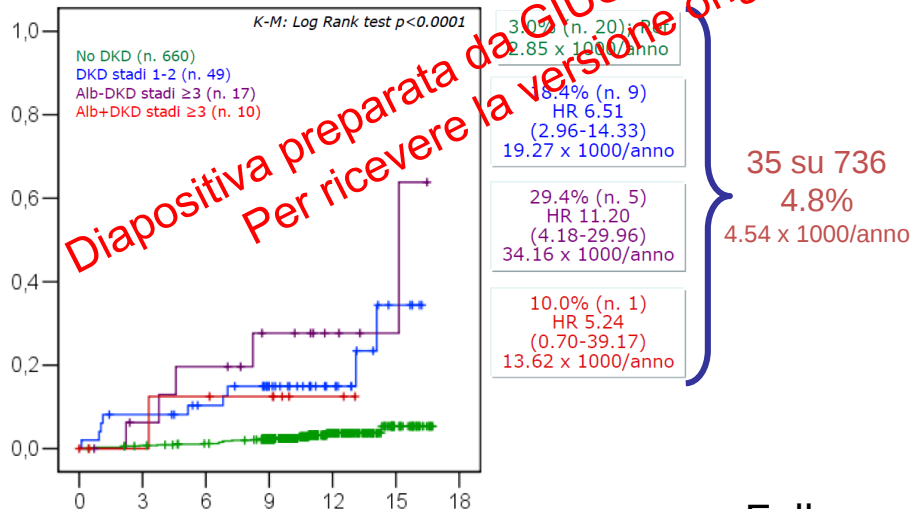
All-cause death *



Major CV events



Coronary events



Follow-up, years

Garofolo M. et al., **J Diabetes Complications** 32: 550-557, 2018*
& unpublished data

DKD IN THE ABSENCE OF ALBUMINURIA

ALB- DKD, MORTALITY & CVD (Type 2 DM; *shortly*)

ALB- DKD, MORTALITY & CVD (Type 1 DM; *shortly*)

PROGRESSION TO ALB- DKD (Type 1 DM)

I° CONVEGNO

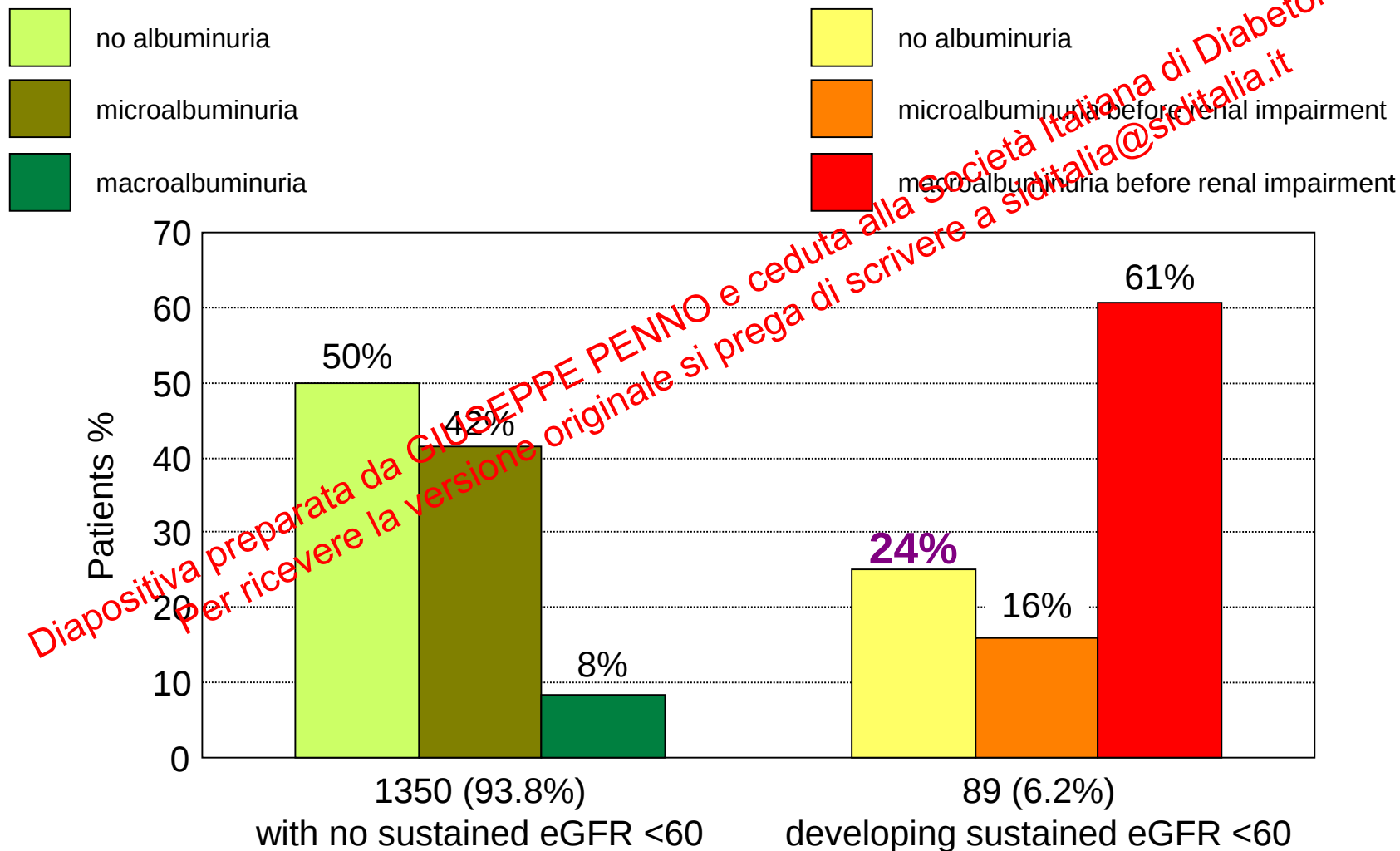
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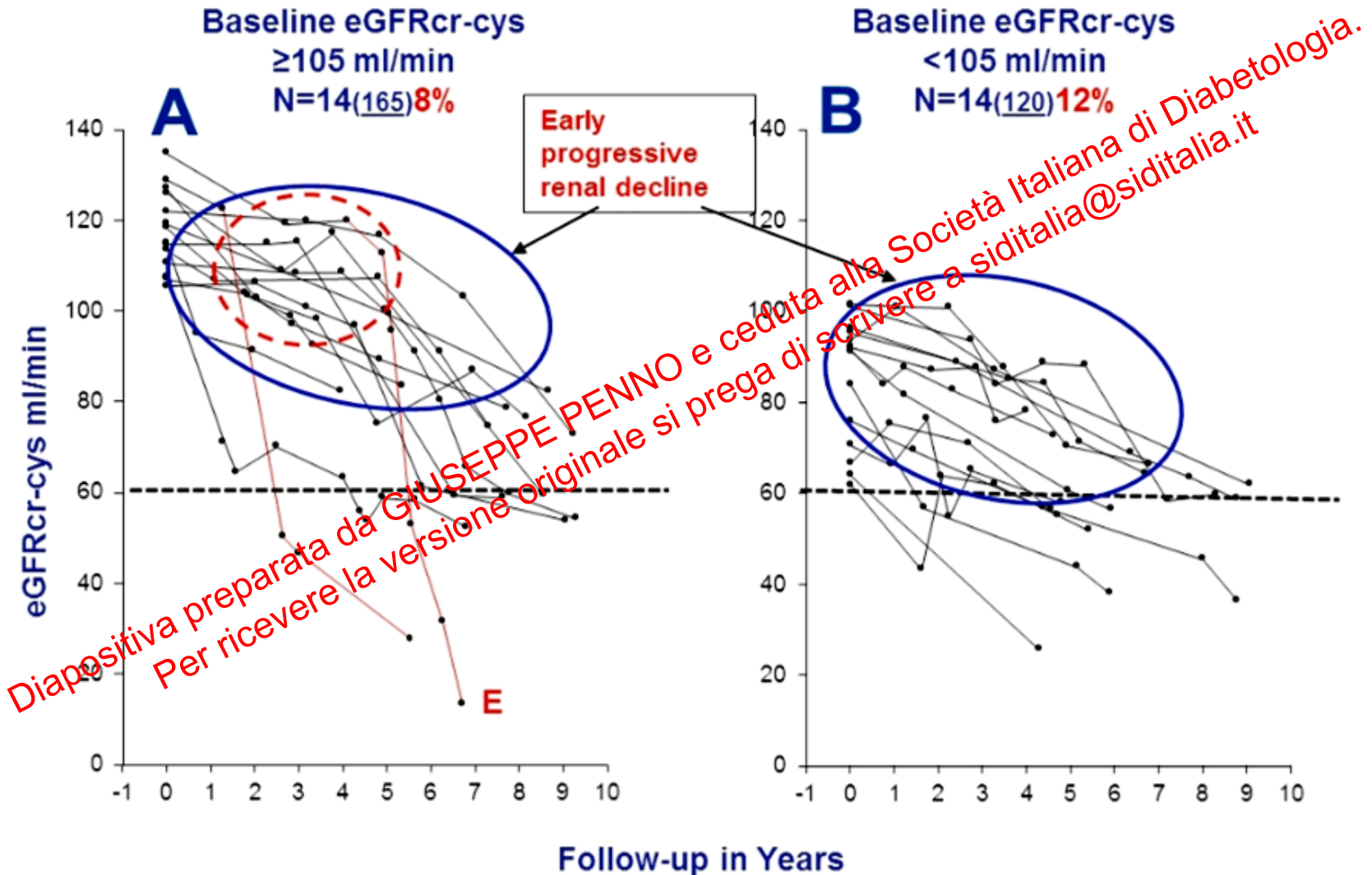
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Challenging conventional paradigms: Diabetic kidney disease with and without albuminuria

DCCT/EDIC; 1439 type 1 DM patients
followed over a median of 19 years



Early Progressive Renal Decline was observed in 10% of 280 T1D patients with Normoalbuminuria during 6-10 years of follow-up.



