La stratificazione precoce del rischio renale nel diabete

Roberto Trevisan

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

Direttore SC Malattie Endocrine – Diabetologia
ASST Papa Giovanni XXIII, Bergamo

Il dr. ROBERTO TREVISAN dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

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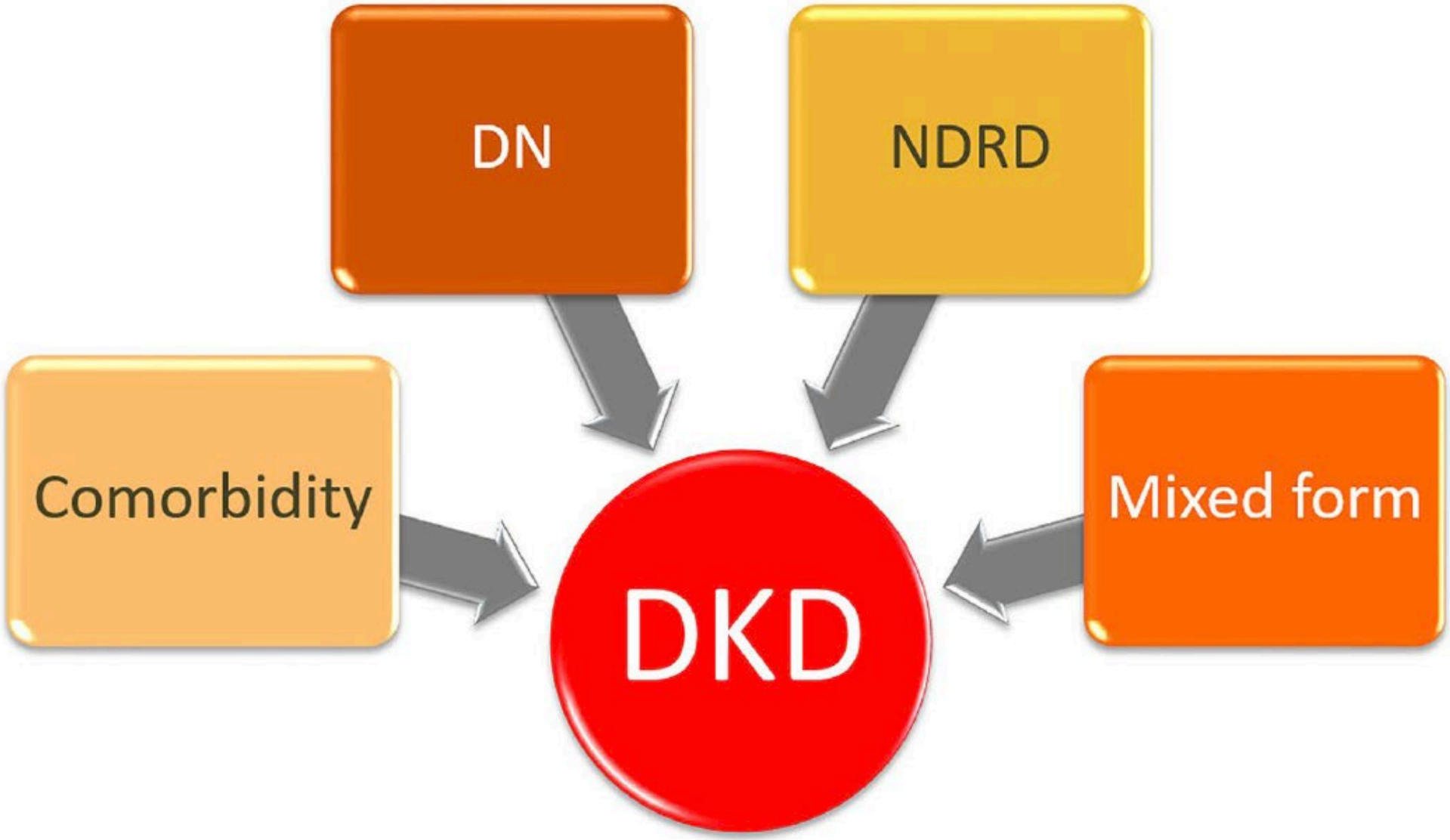
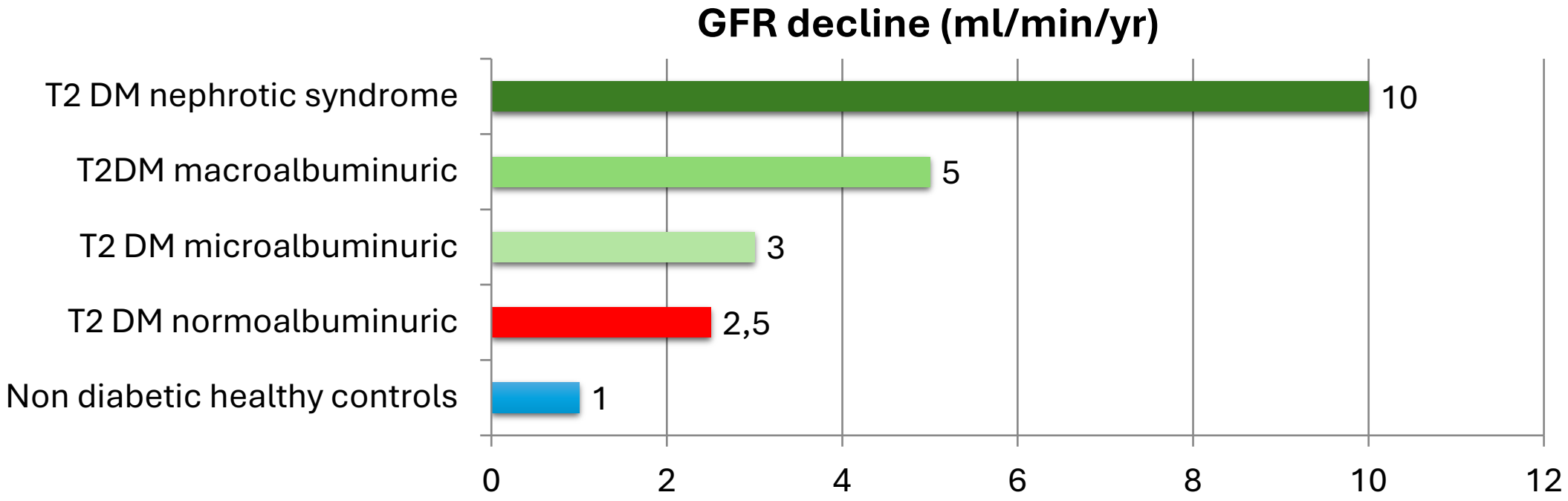

DN
NDRD
Comorbidity
DKD
Mixed form

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

Lancet Diabetes Endocrinol 2015

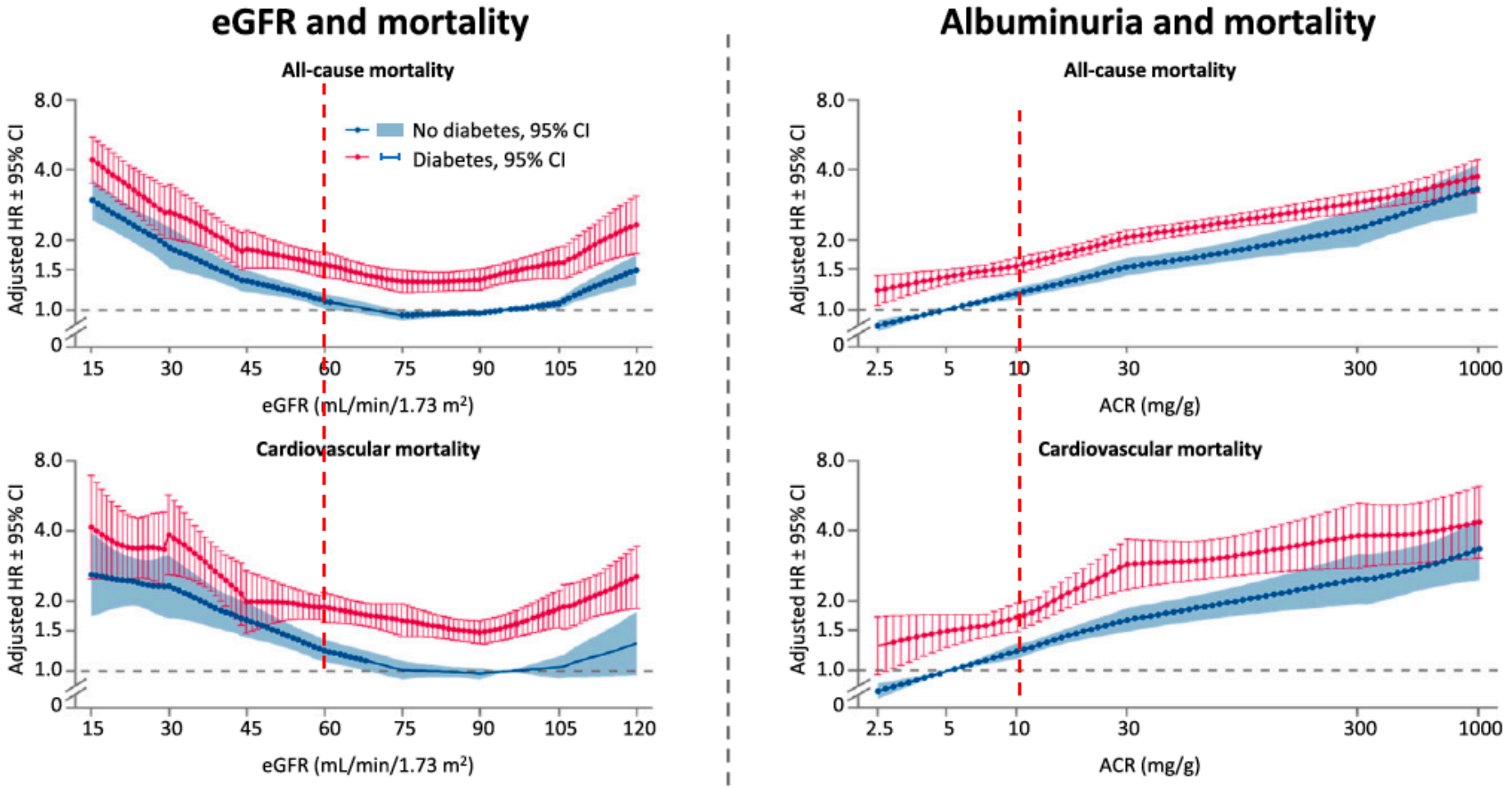
Biomarker definition

- A BIOMARKER is a measurable indicator of the severity or presence of some disease state.
- Biomarkers may help in early diagnosis, disease prevention, drug target identification and drug response.

