



SHARING EVENTS

Impact of diabetes drugs on cardiovascular and renal disease in type 2 diabetes

La diagnosi di nefropatia diabetica
C. Zoccali



Evoluzione della diagnosi di nefropatia diabetica, storia naturale della malattia, l'albuminuria come elemento centrale per strategie preventive

Oltre l'albuminuria, strumenti di «precision nephrology»

Autopsy study: eight patients who died of renal failure

hypertension, heavy albuminuria, and edema

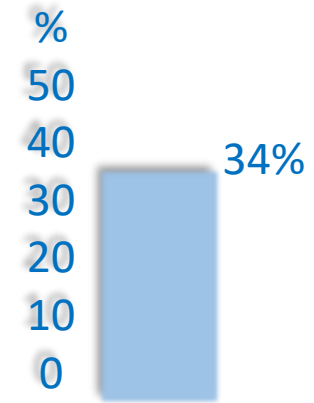
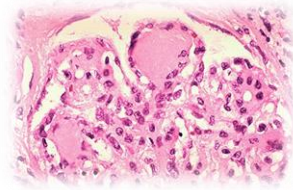
Seven out eight were diabetic



The archetype lesion of diabetic nephropathy

Kimmelstiel P, Wilson C. Intercapillary lesions in glomeruli of kidney. *Am J Pathol.* 1936;12:83.

!! Highly specific to diabetes



← only three other patients →

105 patients with diabetes

100 patients with hypertension

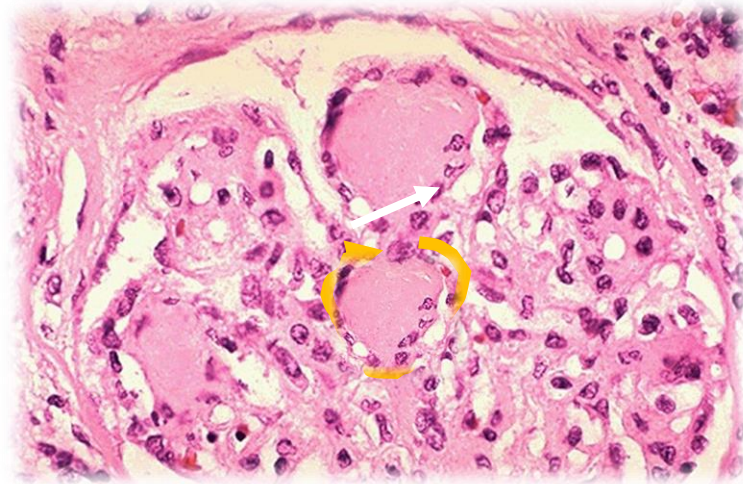
100 patients without hypertension or diabetes

34 patients with glomerulonephritis

Arthur C Allen. So-called intercapillary glomerulosclerosis—a lesion associated with diabetes. Arch Pathol. 1941;32:33–51.

Autopsy study: eight patients who died of renal failure

hypertension, heavy albuminuria edema
Seven out eight were diabetic



Kimmelstiel P, Wilson C. Intercapillary lesions in glomeruli of kidney. *Am J Pathol.* 1936;12:83.

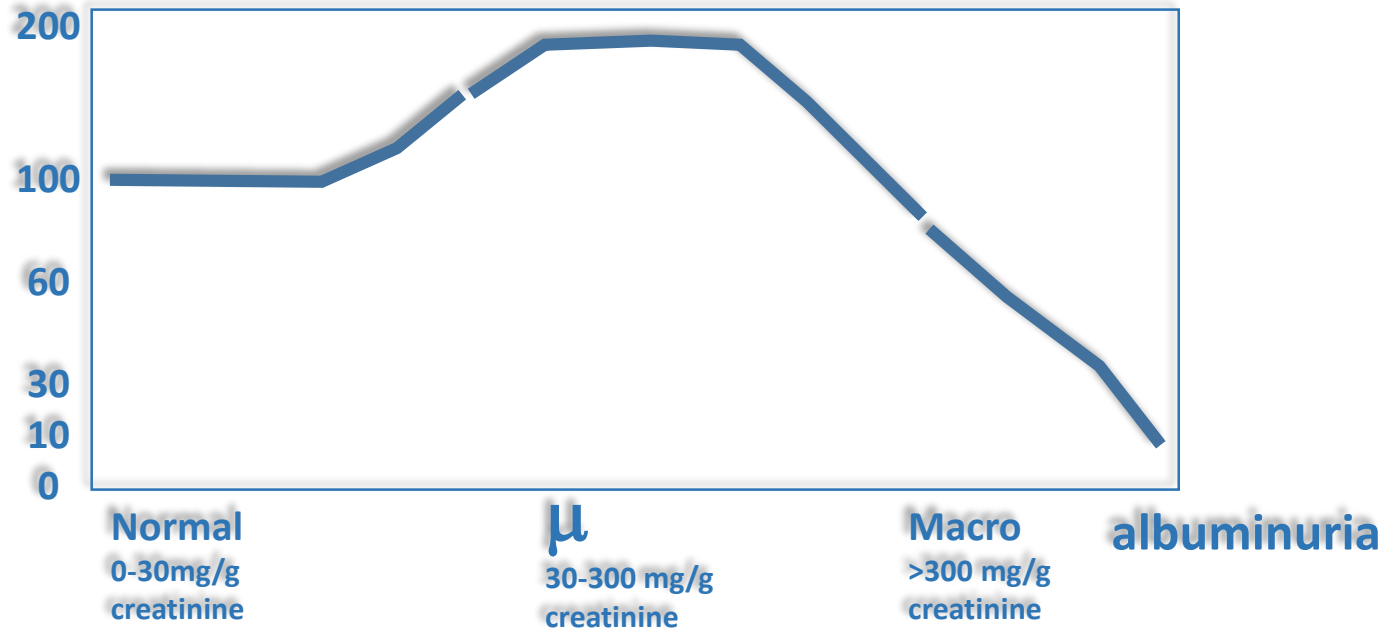
1945-1980...a flurry of studies on proteinuria in diabetes...>400 papers in PubMed



Mechanistic and cohort studies of the etiologic and prognostic role of albuminuria in patients with type 1 and 2 diabetes in Denmark in '70-'80

Copenhagen Aarhus

GFR (ml/min/1.73 m²)