Krolewski AS et al., Early progressive renal decline precedes the onset of microalbuminuria and its progression to macroalbuminuria. **Diabetes Care** 37: 226-234, 2014.

Progression and categories of progression of eGFR decline in patients with **T1DM** according to strata of albuminuria at entry into follow-up. *At entry, eGFR was normal in all patients.*

Patients from the First and Second Joslin Kidney Studies in T1DM: 6-10 years of follow-up				
eGFR decline per ml/yr	Normo-albuminuria %	Micro-albuminuria %	Macro-albuminuria %	Total %
<2.9	91%	78%	49%	81%
3-4.9	6%	11%	16%	8%
5-9.9	9% 2%	22% 7%	51% 19%	19% 7%
>10	1%	4%	16%	4%
Total (n)	932	525	275	1,732

Patients from the SDRN T1BIO in Scotland: 11.6 years of observation*				
eGFR decline per ml/yr	Normo-albuminuria %	Micro-albuminuria %	Macro-albuminuria %	Total %
at least 3.0	10.7%	20.7%	54.5%	12,2%
Total (n)	4,870	422	93	5,385

Progressive Renal Decline. The New Paradigm of Diabetic Nephropathy in Type 1 Diabetes.

At entry, in a subgroup, eGFR was 30-59 ml/min/1.73 m².

Patients from the Second Joslin Kidney Studies in T1DM: 4-10 years of follow-up		
Frequency of decliners (eGFRcr-cys ≥3.3%/year)		
eGFRcr-cys, ml/min	Normo-albuminuria	Micro-albuminuria
≥90	505 (7%)	329 (24%)
60-89	71 (18%)	106 (40%)
30-59	19 (21%)	78 (48%)
All	595 (10%)	513 (32%)

DKD IN THE ABSENCE OF ALBUMINURIA

ALB- DKD, MORTALITY & CVD (Type 2 DM; *shortly*)

ALB- DKD, MORTALITY & CVD (Type 1 DM; *shortly*)

PROGRESSION TO ALB- DKD (Type 1 DM)

PROGRESSION TO ALB- DKD (Type 2 DM)

I° CONVEGNO

La Malattia Renale Diabetica (DKD):

Presente e Futuro dell'Approccio
Integrato Nefro-Diabetologico

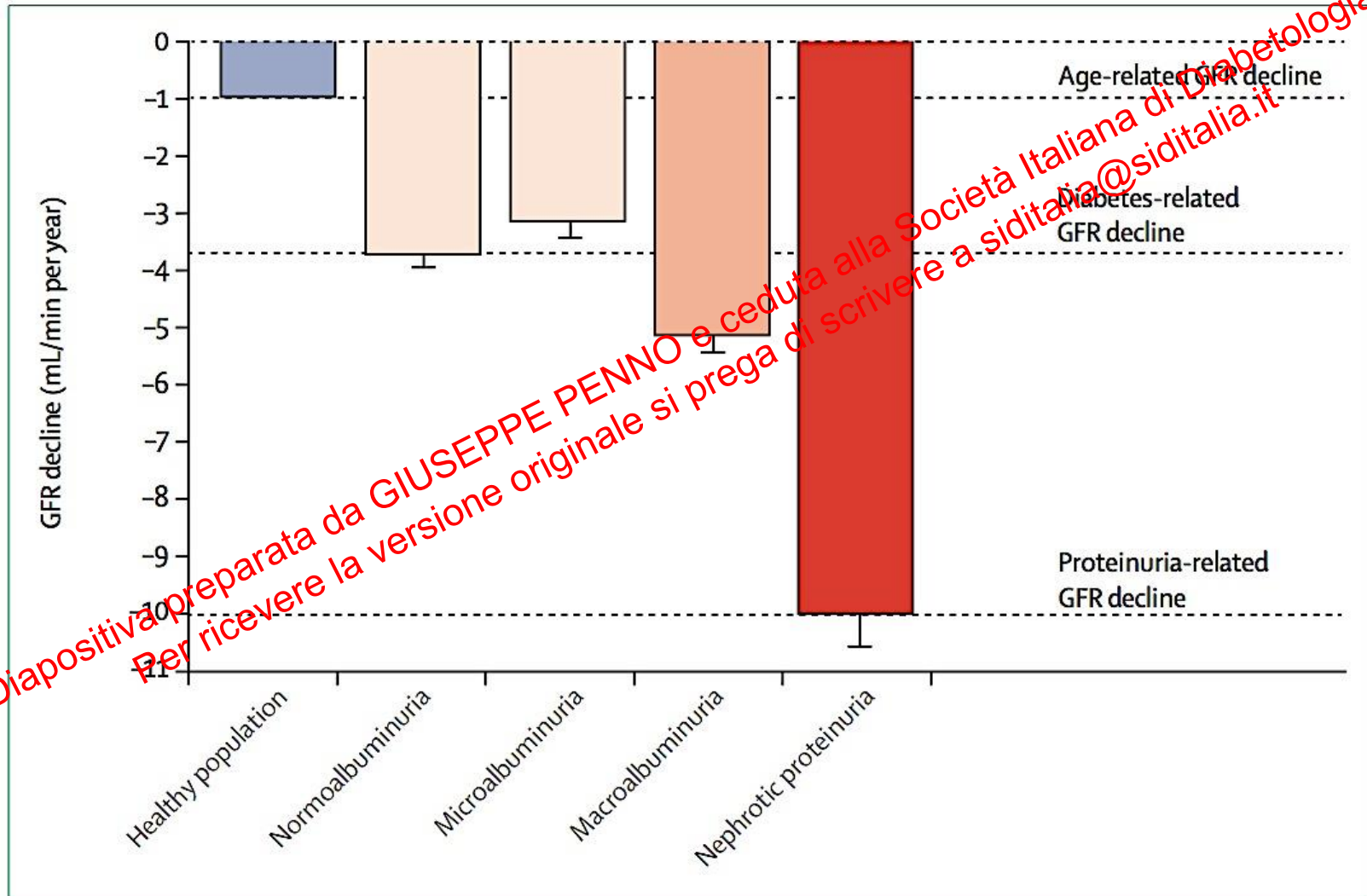
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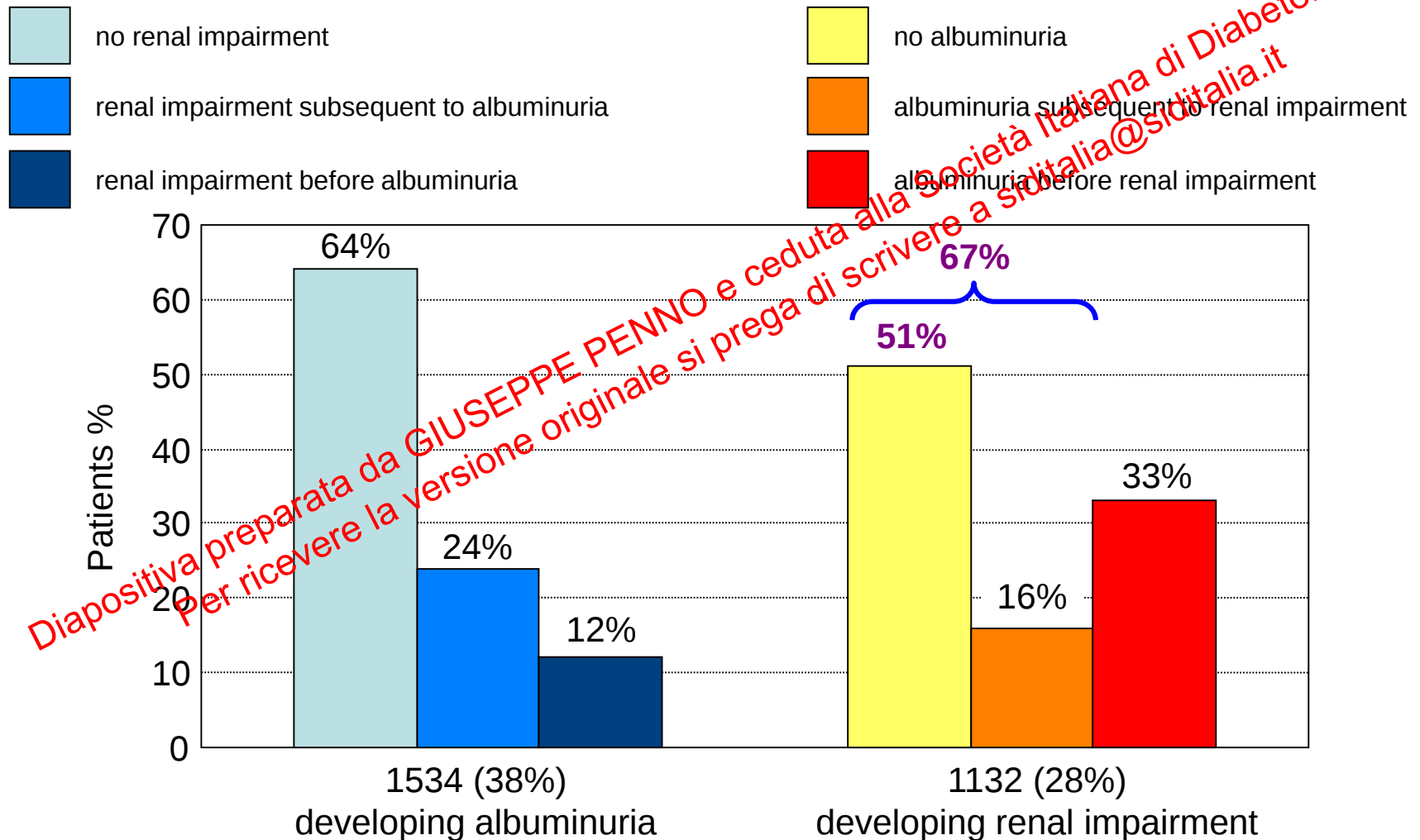
GFR in healthy patients compared with patients with T2DM and normo-, micro-, macro-albuminuria, or severe proteinuria

