

Proteinuria: Significance and Treatment

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Objectives

- To become familiar with the ways to measure proteinuria
- To recognize that proteinuria is associated with an increased risk of death and kidney failure
- To be able to modify the treatment of people with proteinuria to reduce the risk of cardiovascular events and kidney failure

Proteinuria: Measurement Considerations



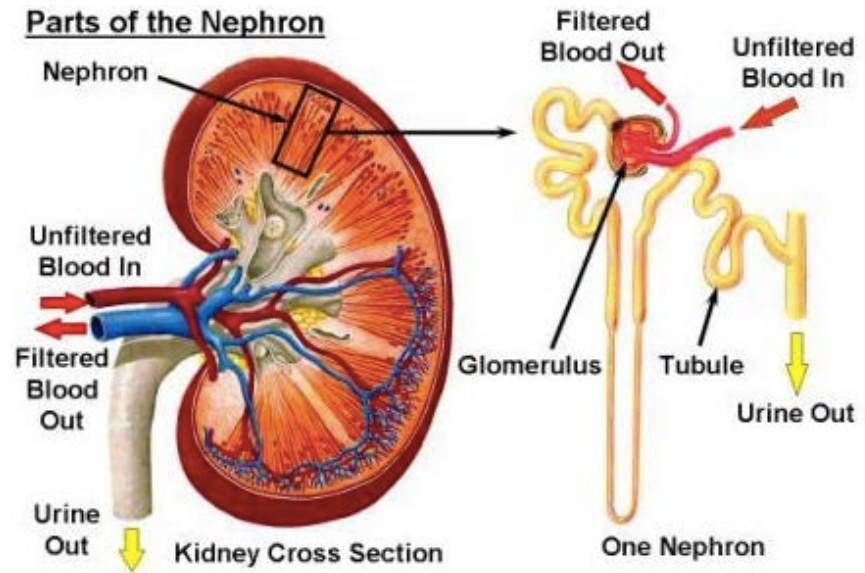
A Small Amount of Protein in the Urine is Normal

- Small amount of low molecular weight proteins and albumin are excreted in the urine
- “Normal” daily protein excretion
 - Protein <150 mg /day
 - Albumin <30 mg/day
 - In reality, “normal” is actually lower than these cutoffs

Proteinuria is a common manifestation of kidney disease

- Causes:

- Glomerular
- Tubular
- Overflow



Transient Proteinuria

- Common!
- Many situations/conditions can transiently increase urine protein levels:
 - Exercise
 - Febrile illness
 - Decompensated CHF
 - Urinary tract infection
 - Urologic or menstrual bleeding
 - Acute severe elevations in blood pressure or blood sugar
- It important to CONFIRM the presence of proteinuria by repeating the urine test 1 -2 weeks later

Methods of Urine Protein Measurement

- Qualitative – ignores urine concentration
 - Urine dipstick
- Quantitative - accounts for urine concentration
 - Albumin to Creatinine Ratio (ACR) on spot sample
 - Protein to Creatinine Ratio (PCR) on spot sample
 - 24 hour urine collection – the “gold standard”

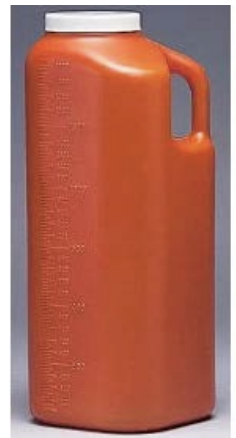
Urine ACR versus PCR

Which one should I order?

- Both affected by day to day variability, circadian variability, posture and physical activity
 - Early morning specimens are preferred (ideally first void)
 - **Be careful not to overinterpret small changes**
- ACR recommended for screening and in diabetes
 - Included in CKD classification system
- PCR may be more useful in some cases
 - Where the main protein excreted is NOT albumin e.g. tubulointerstitial diseases

When should I order a 24 hour urine collection for protein?

- Disadvantages: cumbersome, prone to errors in collection
- Most accurate method if performed correctly
- Often used for follow up of **glomerulonephritis** treatment
 - Spot specimens (ACR, PCR) not validated
- Always include a 24 hour urine **creatinine** to assess the completeness of collection