... incipient diabetic nephropathy (DN) is classically defined by increasing albuminuria, heralding a decline in glomerular filtration rate (GFR)

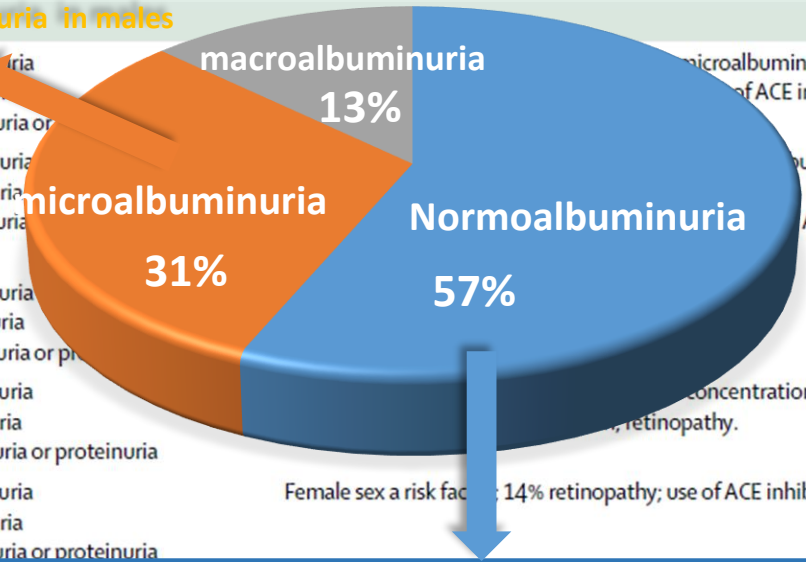
... which usually does not occur until the transition to macroalbuminuria (overt DN).

Porrini et al., *Lancet Diabetes Endocrinol* 2015; 3: 382–91

1988-2014 Community-based surveys of the occurrence of low GFR and albuminuria in type 2 diabetics

N	Outcomes		Comments
	GFR < 60 mL/min per 1.73 m ²	Albuminuria/proteinuria	
Cross-sectional studies	Higher risk for progression to macroalbuminuria in males		
Kramer et al (2003) ¹⁷ (NAHNES 1988-1994)	1197	171 (14%)	36% normoalbuminuria 45% microalbuminuria 19% macroalbuminuria or proteinuria
MacIsaac et al (2004) ¹⁸	301	109 (36%)*	39% normoalbuminuria 35% microalbuminuria 26% macroalbuminuria or proteinuria
So et al (2006) ¹⁹	4421	528 (12%)	14% normoalbuminuria 26% microalbuminuria 60% macroalbuminuria or proteinuria
Yokoyama et al (2009) ²⁰	3297	506 (15%)	52% normoalbuminuria 21% microalbuminuria 27% macroalbuminuria or proteinuria
Thomas et al (2009) ²¹ (NEPHRON 11)	3892	920 (23%)	55% normoalbuminuria 32% microalbuminuria 13% macroalbuminuria or proteinuria
Penno et al (2011) ²² (RIACE study)	15773	2959 (19%)	57% normoalbuminuria 31% microalbuminuria 13% macroalbuminuria or proteinuria
Dwyer et al (2012) ²³ (DEMAND study)	11573	2586 (22%)	40% normoalbuminuria 47% microalbuminuria 13% macroalbuminuria or proteinuria
Mottl et al (2013) ²⁴ (NAHNES 2001-2008)	2798	575 (21%)	52% normoalbuminuria 48% microproteinuria
Boronat et al (2014) ²⁵	..	78 (GFR <30 ml/min)	22% normoalbuminuria 20% microalbuminuria 58% proteinuria

19% GFR < 60 ml/min/.1.73 m²



Risk factors: female sex, obesity, triglyceride concentrations, hypertension
32% retinopathy; 43% no retinopathy plus microalbuminuria or proteinuria; use of ACE inhibitors >70%

Risk factors: female sex, hypertension, retinopathy, dyslipidaemia, smoking, hyperglycaemia

Chronic kidney disease, normoalbuminuria and microalbuminuria more frequent in women than in men; hypertension and hyperglycaemia were protective factors

Female sex a risk factor; hyperglycaemia and polyneuropathy were protective factors; 29% retinopathy in normoalbuminuria, 53% in microalbuminuria or proteinuria

UK Prospective Diabetes Study (UKPDS-74)



14% normoalbuminuric patients developed GFR <60 mL/min/1.73 m² as the sole alteration

Follow up 15 years

Diabetes 2006; 55: 1832–39.

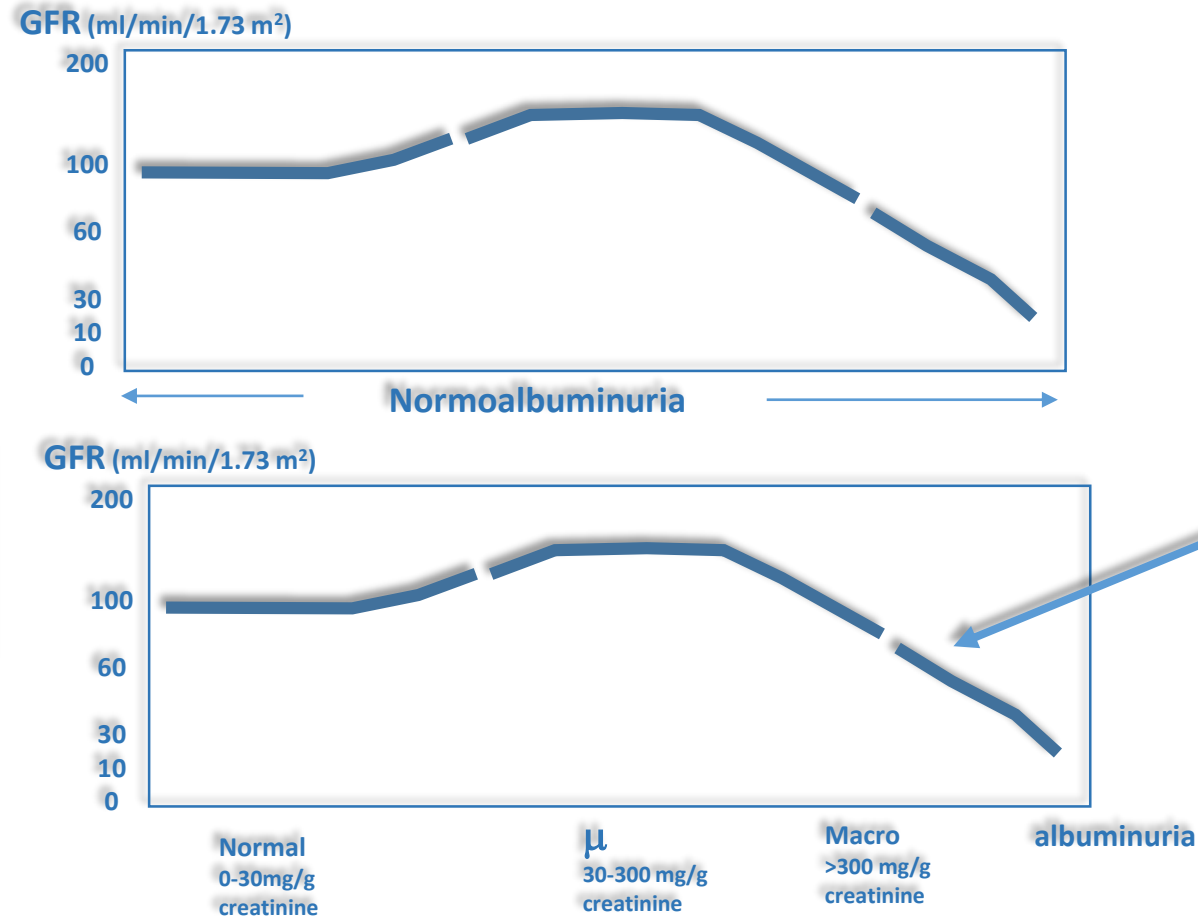
Atherosclerosis in the community (ARIC)