Data from studies that did repeated measurements of GFR using gold standard procedures in patients with normo- or micro-, macro-albuminuria, and severe proteinuria



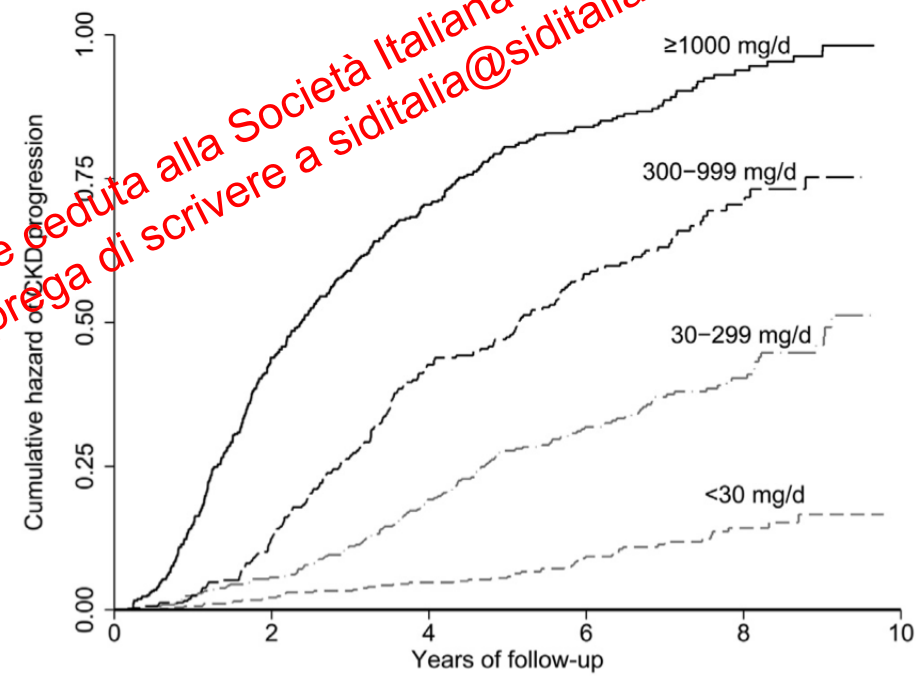
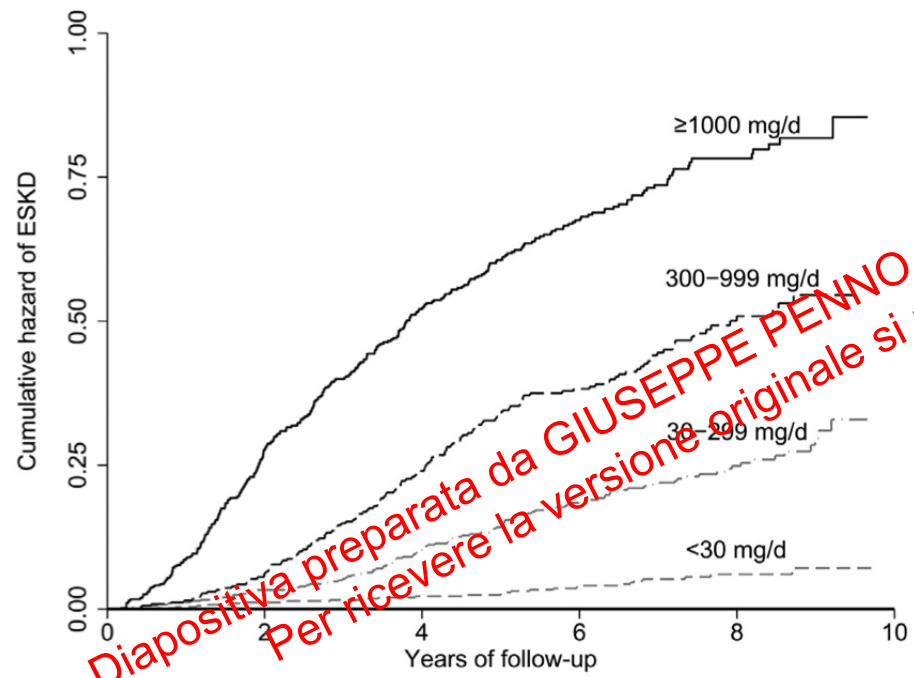
Challenging conventional paradigms: Diabetic kidney disease with and without albuminuria

UKPDS; 4006 type 2 DM patients
followed over a median of 15 years



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

1,908 participants **with diabetes and reduced GFR** enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study in the United States



Crude rates of ESKD were 7.4, 34.8, 78.7, and 178.7 per 1,000 person-years

CKD progression rates (ESKD or 50% reduction in eGFR from baseline) were 17.0, 61.4, 130.5, and 295.1 per 1,000 person-years

Progression and categories of progression of eGFR decline in patients with **T2DM** according to strata of albuminuria at entry into follow-up. *At entry, eGFR was normal in all patients.*

Patients from the Second Joslin Kidney Studies in T2DM: 6-10 years of follow-up				
eGFR decline per ml/yr	Normo-albuminuria %	Micro-albuminuria %	Macro-albuminuria %	Total %
<2.9	80%	67%	82%	72%
3-4.9	13%	18%	17%	15%
5-9.9	20% { 6%	33% { 12%	68% { 30%	28% { 10%
>10	1%	3%	21%	3%
Total (n)	681	418	82	1,181

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DKD IN THE ABSENCE OF ALBUMINURIA

ALB- DKD, MORTALITY & CVD (Type 2 DM; *shortly*)

ALB- DKD, MORTALITY & CVD (Type 1 DM; *shortly*)

PROGRESSION TO ALB- DKD (Type 1 DM)

PROGRESSION TO ALB- DKD (Type 2 DM)

LAST MINUTE DATA (Type 1 and Type 2 DM)

I° CONVEGNO

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Progressive Decline in Estimated Glomerular Filtration Rate in Patients With Diabetes After Moderate Loss in Kidney Function - **Even Without Albuminuria**

Steno Diabetes Center, Copenhagen

- 2919 persons with diabetes with at least one measurement of eGFR in DKD3 (eGFR <60 ml/min/1.73 m²)
- during up to 16 years of follow-up
 - 935 with T1DM, median follow-up of 5.1 years
 - 1,984 with T2DM, median follow-up of 3.7 years
- *eGFR trajectories have been adjusted for sex, age at diabetes diagnosis, DD, use of RAS-blockers, retinopathy status, HbA1c, antihypertensive treatment, BP, current smoking, and lipid-lowering treatment.*

Progressive Decline in Estimated Glomerular Filtration Rate in Patients With Diabetes After Moderate Loss in Kidney Function - Even Without Albuminuria

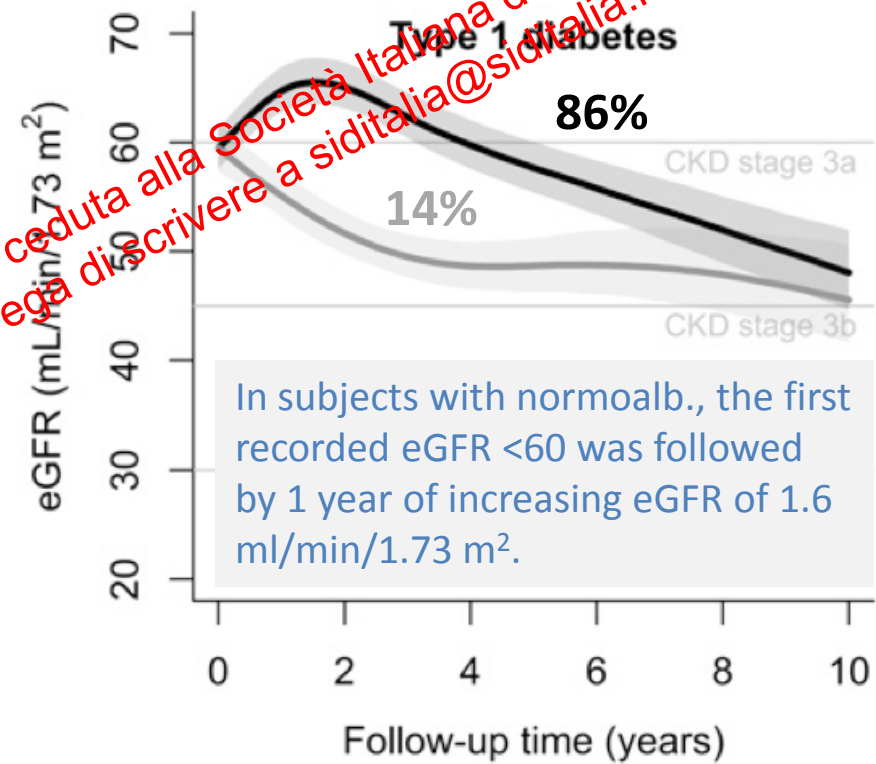
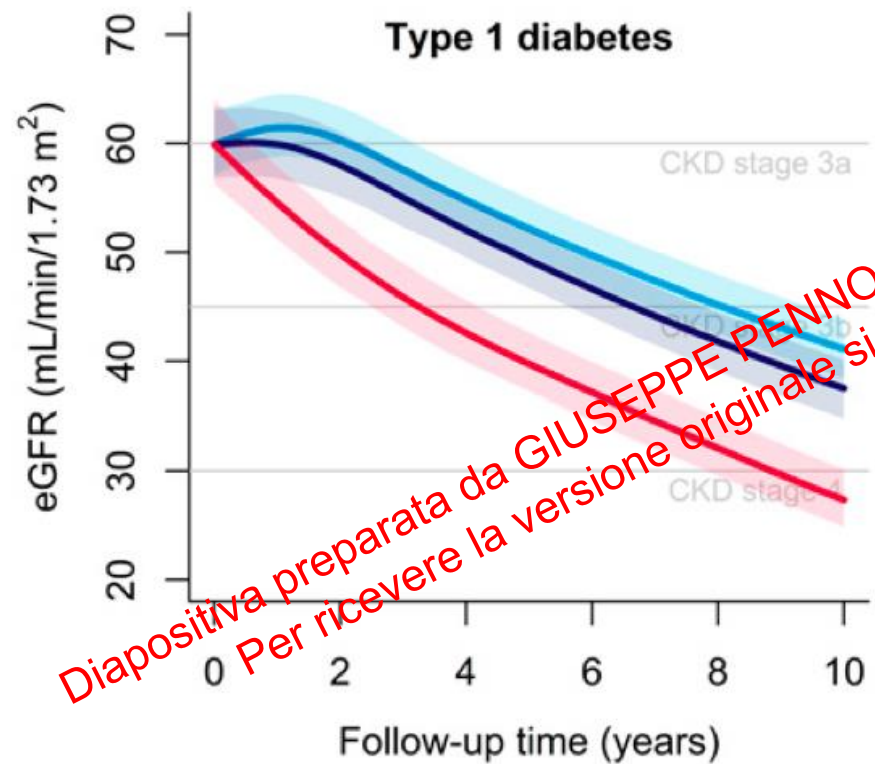
TYPE 1 DIABETES, at baseline