Stratificazione precoce del rischio renale

Albuminuria e eGFR

Declining eGFR and increasing albuminuria are associated with mortality in individuals with diabetes. ACR, albumin-to-creatinine ratio



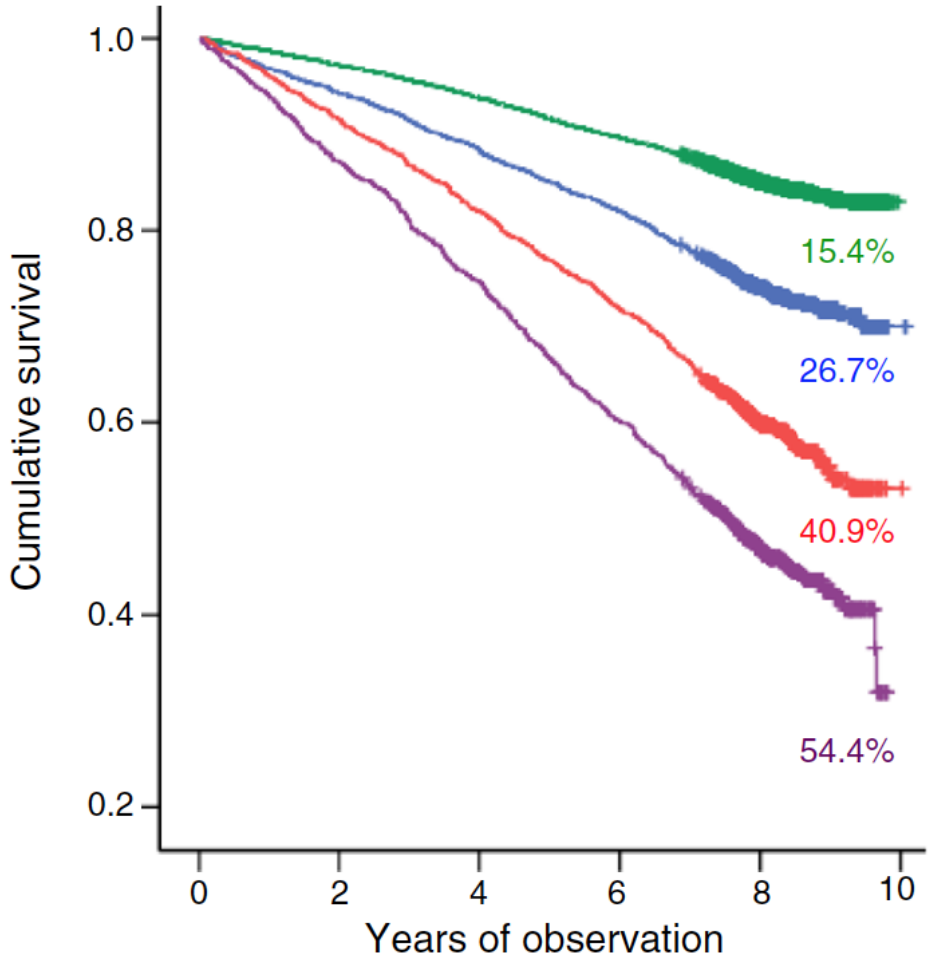
Lancet 2012;380:1662–1673

The RIACE Study

Cumulative survival by Kaplan–Meier analysis according to DKD phenotype

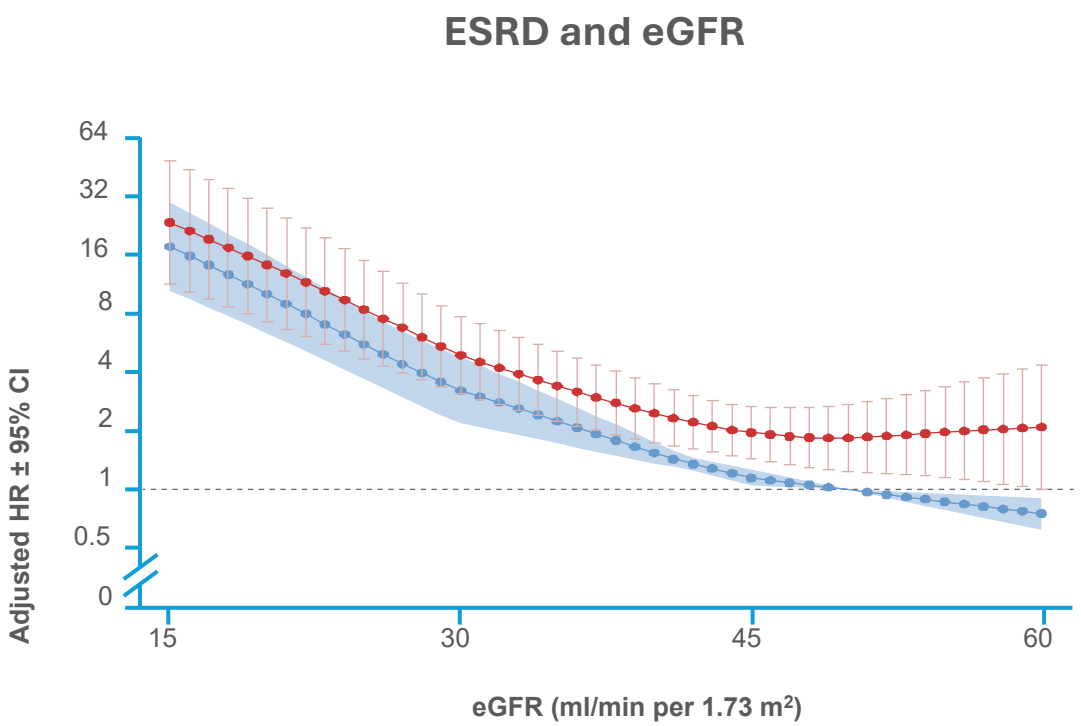
Diabetologia (2018) 61:2277–2289

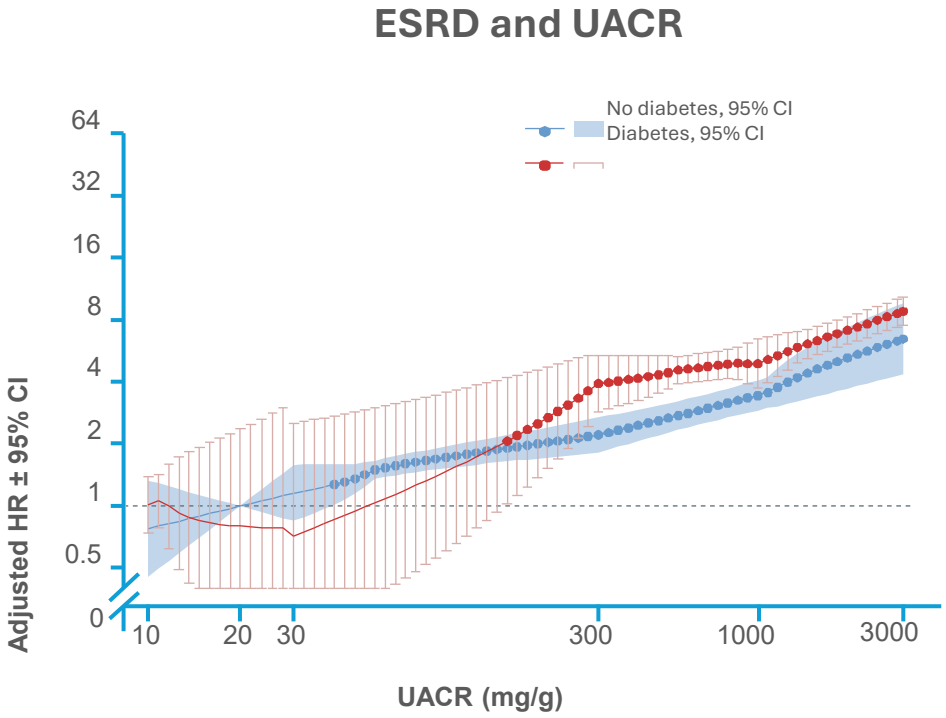
Green, Alb−/eGFR− (no DKD)
Blue, Alb+/eGFR− (albuminuric DKD with preserved eGFR)
Red, Alb−/eGFR+ (non-albuminuric DKD)
Purple, Alb+/eGFR+ (albuminuric DKD with reduced eGFR)



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

Declining eGFR and Increasing UACR are associated with ESRD in diabetes





HRs adjusted for age, sex, race, smoking, history of cardiovascular disease, serum total cholesterol concentration, body-mass index and albuminuria

Includes data from participants with type 1 and type 2 diabetes

Fox CS *et al*. *Lancet* 2012;380:1662

Stratificazione precoce del rischio renale

KDIGO Guidelines

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is defined as abnormalities of kidney structure or function, present for a minimum of 3 months

KDIGO: Prognosis of CKD by GFR and albuminuria categories

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk. GFR, glomerular filtration rate.

Kidney International (2024) 105 (Suppl 4S), S117–S314

Evaluation – Diagnosis of CKD in Older Adults

Epidemiological population data support retaining the threshold GFR of 60 ml/min/1.73 m2 for diagnosis of CKD in older adults, even in the absence of significant albuminuria, with consistently elevated and increasing relative risk of adverse outcomes below this threshold.

