







PROTEINURIA (ASPECTOS FISIOPATOLOGICOS Y SIGNIFICADO CLINICO)

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ERC: Antecedentes generales

- ERC afecta 5-7% de la población mundial
 - ERC es un grupo de alto riesgo de hospitalización
 - ERC es un grupo de alto RCV (peor que tener antecedentes de evento CV o DM)
 - El 80% de los ERC desconoce su condición y progresa en su enfermedad sin percatarse de ello
 - La mitad de los sujetos con ERC mueren de eventos CV antes de requerir TSR
 - Dos de cada 3 sujetos con ERC mueren dentro de los primeros 5 años de diálisis (peor expectativa de vida que la ICC o muchos cánceres)

¿CÓMO DEFINIMOS ERC?

- 1. Daño renal por ≥3 meses, definido por anormalidades estructurales o funcionales del riñón, con o sin disminución de la VFG, manifestado por:
 - Anormalidades anátomo o histopatológicas, o
 - Marcadores de daño renal, incluyendo anormalidades sanguíneas o urinarias, o anormalidades en exámenes imagenológicos.
- 2. VFG <60 mL/min/1,73 m² por ≥3 meses, con o sin daño renal.

EVALUACIÓN DE DAÑO RENAL

- 1. Proteinuria
- 2. Sedimento urinario
- 3. Estimación de la filtración glomerular
- 4. Imágenes renales
- 5. Evidencia histológica (Biopsia renal)

Proteinuria (medición)

- Examen de orina completo (utilizando tiras reactivas)
- Determinación de los niveles de albuminuria (ensayos inmunológicos con mayor sensibilidad)
- Cuantificación de la proteinuria (aislada o de 24 horas)
- Indice Albuminuria/Creatininuria en muestra aislada:
 - Corrige los errores del volumen urinario
 - Excelente correlación con los análisis de 24 horas.

Medición de la albuminuria (microalbuminuria)

- NO sirve el ex de orina corriente (sensibilidad 300 mg/día)
- Muestra aislada de orina (idealmente matinal, con medición concomitante de creatininuria para corregir cambios de concentración urinaria).

Expresar en mg albúmina/g de creatinina

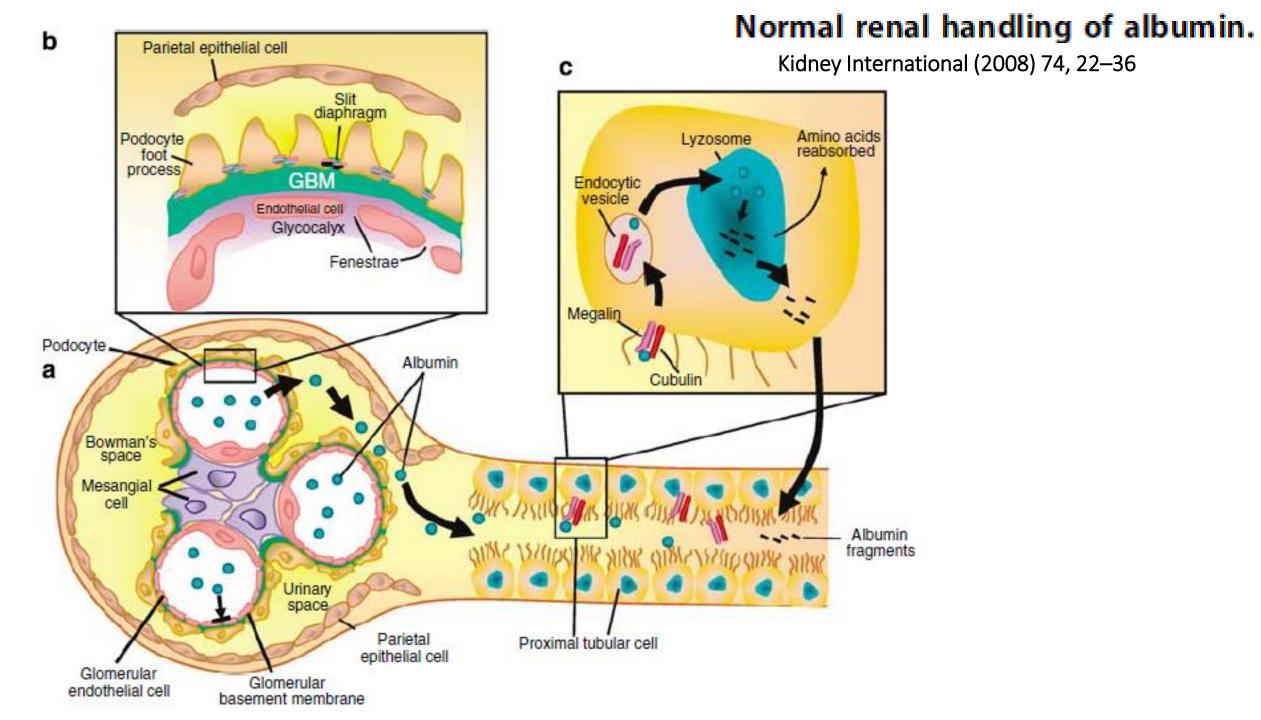
• Evitar toma de muestra con ejercicio e infecciones (no sólo ITU)

Evitar el término "microalbuminuria". (VN sería ahora hasta 10 mg/g)

Definición de Proteinuria y Albuminuria

CATEGORÍA	Valor (mg/24 h)	Valor (mg/ g creatinina)
Excreción de Proteína		P/C
Normal	<150	<200
Proteinuria	>150	>200
Proteinuria nefrótica	>3.500	>3.500
Excreción de Albúmina		A/C
Normal	< 30	<30
Microalbuminuria	30-300	30-300
Macroalbuminuria	>300	>300

P/C: cuociente proteína-creatinina, A/C: cuociente albúmina-creatinina.