	Total	Normo	Micxro	Macro
N (%)	935	427 (46%)	264 (28%)	244 (26%)
Male sex (%)	48.9	37.2	55.8	63.9
Age, years	59.2	65.0	59.5	48.9
Age at diagnosis, years	24.5	31.0	23.2	14.5
HbA1c, %	8.8	8.5	8.8	9.2
Systolic BP, mmHg	140	138	139	145
Diastolic BP, mmHg	75	73	74	80
LDL cholesterol, mmol/L	2.7	2.7	2.5	3.1
Severe retinopathy, %	64.2	51.3	68.1	85.0
Active smoking, %	41.9	34.5	44.9	57.0
RAS blockers, %	62.8	59.5	62.1	69.3
No differences in: DD, BMI, eGFR, degree of antihypertensive treatment, and follow-up time				

Progressive Decline in Estimated Glomerular Filtration Rate in Patients With Diabetes After Moderate Loss in Kidney Function - **Even Without Albuminuria**

TYPE 1 DIABETES

Normoalb.	-1.9 ml/min/1.73 m ²	} <i>p</i> <0.001
Microalb.	-2.2 ml/min/1.73 m ²	
Macroalb.	-3.3 ml/min/1.73 m ²	



In subjects with normoalb., the first recorded eGFR <60 was followed by 1 year of increasing eGFR of 1.6 ml/min/1.73 m².

No modifying effect of RAS blockers on the eGFR development over time (*p*≥0.60)

Background population with no CKD: eGFR decline = 1 ml/min/1.73 m²

Healthy population of white ethnicity and no diabetes: eGFR decline = 0.4 ml/min/1.73 m²

Progressive Decline in Estimated Glomerular Filtration Rate in Patients With Diabetes After Moderate Loss in Kidney Function - Even Without Albuminuria

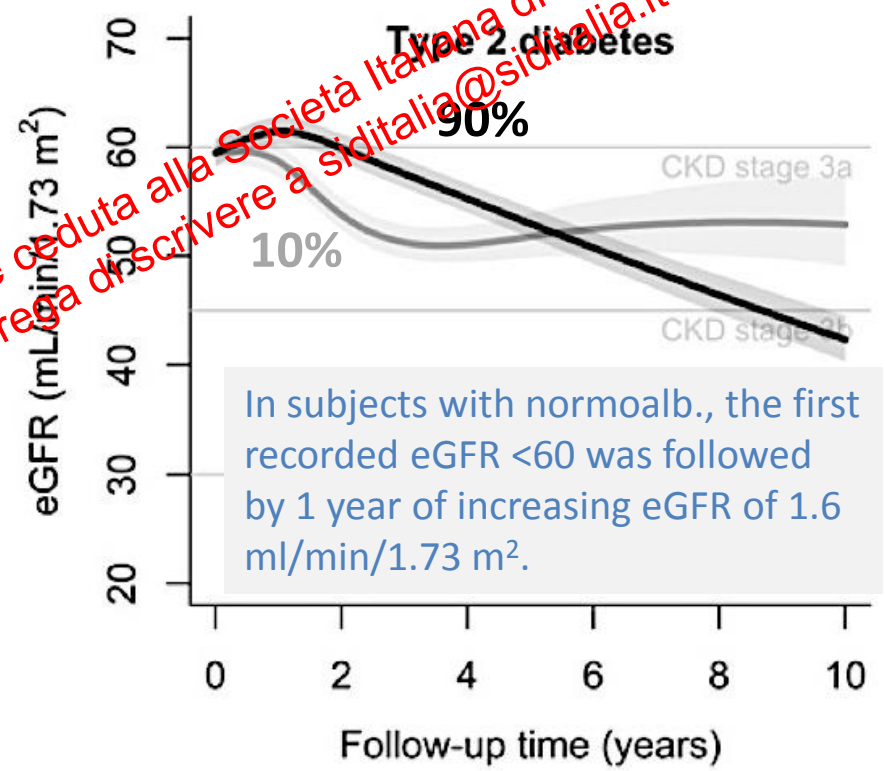
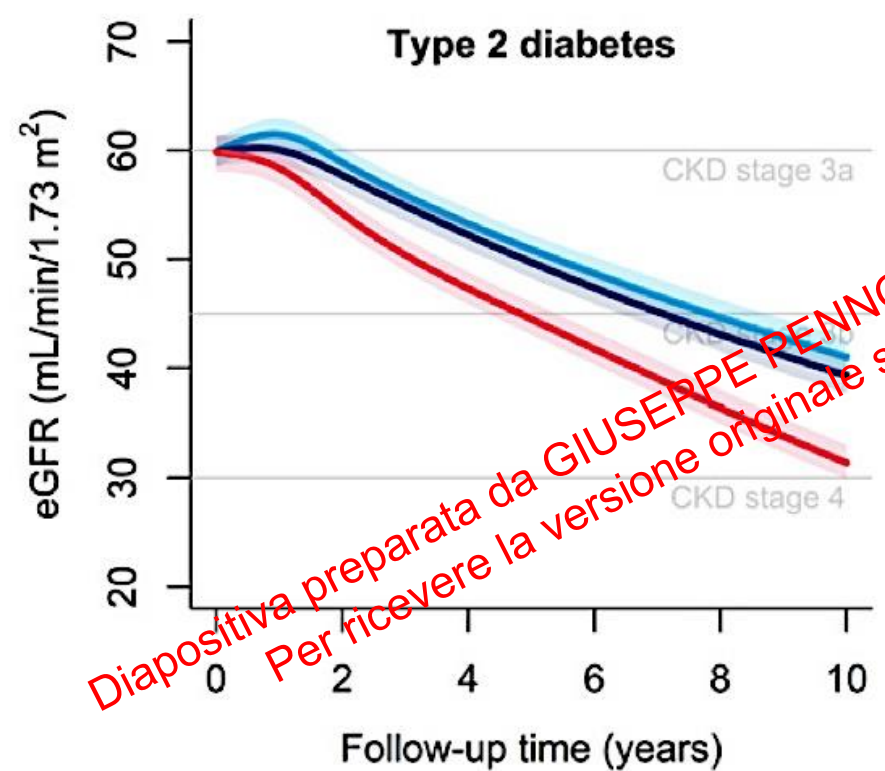
TYPE 2 DIABETES, at baseline

	Total	Normo	Micxro	Macro
N (%)	1,984	942 (48%)	664 (33%)	378 (19%)
Male sex (%)	57.6	47.7	64.0	70.7
Age, years	69.3	70.3	69.5	66.1
Age at diagnosis, years	55.7	57.4	55.3	51.3
HbA1c, %	8.2	8.1	8.3	8.6
Systolic BP, mmHg	141	137	142	152
Diastolic BP, mmHg	75	74	76	79
LDL cholesterol, mmol/L	2.5	2.4	2.4	2.8
Severe retinopathy, %	36.4	28.7	37.3	54.3
Active smoking, %	34.0	31.3	33.4	43.7
RAS blockers, %	55.2	52.4	58.9	55.7
No differences in: DD, BMI, eGFR, degree of antihypertensive treatment, and follow-up time				

Progressive Decline in Estimated Glomerular Filtration Rate in Patients With Diabetes After Moderate Loss in Kidney Function - Even Without Albuminuria

TYPE 2 DIABETES

Normoalb.	-1.9 ml/min/1.73 m ²	} p<0.001
Microalb.	-2.1 ml/min/1.73 m ²	
Macroalb.	-2.9 ml/min/1.73 m ²	



In subjects with normoalb., the first recorded eGFR <60 was followed by 1 year of increasing eGFR of 1.6 ml/min/1.73 m².

