

Early proteinuria and urinary albumin excretion in renal transplantation

Pr Jean-Michel Halimi, Tours, France

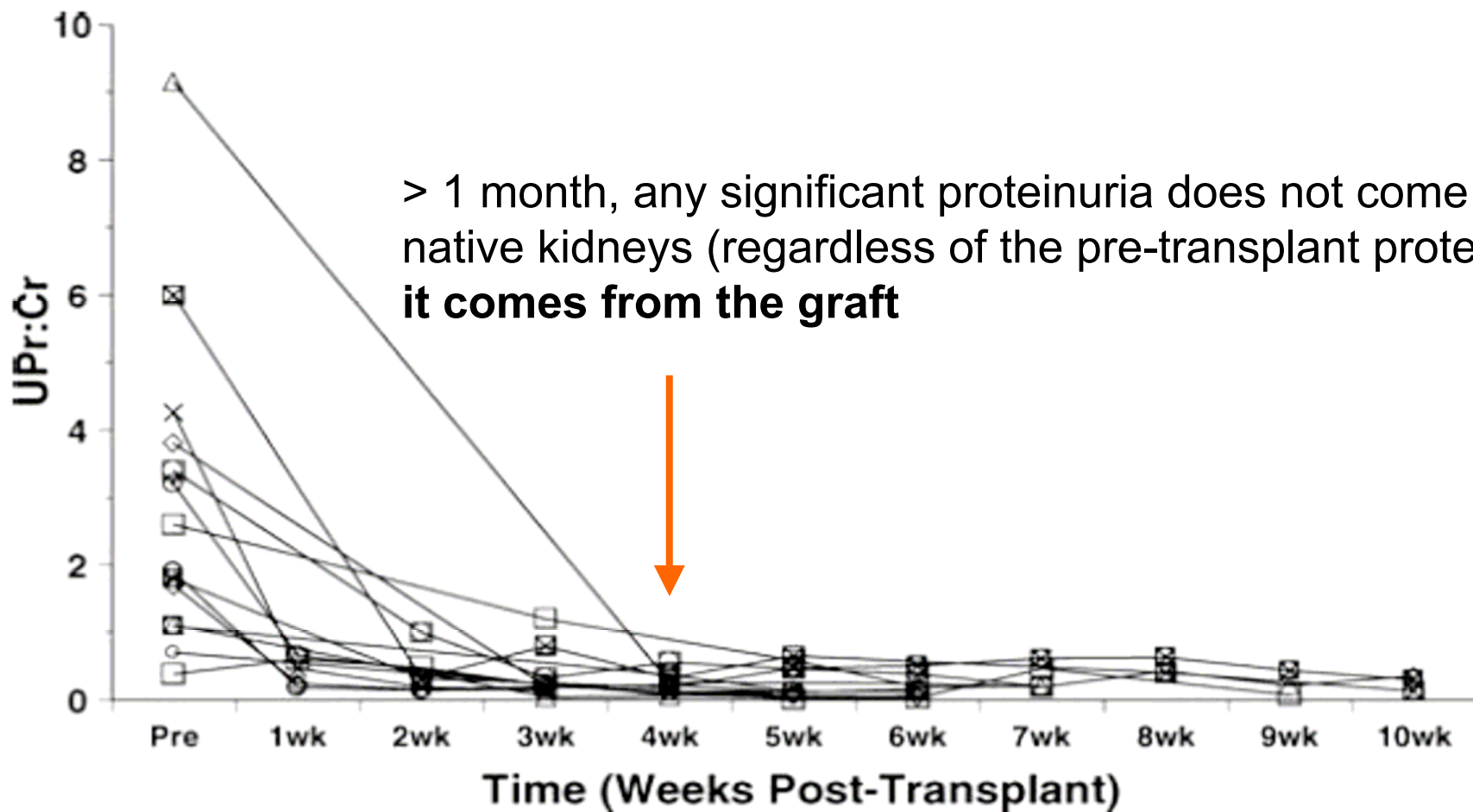
Proteinuria: some of the questions...

- What is the source of early proteinuria: native kidneys or the graft ?
- What early low-grade proteinuria (or albuminuria) can tell us about long-term outcome ?
- Has proteinuria a different meaning in transplantation as compared to other areas of nephrology
- Perspectives (for rich people and other people...)

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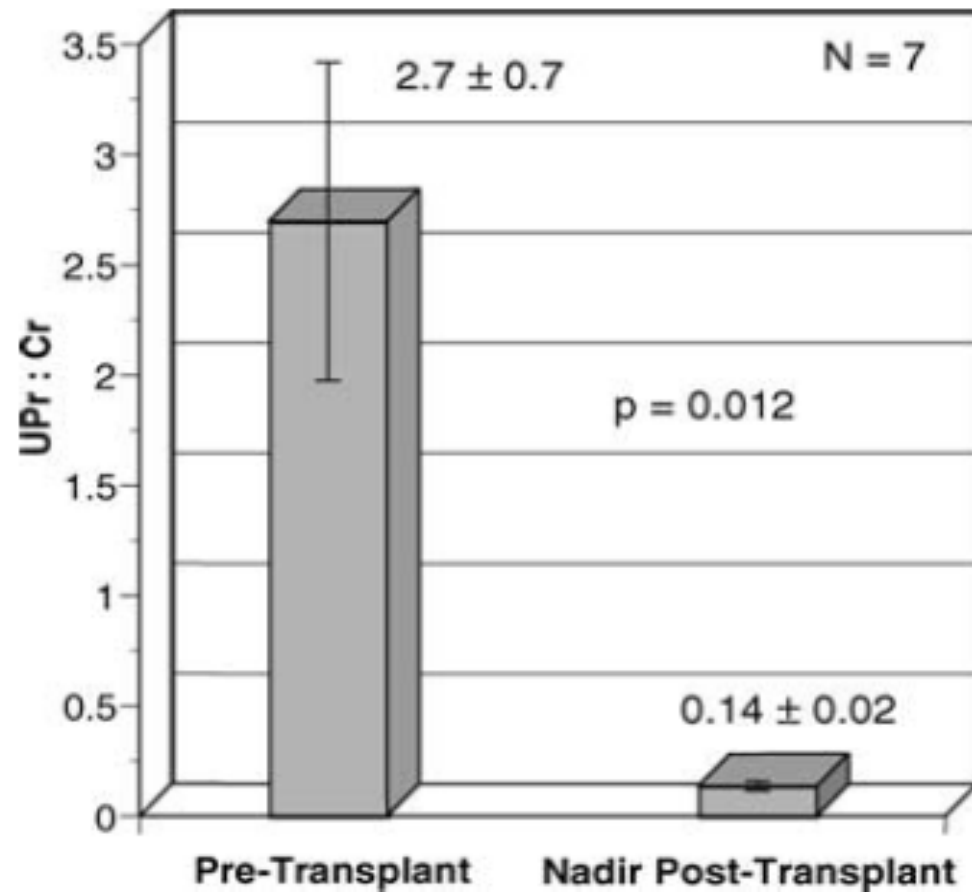
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When does proteinuria disappear after transplantation?