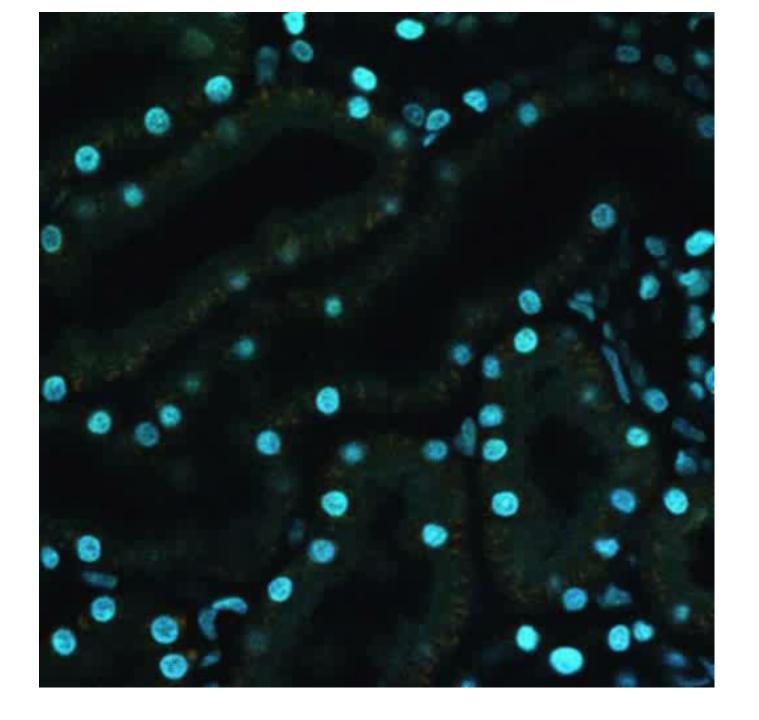


Figura 1 Rápida aparición de albúmina en el ribete en cepillo

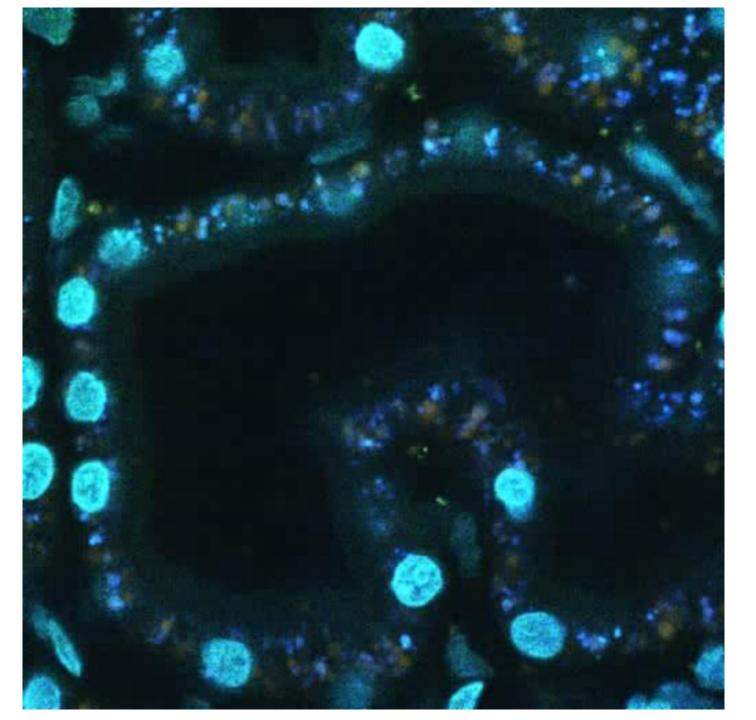


Figura 2 Albúmina pasa a la base del ribete en cepillo

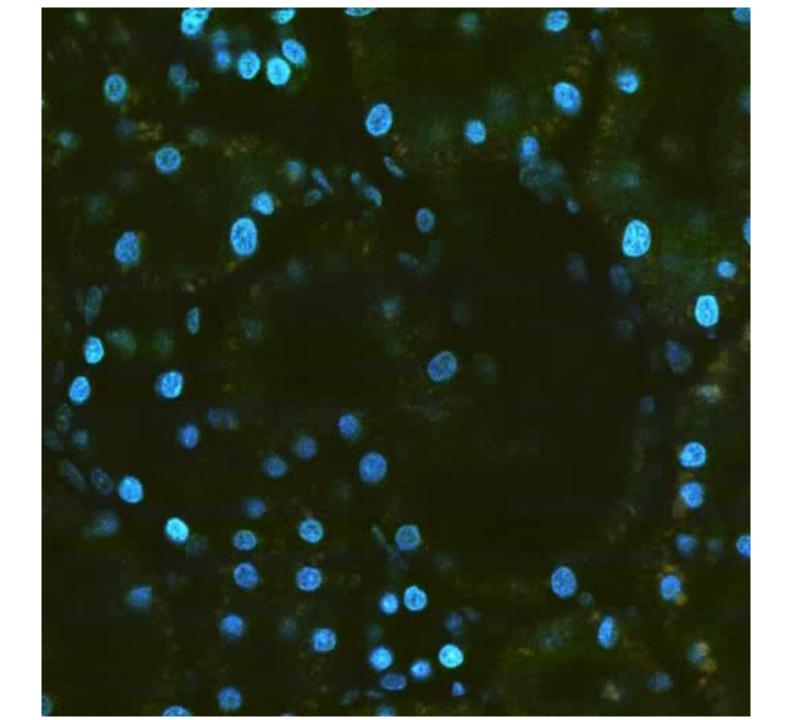


Figura 3 Albúmina en la base del ribete en cepillo

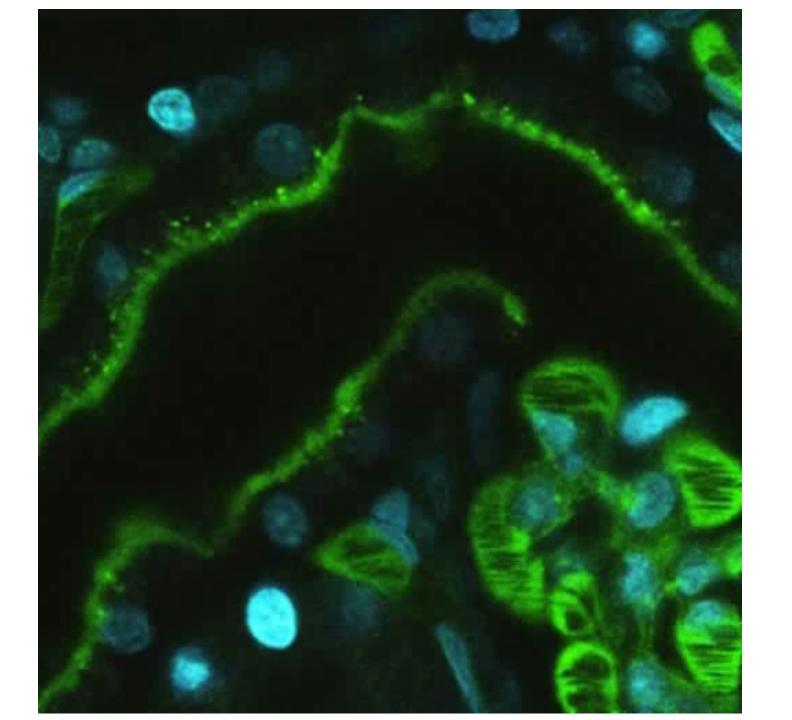
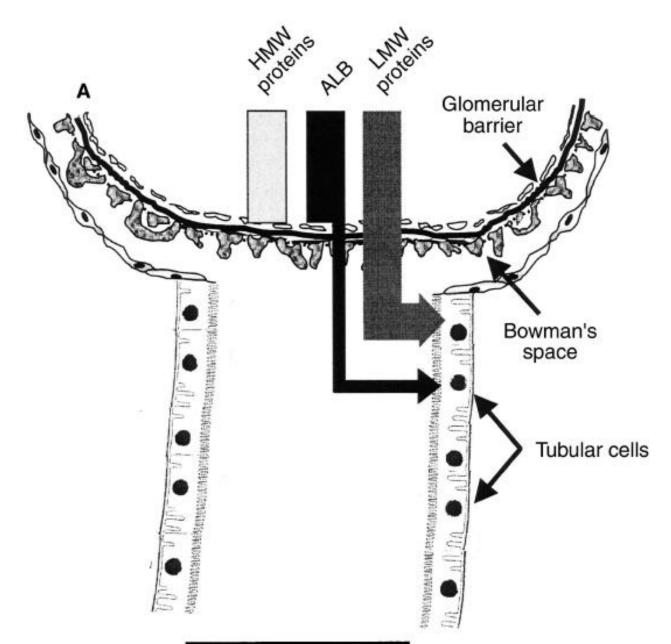
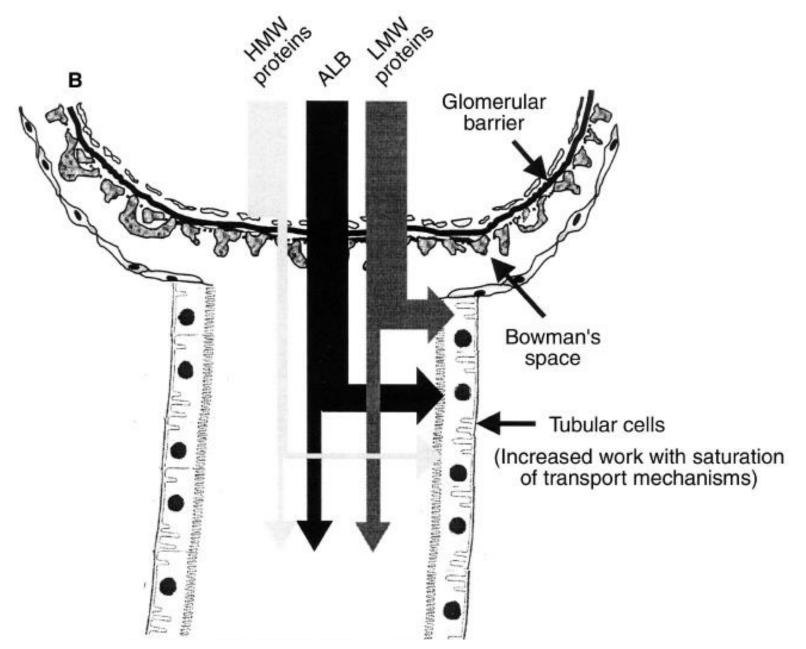