No modifying effect of RAS blockers on the eGFR development over time (p≥0.60)

Background population with no CKD: eGFR decline = 1 ml/min/1.73 m²

Healthy population of white ethnicity and no diabetes: eGFR decline = 0.4 ml/min/1.73 m²

DKD IN THE ABSENCE OF ALBUMINURIA

ALB- DKD, MORTALITY & CVD (Type 2 DM; *shortly*)

ALB- DKD, MORTALITY & CVD (Type 1 DM; *shortly*)

PROGRESSION TO ALB- DKD (Type 1 DM)

PROGRESSION TO ALB- DKD (Type 2 DM)

LAST MINUTE DATA (Type 1 and Type 2 DM)

TAKE HOME MESSAGES

I° CONVEGNO

La Malattia Renale Diabetica (DKD):

Presente e Futuro dell'Approccio

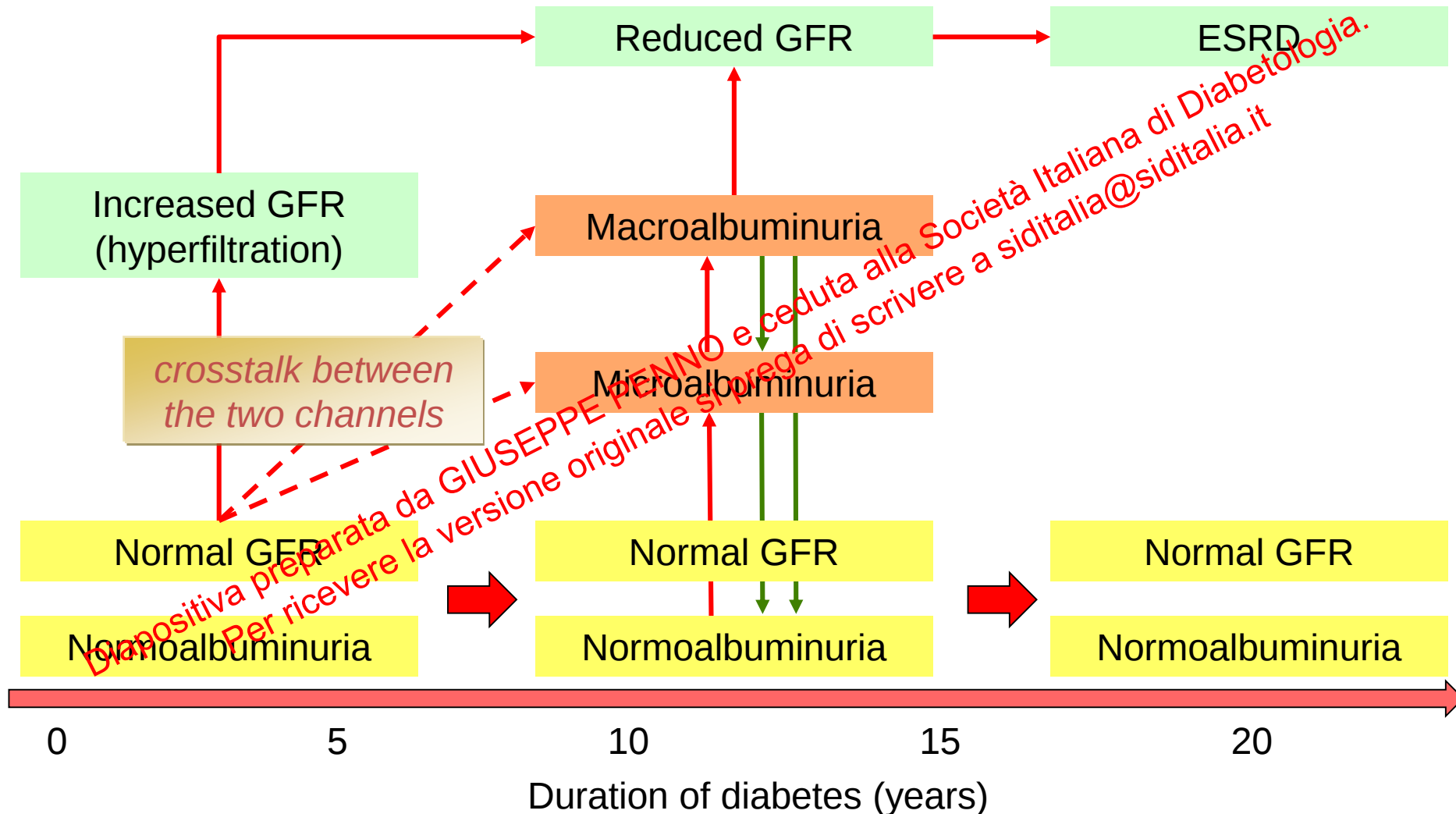
Integrato Nefro-Diabetologico

TEAM WORK FOR WORK SUCCESS

RIMINI, 2 OTTOBRE 2019

Diapositiva preparata da GIUSEPPE PENNO e ceduta alla Società Italiana di Diabetologia.
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Schematic presentation of variable clinical courses of diabetic kidney disease



Common biomarkers predictive of DKD and mechanistic hypothesis

Parechimal resistance index (resistance of the intrarenal arteries), increased to a similar extent regardless of albuminuria (*MacIsaac RJ et al., Diabetes Care 2006*)

T1DM: CD27, alpha1-microglobulin and KIM-1 associated with decline in eGFR (*Colombo M et al., Diabetologia 62: 1616-1627, 2019*)

Subjects with eGFR <60: those with normo- (or micro-) albuminuria have fewer (T2DM*) or equal (T1DM**) of the typical morphological features described for DKD associated with proteinuria (**Yamanouchi M et al., Diabetes Care 2019*; ***Caramori ML et al., Diabetes 2003*)

Serum tumor necrosis factor receptors associated with reduced eGFR in normo T2DM (*Gohda T et al., Diab Res Clin Practice 2018*)

Inflammation/endothelial damage/fibrosis

α_1 -Antitrypsin
 TGF- β 1
 MCP-1
 VEGF
 MR-proADM
 NT-proBNP
 TNF-R1, TNFR2
 SDMA/ADMA
 FGF21
 CKD273
 CD5L
 MMPs
 Endostatin

Glomerulus

Cystatin C
 α_1 -Microglobulin
 β_2 -Microglobulin
 Albumin

Proximal tubule

KIM-1
 NGAL
 L-FABP
 FGF23

Loop of Henle

Osteopontin
 Uromodulin
 (Tamm-Horsfall protein)

Distal tubule

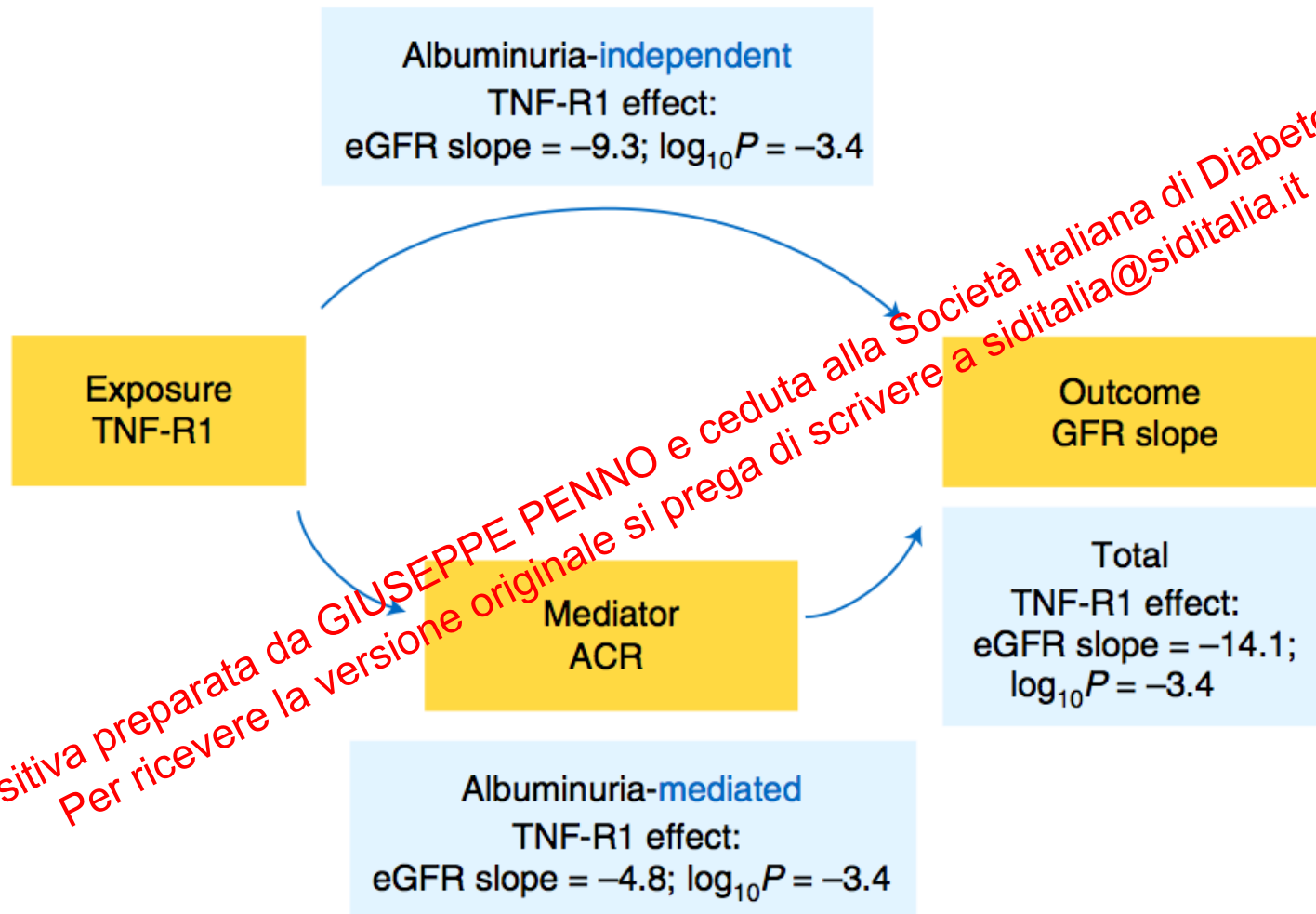
Osteopontin
 NGAL
 Copeptin

T2DM: B2M and KIM-1 associated with decline in eGFR after adjustment for baseline eGFR and albuminuria (*Colombo M et al., Diabetologia 62: 156-168, 2019*)

Collecting duct

Copeptin

A signature of circulating inflammatory proteins and development of end-stage renal disease in diabetes



The proportion of the albuminuria-independent effect of TNF-R1 was 66%.