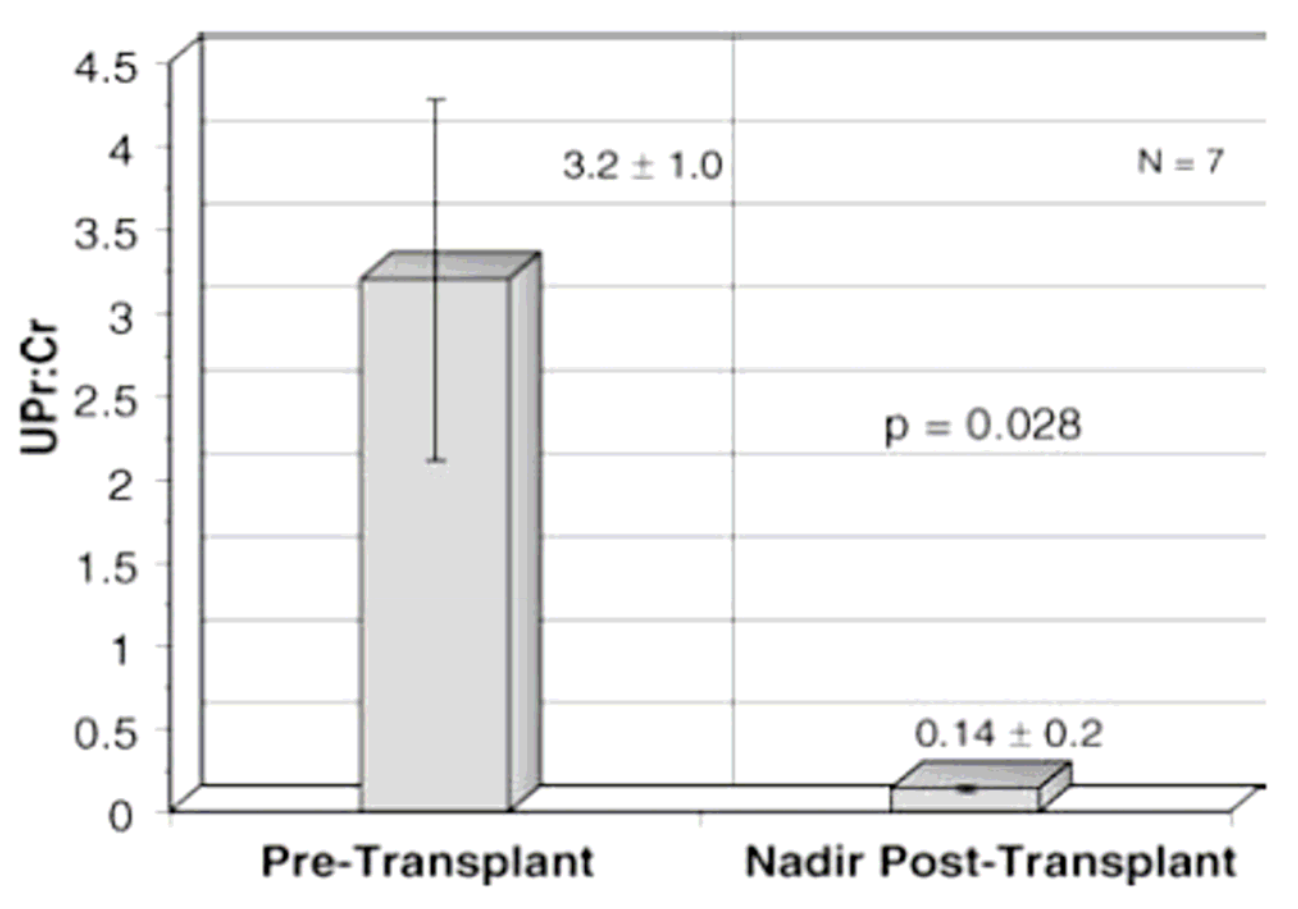


14 patients (living donors)
D'Cunha, AJT 2005

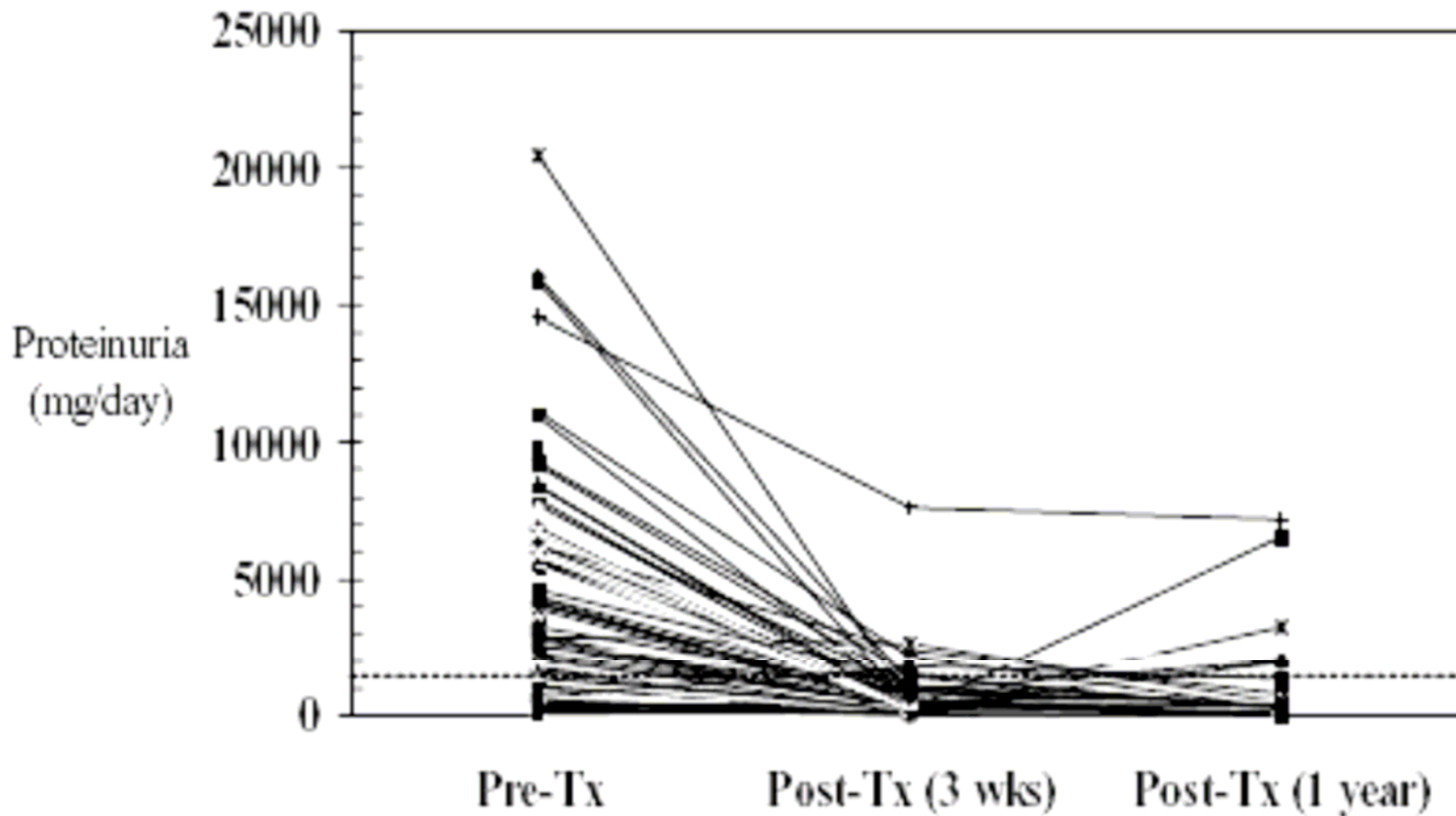
Pre-and post-transplant proteinuria in the 7 patients who were dialysed before transplantation



Pre-and post-transplant proteinuria in the 7 patients with pre-emptive transplantation

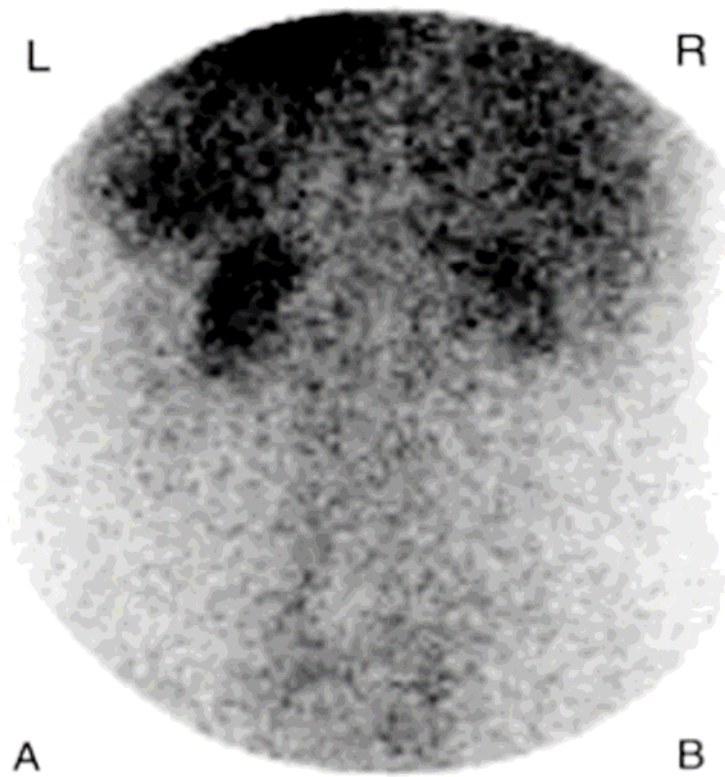


True in 85 patients who benefited from a pre-emptive transplantation: > 1 month, any significant proteinuria does not come from the native kidneys



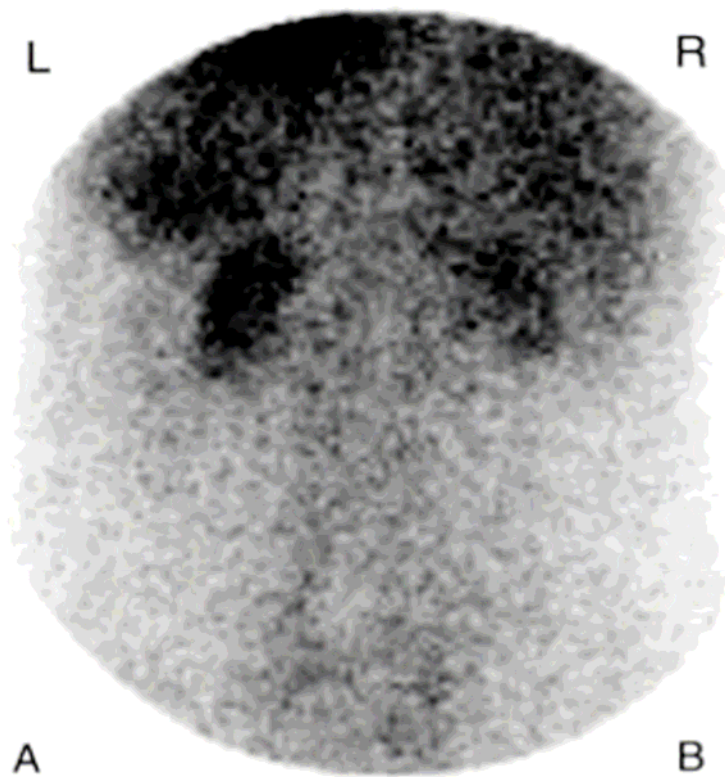
85 patients with pre-emptive grafts; 30 dialysis < 3 months
Myslak, AJT 2006

Why ?