Figura 3 Albúmina en vesículas intracitoplasmáticas

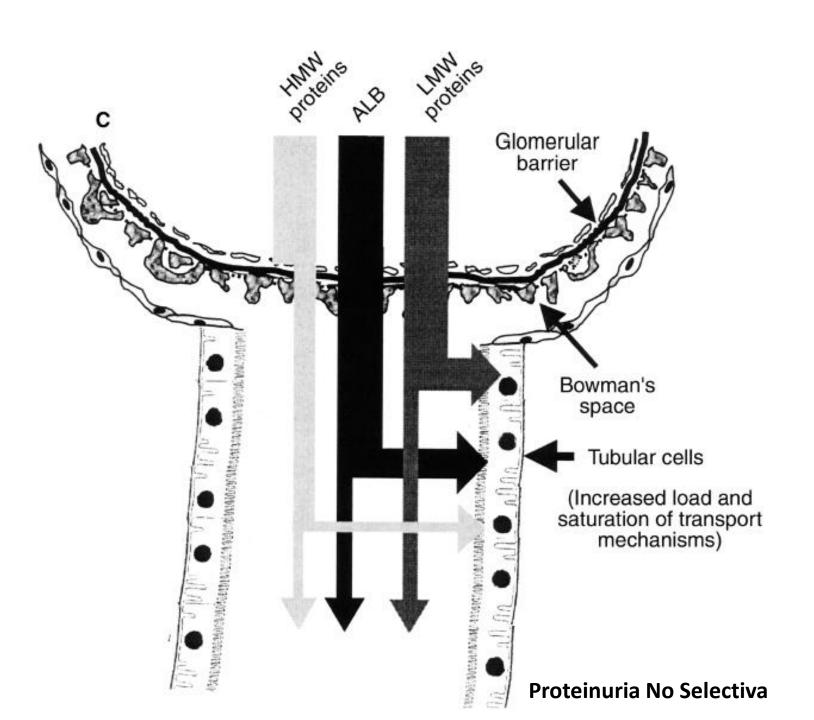


Absence of proteinuria

Kidney International, Vol. 63 (2003), pp. 809–825



Proteinuria Selectiva



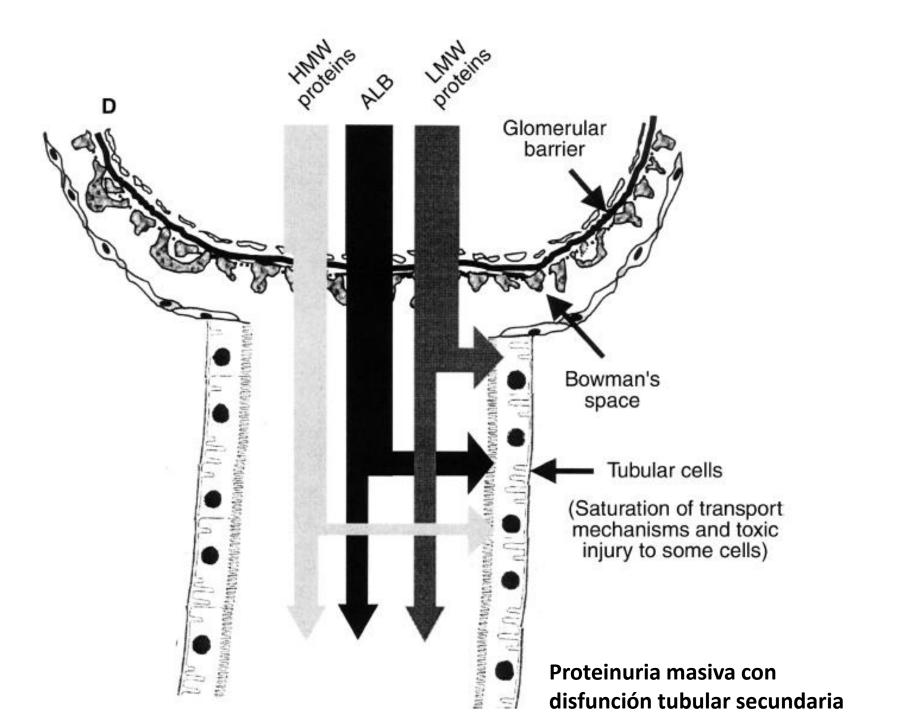
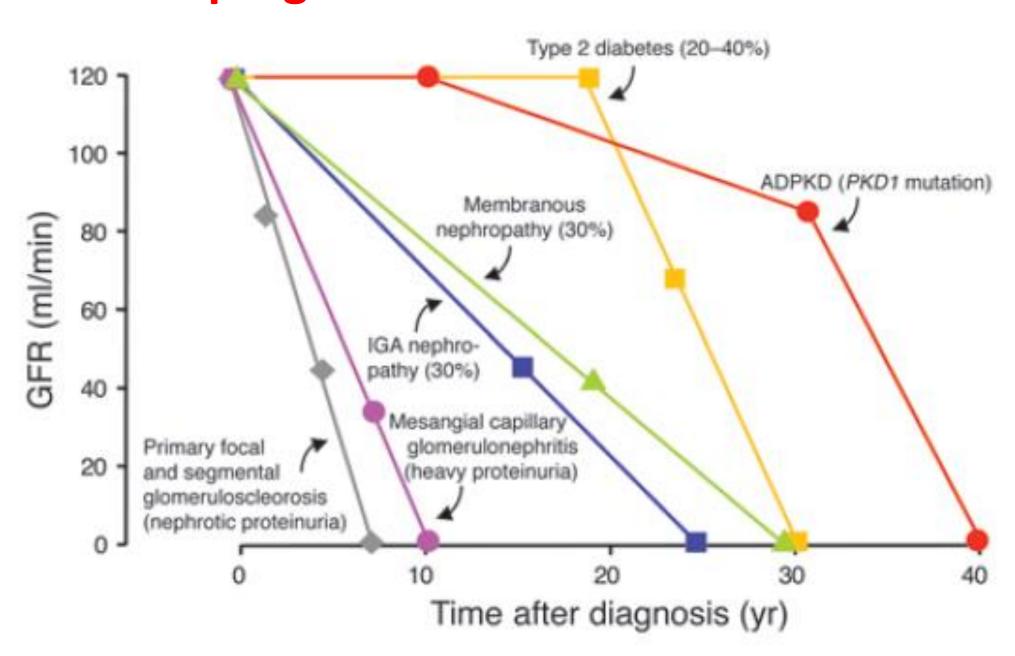


Table 1 | Mechanisms of proteinuria in DKD

Site of injury	Effect	Underlying mechanisms
Glomerular hemodynamics	Glomerular hyperfiltration	Afferent arteriole vasodilatation
		Efferent arteriole vasoconstriction
		†glomerular capillary pressure
Glomerular endothelial cell	Endothelial cell injury	Hyperglycemia, AGE, ROS
	Diminished endothelial glycocalyx	Endothelial cell injury or enzymatic cleavage
	Altered VEGF signaling	Podocyte injury or loss
GBM	Irregular thickening	↓production and/or ↑degradation of extracellular matrix proteins
	Decreased negative charge	↓ production and/or ↑ degradation of HSPG
Podocyte	Podocytopenia	Detachment
•		Apoptosis
		Lack of proliferation
	Loss of slit diaphragm integrity	Decrease or changes in subcellular localization of nephrin
	Foot process widening and effacement	Disrupted actin cytoskeleton
		Loss of slit diaphragm integrity
		Impaired podocyte GBM interaction
	Loss negative charge	↓ Podocalyxin
Proximal tubule	Decreased protein reabsorption	Tubular injury and interstitial fibrosis

Proposed schema unifying the mechanisms of proteinuria and decrease in GFR in DKD Kidney International (2008) 74, 22–36

La naturaleza progresiva de la ERC



La proteinuria como el principal factor de riesgo de progresión en ERC (screening de 107.192 sujetos adultos) Iseki, KI 1996

Table 3. Logistic regression analysis of clinical predictors of end-stage renal disease over 10 years among the participants of the mass screening on 1983 in Okinawa, Japan

	Odds ratio (95% confidence interval)	
Prognostic factor	Not adjusted	Adjusted ^a
Male (vs. female)	1.31 (0.99-1.74)	1.41 (1.04-1.92)
Age (vs. 18-39 years)	1.25 (1.14-1.37)	1.11 (0.99-1.24)
10 year increments	, ,	, ,
Proteinuria (vs. normal)	22.9 (17.2-30.6)	14.9 (10.9-20.2)
Hematuria (vs. normal)	2.30 (1.72-3.07)	2.30 (1.62-3.28)
Systolic blood pressure	1.51 (1.39-1.65)	1.10 (0.96-1.26)
(vs. less than 119 mm Hg) 10 mm Hg increments		
Diastolic blood pressure	1.88 (1.68-2.11)	1.39 (1.17–1.64)
(vs. less than 69 mm Hg) 10 mm Hg increments		

Proteinuria and hematuria

2,000

Proteinuria

Proteinuria

Normal

0.0

Time after screening, years

Fig. 4. Relationship between the cumulative incidence of ESRD and the duration from the mass screening, in years, is shown according to the results of the mass screening urinalysis.

a Adjusted for other prognostic factors.

Urinary protein excretion rate is the best independent predictor of ESRF in <u>non-diabetic proteinuric</u> chronic nephropathies. Ruggenenti, KI, 1998

Table 2. Univariate analysis of the correlation between baseline parameters, decline in glomerular filtration rate (Δ GFR) and progression to end-stage renal failure (ESRF)

	ΔGFR		ESRF	
Baseline parameters	r coefficient	P value	P value	
Clinical parameters				
Age	-0.03	0.62	0.72	
Sex	0.01	0.84	0.31	
Systolic blood pressure	-0.21	0.0002	0.001	
Diastolic blood pressure	-0.17	0.003	0.003	
Mean blood pressure	-0.21	0.0002	0.0002	
Diagnosis	0.03	0.29	0.28	
Laboratory parameters				
Urinary protein excretion	-0.22	0.0001	0.0001	
GFR	-0.044	0.46	0.0001	
Creatinine clearance	0.13	0.02	0.0001	
Serum creatinine	-0.08	0.16	0.0001	
Total cholesterol	-0.048	0.41	0.23	
Triglycerides	-0.07	0.22	0.48	

Table 3. Multivariate analysis of the correlation between baseline parameters, decline in glomerular filtration rate (ΔGFR) and progression to end-stage renal failure (ESRF)

Baseline parameters	ΔGFR	ESRF
Clinical parameters		
Age	0.37	0.54
Sex	0.69	0.26
Mean blood pressure	0.0002	0.0037
Diagnosis	0.69	0.07
Laboratory parameters		
Urinary protein excretion	0.0001	0.0001
GFR	0.08	0.0001
Total cholesterol	0.35	0.06
Triglycerides	0.87	0.54

Urinary protein excretion rate is the best independent predictor of ESRF in *non-diabetic proteinuric* chronic nephropaties.

Ruggenenti et al, Kidney International, Vol. 53 (1998), pp. 1209–1216

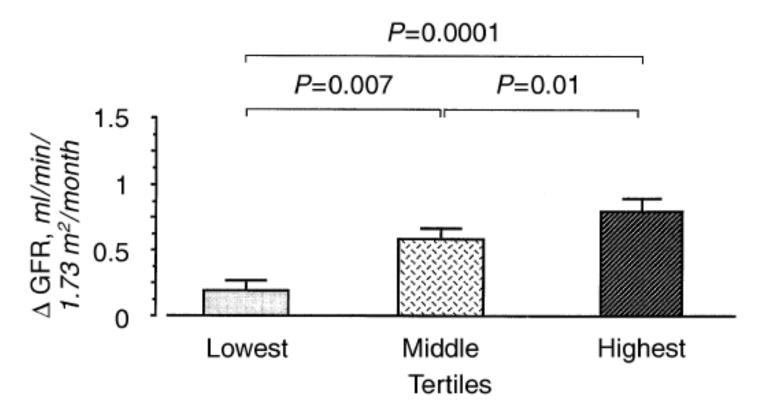
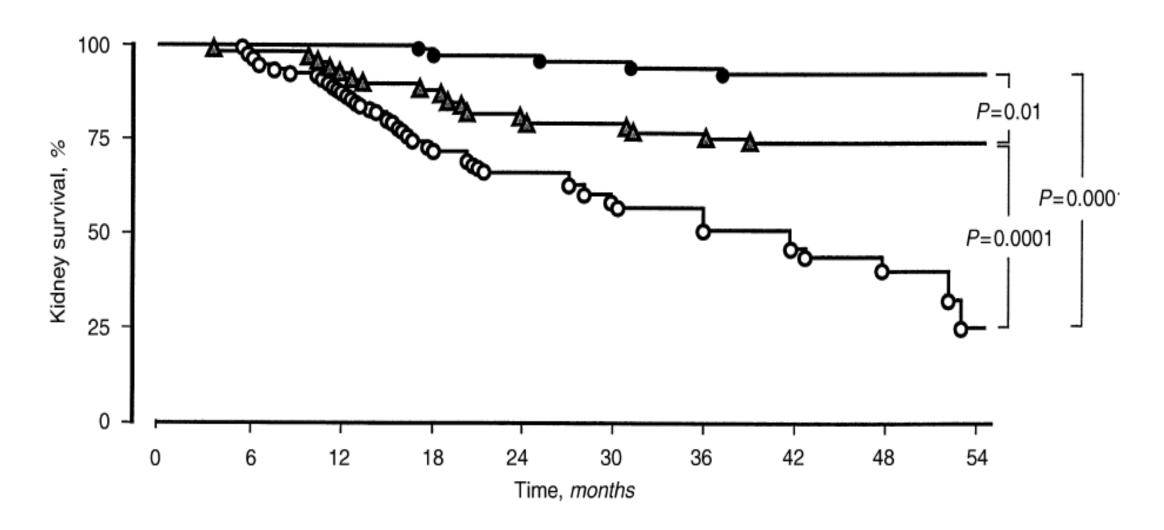