Age 65+	ACR, mg/g				ACR, mg/g			
eGFRcr-cys	<10	10–29	30–299	300+	<10	10–29	30–299	300+
	All-cause mortality				Myocardial infarction			
105+	1.2	1.4	1.9	3.5	0.97	1.4	2.0	19
90–104	ref	1.2	1.4	2.0	ref	1.2	1.1	1.9
60–89	1.2	1.5	1.8	2.3	1.1	1.4	1.5	1.9
45–59	1.6	2.0	2.4	2.9	1.6	1.9	2.3	3.4
30–44	2.0	2.4	3.2	4.1	2.1	2.6	3.1	3.8
<30	3.4	4.1	5.1	6.5	4.9	3.0	5.1	5.0
	Cardiovascular mortality				Stroke			
105+	1.1	1.5	2.0	12	1.2	1.3	1.5	3.3
90–104	ref	1.4	1.4	3.4	ref	1.3	1.3	2.8
60–89	1.2	1.7	2.2	3.1	1.1	1.4	1.8	2.5
45–59	1.7	2.4	3.0	4.3	1.5	1.7	2.0	2.3
30–44	2.4	3.1	4.5	5.8	1.5	2.0	2.1	2.3
<30	5.7	5.2	5.1	7.8	1.7	2.0	2.4	4.8
	Kidney failure replacement therapy				Heart failure			
105+	2.0	1.0	2.1		0.99	1.5	1.7	7.0
90–104	ref	1.9	4.7	10	ref	1.3	1.5	2.2
60–89	1.4	2.6	6.2	19	1.2	1.5	2.0	3.2
45–59	3.7	7.9	16	42	1.6	2.0	2.9	4.1
30–44	14	14	46	137	2.3	2.9	3.5	6.1
<30	87	364	241	406	4.4	4.1	5.5	7.2
	Acute kidney injury				Atrial fibrillation			
105+	0.91	1.1	1.3	1.9	0.95	1.1	1.0	3.7
90–104	ref	1.3	1.4	3.9	ref	1.2	1.3	2.4
60–89	1.5	2.1	2.7	4.7	1.1	1.2	1.5	2.0
45–59	3.6	4.3	5.1	7.3	1.2	1.4	1.7	1.9
30–44	5.7	5.9	7.2	9.8	1.5	1.8	2.0	2.2
<30	10	11	11	22	1.8	1.8	2.2	3.2
	Hospitalization				Peripheral artery disease			
105+	1.0	1.1	1.2	2.2	1.1	2.3	2.9	4.9
90–104	ref	1.1	1.3	1.4	ref	1.3	2.0	4.8
60–89	1.1	1.2	1.3	1.5	1.3	1.6	2.0	3.2
45–59	1.2	1.2	1.4	1.6	2.0	2.8	3.1	3.1
30–44	1.5	1.4	1.6	2.0	3.5	2.8	3.8	5.9
<30	1.9	1.9	2.0	2.6	8.4	4.1	5.9	10

JAMA. 2023;330(13):1266–1277.
Kidney International (2024) 105 (Suppl 4S), S117–S314

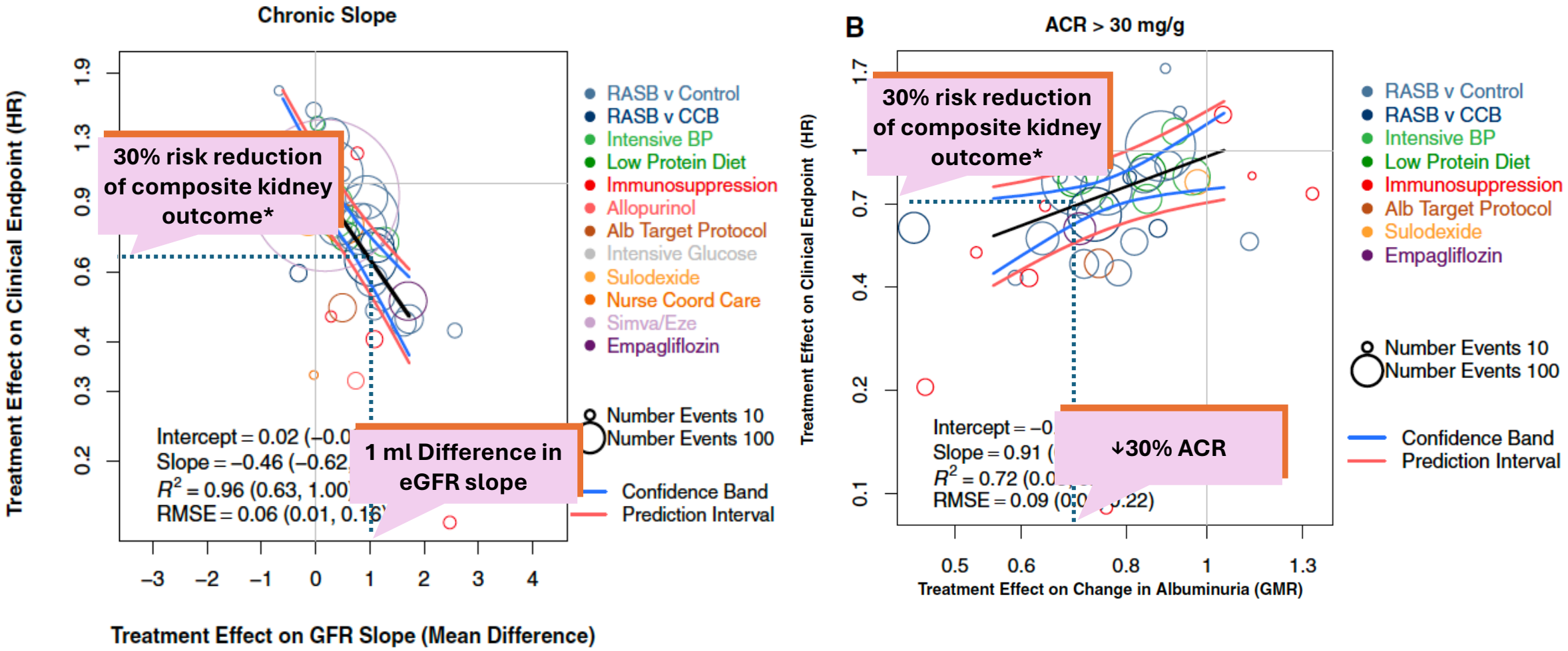
Stratificazione precoce del rischio renale

eGFR slope and early ACR change

The ADA and FDA have acknowledged GFR slope and early ACR change as a valid treatment target to slow CKD progression

Meta-analysis of 41 clinical trials including 29,979 participants

The clinical end point is defined as ESRD, doubling of creatinine level, or GFR of 15 mL/min/1.73 m^2

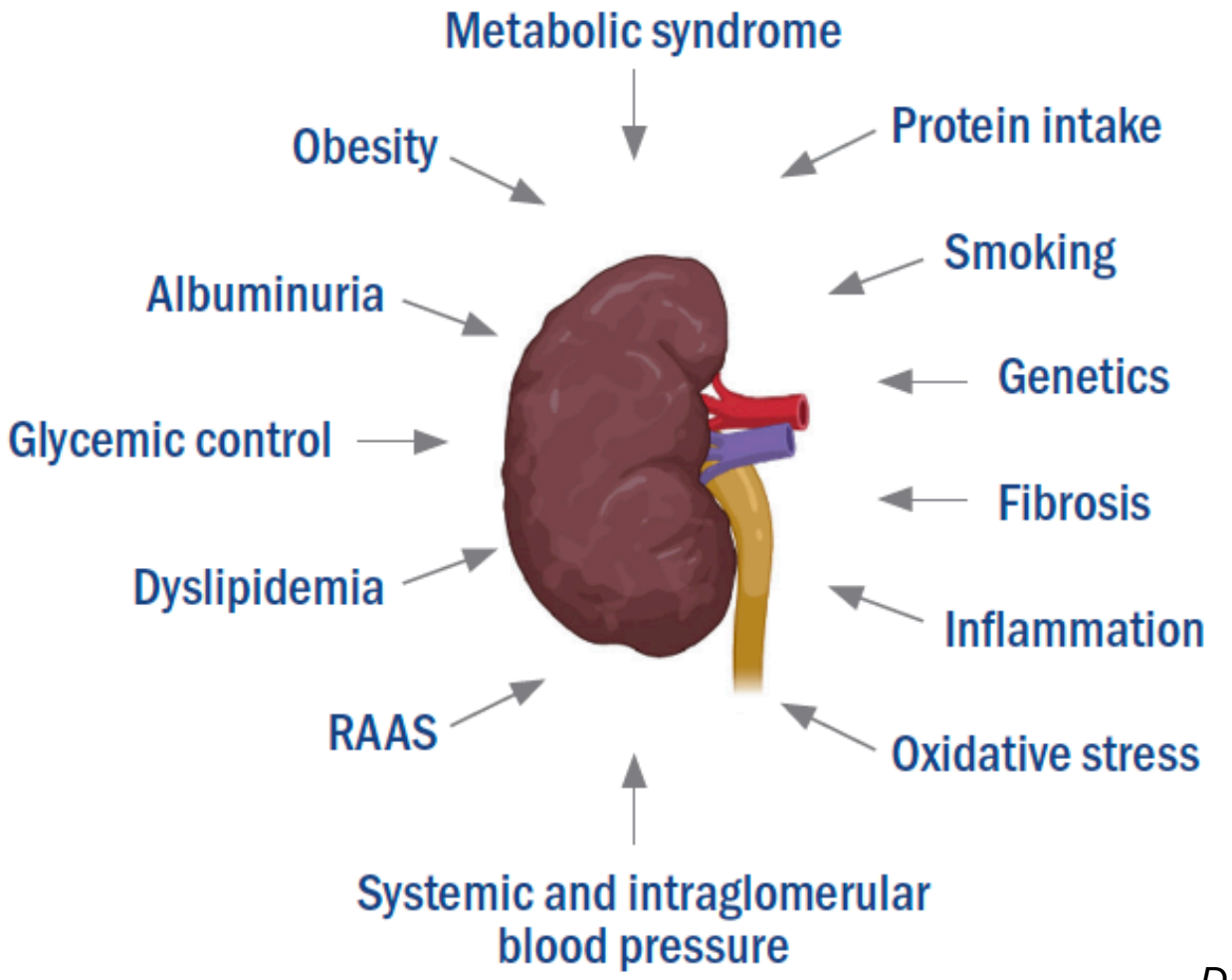


1. American Diabetes Association. Diabetes Care 2022;45;S175–S184; 2. Levey AS, et al. Am J Kidney Dis 2020;75:84–104

Stratificazione precoce del rischio renale

Ruolo dei fattori di rischio

Putative promoters of CKD progression in diabetes



Diabetes 2021;70:39–50.