CKD PREVALENCE: 10%-15%, likely stable

In the general population as well in high-risk populations any stage of CKD is associated with progressive increase in all-cause mortality, all-cause hospitalization, hospitalization for CVD, and heart failure

Increased albuminuria and reduced eGFR are independently associated with all-cause death, cardiovascular outcomes (and ESRD)

Prevalence of DKD is higher (30-40%) but likely decreasing

In both T1DM and T2DM any DKD phenotype is associated with an increased risk of all-cause mortality and an increased risk of CV outcomes

A substantial number of persons entering DKD3 will have normoalbuminuria and, especially in T2DM, the prevalence of this phenotype is increasing

It is debated whether the Alb-DKD3 phenotype reflects ...

- normal age-related decline in renal function
- DKD with previous albuminuria normalized by treatments
- a new phenotype of kidney disease in diabetes

For both type of diabetes, eGFR levels move on a progressive declining trajectory when persons enter DKD3

For both types of diabetes, this was also true for subjects with normoalbuminuria, although with a less steep decline in eGFR compared with micro- and macroalbuminuria

Thus, following DKD3 entering, a diabetes-dependent decline in eGFR exists even without albuminuria

Many patients with T1DM or T2DM can follow a non-albuminuric pathway to renal function loss, even accounting for the use of renoprotective agents

At least 20% of subjects progressing to ESKD (eGFR <15) did so without the transition to macroalbuminuria

The pathological drivers and structural basis of renal function decline in non-albuminuric DKD still remain to be elucidated

New markers are needed to identify people who are at greatest risk for the progression of the normoalbuminuric DKD

TEAM WORK FOR WORK SUCCESS

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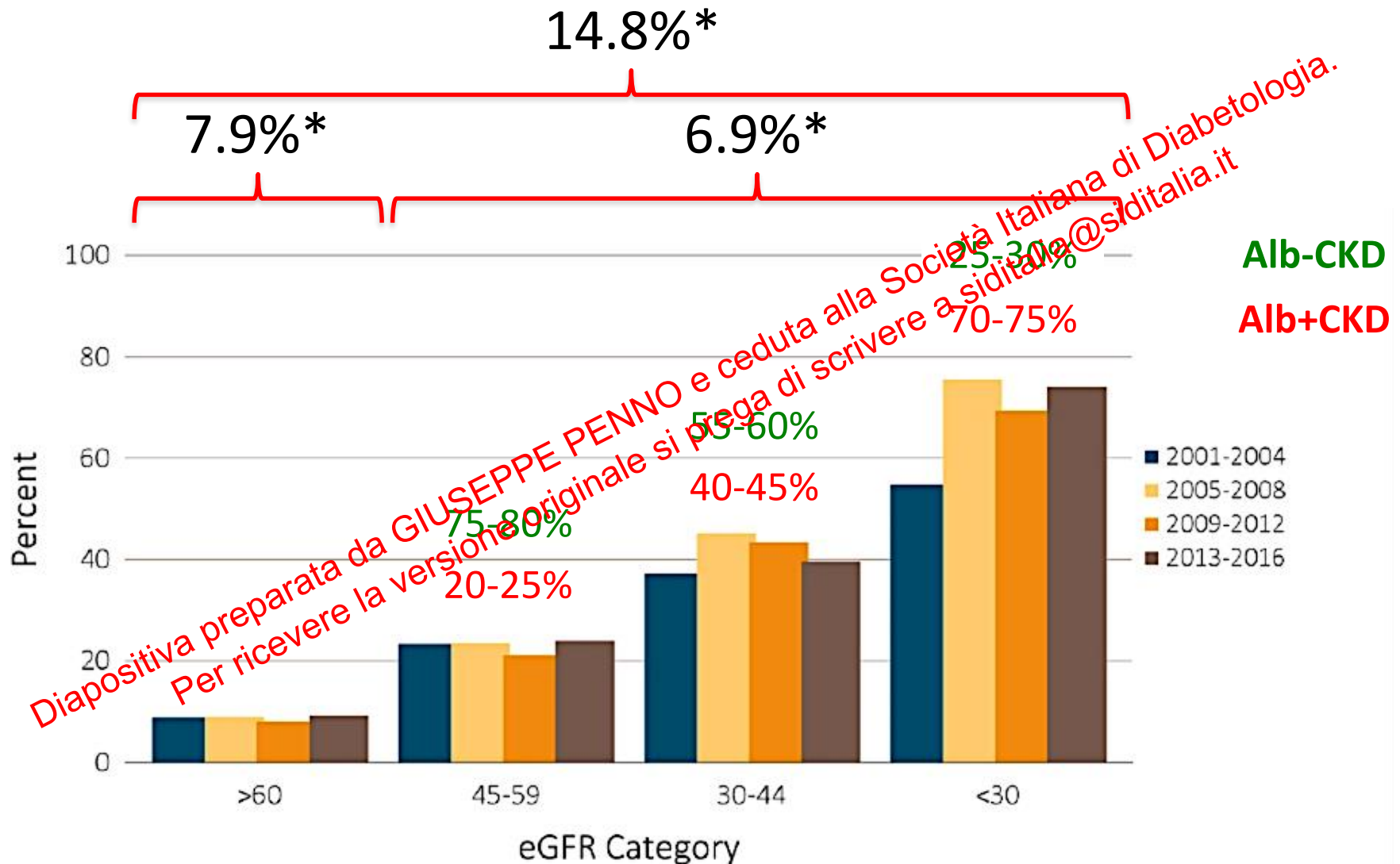
unite for diabetes

Thank for your
attention!

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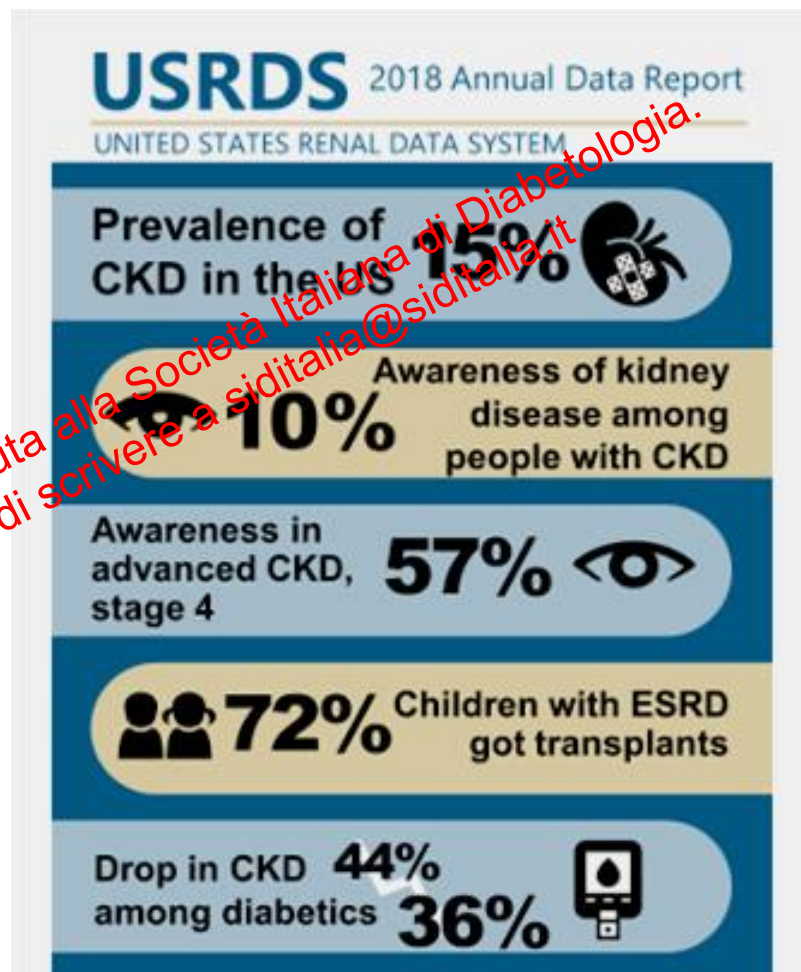
Percentage of NHANES (2001-2016) participants with ACR >30 mg/g, by eGFR category