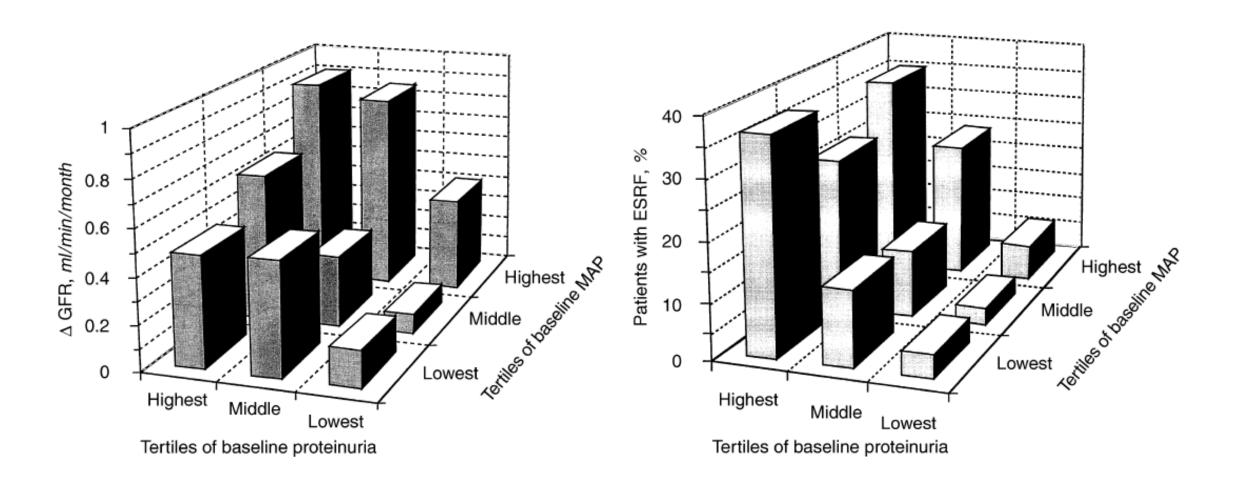
Fig. 1. Rate of glomerular filtration rate (GFR) decline per tertile of baseline urinary protein excretion rate. Δ GFR for: lowest is 0.16 \pm 0.07; middle is 0.55 \pm 0.09; highest is 0.70 \pm 0.11.

La proteinuria además aumenta la mortalidad CV y total

Urinary protein excretion rate is the best independent predictor of ESRF in *non-diabetic proteinuric* chronic nephropathies. Ruggenenti, KI, 1998



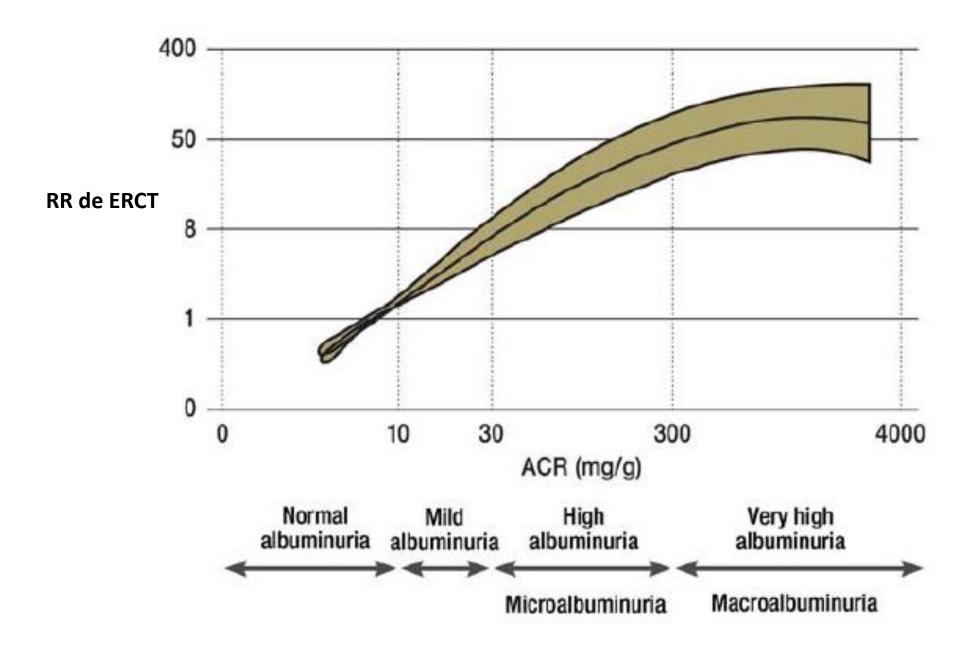
Urinary protein excretion rate is the best independent predictor of ESRF in *non-diabetic proteinuric* chronic nephropathies. Ruggenenti, KI, 1998



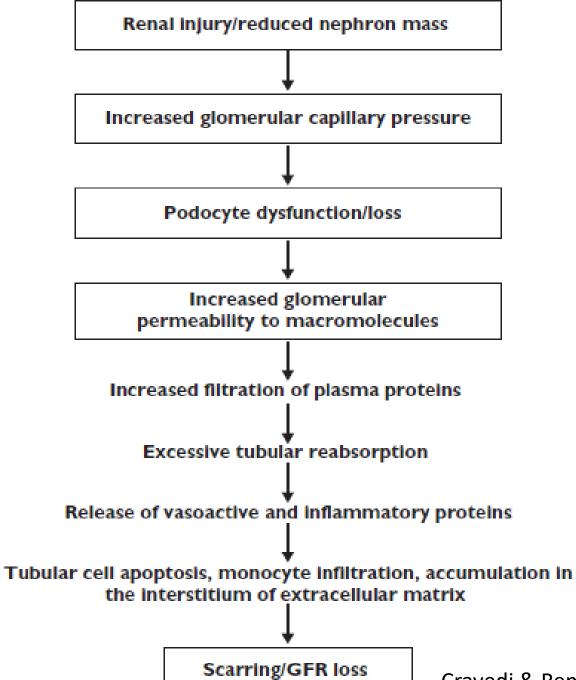
En Diabetes

- UKPDS 74 (diabéticos tipo 2 sin albuminuria).
 Niveles más altos de albuminuria, dentro del rango normal, se asocian con:
 - Aparición de microalbuminuria persistente
 - Compromiso funcional renal
- En diabéticos CON nefropatía diabética:
 - RAC basal es un buen predictor de ERCT

Albuminuria como marcador pronóstico de ERCT (NKF)



La naturaleza progresiva de la ERC



Cravedi & Remuzzi, Br J Clin Pharmacol 2013

Mecanismos de daño por proteinuria

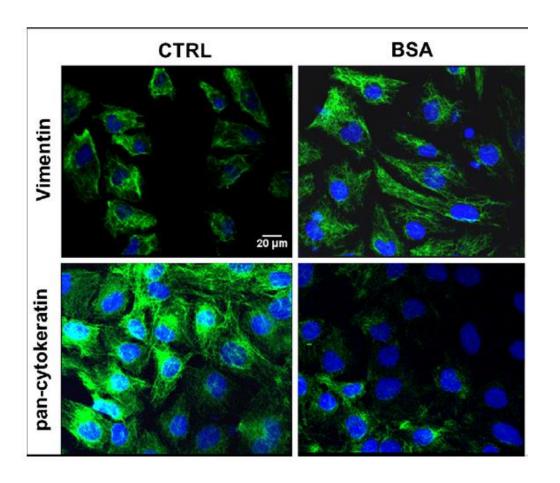
- Injuria o apoptosis podocitaria
- Toxicidad mesangial
- Sobrecarga tubular e hiperplasia
- Toxicidad específica (transferrina/hierro ó albúmina/ácidos grasos)
- Inducción de citoquinas proinflamatorias/profibróticas (MCP-1, TGF-β,
 PDGF, etc.)
- Inducción de transición epitelio-mesenquimática

Transición epitelio-mesenquimática inducida por albúmina in vitro

HK-2 morphology	Untreated	BSA
% Fusiform cells	13 <u>+</u> 3.5	72 <u>+</u> 5*
Active TGF-β (pg / ml / mg protein)	260 <u>+</u> 25	624 <u>+</u> 76*
α-SMA (fold increase)	1.0	3.2 <u>+</u> 0.1*