56% who developed GFR <60 mL/min/1.73 m² were initially normoalbuminuric

Follow up 11 years

Arch Intern Med 2008; 168: 2440–47.

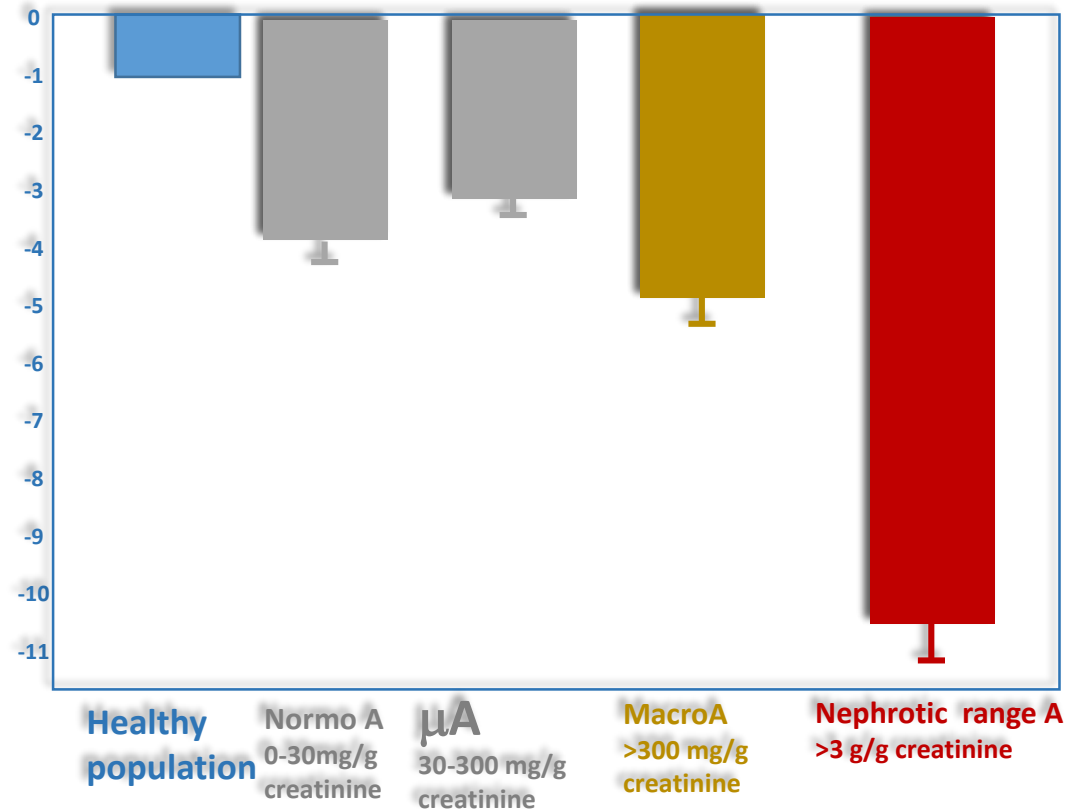


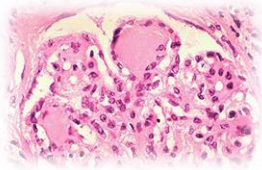
When present, macroalbuminuria is a strong predictor of faster GFR loss in diabetes

Diabetic Kidney Disease: evidence of renal dysfunction (i.e. GFR loss) and/or damage (albuminuria) in patients with diabetes

GFR decline (ml/min/1.73 m²) and albuminuria

data from studies that did repeated golden standard GFRs



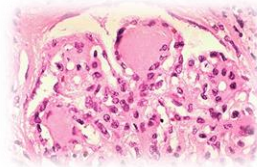


Clino-Pathological relationship

Strong relation with albuminuria in the seminal small series by Kimmelstiel

Renal Structure in Normoalbuminuric and Albuminuric Patients With Type 2 Diabetes and Impaired Renal Function

EKINCI IF et al., *Diabetes Care* 36:3620–3626, 2013



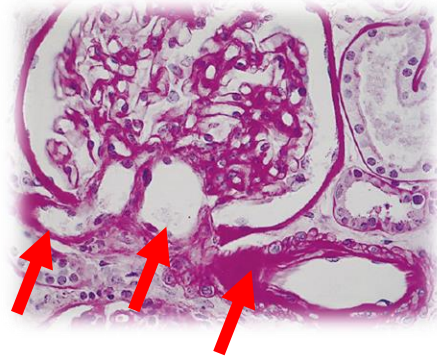
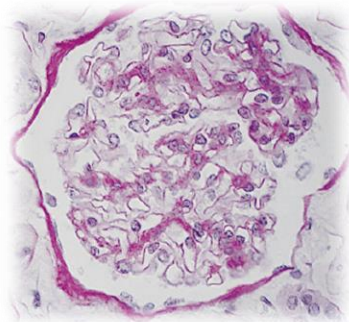
Type 2 diabetics CKD stage G3-4