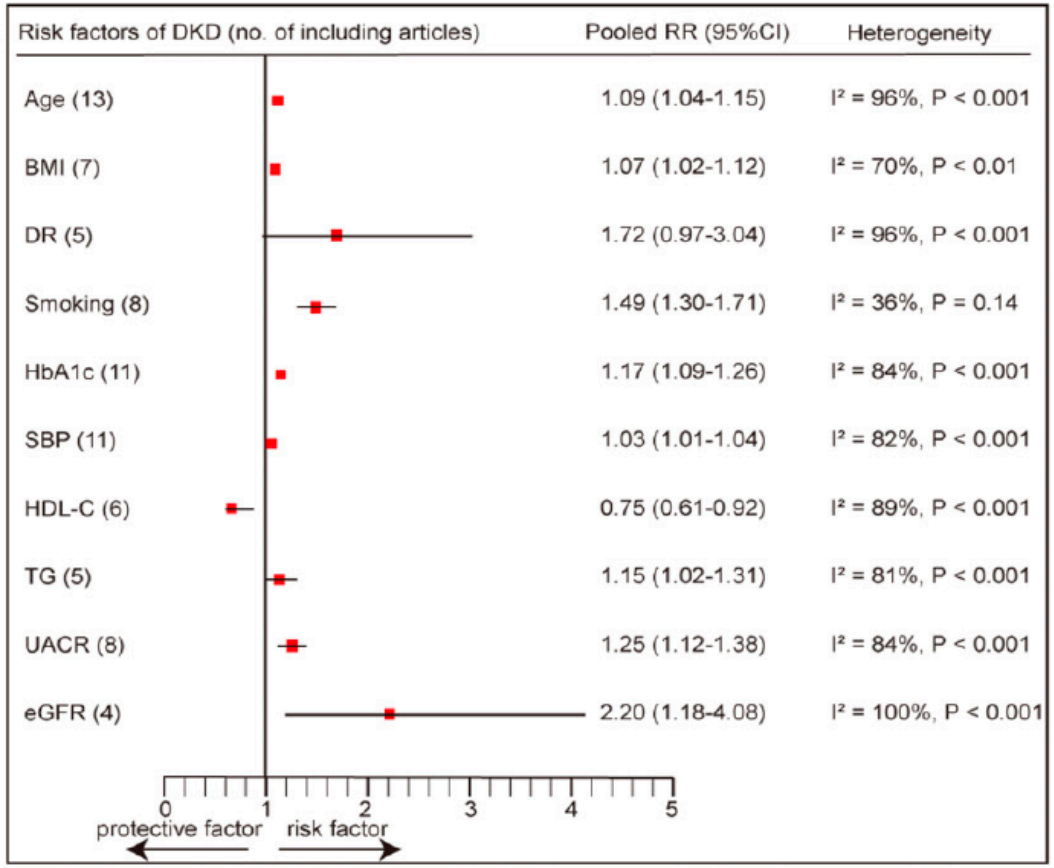
Perché i diabetici perdono funzione renale anche in assenza di nefropatia proteinurica?

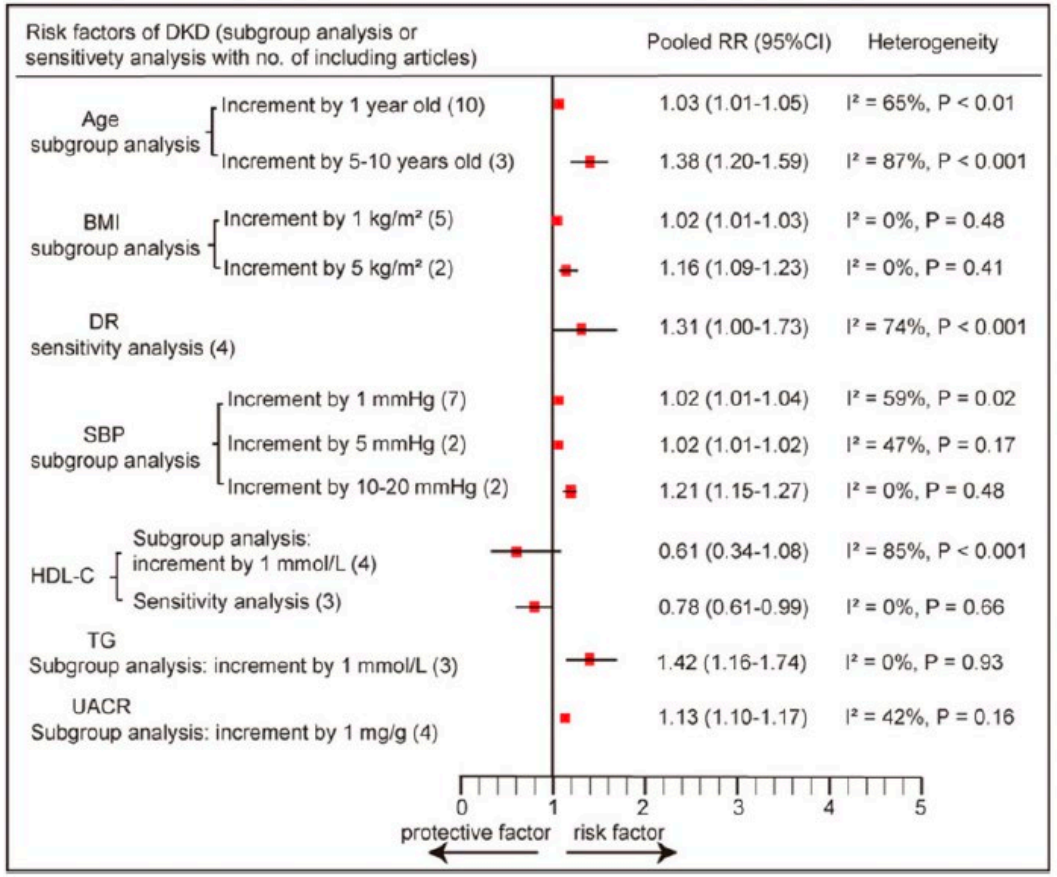
- Nefroangiosclerosi
- Nefropatia ischemica
- Danno da farmaci
- Insufficienza cardiaca
- Proteinuria «prevenuta» dal trattamento precoce con ACE/ARBs
- Altre malattie renali

Fattori di rischio di danno renale:

- Glicemia
- Pressione arteriosa
- Iperlipidemia
- Fumo
- Introito di sale nella dieta
- Obesità
- Insulino-resistenza

Pooled RRs and their corresponding 95% CIs for risk factors of DKD development that were statistically significant in the systematic review and meta-analysis of 20 Cohorts





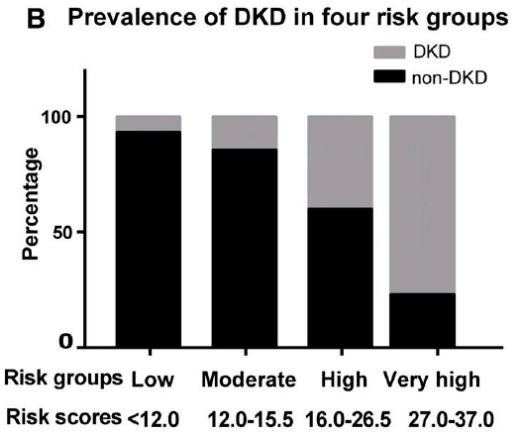
Diabetes Care 2020;43:925–933

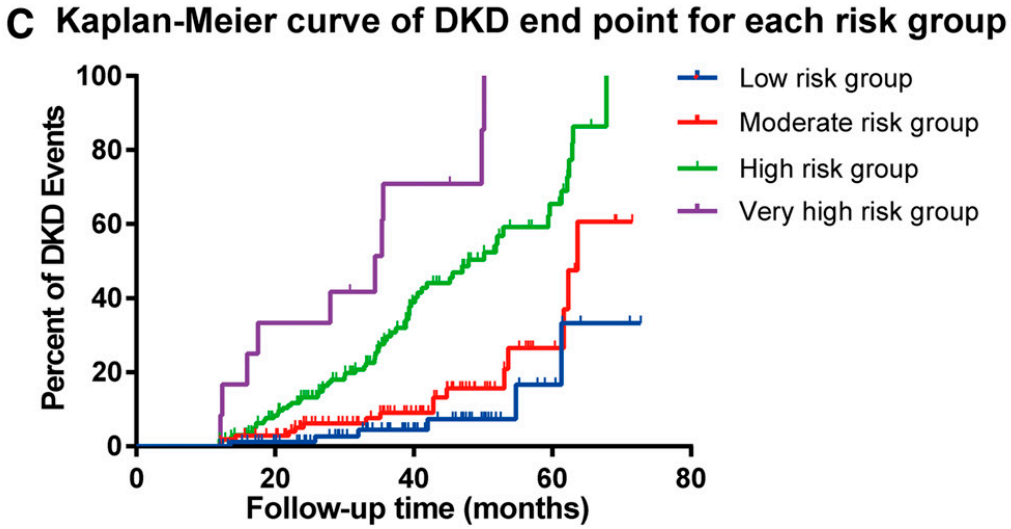
Risk Prediction Model for Early Diabetic Kidney Disease Based on a Systematic Review and Meta-Analysis of 20 Cohorts