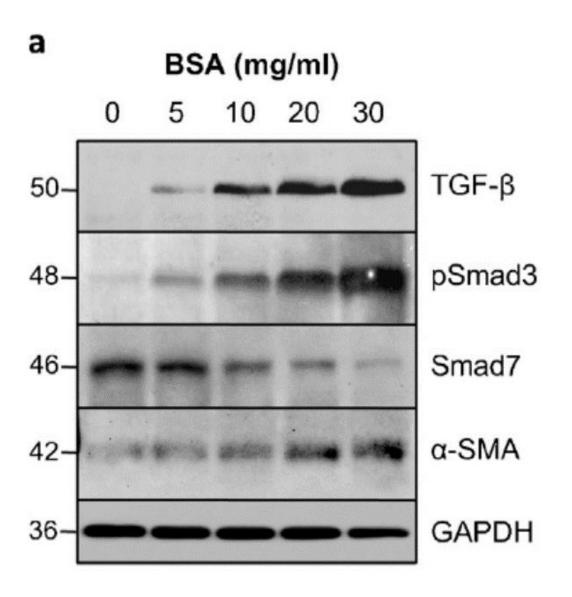
Antihypertensive and renoprotective effect of the kinin pathway activated by potassium in a model of salt sensitivity following overload proteinuria
Leopoldo Ardiles, Areli Cardenas, María E. Burgos, Alejandra Droguett, Pamela Ehrenfeld, Daniel Carpio, Sergio Mezzano and Carlos D. Figueroa

Am J Physiol Renal Physiol 304:F1399-F1410, 2013. First published 3 April 2013; doi: 10.1152/ajprenal.00604.2012

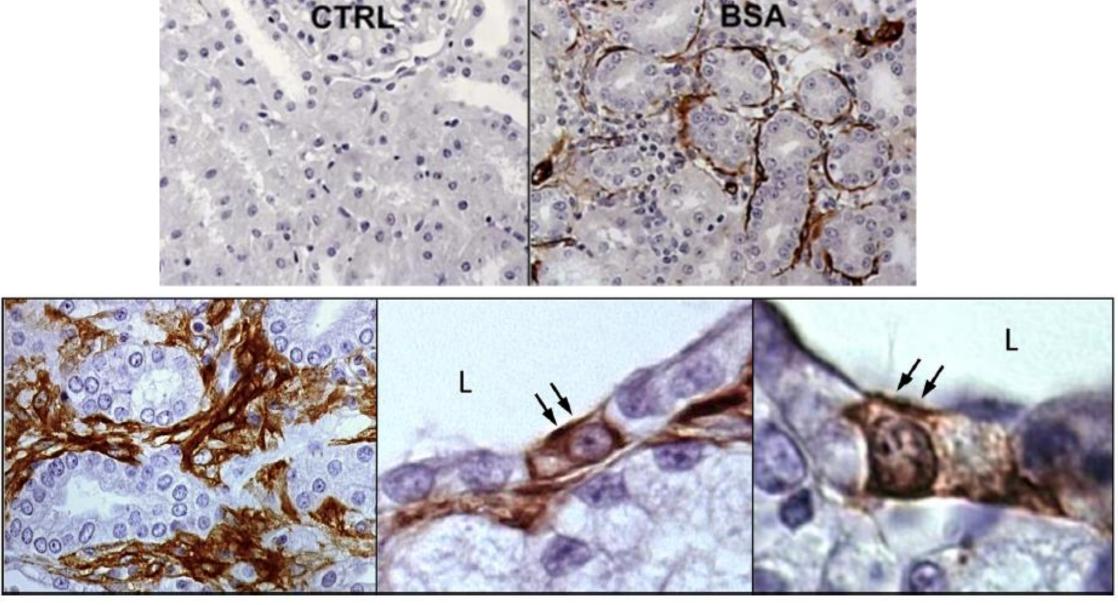


A. Cárdenas et al. / Peptides 73 (2015) 7-19

Activación de cascada TGF-β/Smad en células TCP por proteína in vitro



Inmunohistoquímica alfa actina músculo liso (ratas)



Proteinuria



TGF-β1 ↑ mRNA ↑ protein ↑ active peptide



Active TGF-β1



ΤβΡΙ/ΤβΡΙΙ



pSmad2/3/4



↑ α-SMA, vimentin

 \downarrow E-cadherin, cytokeratin

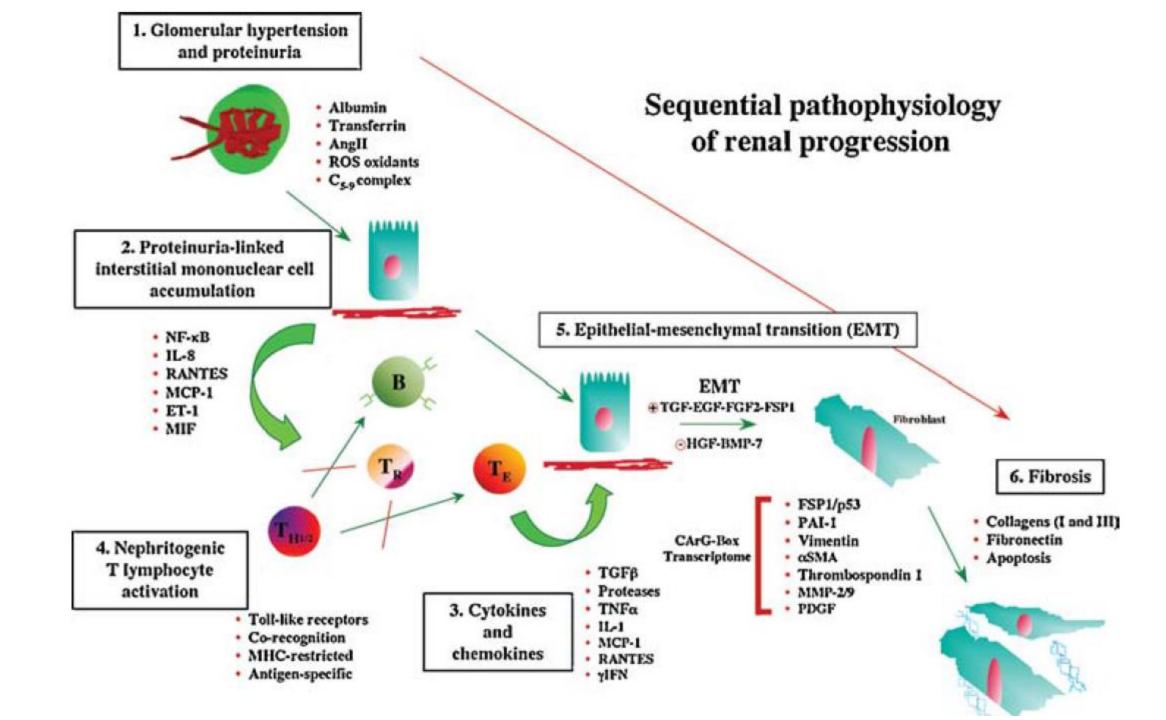


Tubulointerstitial fibrosis

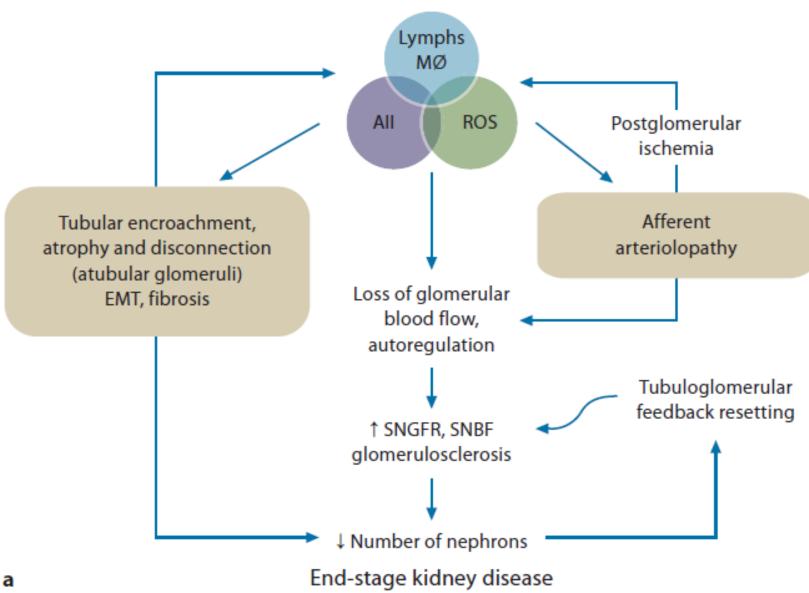


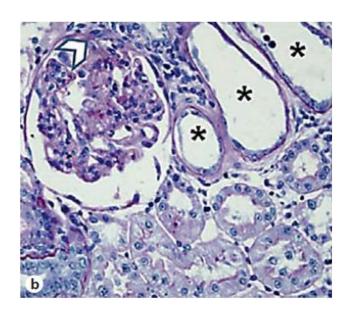
Chronic Kidney Disease

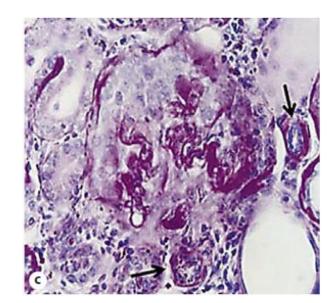
A. Cárdenas et al. / Peptides 73 (2015) 7-19