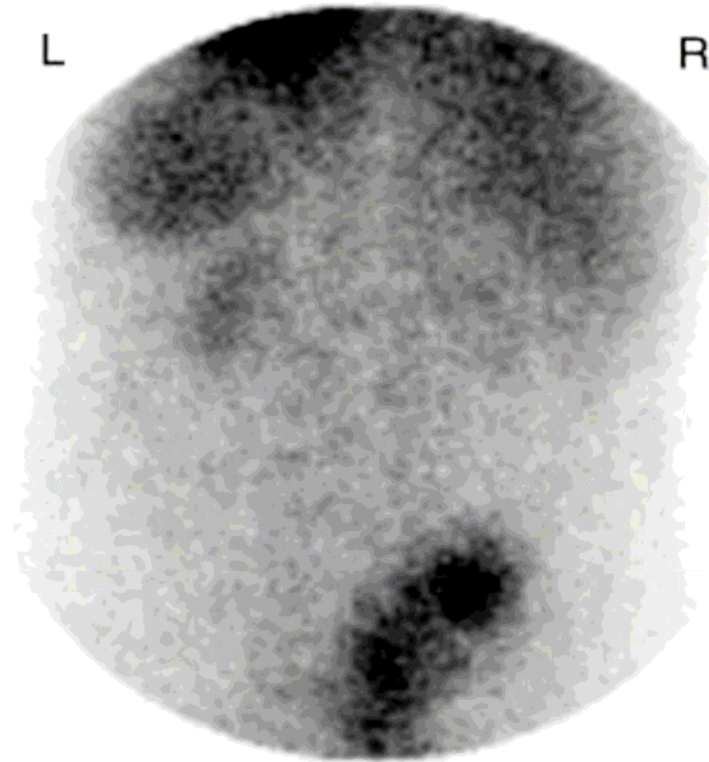


1 week before graft

Why ? The native kidneys no longer function 3 weeks following transplantation

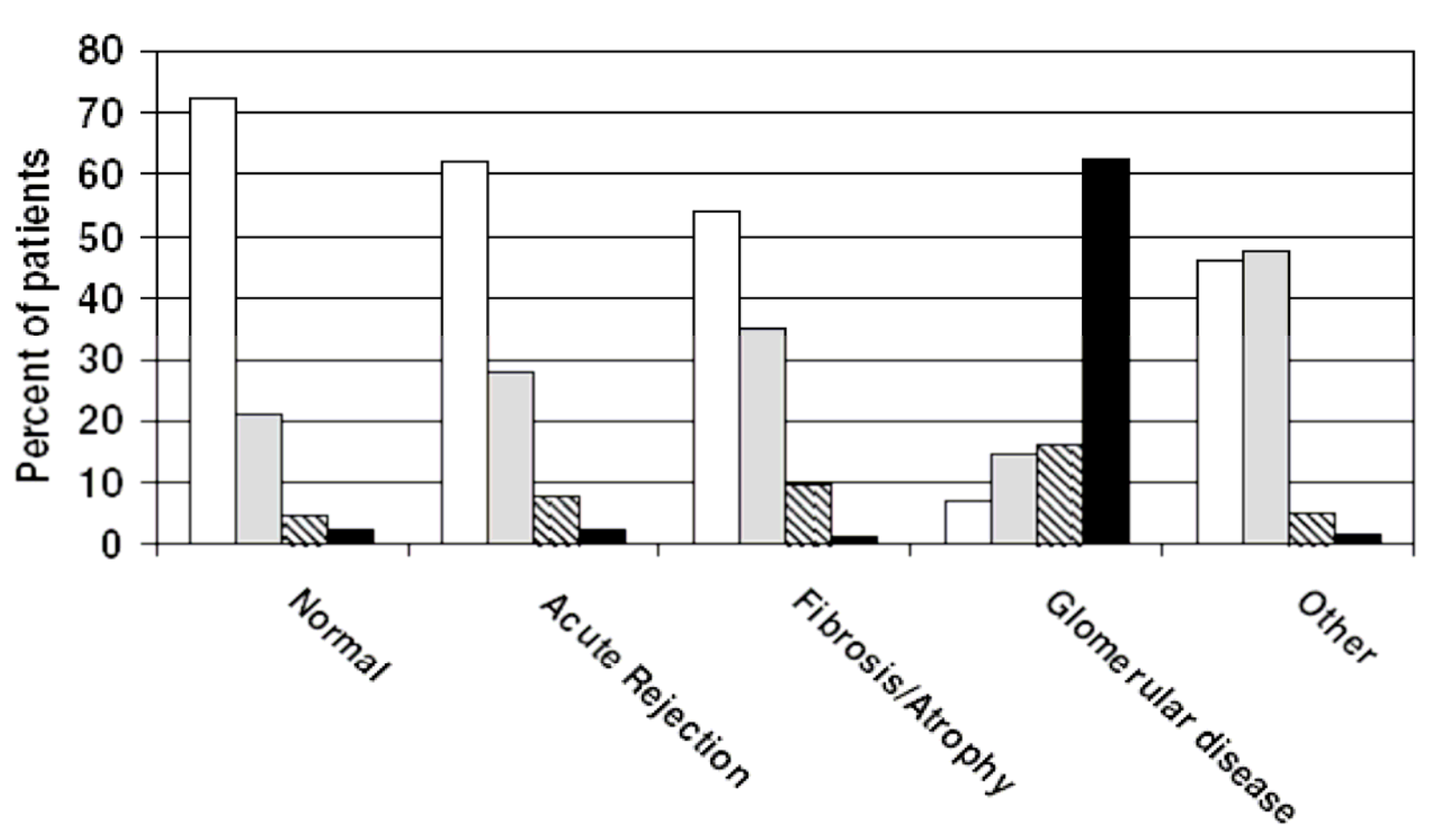


1 week before graft



3 weeks after graft

Relationship with histology findings



<150 mg/day; 150-500 mg/day; 500-1500 mg/day; >1500 mg/day

Proteinuria at 1 yr
Amer, AJT 2007

Proteinuria: some of the questions...

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- Has proteinuria a different meaning in transplantation as compared to other areas of nephrology ?
- Perspectives (for rich people and other people...)

Early proteinuria is associated with donor CV parameters and ischemia-reperfusion injury lesions

	At 1 month		
	OR	95% CI	p-values
Donor age >60 (yes vs. no)	4.43	1.61–14.13	0.003
Donor cardiovascular death (yes vs. no)	1.98	1.20–3.14	0.002
Warm ischemia time >60 min (yes vs. no)	2.23	1.39–3.66	0.001
Cold ischemia time >24 h (yes vs. no)	1.77	1.17–2.73	0.006
Delayed graft function (yes vs. no)	1.21	0.97–1.51	0.09

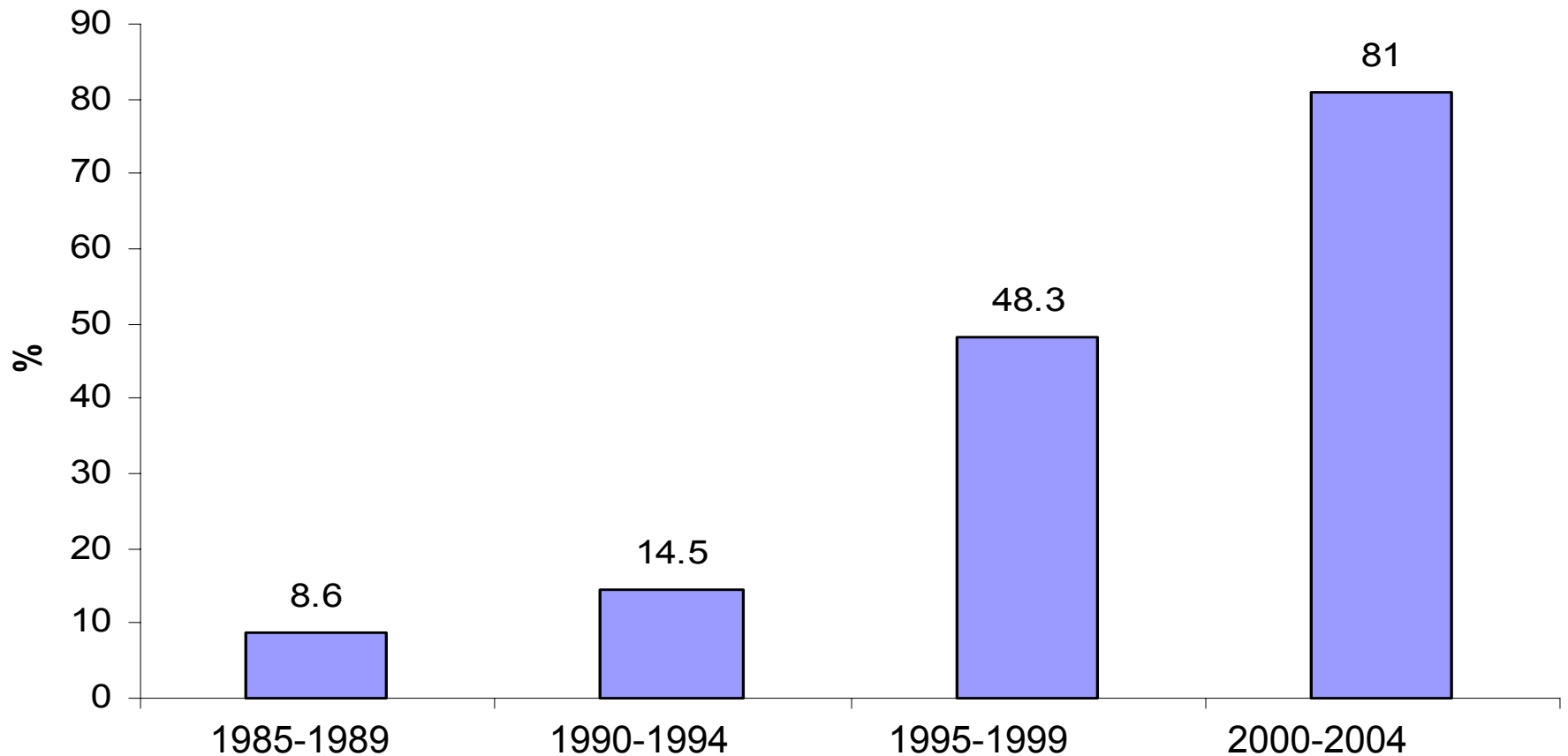
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	At 3 months		
	OR	95% CI	p-values
Donor age >60 (yes vs. no)	4.70	2.10–14.65	0.002
Donor cardiovascular death (yes vs. no)	1.72	1.39–3.67	0.01
Warm ischemia time >60 min (yes vs. no)	1.66	0.99–2.62	0.04
Cold ischemia time >24 h (yes vs. no)	1.77	1.16–2.75	0.008
Delayed graft function (yes vs. no)	1.20	0.96–1.51	0.11