~37% ~83% ~100%

Normo A
0-30mg/g
creatinine

μ A
30-300 mg/g
creatinine

MacroA
>300 mg/g
creatinine

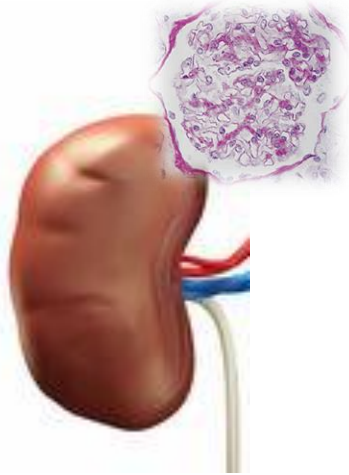




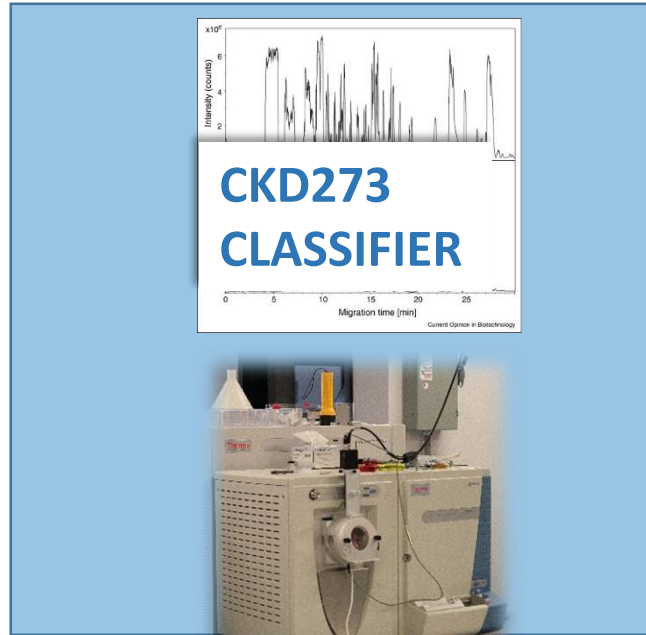
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Oltre l'albuminuria, strumenti di «precision nephrology»

Pathway to Diabetic Nephropathy and Kidney failure



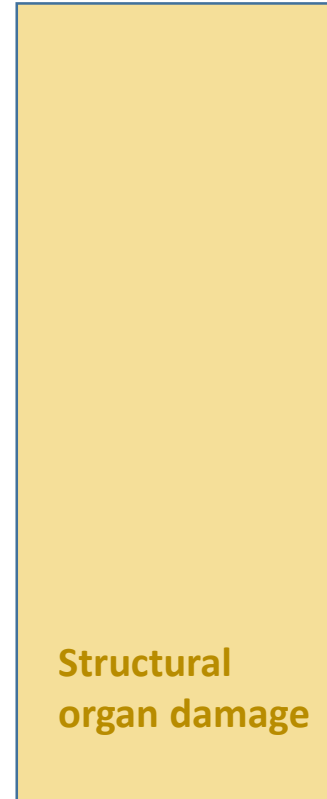
Healthy
KIDNEY



Molecular
Alterations

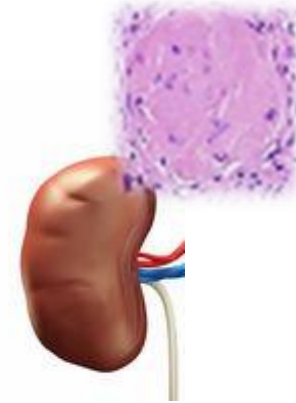
Minor
structural
damage

PROTEOMICS



Structural
organ damage

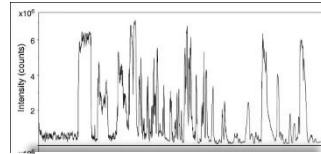
μ A



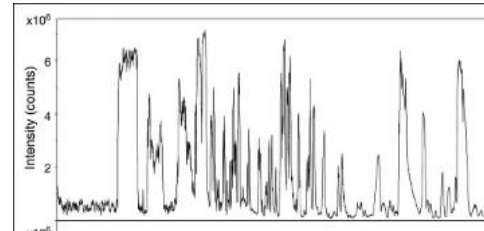
Organ
failure



5010 peptides



**CKD273
CLASSIFIER**



CKD patients

273 peptides \Rightarrow CKD273

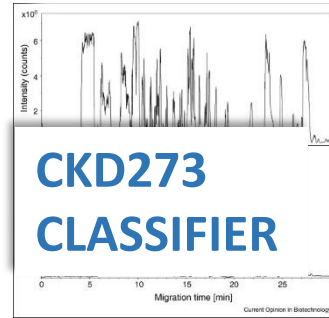
74% collagen fragments. Reduced peaks of most of these these fragments was the most prominent difference between Healthy subjects and CKD patients.

Interpretation: due to reduced degradation (by metalloproteinases) collagen accumulates in the extracellular matrix leading to kidney fibrosis.