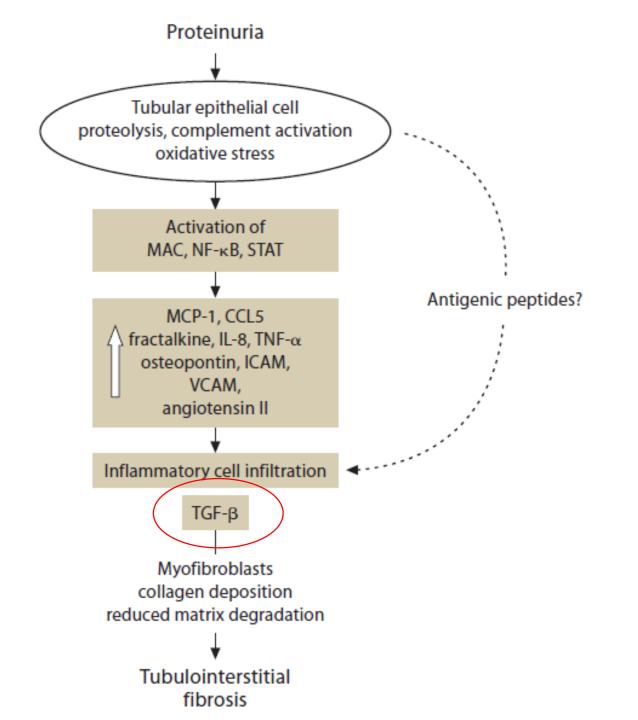


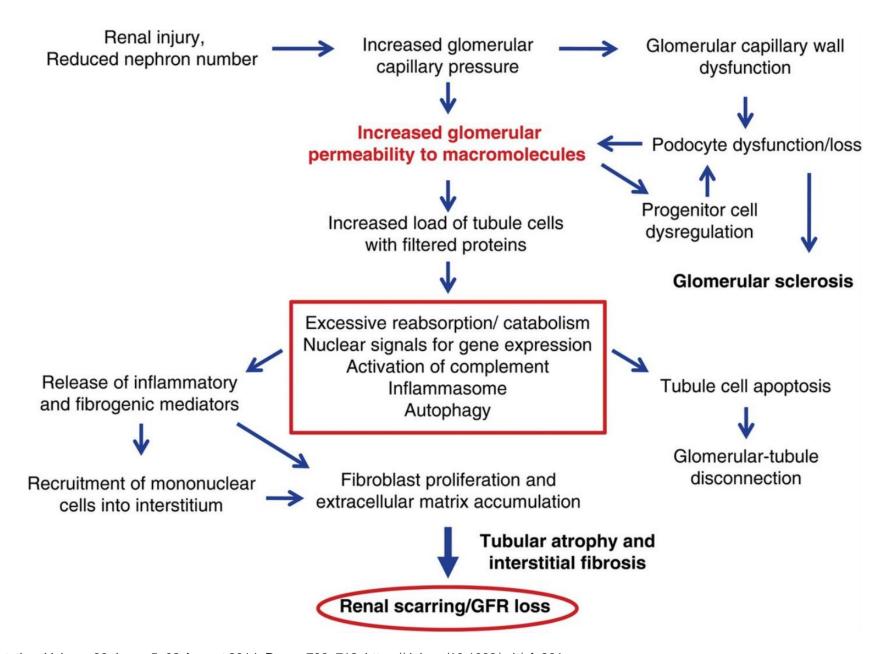
Tubulointerstitial inflammation

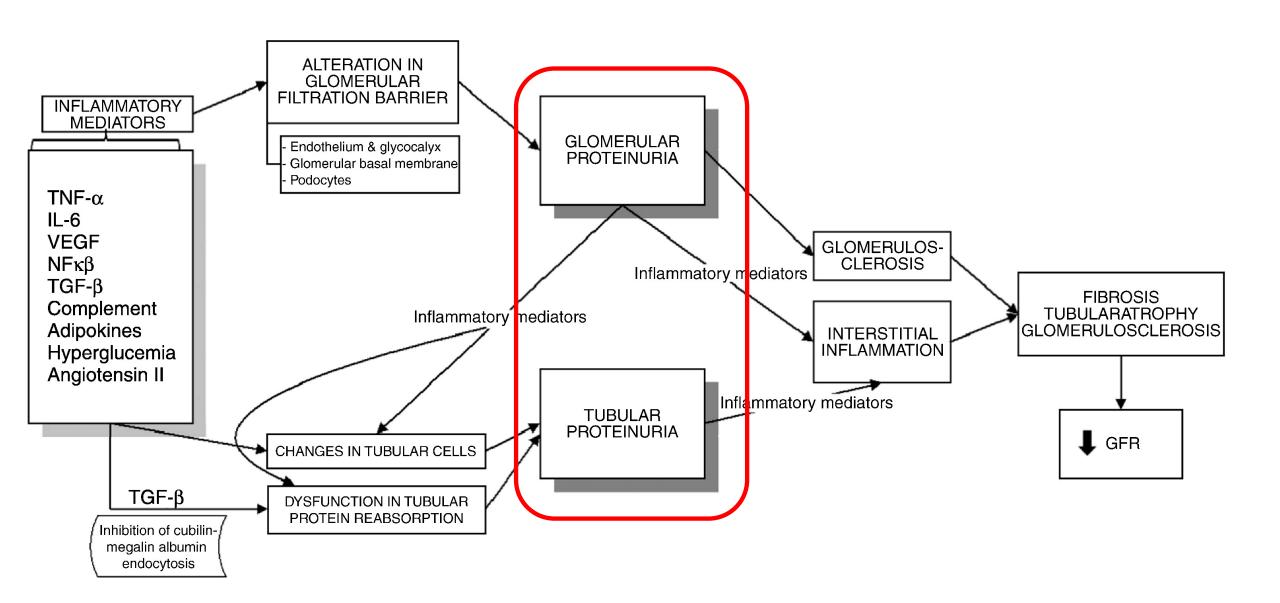


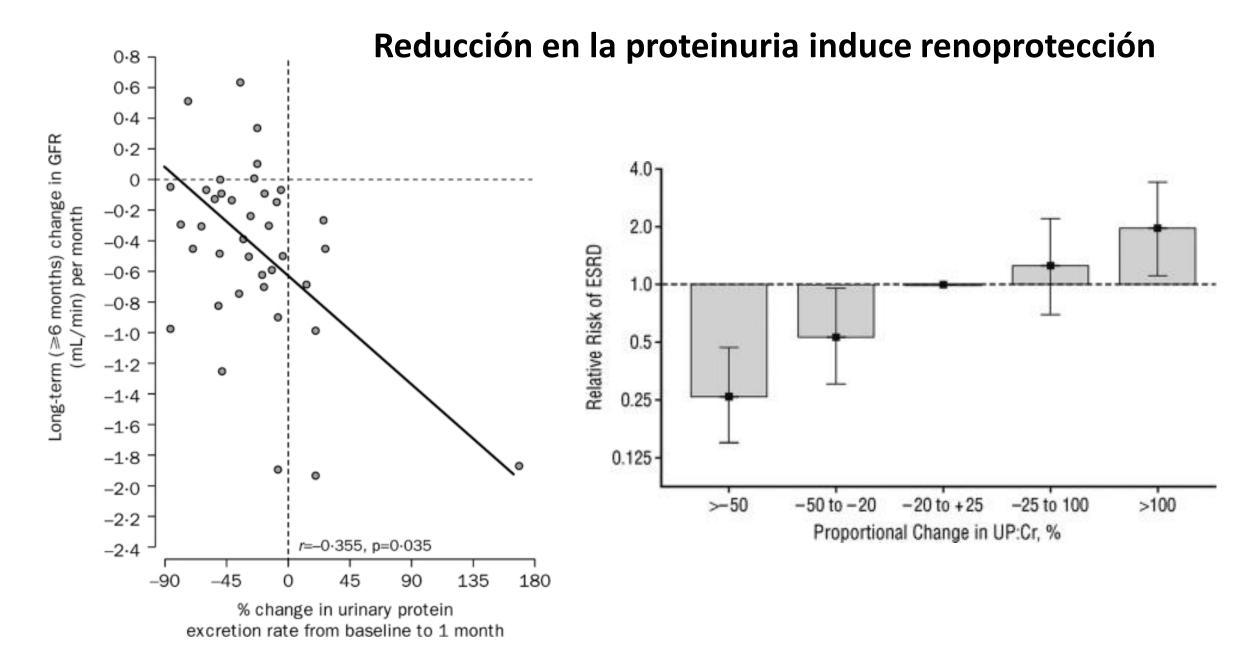


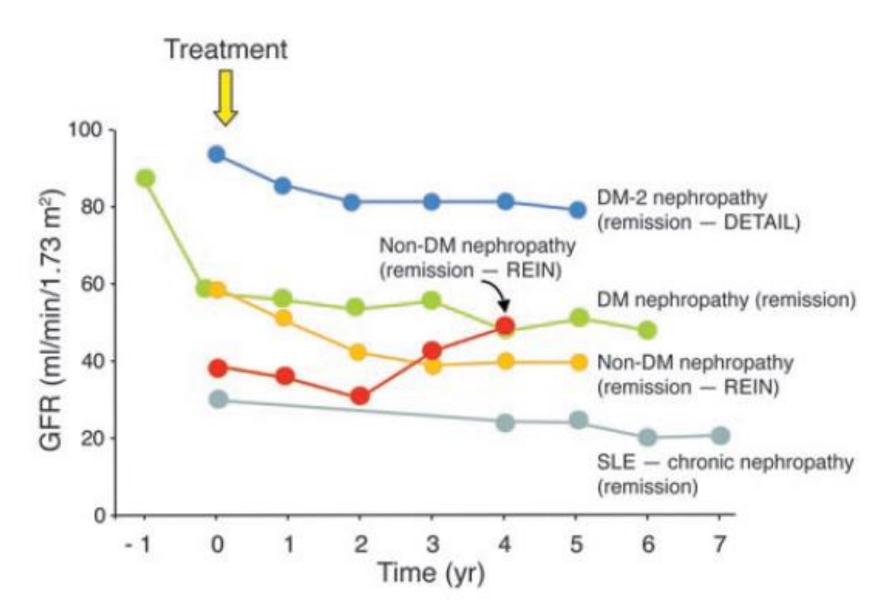




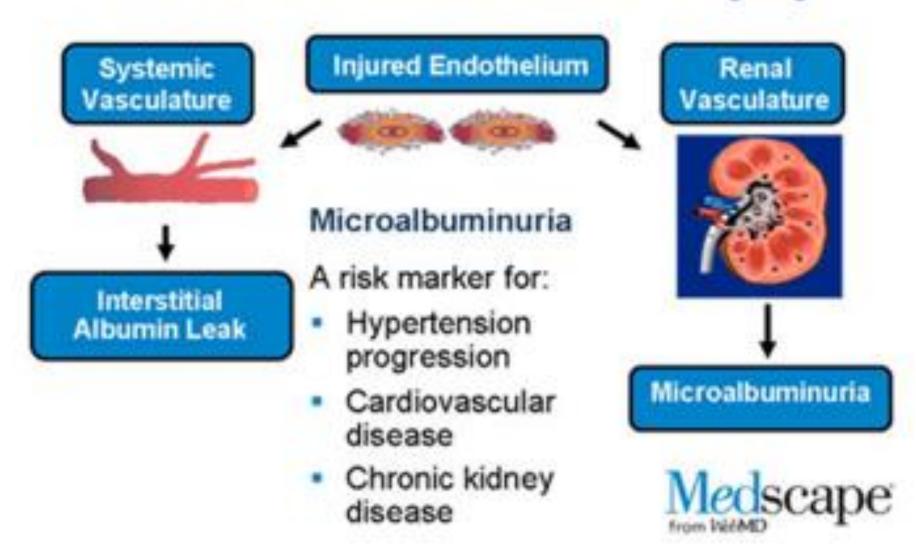


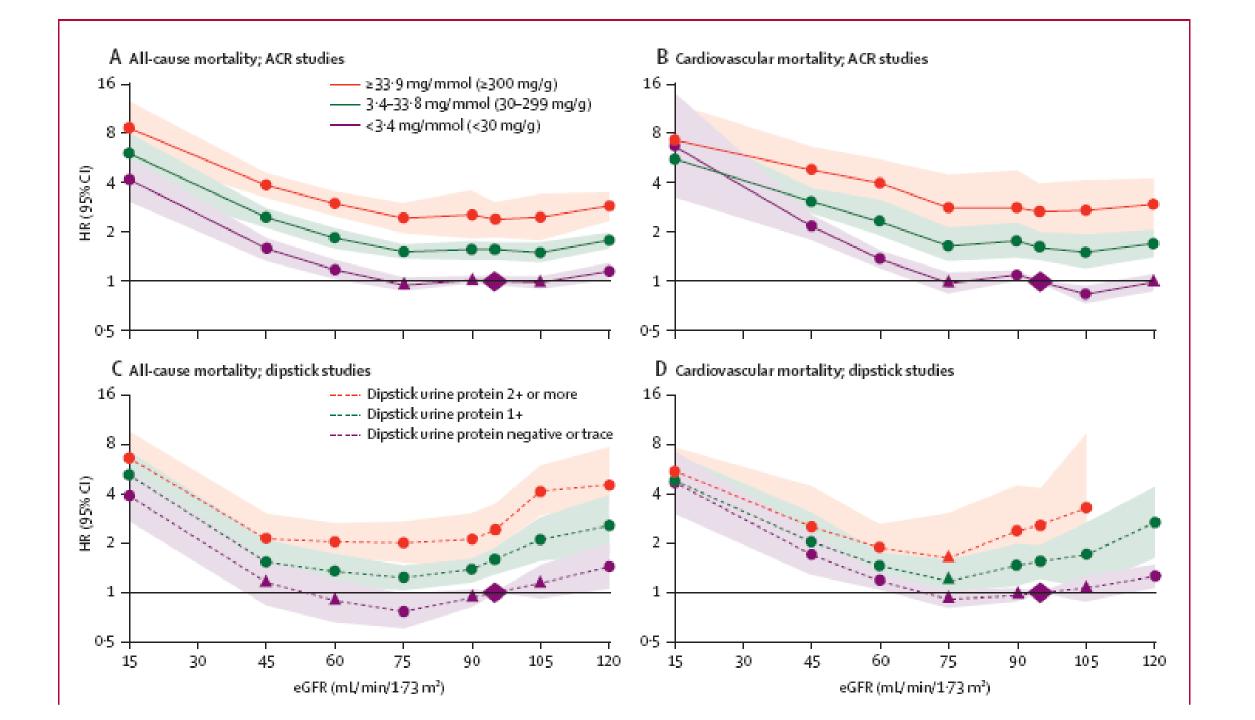




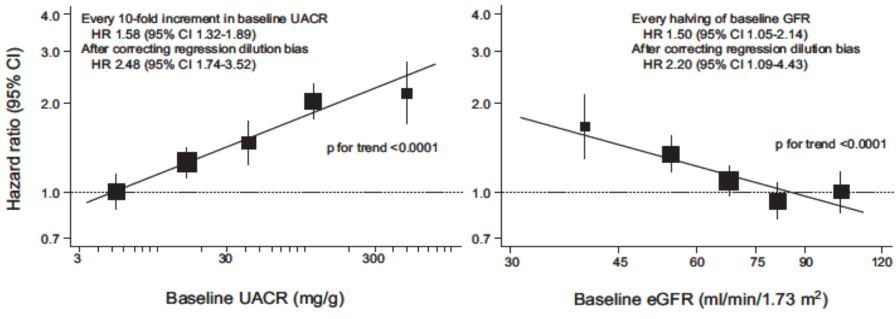