Our patients have changed
within the last 25 years

Donors as well as recipients...

Quality of the graft from 1980's until now: proteinuria may tell us something....

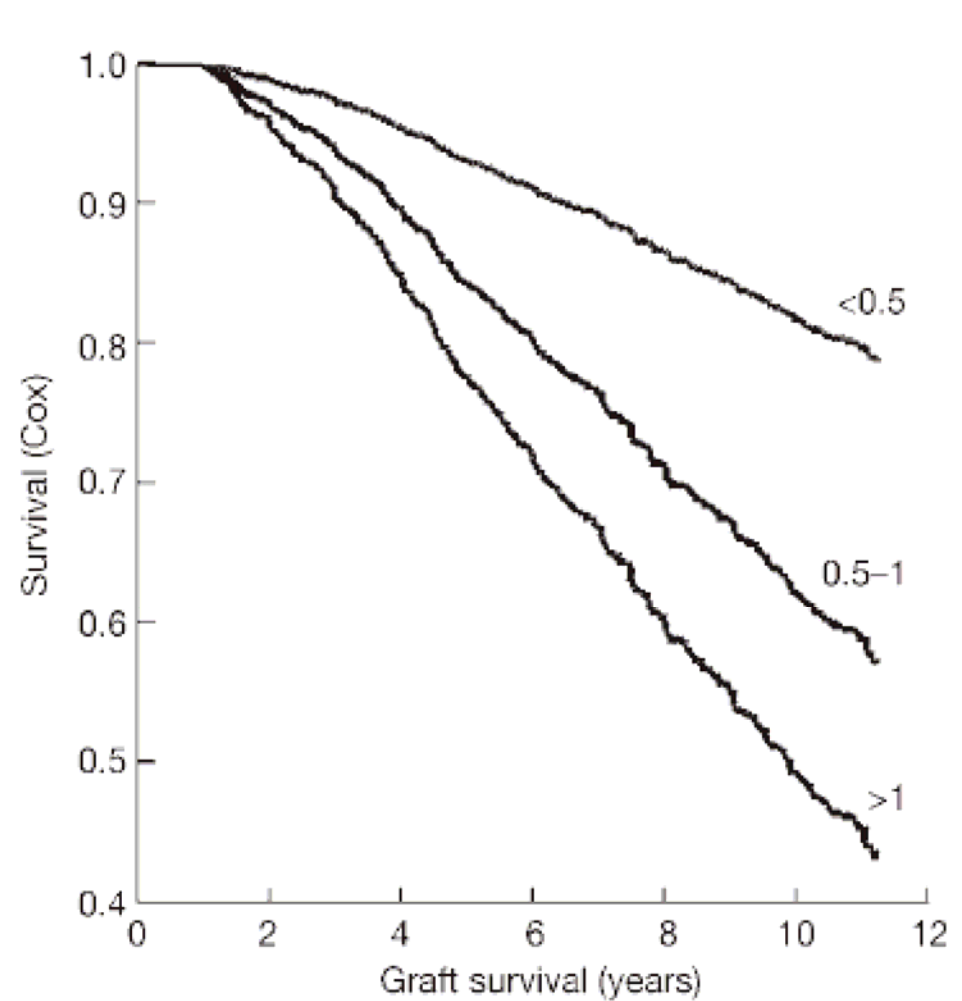
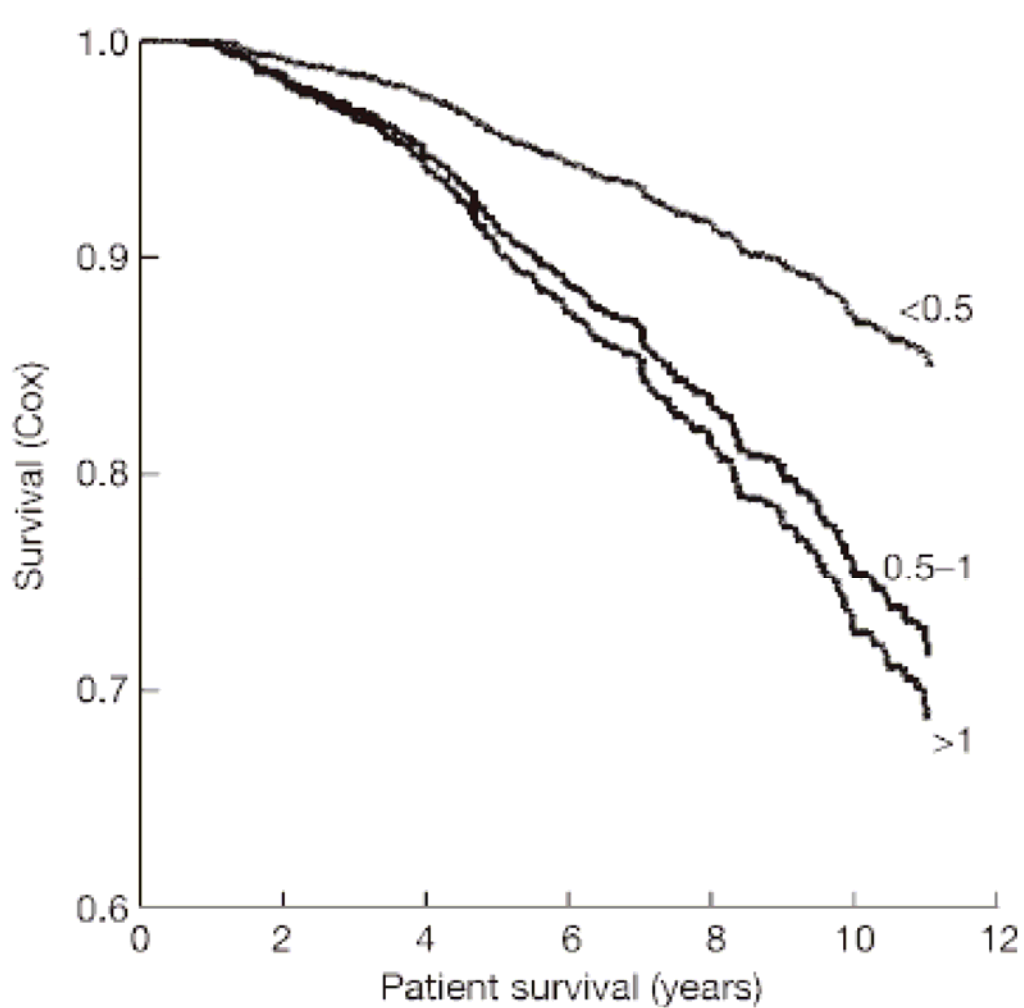


Roland et al, n=828 patients, AJT 2008
Prevalence of proteinuria at 3 months
Threshold limit: >0.007 g/L