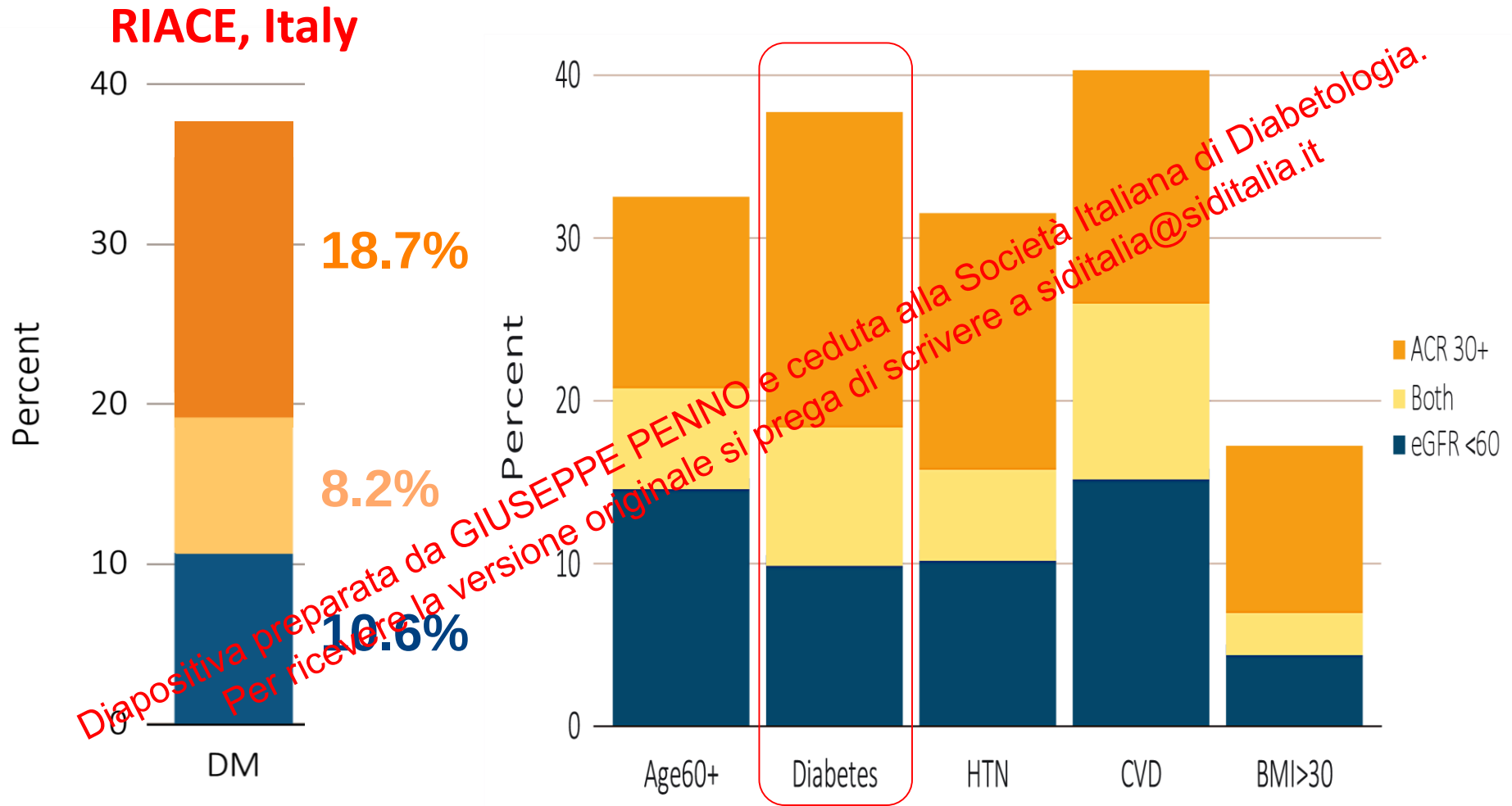
* 2016

Prevalence (%) of CKD in NHANES population within age, sex, race/ethnicity, & risk factor categories, 2001-2016

	All CKD			
	2001-2004	2005-2008	2009-2012	2013-2016
Age				
20-39	5.4	6.1	5.5	6.3
40-59	9.7	10.1	8.3	10.4
60+	38.8	34.5	33.1	32.2
Sex				
Male	12.7	12.1	12.3	12.9
Female	15.5	16.3	14.6	16.7
Race/Ethnicity				
Non-Hispanic White	14.3	14.4	13.6	15.6
Non-Hispanic Black/African American	14.7	16.3	16.1	15.9
Mexican American	11.4	11.8	11.9	12.6
Other Hispanic	13.1	14.9	11.5	11.4
Other Non-Hispanic	15.9	11.4	11.7	12.6
Risk Factor				
Diabetes	43.6	40.1	38.6	36.0
Self-reported diabetes	43.8	41.8	39.5	37.1
Hypertension	32.7	31.6	30.9	31.2
Self-reported hypertension	27.2	26.6	26.1	26.6
Self-reported cardiovascular disease	42.2	40.6	40.8	40.3
Obesity (BMI ≥30)	16.5	17.2	16.5	16.8
All	14.2	14.3	13.5	14.8



Distribution of markers of CKD in RIACE participants with DM and in NHANES participants with age 60+, DM, hypertension, self-reported CVD, & obesity, 2013-2016



Data Source: National Health and Nutrition Examination Survey (NHANES), 2013-2016 participants age 20 & older. Single-sample estimates of eGFR & ACR; eGFR calculated using the CKD-EPI equation.

Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis

Data for 1 024 977 participants (128 505 with diabetes) from 30 general population and high-risk cardiovascular cohorts and 13 chronic kidney disease cohorts

	Individuals with diabetes				Overall
	ACR <10, PCR <15, or dipstick negative	ACR 10–29, PCR 15–49, or dipstick trace	ACR 30–299, PCR 50–499, or dipstick 1+	ACR ≥300, PCR ≥500, or dipstick ≥2+	
All-cause mortality					
eGFR ≥105	1.27*; 1.07–1.51	1.58*; 1.29–1.94	2.43*; 1.90–3.11	4.38*; 2.97–6.46	1.21*; 1.06–1.39
eGFR 90–104	Reference	1.41*; 1.24–1.59	1.78*; 1.45–2.05	2.95*; 2.22–3.91	Reference
eGFR 75–89	0.94; 0.87–1.01	1.33*; 1.16–1.54	1.59*; 1.35–1.87	2.42*; 1.89–3.11	0.95; 0.90–1.01
eGFR 60–74	0.99; 0.93–1.07	1.32*†; 1.16–1.49	1.86*; 1.60–2.16	2.98*; 2.36–3.76	1.04; 0.97–1.12
eGFR 45–59	1.15*; 1.01–1.30	1.82*; 1.60–2.07	1.97*; 1.65–2.35	3.23*; 2.51–4.15	1.18*†; 1.07–1.30
eGFR 30–44	1.81*; 1.35–2.44	2.25*; 1.87–2.70	3.13*; 2.57–3.80	4.61*; 3.64–5.84	1.65*; 1.48–1.83
eGFR 15–29	2.69*; 1.78–4.06	3.30*; 2.43–4.46	4.96*; 3.19–7.72	6.80*; 4.76–9.70	2.28*; 1.91–2.72
eGFR <15	12.0*; 3.02–47.6	5.88*; 2.43–14.2	9.55*; 4.53–20.1	14.5*; 8.84–23.8	4.46*; 3.26–6.10
Overall	Reference	1.35*; 1.27–1.44	1.73*; 1.61–1.86	2.67*; 2.31–3.08	..

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Data for 1 024 977 participants (128 505 with diabetes) from 30 general population and high-risk cardiovascular cohorts and 13 chronic kidney disease cohorts

	Individuals with diabetes				Overall
	ACR <10, PCR <15, or dipstick negative	ACR 10–29, PCR 15–49, or dipstick trace	ACR 30–299, PCR 50–499, or dipstick 1+	ACR ≥300, PCR ≥500, or dipstick ≥2+	
Cardiovascular mortality					
eGFR ≥105	1.19; 0.76–1.89	1.93*; 1.12–3.33	3.00*; 1.45–6.03	5.07*; 1.86–13.8	1.16; 0.84–1.62
eGFR 90–104	Reference	1.28; 0.95–1.74	1.74; 1.28–2.36	3.03*; 1.90–4.84	Reference
eGFR 75–89	1.04; 0.88–1.23	1.70*; 1.29–2.23	1.79*; 1.41–2.28	2.69*; 1.91–3.78	1.10; 0.97–1.23
eGFR 60–74	1.25*; 1.06–1.47	1.56*; 1.21–2.00	2.53*; 2.00–3.20	3.21*; 2.42–4.27	1.27*; 1.12–1.44
eGFR 45–59	1.33*; 1.05–1.68	1.75*; 1.31–2.35	2.27*; 1.70–3.01	3.24*; 2.41–4.35	1.32*†; 1.14–1.53
eGFR 30–44	2.12*; 1.55–2.89	2.49*; 1.62–3.85	3.62*; 2.50–5.24	5.57*; 4.08–7.59	2.08*; 1.73–2.50
eGFR 15–29	4.10*; 1.75–9.61	3.39*; 1.56–7.34	5.64*; 2.64–12.1	7.96*; 4.89–13.0	2.57*; 1.94–3.40
eGFR <15	19.9*; 1.79–220	NA	NA	21.6*; 4.65–99.9	6.38*; 1.87–21.8
Overall	Reference	1.43*; 1.25–1.64	1.81*; 1.62–2.01	2.44*; 1.99–2.98	..