Urinary Proteomics for Early Diagnosis in Diabetic Nephropathy

Petra Züribig,¹ George Jerums,² Peter Hovind,³ Richard J. MacIsaac,⁴ Harald Mischak,^{1,5} Stine E. Nielsen,³ Sianna Panagiotopoulos,² Frederik Persson,³ and Peter Rossing³

Diabetes 61:3304–3313, 2012



316 urine samples Samples were available from patients with type 1 (n = 16) or type 2 (n = 19)

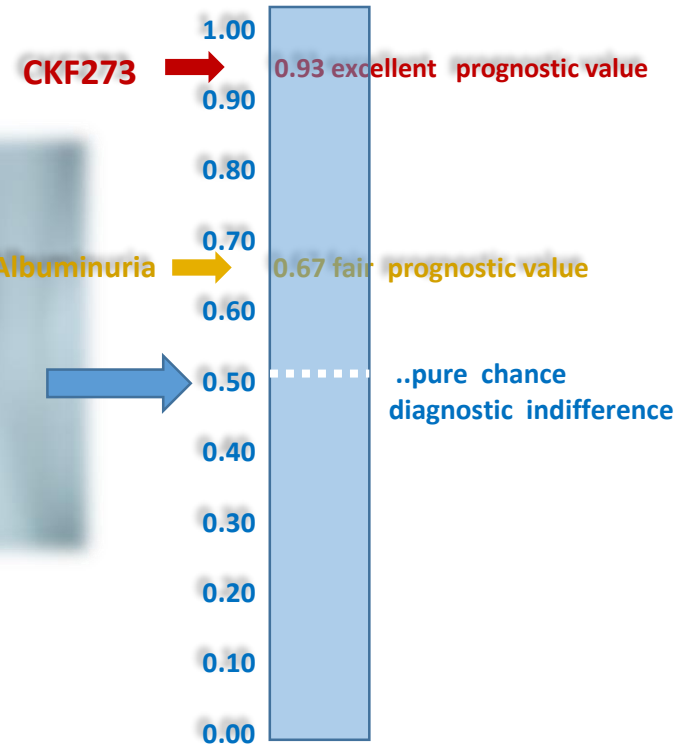


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Diabetes 61:3304–3313, 2012

Correct Prediction of Macroalbuminuria



Prediction Time

μ-albuminuria

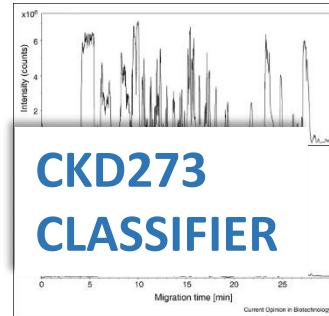
3.4 years earlier

Macro Albuminuria

4.9 years earlier

CKD273
classifier





Cost-effectiveness of screening type 2 diabetes patients for chronic kidney disease progression with the CKD273 urinary peptide classifier as compared to urinary albumin excretion

Elena Critselis¹, Antonia Vlahou¹, Vianda S. Stel² and Rachael L. Morton³

¹Proteomics Laboratory, Center for Basic Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece, ²ERA-EDTA Registry, Department of Medical Informatics, Academic Medical Center, University of Amsterdam, Amsterdam Public Health Research Institute, Amsterdam, The Netherlands and ³National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Sydney, Australia



DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: June 14, 2016

ATTN: Harald Mischak, Dr. Med. Habil, Ph.D.
Mosaiques-diagnostics GmbH
Rotenburger Str. 20
D-30659 Hannover
GERMANY

Subject: Biomarker Letter of Support

Dear Dr. Mischak,

We are issuing this Letter of Support to Mosaiques Diagnostics GmbH to encourage the further development of CKD273, a prognostic enrichment biomarker panel composed of 273 urinary peptides, to be used in combination with current measures (i.e., albuminuria, serum creatinine) in early phase clinical trials in diabetic kidney disease (DKD) to identify patients with early stage disease who may be more likely to progress. For a listing of the components of the CKD273 biomarker panel, please see Appendix 1.

**CKD273 use approved in Germany
..already available as an *in vitro* diagnostic
device for the early detection of CKD in
diabetic patients.**

**urine sample is shipped overnight to the analytical
laboratory, and the results are reported back to the
sender within 5 days.**

**cost still covered by some private health insurance
companies only.**

S & C

Diabetic nephropathy is a structurally and pathophysiologically heterogeneous disease and may evolve into kidney failure both in albuminuric and non-albuminuric patients

the severity of albuminuria goes along with the rate of GFR loss.

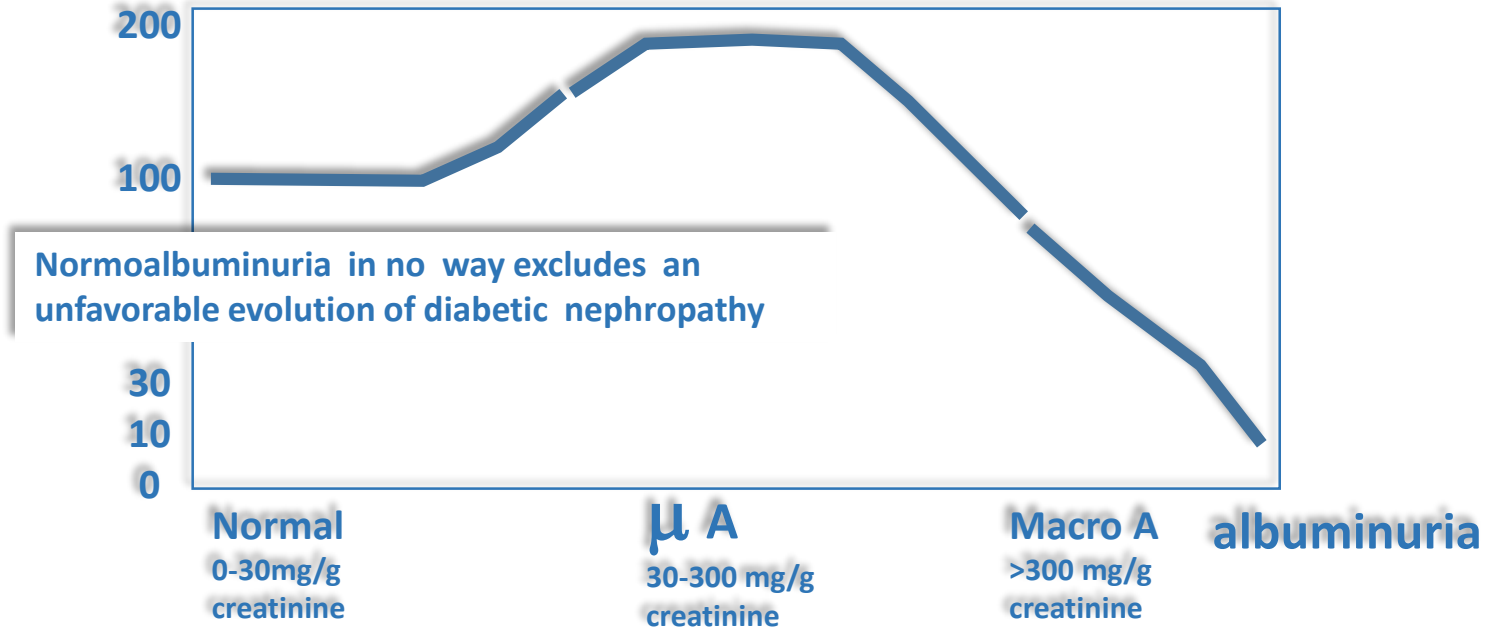
In normoalbuminuric patients female gender, hypertension, overweight-obesity, are the main risk factors for the risk of CKD

A new peptidomic classifier outperforms albuminuria for the prediction of Macro-Albuminuria. Initial cost-effectiveness analyses support further development of this classifier.