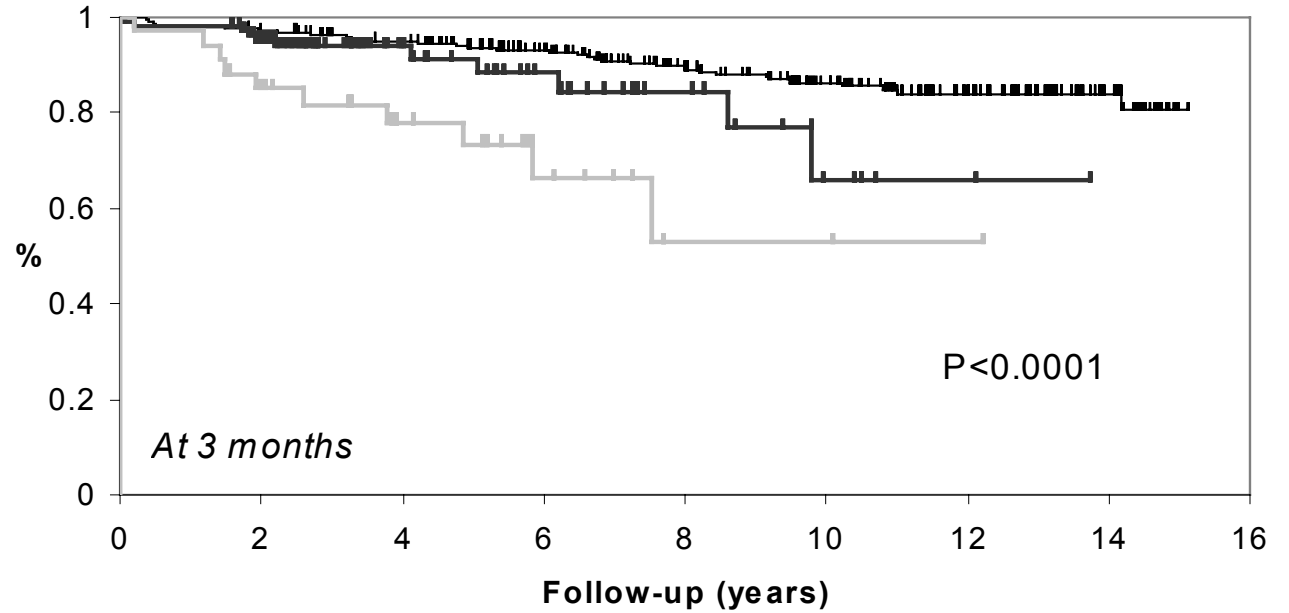
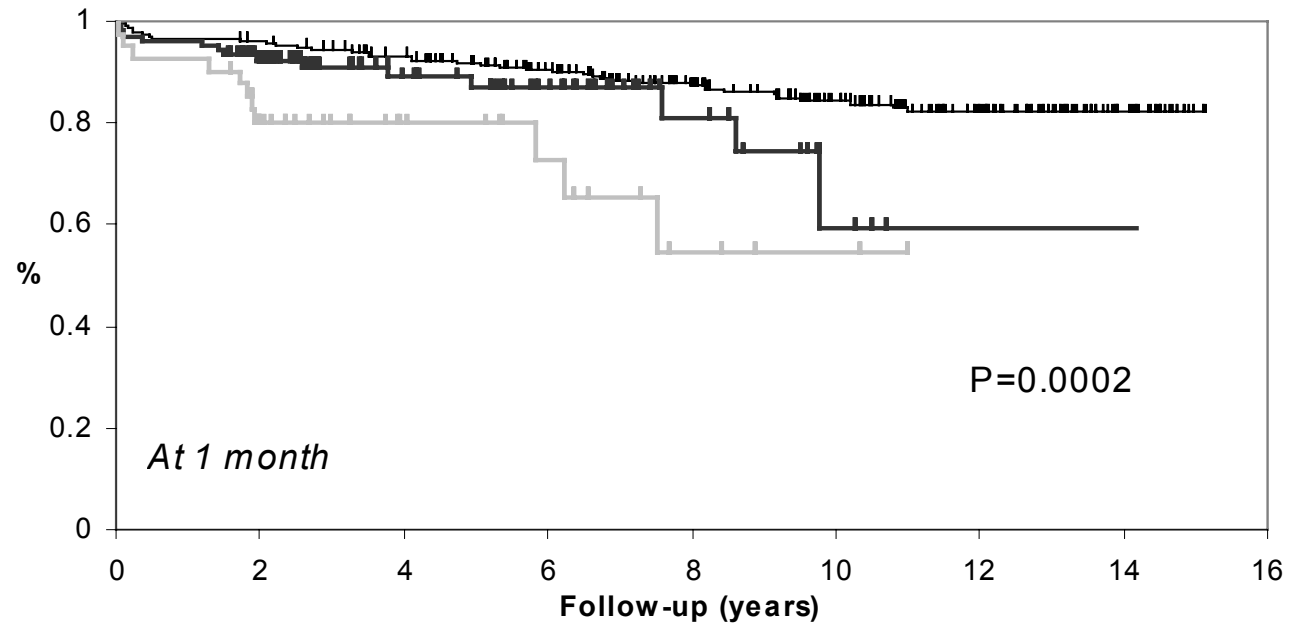
Early low-grade proteinuria and/or urinary albumin excretion are predictors of

- Long-term graft survival
- Long-term patient survival
- Cardiovascular morbidity and mortality
- Mortality by cancer or PTLD
- New-onset diabetes mellitus (NODAT)

Proteinuria $> 1\text{g/day}$ vs $< 1\text{g/day}$ modulates graft and patient survival



« Low-grade » proteinuria and graft survival



Early low-grade proteinuria: each 100 mg/day increases the risk of graft loss by ~ 20%

Subjects with proteinuria < 1 g/day

	Hazard ratio	95% CI	p-values
Proteinuria at 1 month	1.20	1.10–1.31	0.0001
Proteinuria at 3 months	1.26	1.15–1.38	0.0001
Proteinuria at 6 months	1.22	1.09–1.37	0.0004
Proteinuria at 12 months	1.25	1.11–1.41	0.0002

Urinary albumin excretion: predicts graft loss even after multiple adjustments

Macroalbuminuria vs. microalbuminuria

OR** 95% CI p-value

Risk of graft loss after adjustment on the following parameters:

Recipient age (years)	16.74	7.61–36.80	<0.0001
Cold ischemia time (min)	19.31	8.41–44.34	<0.0001
Warm ischemia time (min)	17.21	7.81–35.96	<0.0001
Creatinine clearance (>60 mL/min vs. ≤60 mL/min)	14.75	6.68–32.58	<0.0001
Plasma reactive antibodies (≥50% vs. <50%)	16.63	7.57–36.54	<0.0001
History of acute rejection (yes vs. no)	18.38	8.21–41.12	<0.0001
Delayed graft function (yes vs. no)	16.22	7.44–35.34	<0.0001
Systolic arterial pressure (mmHg)	16.21	7.32–35.90	<0.0001
Cyclosporine use (yes vs. no)	16.19	7.33–35.78	<0.0001
Steroid use (yes vs. no)	16.85	7.15–35.10	<0.0001
Rapamycine use (yes vs. no)	17.02	7.76–37.36	<0.0001
ACEI or ARB use (yes vs. no)	17.51	7.92–38.70	<0.0001

Halimi et al, AJT 2007
N=616 patients

Urinary albumin excretion: predicts graft loss even after multiple adjustments

	Macroalbuminuria vs. microalbuminuria			Microalbuminuria vs. normoalbuminuria		
	OR**	95% CI	p-value	OR*	95% CI	p-value
Risk of graft loss after adjustment on the following parameters:						
Recipient age (years)	16.74	7.61–36.80	<0.0001	14.31	3.89–52.63	<0.0001
Cold ischemia time (min)	19.31	8.41–44.34	<0.0001	20.32	5.21–79.32	<0.0001
Warm ischemia time (min)	17.21	7.81–35.96	<0.0001	12.29	3.32–45.51	0.0002
Creatinine clearance (>60 mL/min vs. ≤60 mL/min)	14.75	6.68–32.58	<0.0001	12.62	3.45–46.19	0.0001
Plasma reactive antibodies (≥50% vs. <50%)	16.63	7.57–36.54	<0.0001	14.47	3.93–53.20	<0.0001
History of acute rejection (yes vs. no)	18.38	8.21–41.12	<0.0001	12.75	3.45–47.2	0.0001
Delayed graft function (yes vs. no)	16.22	7.44–35.34	<0.0001	12.87	3.47–47.68	0.0001
Systolic arterial pressure (mmHg)	16.21	7.32–35.90	<0.0001	13.51	3.65–50.00	<0.0001
Cyclosporine use (yes vs. no)	16.19	7.33–35.78	<0.0001	14.08	3.79–52.32	<0.0001
Steroid use (yes vs. no)	16.85	7.15–35.10	<0.0001	12.69	3.44–46.81	0.0001
Rapamycine use (yes vs. no)	17.02	7.76–37.36	<0.0001	14.62	3.98–53.80	<0.0001
ACEI or ARB use (yes vs. no)	17.51	7.92–38.70	<0.0001	14.83	4.05–54.32	<0.0001

Halimi et al, AJT 2007
N=616 patients

Relationship between proteinuria and urinary albumin excretion

Proteinuria (g/day)	Number of patients	Urinary albumin excretion (mg/day)	Nonalbumin (%)
0	219	19.6±58.3	0
0.01 to 0.25	172	37±32	76±24
0.26 to 0.50	107	116±78	66±21
0.51 to 0.75	40	210±113	64±19
0.76 to 1	15	376±156	57±17
>1	63	1318±855	44±18

Some patients without proteinuria may have normo, microalbuminuria or macroalbuminuria

Proteinuria: colorimetric method
Urinary albumin excretion: nephelometric method

Risk of graft loss associated with macroalbuminuria vs microalbuminuria *(in the subgroup of patients with no proteinuria)*

	OR*	95% CI	p-value
Crude risk	23.09	1.93–276.4	0.0132
Model 1	28.54	2.24–364.3	0.0099
Model 2	39.48	1.59–981.9	0.0250
Model 3	21.97	1.55–310.6	0.0223
Model 4	20.11	1.40–289.0	0.0273
Model 5	24.96	1.16–537.6	0.0399

If proteinuria is present in the
urine...