Diapositiva preparata da GIUSEPPE PENNO e ceduta alla Societa Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis

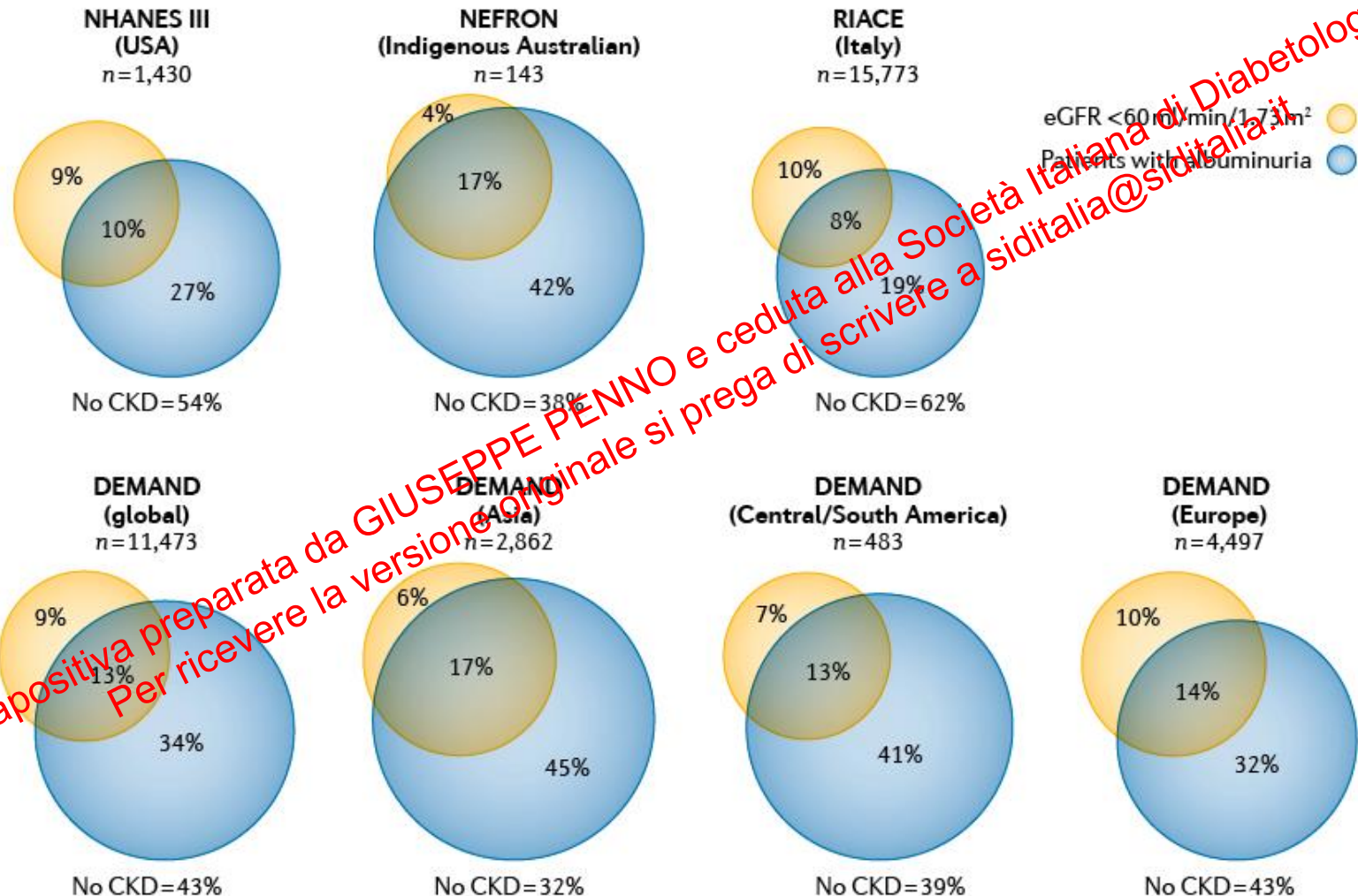
Data for 1 024 977 participants (128 505 with diabetes) from 30 general population and high- risk cardiovascular cohorts and 13 chronic kidney disease cohorts

HR for ESRD in chronic kidney disease populations according to eGFR and albuminuria

	Individuals with diabetes				
	ACR <30, PCR <50, or dipstick negative or trace	ACR 30–299, PCR 50–499, or dipstick 1+	ACR 300–999, PCR 500–1499, or dipstick 2+	ACR ≥1000, PCR ≥1500, or dipstick ≥3+	Overall
eGFR ≥75	1.47; 0.63–3.41	2.47*; 1.29–4.73	3.43*†; 1.58–7.47	4.42*; 2.20–8.86	0.81†; 0.21–3.17
eGFR 45–74	Reference	1.76*; 1.05–2.95	2.84*; 1.11–7.27	8.01*; 3.62–17.7	Reference
eGFR 30–44	2.11*†; 1.26–3.51	3.35*; 2.07–5.41	5.71*; 3.57–9.13	8.56*; 5.27–13.9	1.86*; 1.58–2.19
eGFR 15–29	2.98*; 1.68–5.28	8.25*; 5.19–13.1	23.7*; 8.09–69.3	33.7*; 13.8–82.4	5.23*; 3.81–7.17
eGFR <15	1.74; 0.23–13.1	34.7*; 4.21–285	122*; 4.64–3229	35.7*; 21.5–59.4	9.46*; 5.52–16.2
Overall	Reference	1.60; 0.85–3.02	3.55*; 2.89–4.36	6.79*; 4.36–10.6	..

Diabetic Kidney Disease (DKD)

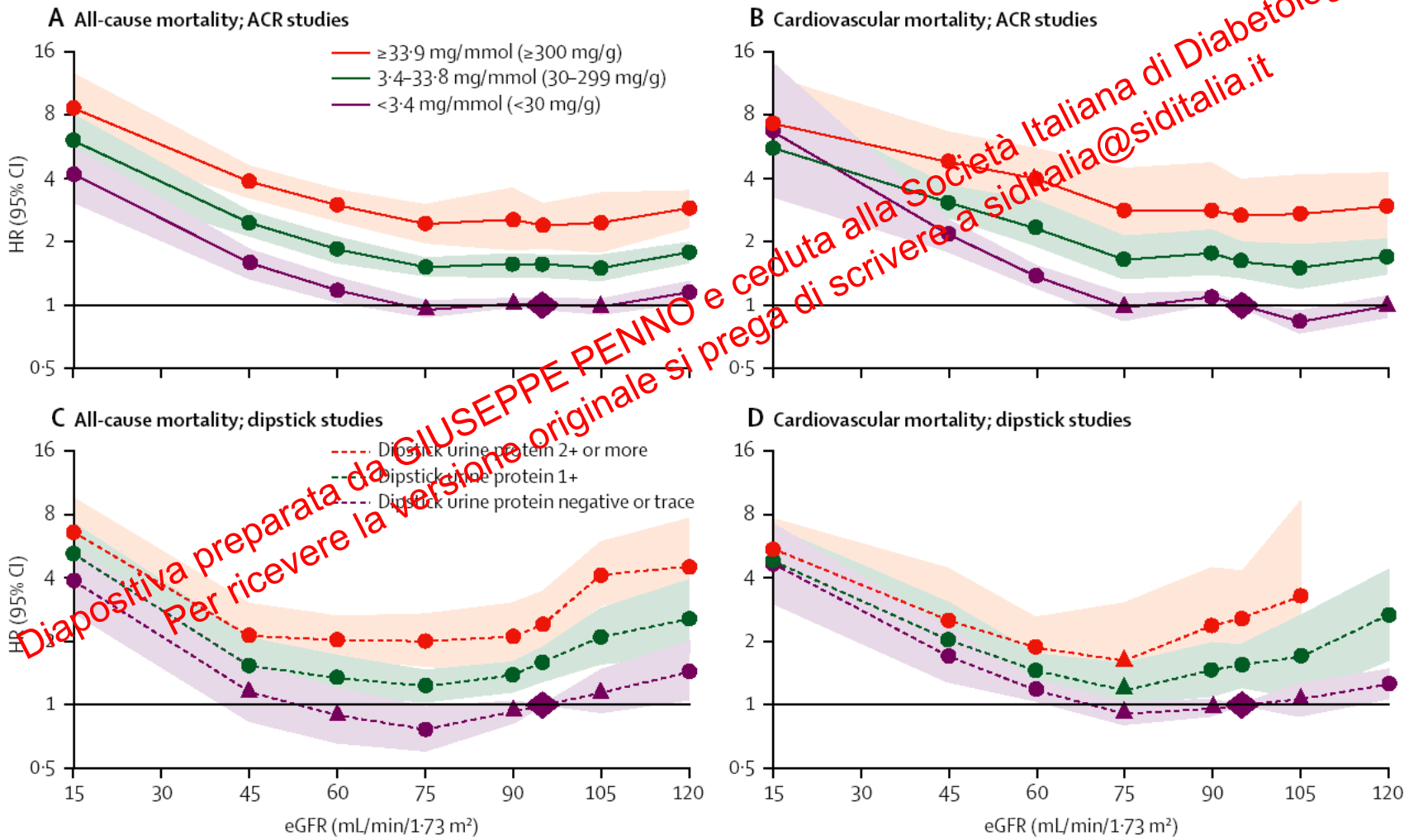
The prevalence of DKD phenotypes in different populations with type 2 DM



Chronic Kidney Disease Prognosis Consortium - collaborative meta-analyses

Lower estimated GFR and higher albuminuria are associated with **all-cause** and **cardiovascular mortality in general population cohorts**

ACR: 105,872 participants; Protein dipstick: 1,128,310 participants



Chronic Kidney Disease Prognosis Consortium - collaborative meta-analyses

Lower estimated GFR and higher albuminuria are associated with

... all cause and CV mortality
in general population cohorts:

105,872 participants from 14 studies
with ACR measurements;
1,128,310 participants from 7 studies
with protein dipstick measurements

CKD Prognosis Consortium.
Lancet 375: 2073-2081, 2010

... all cause and CV mortality
in high-risk population cohorts:

266,975 participants from 15 cohorts
selected because of increased risk
of CKD:
hypertension, diabetes (49.6%, 32.4%), or
cardiovascular disease

CKD Prognosis Consortium.
Kidney Int 79: 1341-1352, 2011

... adverse kidney outcomes
in both general and high-risk
populations:

645,135 participants from 9 general
population cohorts;
173,892 patients from 8 cohorts selected
because of their high risk for CKD
(diabetes 44.5%)

CKD Prognosis Consortium.
Kidney Int 80: 93-104, 2011

... mortality and ESRD in
kidney disease population
cohorts:

21,688 patients from 13 studies selected
for CKD of diverse etiology
(diabetes 33.8%)

CKD Prognosis Consortium.
Kidney Int 79: 1331-1340, 2011