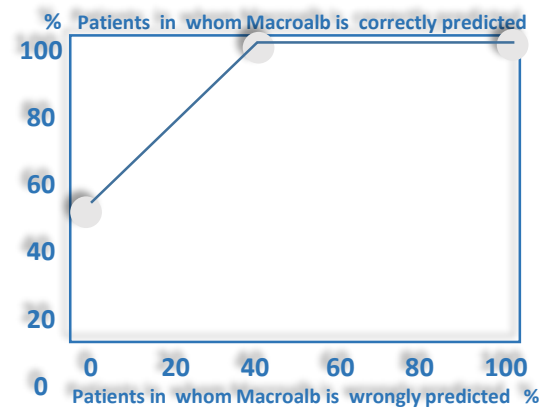
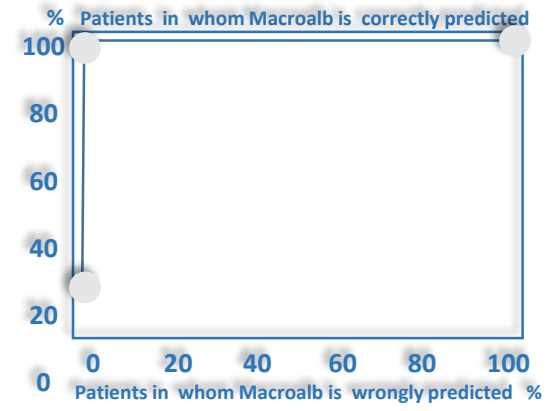
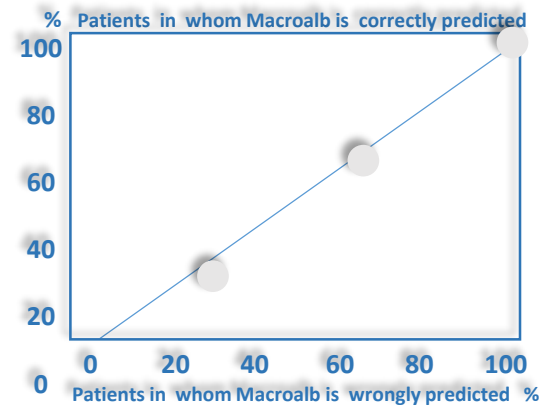
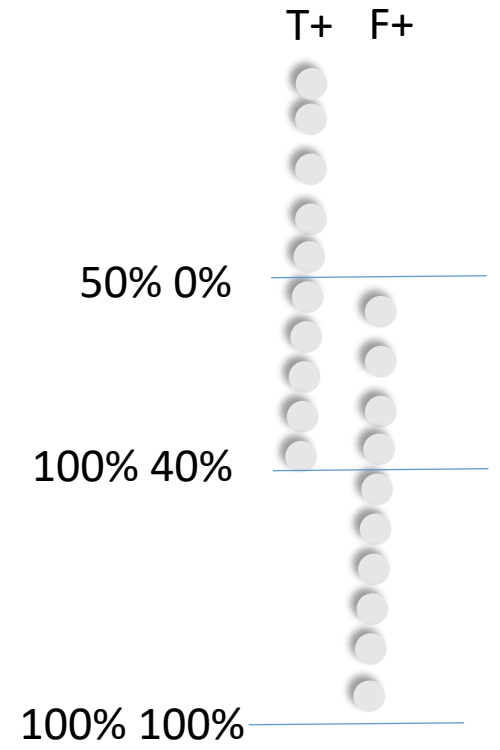
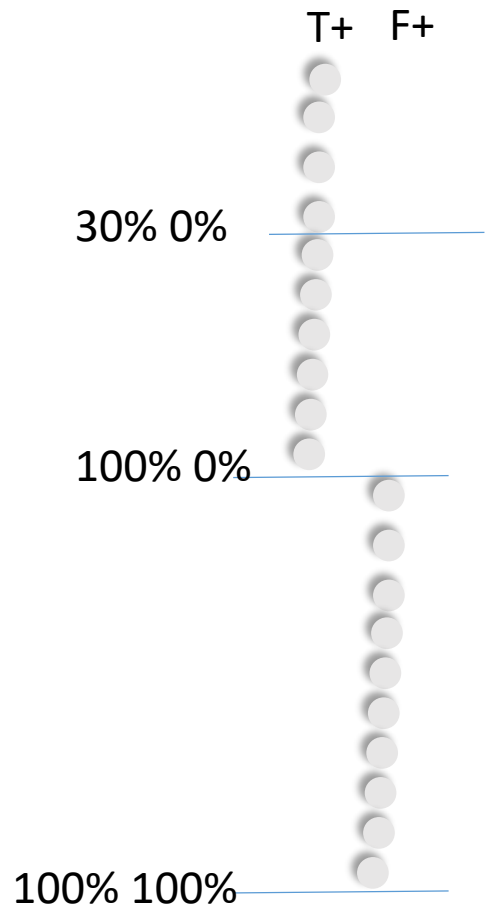
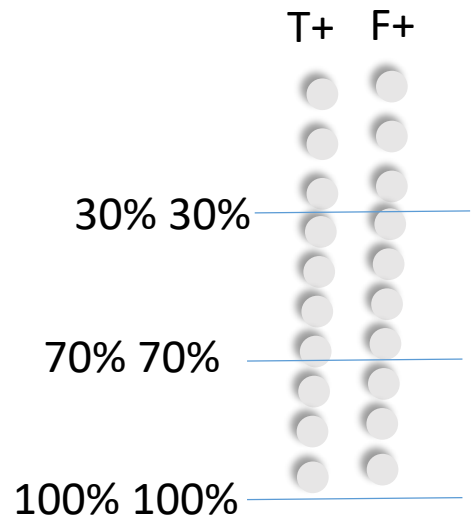
Mechanistic and cohort studies in patients with type 1 and 2 diabetes in Denmark in '70-'80

GFR (ml/min/1.73 m²)



Albuminuria remains the most applied biomarker for prevention of Diabetic Nephropathy

Diabetes 1983; 32 (suppl 2): 64–78.