Table 1—DKD risk prediction model*

Risk factor of DKD	Category	Point
Age** (years)	39–49	0
	50–59	3
	60–75	6
BMI***(kg/m^2)	<25.00	0
	25.00–29.99	1.5
	≥30.00	3
Smoker****	Nonsmoker	0
	Smoker	4
DR	No	0
	Yes	3
HbA_{1c} (% [mmol/mol])	<7.0 [<53]	0
	7.0–7.9 [53–63]	1.5
	8.0–8.9 [64–74]	3
	≥9.0 [≥75]	4.5
SBP (mmHg)	<130	0
	130–139	2
	140–149	4
	≥150	6
HDL-C (mmol/L)	≥1.30	0
	<1.30	2.5
TG (mmol/L)	<1.70	0
	≥1.70	4
UACR (mg/g)	<10.00	0
	10.00–19.99	2
	20.00–29.99	4

*DKD risk prediction model applied to patients with type 2 diabetes without DKD. **Patients in derivation and validation cohorts aged 39–75 years old. ***BMI was categorized as <25.00, 25.00–29.99, and ≥30.00 kg/m^2 in white patients but <24.00, 24.00–27.99, and ≥28.00 kg/m^2 in Asians. ****Smoker was defined as having smoked more than 100 cigarettes in their lifetime.



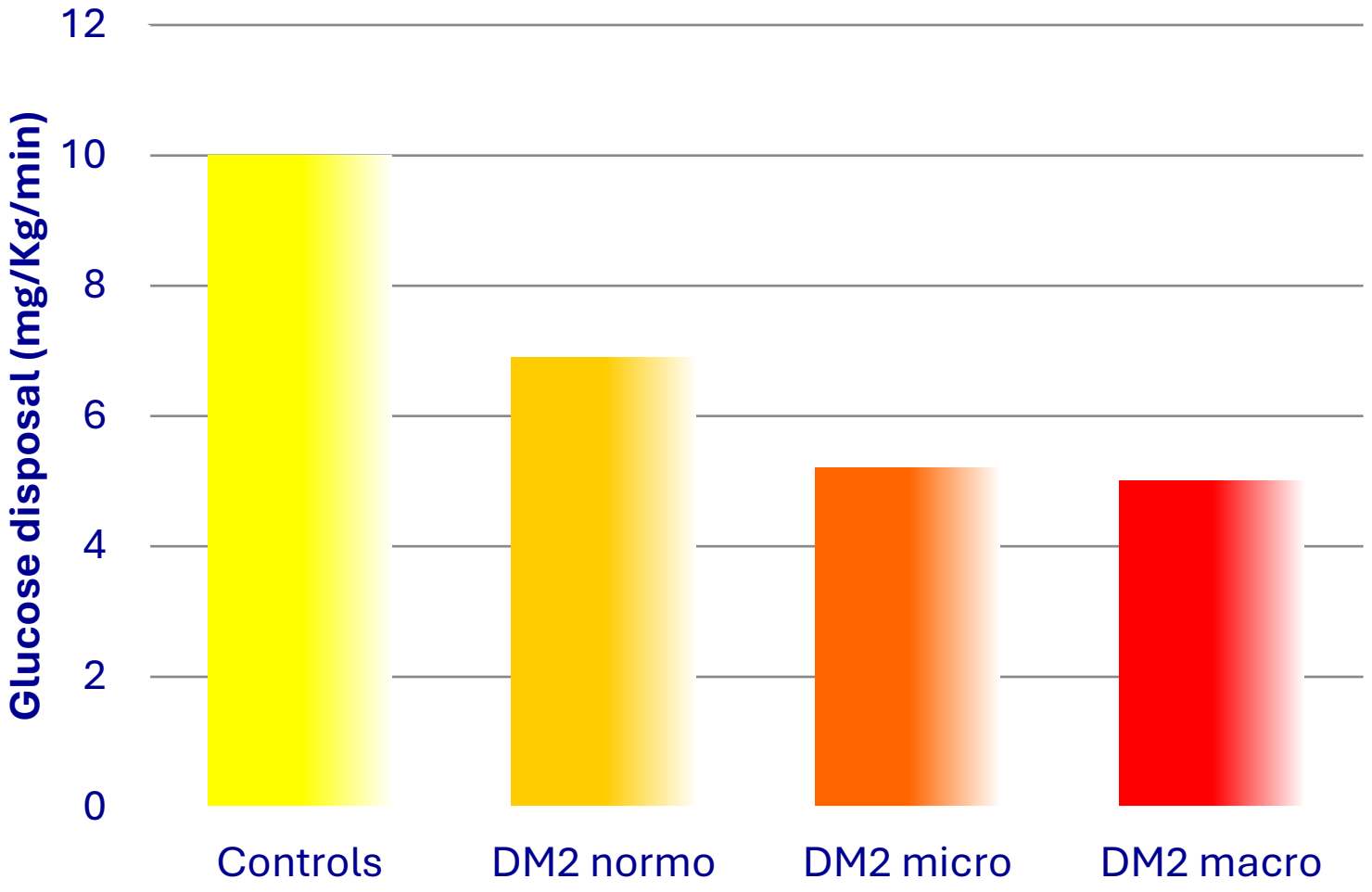


Diabetes Care 2020;43:925–933

Stratificazione precoce del rischio renale

Insulino-resistenza

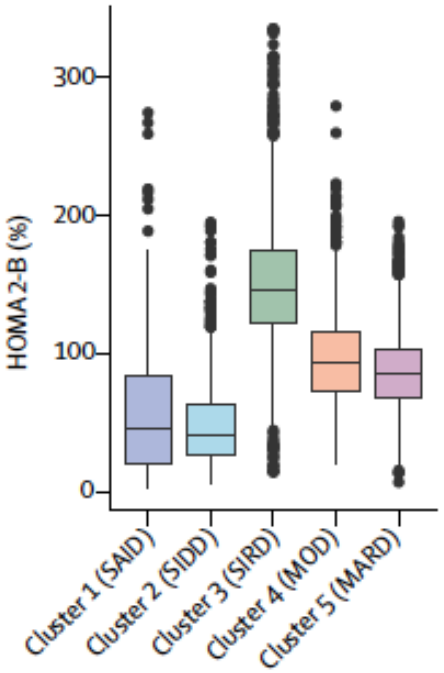
Type 2 diabetic patients with increased AER have a greater insulin resistance



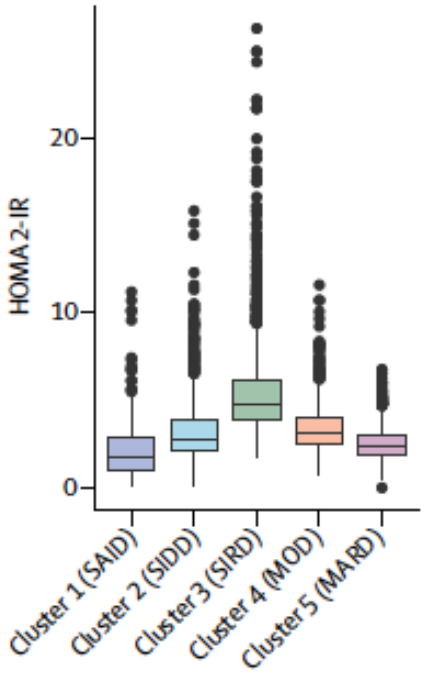
R Trevisan, AR Dodesini, Diabetes 2006

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

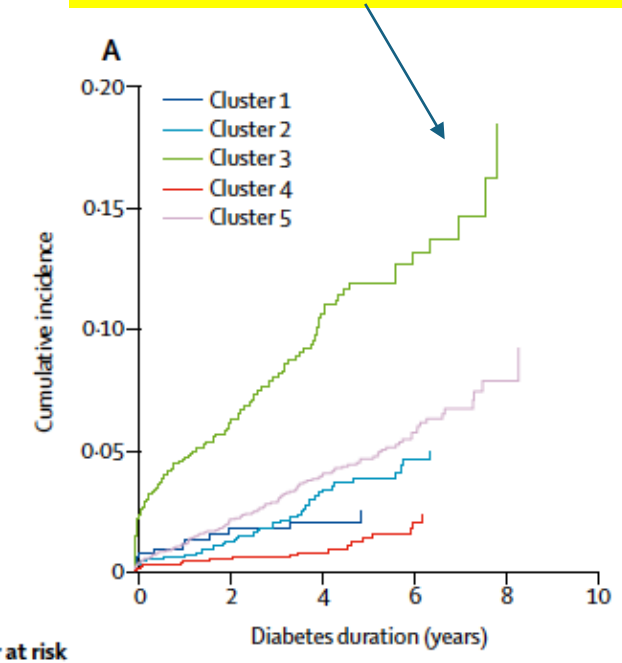
estimates of β-cell function



estimates of insulin resistance

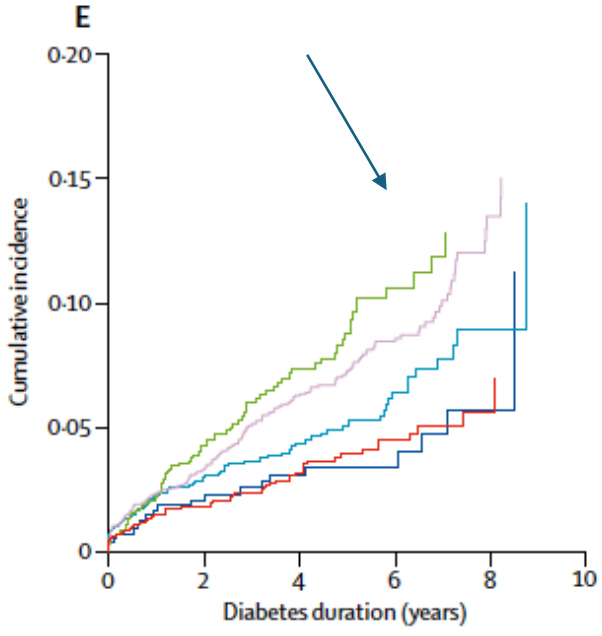


Time to chronic kidney disease (eGFR > 45/ml/1-73 m2))