We may find urinary albumin
excretion and some sort of « non-
albumin » proteins

« Non-albumin proteinuria » vs UAE: respective predictive values for the long-term risk of graft loss

	OR	95% CI	p-Value
<hr/>			
Univariate analyses			
Macroalbuminuria vs. microalbuminuria	16.41	7.49–35.97	<0.0001
Nonalbumin proteinuria (yes vs. no)	29.09	8.80–96.20	<0.0001

« Non-albumin proteinuria » vs UAE: respective predictive values for the long-term risk of graft loss

	OR	95% CI	p-Value
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Macroalbuminuria vs. microalbuminuria	16.41	7.49–35.97	<0.0001
Nonalbumin proteinuria (yes vs. no)	29.09	8.80–96.20	<0.0001
Multivariate analyses			
Nonalbumin proteinuria (yes vs. no)	14.58	4.07–52.25	<0.0001
Macroalbuminuria vs. microalbuminuria (yes vs. no)	6.57	3.05–14.16	<0.0001

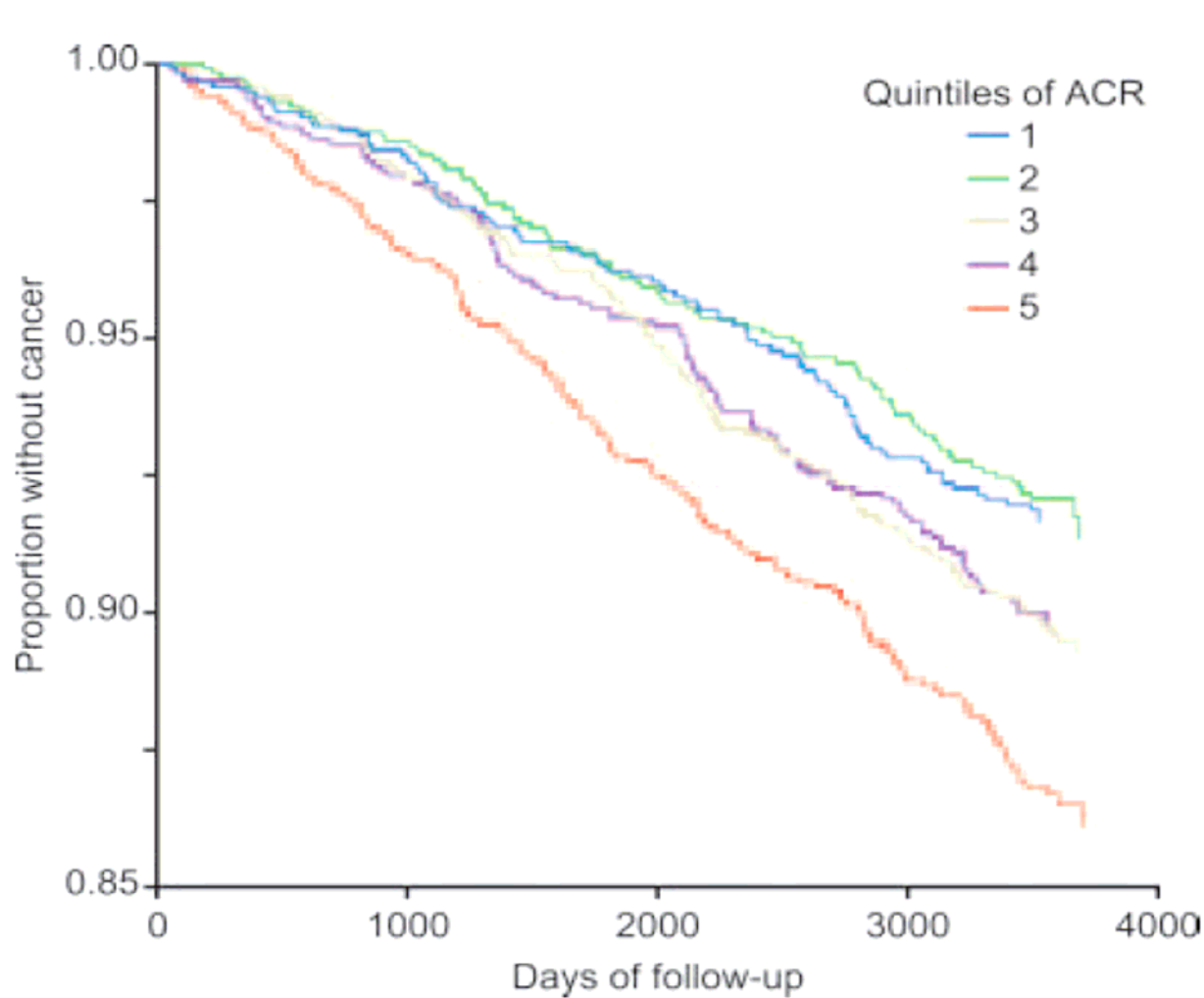
« Non-albumin proteinuria » vs UAE: respective predictive values for the long-term risk of death

- Risk of death
 - Macroalb (vs microalb): HR 4.12 [1.65-10.29], P=0.0024
 - **Non-Alb: HR: 5.37 [2.55-11.34], P<0.0001**

Urinary albumin excretion is associated with the risk of malignancy-related death

Macroalbuminuria (as compared to microalbuminuria) was associated to malignancy-related death [OR: 4.33 (1.01–18.50), $p = 0.0481$].

Albuminuria and the risk of cancer in the general population



Tromso study, 5425 subjects with no history of cancer or diabetes;
590 developed cancer during follow-up (mean: 9.1 yrs)
Jorgensen, JASN 2008

Early low-grade proteinuria is a risk factor for new-onset diabetes mellitus (NODAT)

Risk of NODAT

Proteinuria as a categorical variable

	HR (proteinuria: yes vs no)	95% CI	<i>P</i>
Univariate analysis			
All population	2.52	1.66-3.81	<0.0001
Patients with proteinuria < 1g/day	2.04	1.25-3.33	0.0042
Patients with proteinuria < 0.5g/day	2.38	1.51-3.73	0.0002
Patients with proteinuria < 0.3g/day	2.21	1.32-3.70	0.0025