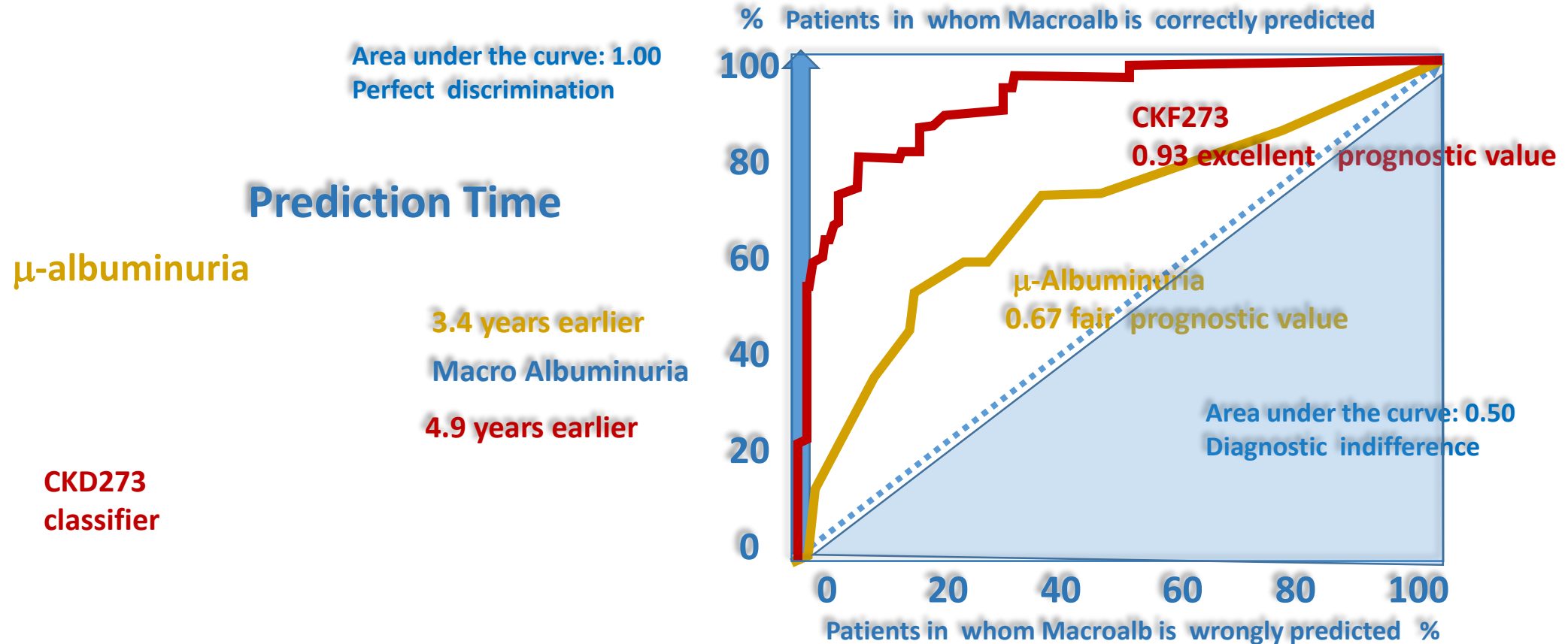


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Diabetes 61:3304–3313, 2012

Prognostic value of μ -albuminuria and CKD273 for Macroalbuminuria

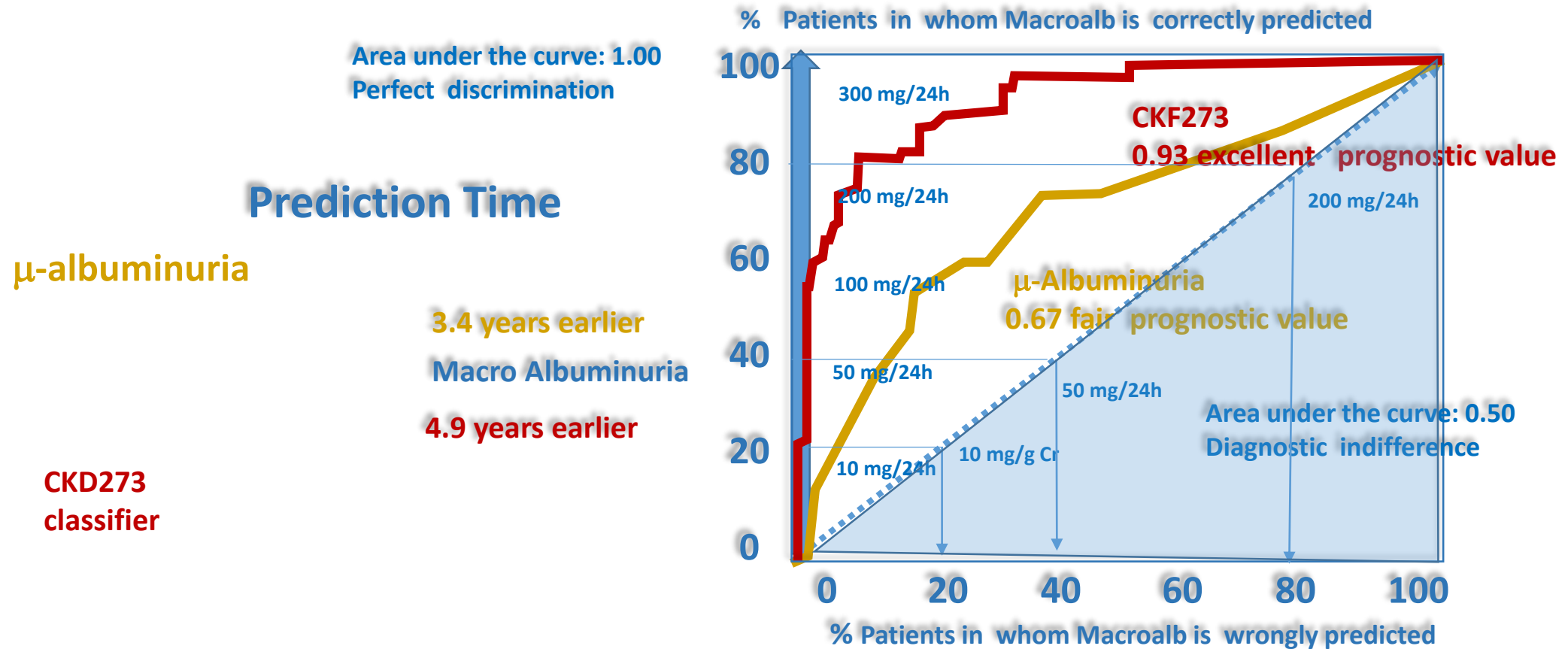


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Non-proteinuric rather than proteinuric renal diseases are the leading cause of end-stage kidney disease