Microalbuminuria: A manifestation of diffuse endothelial cell injury

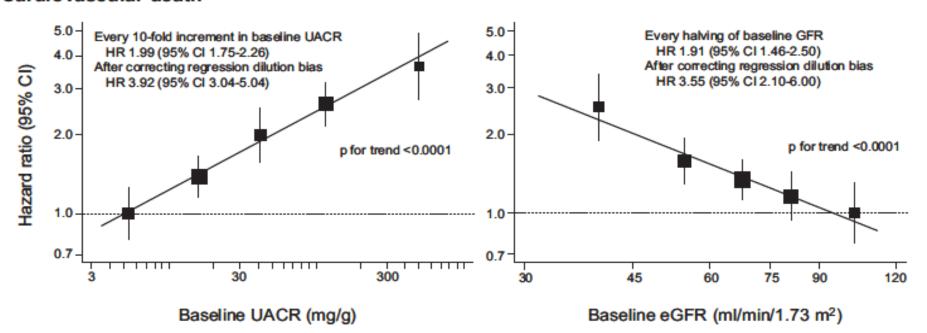




Cardiovascular events



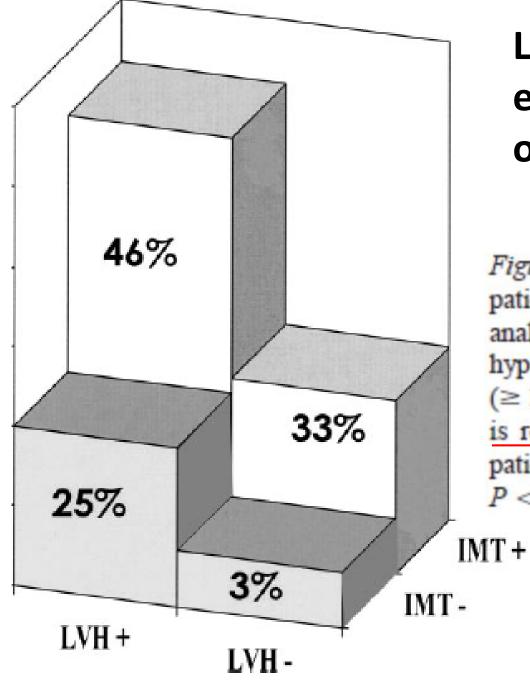
Cardiovascular death



ERC y eventos CV JASN 20: 1813–1821, 2009

Table 1. Association Between Microalbuminuria and Cardiovascular Events in Studies of Patients with Diabetes Mellitus and Hypertension