Risk of NODAT

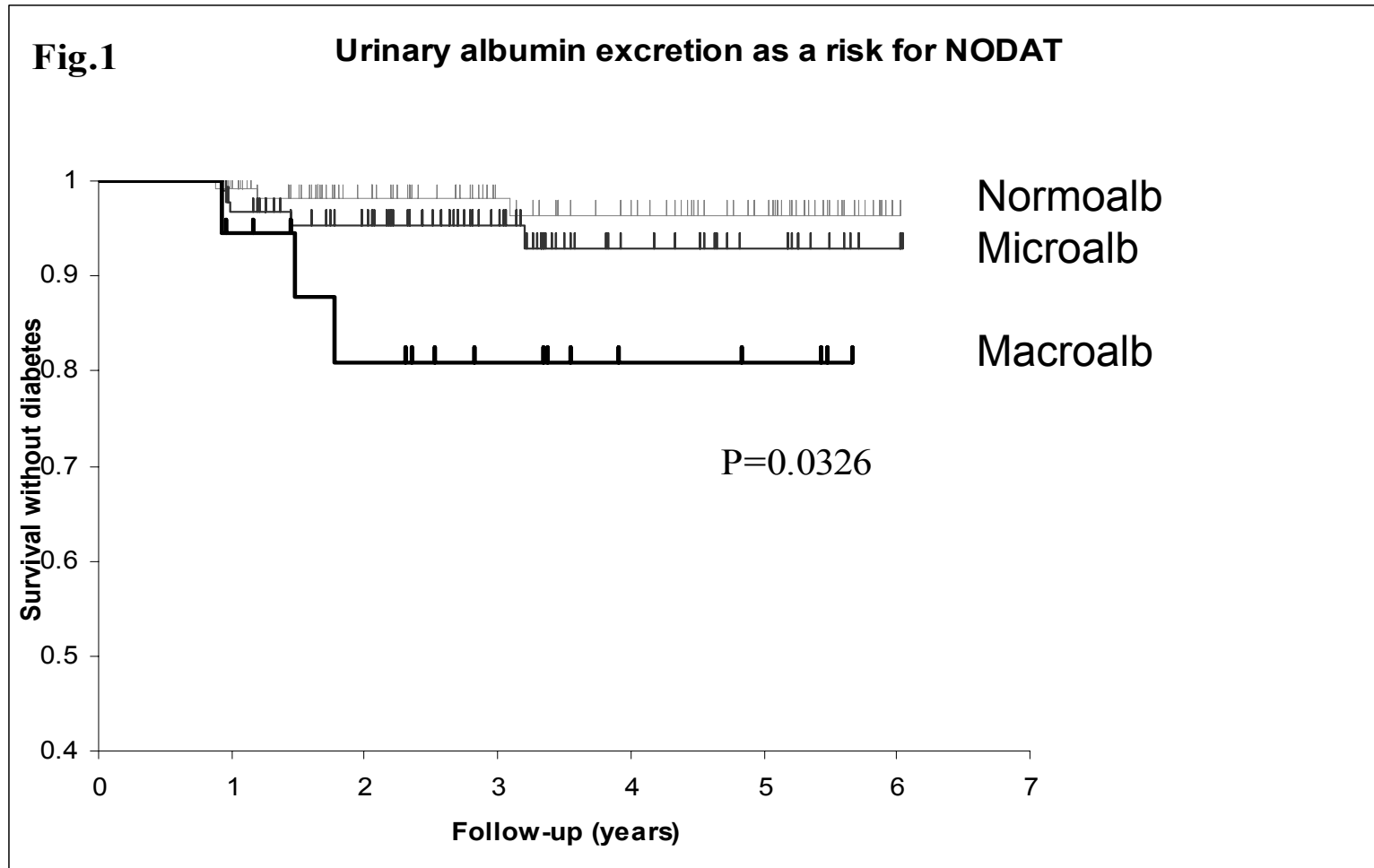
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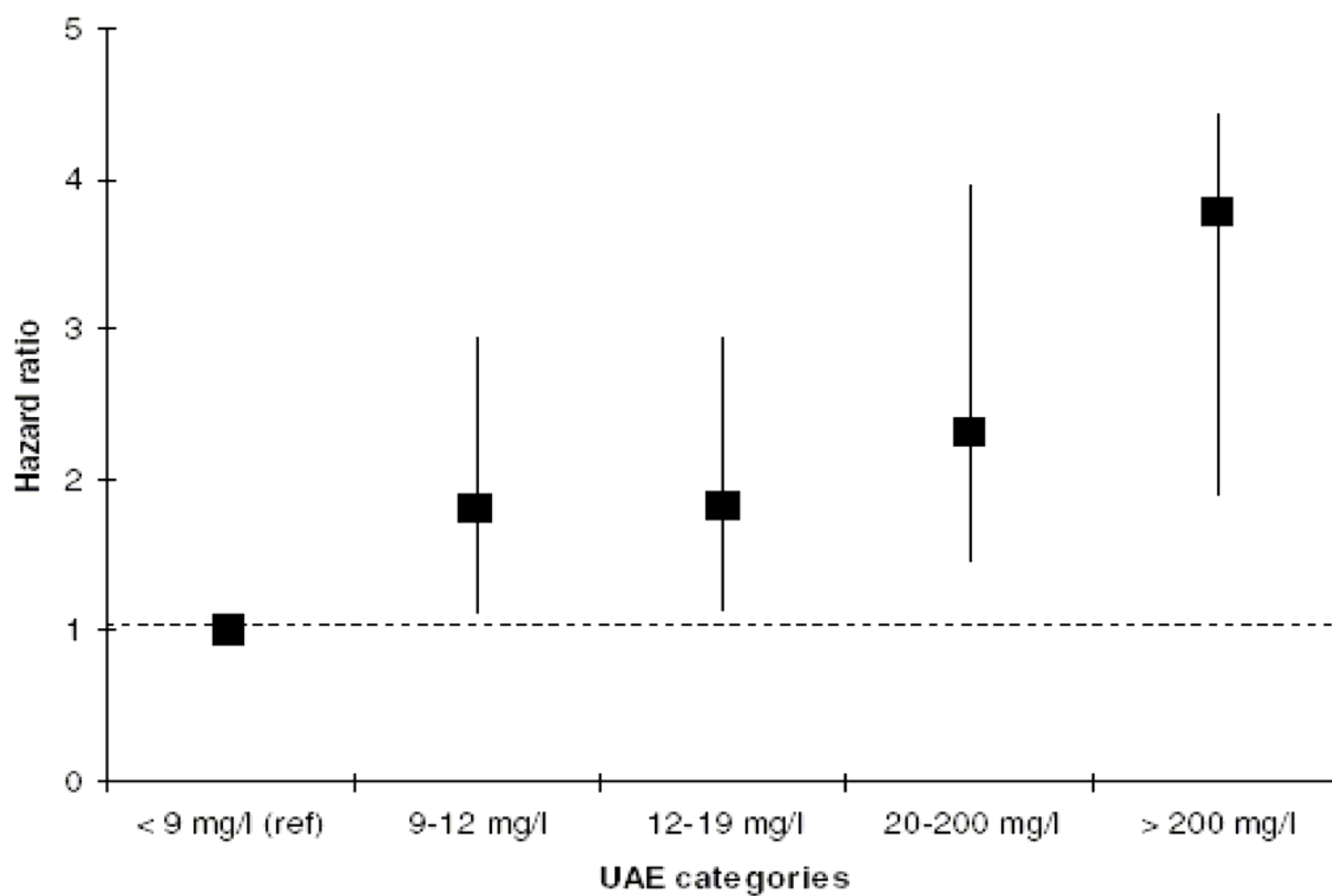
Proteinuria as a quantitative variable

	HR (per 0.1 g/day)	95% CI	<i>P</i>
Univariate analysis			
All population	1.01	1.01-1.03	0.0250
Only patients with proteinuria < 1g/day	1.20	1.12-1.30	<0.0001
Only patients with proteinuria < 0.5g/day	1.31	1.14-1.50	<0.0001
Only patients with proteinuria < 0.3g/day	1.50	1.18-1.91	0.0009
Multivariate analysis			
All population, model 1	1.02	1.01-1.03	0.0114
Proteinuria < 1g/day, model 1	1.12	1.02-1.23	0.0180
Proteinuria < 1g/day, model 2	1.12	1.02-1.23	0.0186
Proteinuria < 1g/day, model 3	1.11	1.01-1.23	0.0287
Proteinuria < 1g/day, model 4	1.11	1.01-1.23	0.0320

UAE and the risk of NODAT



UAE and the risk of diabetes in the general population (DESIR study)



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- Has proteinuria a different meaning in transplantation as compared to other areas of nephrology ?
- Perspectives (for rich people and other people...)

Proteinuria: associations

Renal transplantation Non-transplanted populations

Conditions encountered in both transplanted and non-transplanted populations

Elevated arterial pressure	yes	yes
Elevated serum creatinine	yes	yes
Excessive sodium intake	yes	yes
Body weight or obesity	yes	yes
Active smoking	bordeline significance	-

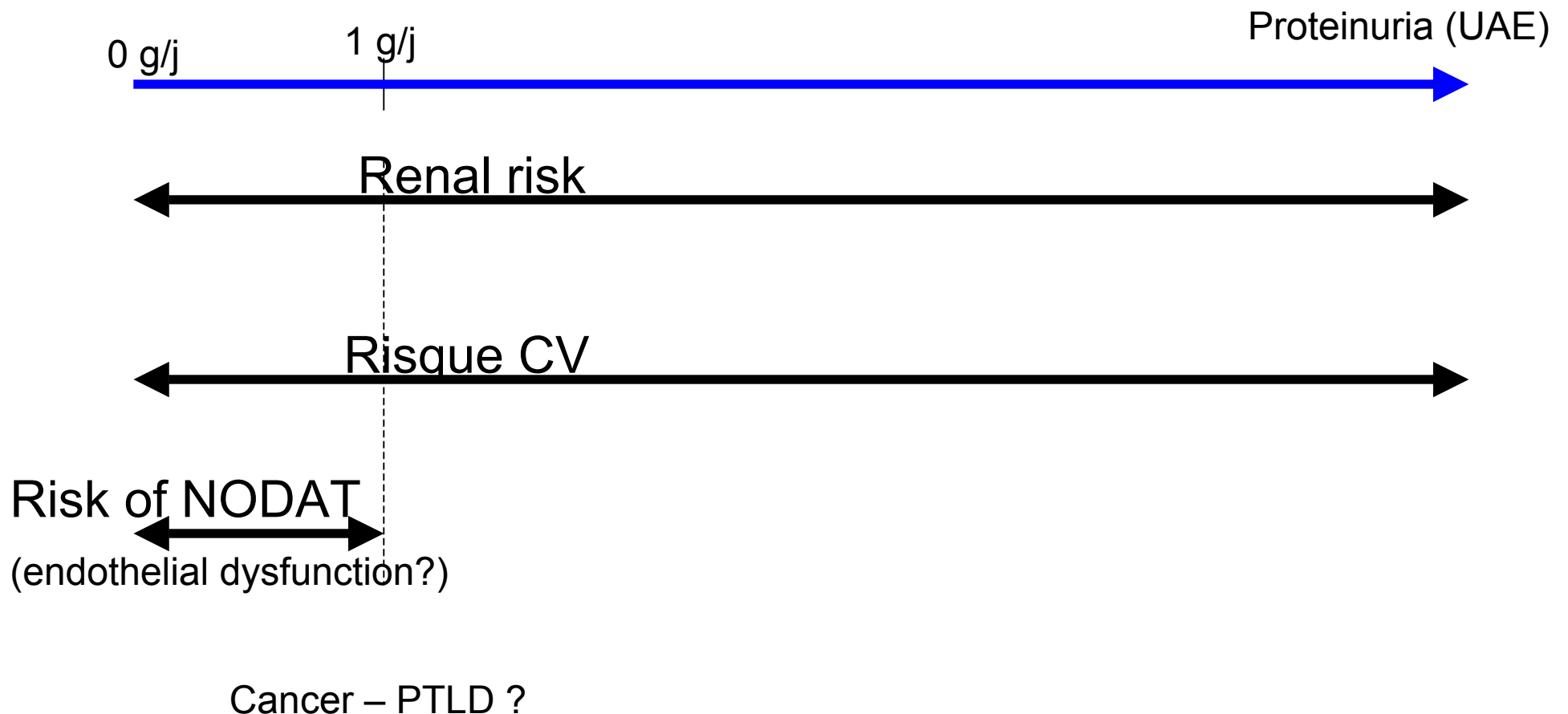
Conditions specific to transplanted populations

Donor age	yes	-
Donor smoking	bordeline significance	-
Donor cardiovascular cause of death	yes	-
Acute rejection	yes	-
Delayed graft function	yes	-
Slow graft function	yes	-
Prolonged cold ischemia time	yes	-
Prolonged warm ischemia ime	yes	-
Glomerular lesions	yes	-
Sirolimus use	yes	-
Everolimus use	yes	-