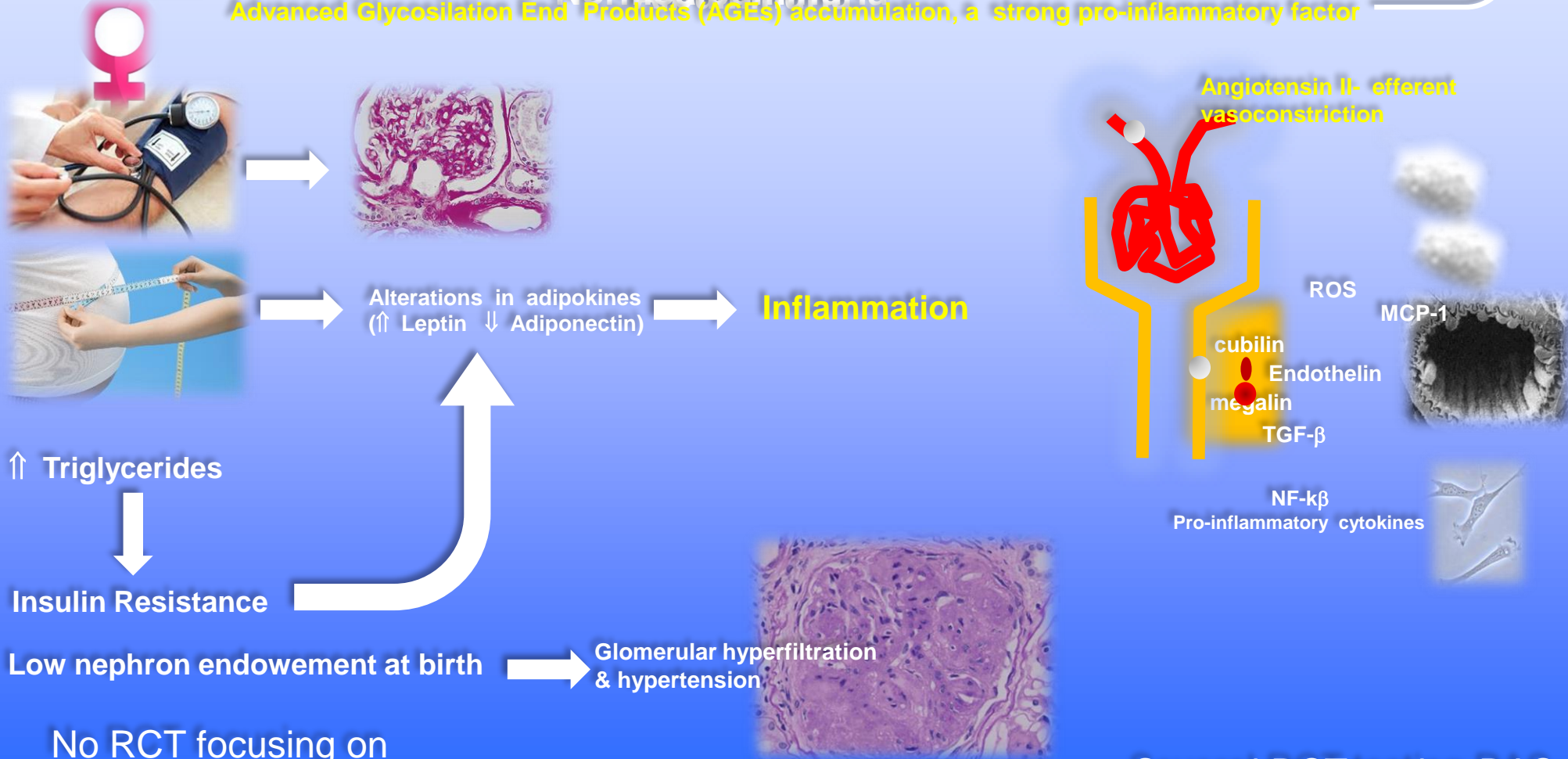
Davide Bolignano and Carmine Zoccali

Clinical Epidemiology and Pathophysiology of Renal Diseases and Hypertension, CNR-IFC, Reggio Calabria, Italy

Nephrol Dial Transplant (2017) 32: ii194–ii199

Normoalbuminuria

Advanced Glycosylation End Products (AGEs) accumulation, a strong pro-inflammatory factor



No RCT focusing on normoalbuminuric patients

Several RCT testing RAS inhibitors and other therapies

Diabetic Kidney Disease

.... incipient diabetic nephropathy (DN) is classically defined by increasing albuminuria, heralding a decline in glomerular filtration rate (GFR)
.... which usually does not occur until the transition to macroalbuminuria (overt DN).

However, a high proportion of patients with either type 1 or type 2 diabetes does not follow this classical albuminuric pathway, instead showing declining renal function in the absence of an elevated albumin excretion rate

Diabetic Kidney Disease: evidence of renal dysfunction (i.e. GFR loss) or damage (albuminuria) in patients with diabetes

Renal Pathology Society classification

Class I Isolated glomerular basement membrane thickening

Class II Mild (class IIa) or severe (class IIb) mesangial expansion

Class III At least one Kimmelstiel-Wilson lesion (nodular intercapillary glomerulosclerosis) is observed on biopsy and there is <50 percent global glomerulosclerosis

Class IV There is >50 percent global glomerulosclerosis that attributable to diabetic nephropathy

Tervaert TW et al. J Am Soc Nephrol. 2010;21(4):556.