Number at risk					
Cluster 1	496	362	220	82	11
Cluster 2	1325	912	511	180	17
Cluster 3	1061	669	337	105	13
Cluster 4	1607	1082	596	206	27
Cluster 5	2880	1968	1128	414	55

Time to coronary events



499	376	245	106	16
1325	936	557	215	32
996	658	349	118	20
1594	1115	647	252	43
26415	18450	1095	444	77

Cluster 1: severe autoimmune diabetes
Cluster 2: severe insulin-deficient diabetes
Cluster 3: severe insulin-resistant diabetes
Cluster 4: mild obesity-related diabetes
Cluster 5: mild age-related diabetes

Lancet Diabetes Endocrinol 2018

MASLD e rischio di malattia renale

Diabetes and Metabolism 50 (2024) 101506

Contents lists available at ScienceDirect

Diabetes & Metabolism

journal homepage: www.elsevier.com/locate/diabet

Review

Steatotic liver disease, MASLD and risk of chronic kidney disease

Josh Bilson [a,b,1], Alessandro Mantovani [c,1], Christopher D. Byrne [a,b,1], Giovanni Targher [d,e,1,*]

diabetesresearchandclinicalpractice 227 (2025) 112418

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.journals.elsevier.com/diabetes-research-and-clinical-practice

Association of chronic kidney disease and type 2 diabetes mellitus with metabolic dysfunction-associated steatotic liver disease and liver fibrosis assessed by transient elastography: a cross-sectional study based on NHANES 2017–2020

The Journal of Clinical Endocrinology & Metabolism, 2022, **107**, e3661–e3669
https://doi.org/10.1210/clinem/dgac382
Advance access publication 29 June 2022
Clinical Research Article

Fibrosis Risk in Nonalcoholic Fatty Liver Disease Is Related to Chronic Kidney Disease in Older Type 2 Diabetes Patients

The Journal of Clinical Endocrinology & Metabolism, 2024, **109**, 1308–1317
https://doi.org/10.1210/clinem/dgad682
Advance access publication 22 November 2023
Clinical Research Article

METHODS

Development of a New Model of Insulin Sensitivity in Patients With Type 2 Diabetes and Association With Mortality

Stefano Ciardullo,[1,2,*] Alessandro Roberto Dodesini,[3,*] Giuseppe Lepore,[3] Anna Corsi,[3] Cristiana Scaranna,[3] Gianluca Perseghin,[1,2] and Roberto Trevisan[2,3]

Original cohort (n=140) → **GDR Equation** → **1999-2010 NHANES cohort (n=3553)** → **Mortality (Dec 2015)**

log**IS** = 5.3505-0.3697*log(**GGT**, IU/L)-0.2591*log(**triglycerides**, mg/dl)-0.1169*log(**UACR**, mg/g)-(0.0279***BMI**, kg/m2)

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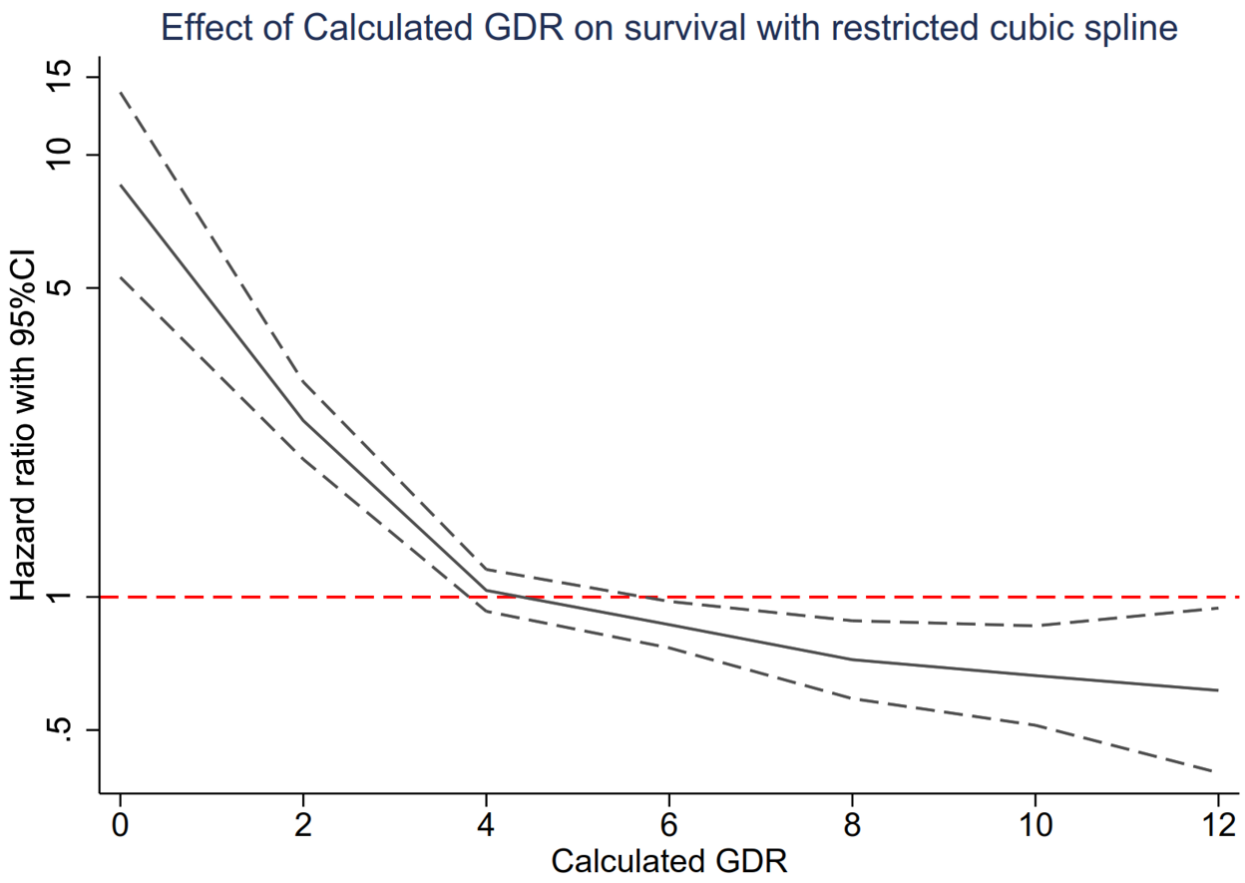
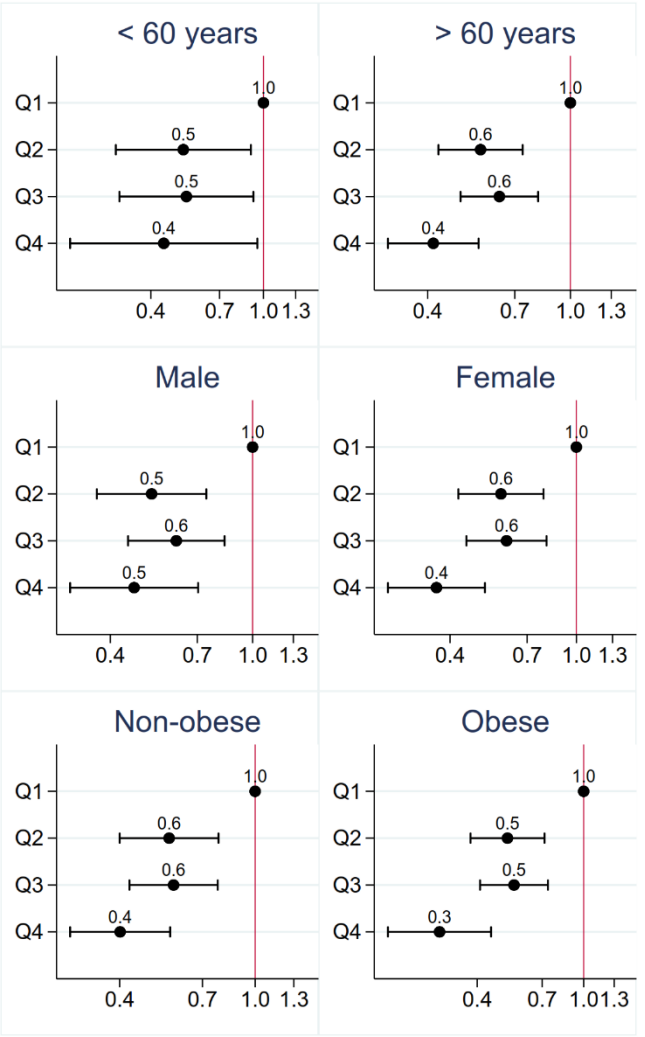
RESULTS