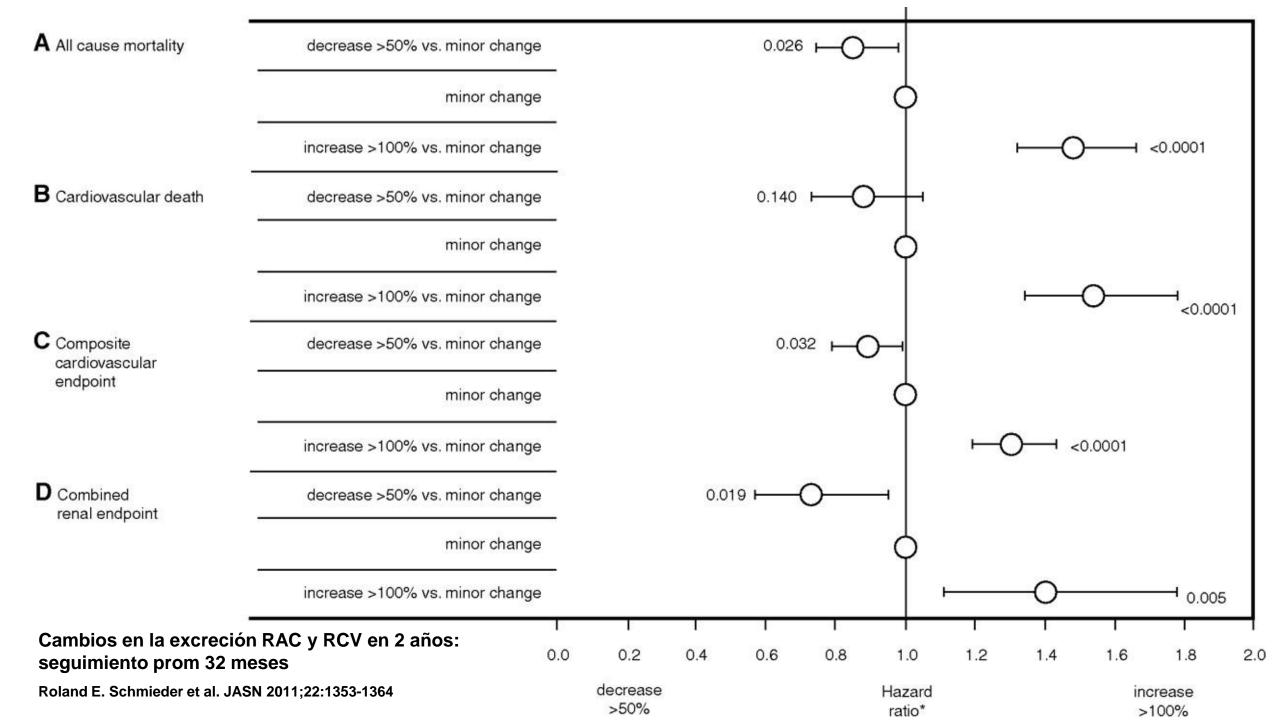
			Time Frame of		
No. of	Diabetes	Hypertension	Evaluation		
Patients	(%)	(%)	(yrs)	End Point	Results ^a
10224	100	100	Baseline	Composite	β = 0.002; CV outcomes
15825	100	53	2	Composite	RR 4.5, 95% CI 2.0–10.3, ^{b, c} CV outcomes
683^{26}	100	68.1	6	CV mortality	RR 2.0, 95% CI 1.2-3.7b
138^{27}	100	62.5	5	All-cause mortality	RR 2.8, 95% CI 0.6-11.6b
141^{28}	100	> 50	3.4	All-cause mortality	RR 7.9, 95% CI 2.5-25.3
218^{29}	100	51	7.59-9.25	All-cause mortality	RR 1.6, 95% CI 1.2-2.2b
400^{30}	100	51	5.9	All-cause mortality	RR 1.87, 95% CI 1.27-2.76



La presencia de albuminuria en HTA esencial anormal predice la presencia de otros daños en órganos blanco

Figure 1. Urinary albumin excretion and target organ damage in 279 patients with essential hypertension. Urinary albumin excretion was analyzed on the basis of the presence/absence of left ventricular hypertrophy (LVH+/LVH−) and increased intima-media thickness (≥ 1.1 mm) (IMT+/IMT−). The prevalence of microalbuminuria (%) is reported in each group. The odds ratio for a microalbuminuric patient of having both LVH and increased IMT is 21 (CI, 5.4 to 190; P < 0.0001).

PONTREMOLI et al, J Am Soc Nephrol 13: S169–S172, 2002 Microalbuminuria and Primary Hypertension



Albuminuria Regression and All-Cause Mortality among Insulin-Treated Patients with Type 2 Diabetes: Analysis of a Large UK Primary Care Cohort (Am J Nephrol 2019)

Cohorte de 11,074 DM2 usuarios de insulina y con nefropatía (ACR ≥300 mg/g) en tratamiento.

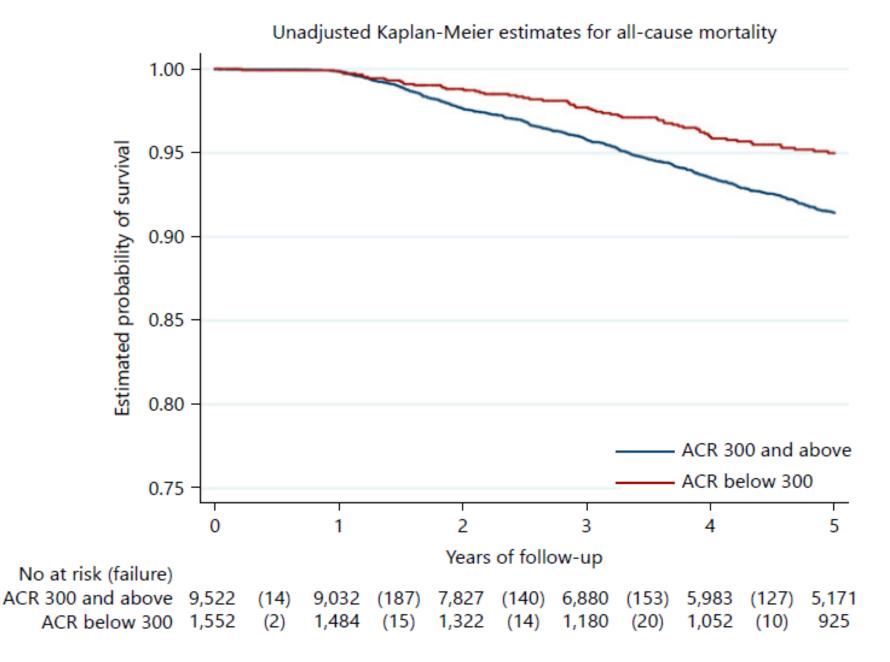
Se separan en dos grupos

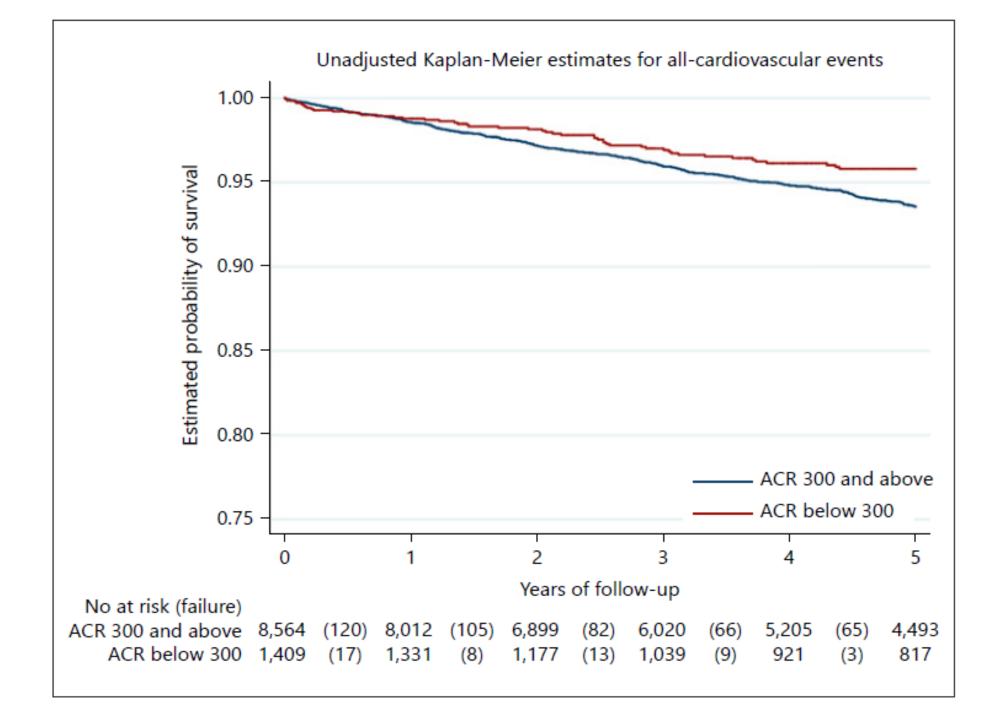
- 1. < 300 mg/g (con regresión de albuminuria)
- 2. >300 mg/g ((sin regresión de albuminuria)

Seguimiento por 5 años:

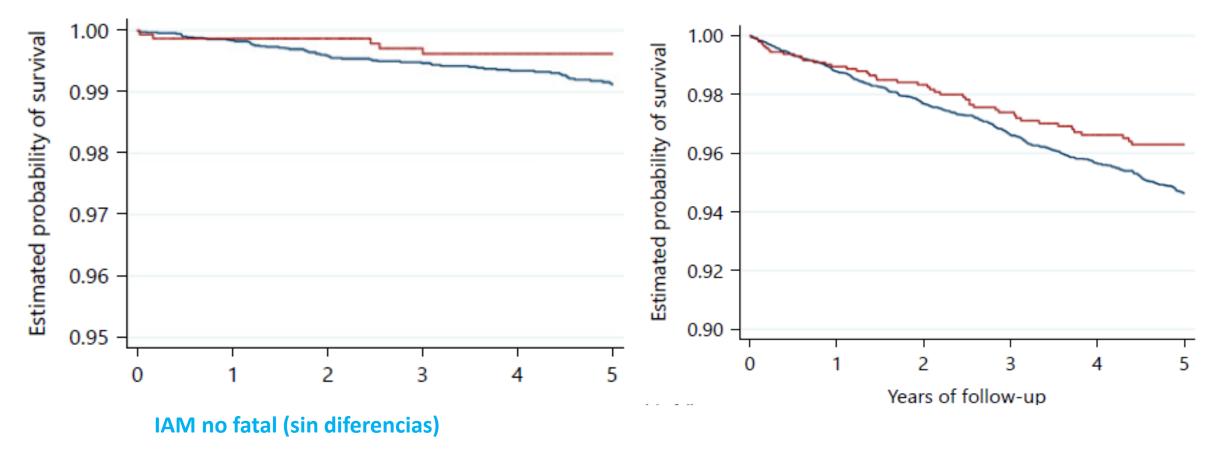
La regression de la albuminuria se asocial con REDUCCIÓN EN LA MORTALIDAD POR CUALQUIER CAUSA

Conclusión: Albuminuria no solo es un marcador de riesgo renal y resgo CV, sino que es un objetivo terapéutico independiente





Eventos CV (p<0.05)



AVE no fatal (p<0.05)





Desierto Florido, Atacama, 2017

Garra de león, Desierto Atacama 2017