Proteinuria (or UAE) predictive value

	Renal transplantation	Non-transplanted populations
Death	yes	yes
Cardiovascular death	yes	yes
Noncardiovascular death	yes	yes
Major cardiovascular events	yes	yes
Renal functional response after intervention for renal artery stenosis	no	yes
ESRD	yes, direct evidence both for proteinuria and microalbuminuria	probable, but no direct evidence for microalbuminuria
Diabetes mellitus	yes	yes

Proteinuria (UAE) : metabolic, cardiovascular, cancer and renal risk



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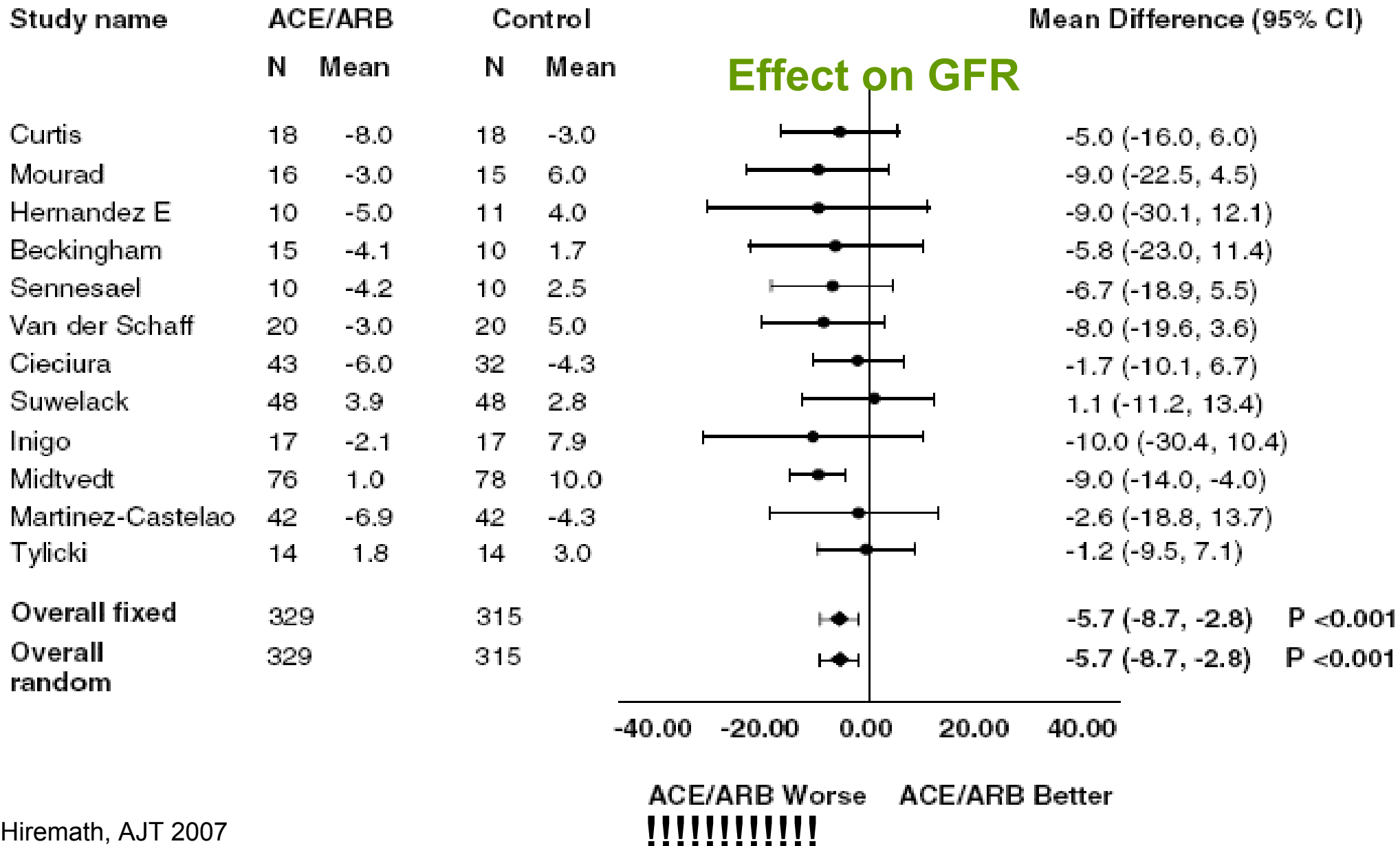
Should we use ACE or ARB in patients
with early low-grade proteinuria ?

I don't know

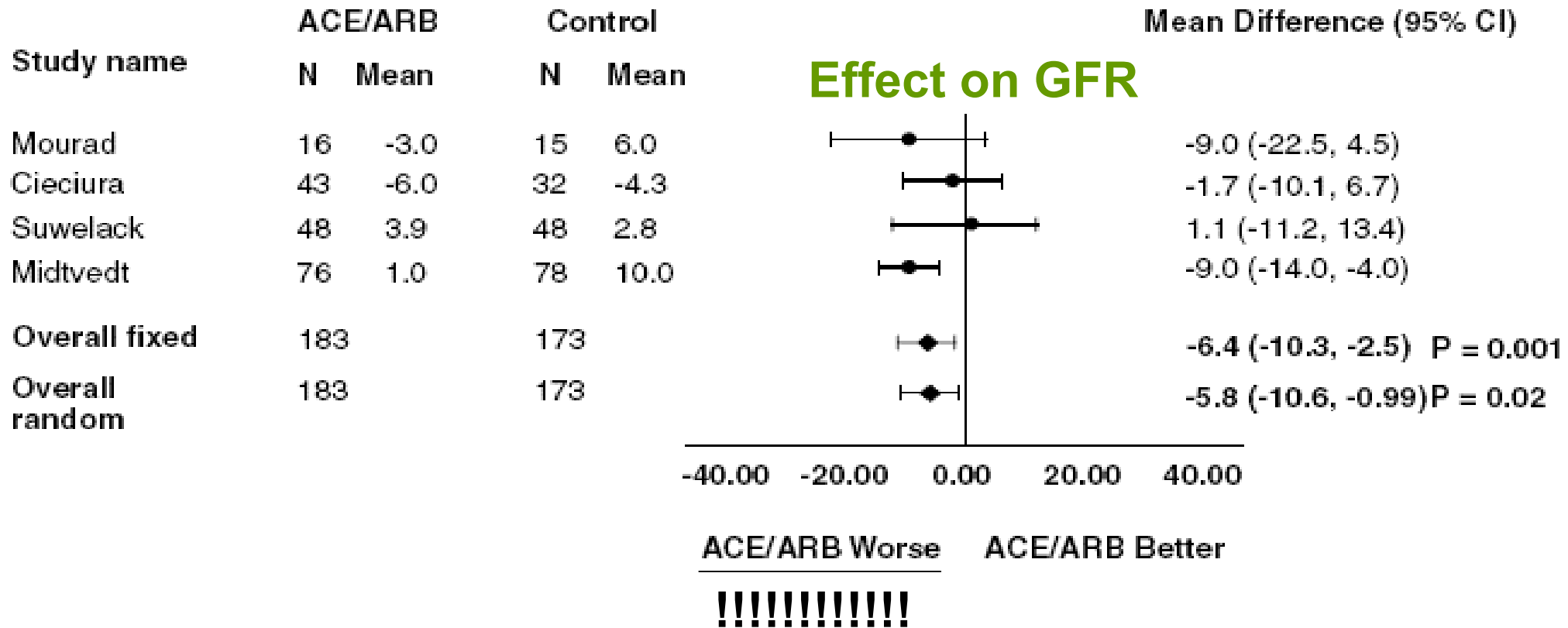
Strong evidence for nephroprotection ?

- Massive proteinuria or chronic allograft nephropathy
 - Several observational studies: **YES, we can!**
 - Some small clinical trials: **YES, we can!**
- No massive proteinuria nor chronic allograft nephropathy
 - Observational (nb studies): **YES: 5 – NO: 2**
 - Clinical trials (nb studies): **YES: 1 – NO: 2.**

Meta-analysis: nephroprotection with IEC/ARB



Meta-analysis (follow-up > 12 months)



Which combinations ?

	Amlodipine	Enalapril	Combination	p, global	p, E vs. AE	p, A vs. AE	p, A vs. E
Unadjusted (%)	-22.2% [-44.8; +10.8]	-60.1 [-72.0; -43.2]	-67.4 [-77.2; -53.2]	0.002	0.709	0.002	0.023
Adjusted (%)	-29.0% [-50.7; +2.2]	-59.5 [-72.1; -41.4]	-64.7 [-75.7; -48.5]	0.023	0.857	0.027	0.076

Perspectives

- For our patients: it may be useful to measure UAE
 - When there is no proteinuria
 - *But certainly not* when there is proteinuria
 - Using 24 hours urine is not mandatory (U. protein/creatinine ratio is OK)
 - To reduce arterial pressure is important.
- Epidemiology
 - « Non-alb » and UAE provide different information on long-term outcome
 - Nature of the « Non-alb »?
 - UAE detected by HPLC method ?
 - ↑-1 µglobulin, NGAL, KIM-1, nephrin, MMPs, TIMP1 ? ... you name it
- Proteomics: you have to be rich
 - 2000 € per sample in Tours (so we stopped for the time being)
 - Metabolomics?