Restricted cubic splines



The Journal of Clinical Endocrinology & Metabolism, 2024, **109**, 1308–1317

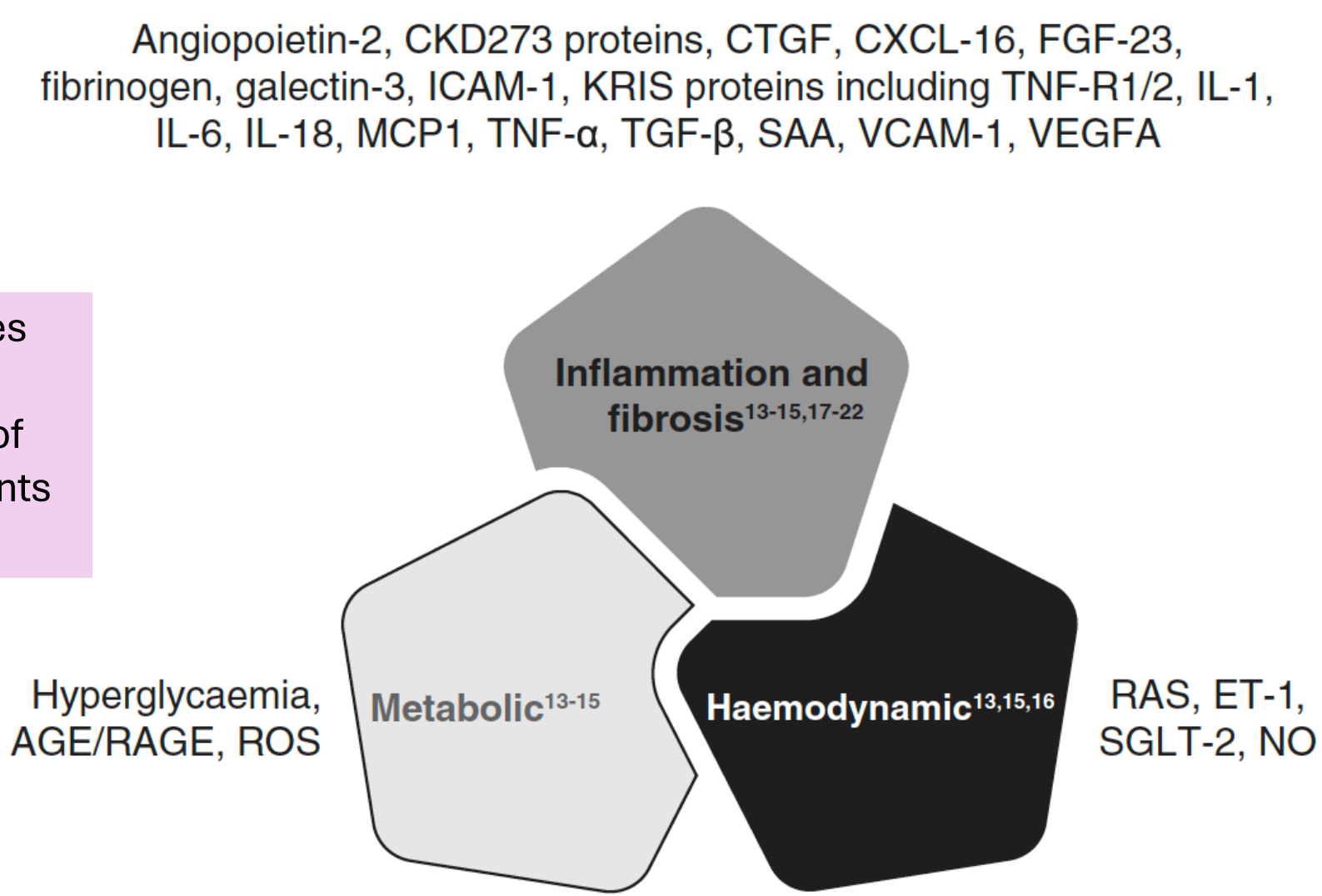
Subgroup analysis



Stratificazione precoce del rischio renale

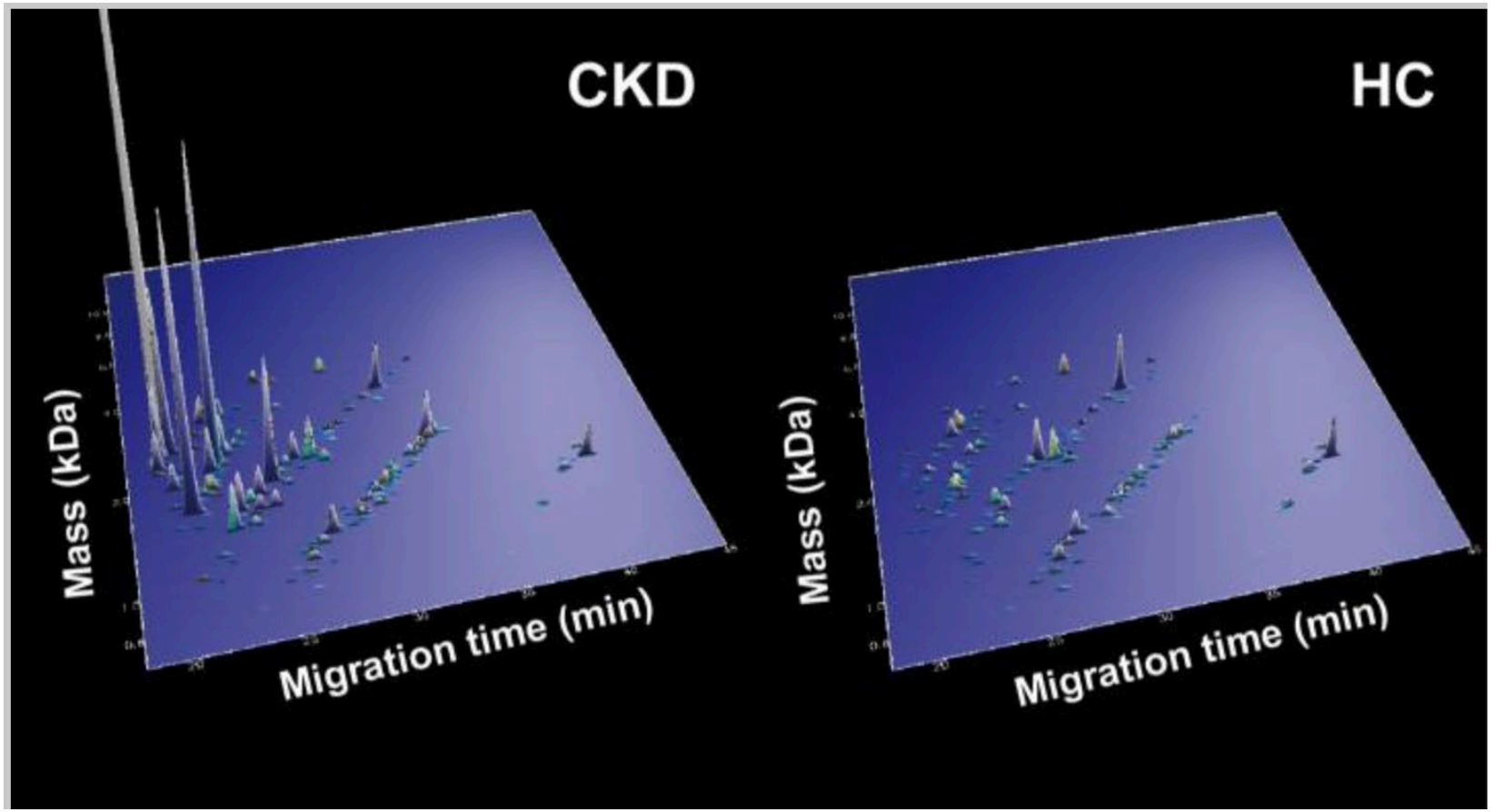
Biomarcatori precoci

Three interconnected processes contribute to the development and progression of chronic kidney disease in patients with type 2 diabetes



Diabetes Obes Metab. 2022;24:365–376.

Applying urinary proteomic analysis with capillary electrophoresis coupled to MS, Good et al. * described a high dimensional **urinary biomarker pattern composed of 273 peptides** associated with overt kidney disease: **CKD273**.
The components of CKD273 include collagen fragments and are assumed to relate to early fibrosis in the kidney.

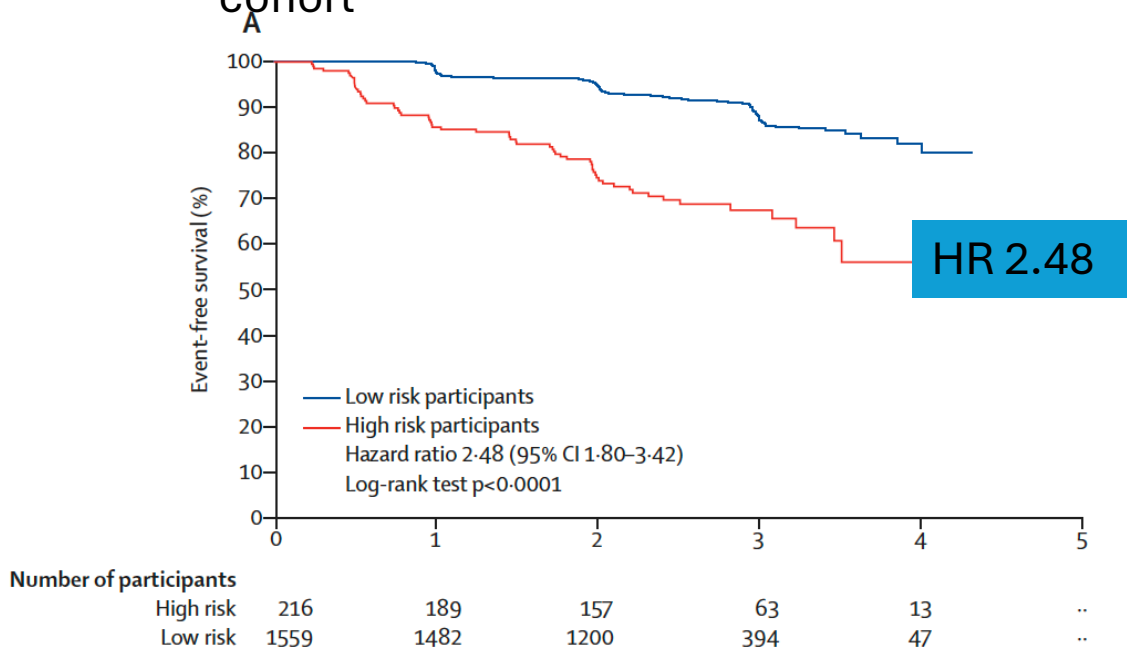


Mol Cell Proteomics 2010; 9:2424–2437

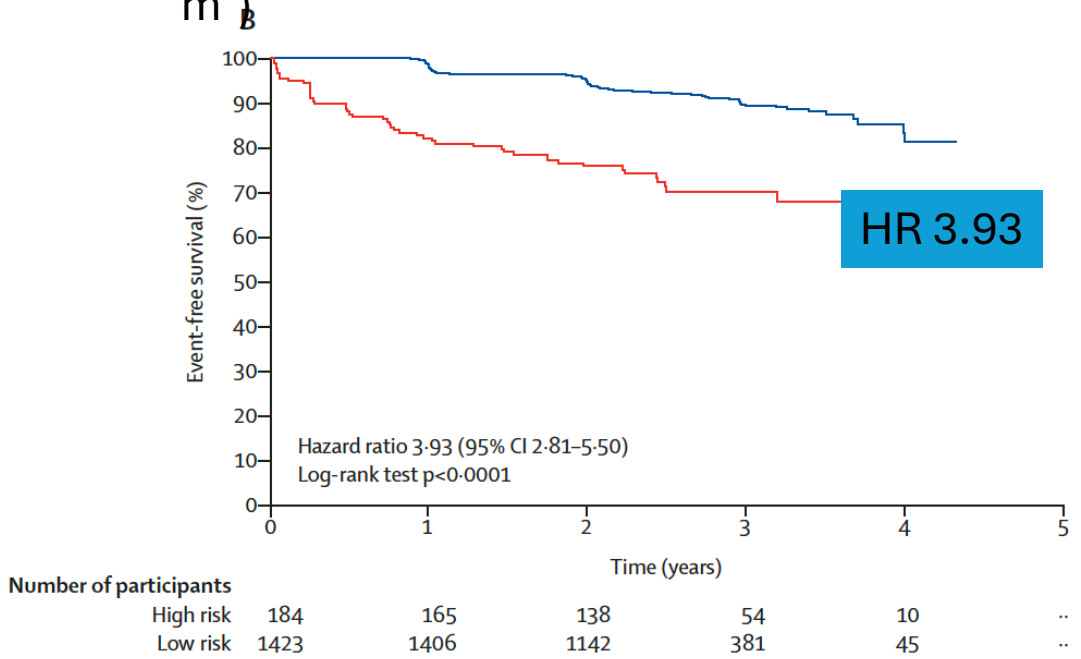
Progression to renal endpoints according to CKD273 risk score status in the observational cohort

1775 participants (people with type 2 diabetes, normal urinary albumin excretion, and preserved renal function)

Microalbuminuria in the observational cohort



Decrease in renal function and progression to CKD stage 3 (eGFR <60 mL/min per 1·73 m^2)



Lancet Diabetes Endocrinol 2020; 8: 301–312

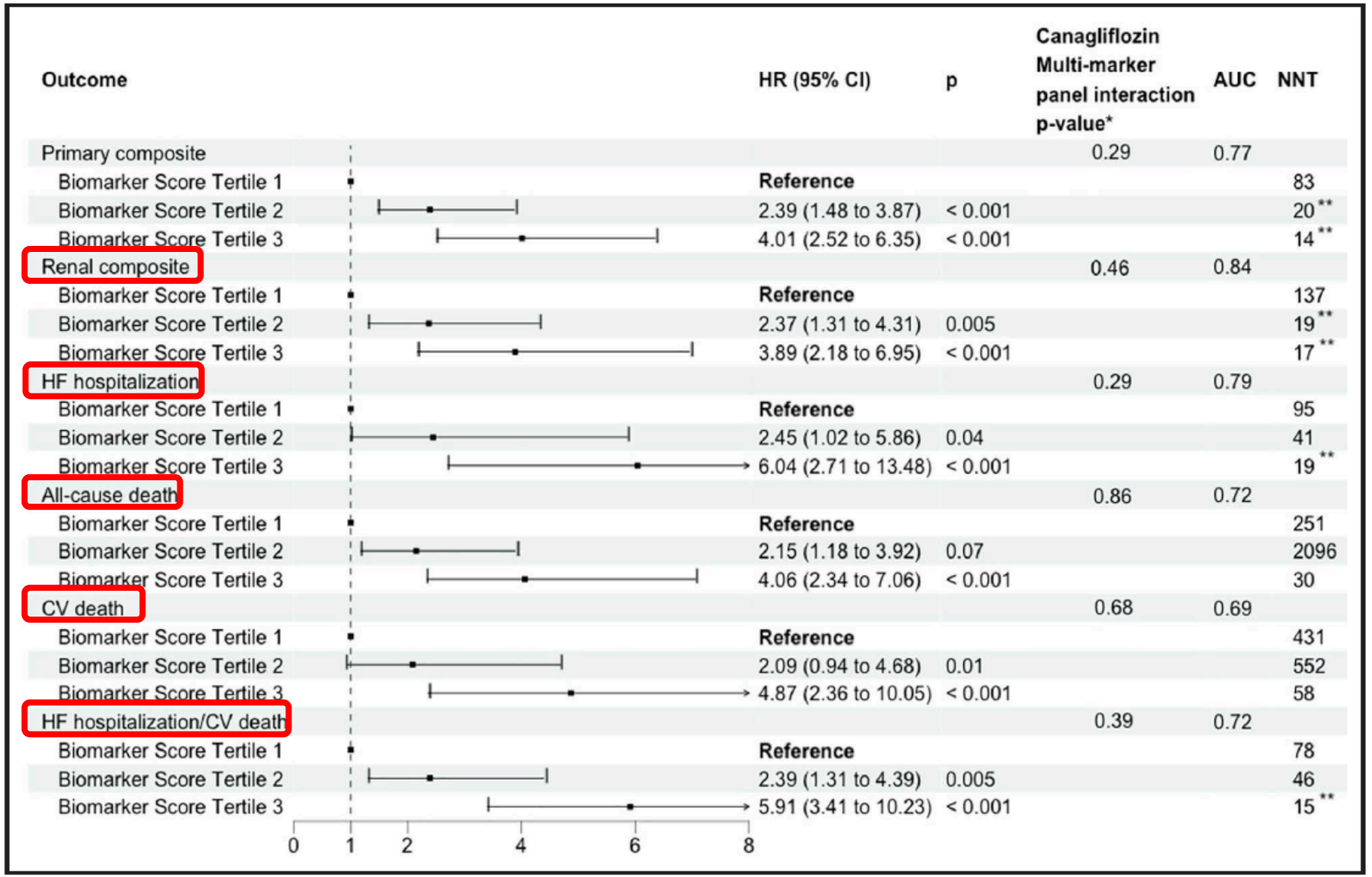
Cardiorenal Biomarkers, Canagliflozin, and Outcomes in Diabetic Kidney Disease: The CREDENCE Trial

Among 2627 study participants in the CREDENCE trial concentrations of the following biomarkers were measured:

- NT-proBNP (N-terminal pro-B-type natriuretic peptide),
- high-sensitivity cardiac troponin T,
- growth differentiation factor-15, and
- IGFBP7 (insulin-like growth factor binding protein 7)

Circulation. 2023;148:651–660.

Forest plot of outcomes of study participants as a function of multibiomarker score at baseline



Outcome	HR (95% CI)	p	Canagliflozin Multi-marker panel interaction p-value*	AUC	NNT
Primary composite			0.29	0.77	
Biomarker Score Tertile 1	Reference				83
Biomarker Score Tertile 2	2.39 (1.48 to 3.87)	< 0.001			20 **
Biomarker Score Tertile 3	4.01 (2.52 to 6.35)	< 0.001			14 **
Renal composite			0.46	0.84	
Biomarker Score Tertile 1	Reference				137
Biomarker Score Tertile 2	2.37 (1.31 to 4.31)	0.005			19 **
Biomarker Score Tertile 3	3.89 (2.18 to 6.95)	< 0.001			17 **
HF hospitalization			0.29	0.79	
Biomarker Score Tertile 1	Reference				95
Biomarker Score Tertile 2	2.45 (1.02 to 5.86)	0.04			41
Biomarker Score Tertile 3	6.04 (2.71 to 13.48)	< 0.001			19 **
All-cause death			0.86	0.72	
Biomarker Score Tertile 1	Reference				251
Biomarker Score Tertile 2	2.15 (1.18 to 3.92)	0.07			2096
Biomarker Score Tertile 3	4.06 (2.34 to 7.06)	< 0.001			30
CV death			0.68	0.69	
Biomarker Score Tertile 1	Reference				431
Biomarker Score Tertile 2	2.09 (0.94 to 4.68)	0.01			552
Biomarker Score Tertile 3	4.87 (2.36 to 10.05)	< 0.001			58
HF hospitalization/CV death			0.39	0.72	
Biomarker Score Tertile 1	Reference				78
Biomarker Score Tertile 2	2.39 (1.31 to 4.39)	0.005			46
Biomarker Score Tertile 3	5.91 (3.41 to 10.23)	< 0.001			15 **

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Stratificazione precoce del rischio renale

- ↑ ACR
- ↑ eGFR
- ↑ Età e durata diabete
- ↑ BP
- ↑ A1c
- ↑ BMI

- ↑ TG and ↓ HDL
- ↑ FIB 4
- Retinopatia
- Rischio CVD (Score 2-Diabetes)

Stratificazione precoce del rischio renale

Sviluppi futuri

Multiomica

Imaging (RM)

Conclusion

- In future treatment and prevention of DKD, a shift towards a more personalised approach is desirable. The overall aim would be a panel of different non-invasive markers, both including omics- and other biomarkers, revealing the aetiology of DKD and guiding the clinician in selection of the intervention that the individual would benefit the most from.
- More studies including several cohorts of patients and human kidney biopsies are warranted to validate these markers and determine their reflection of underlying aetiology.
- Moreover, quantification, automation, reliability and reproducibility among individual laboratories and across countries are continuously being developed and needed before clinical application of these potential biomarkers.
- Hopefully, this will lead to a better stratification and prevention of renal and cardiovascular outcome in the future.


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