Albuminuria Definitions

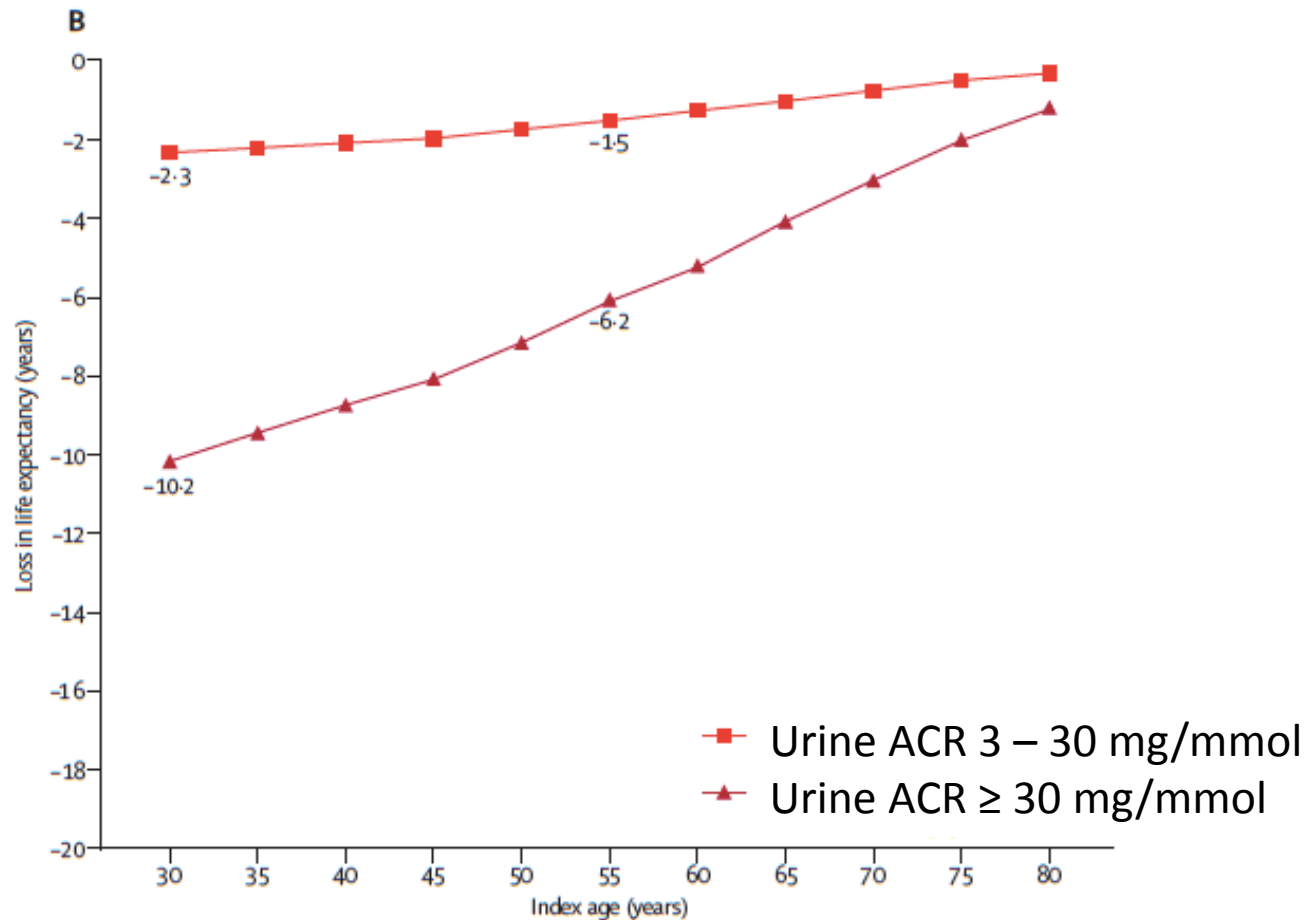
“Old” Terminology	New Terminology (KDIGO 2012)	Amount of Albumin
“Normal”	Normal to mildly increased albuminuria	< 30 mg/day ACR < 3.0 mg/mmol
Microalbuminuria	Moderately increased albuminuria	30 – 300 mg/day ACR 3 – 30 mg/mmol
Macroalbuminuria Overt proteinuria	Severely increased albuminuria	>300 mg/day ACR > 30 mg/mmol
Nephrotic-range proteinuria	Nephrotic-range proteinuria	≥3.5 grams/day protein ACR >220-300 mg/mmol

Significance of Proteinuria (Albuminuria)

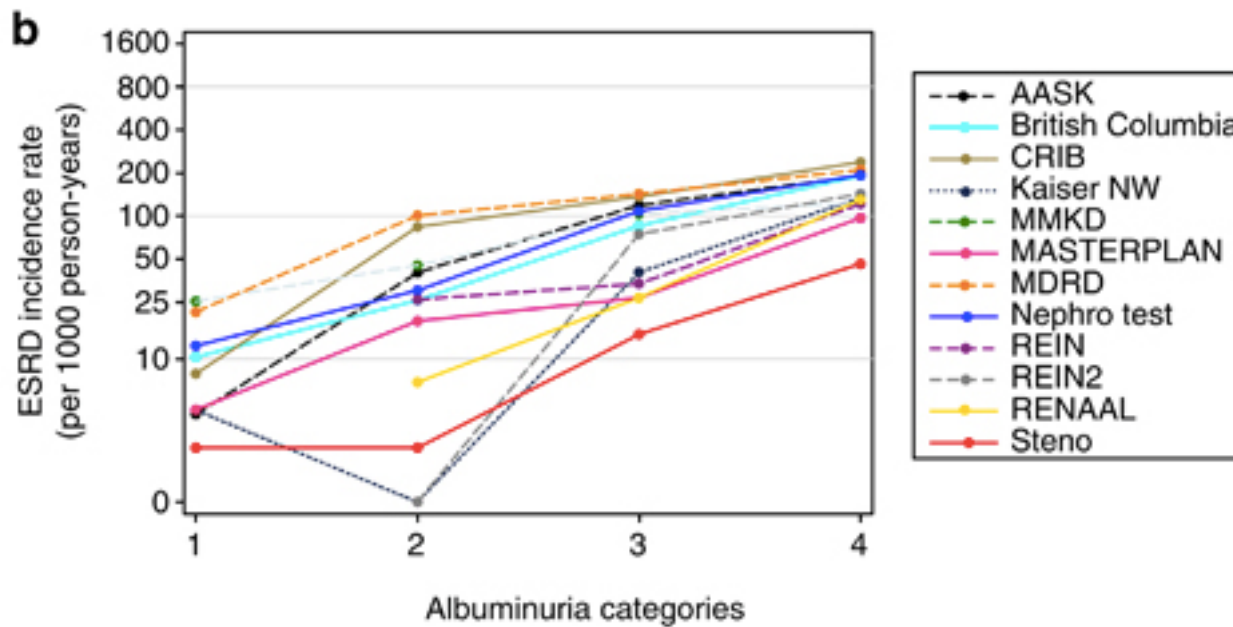
Albuminuria predicts adverse outcomes in CKD

- Increased risk of:
 - Cardiovascular events
 - Mortality
 - CKD progression

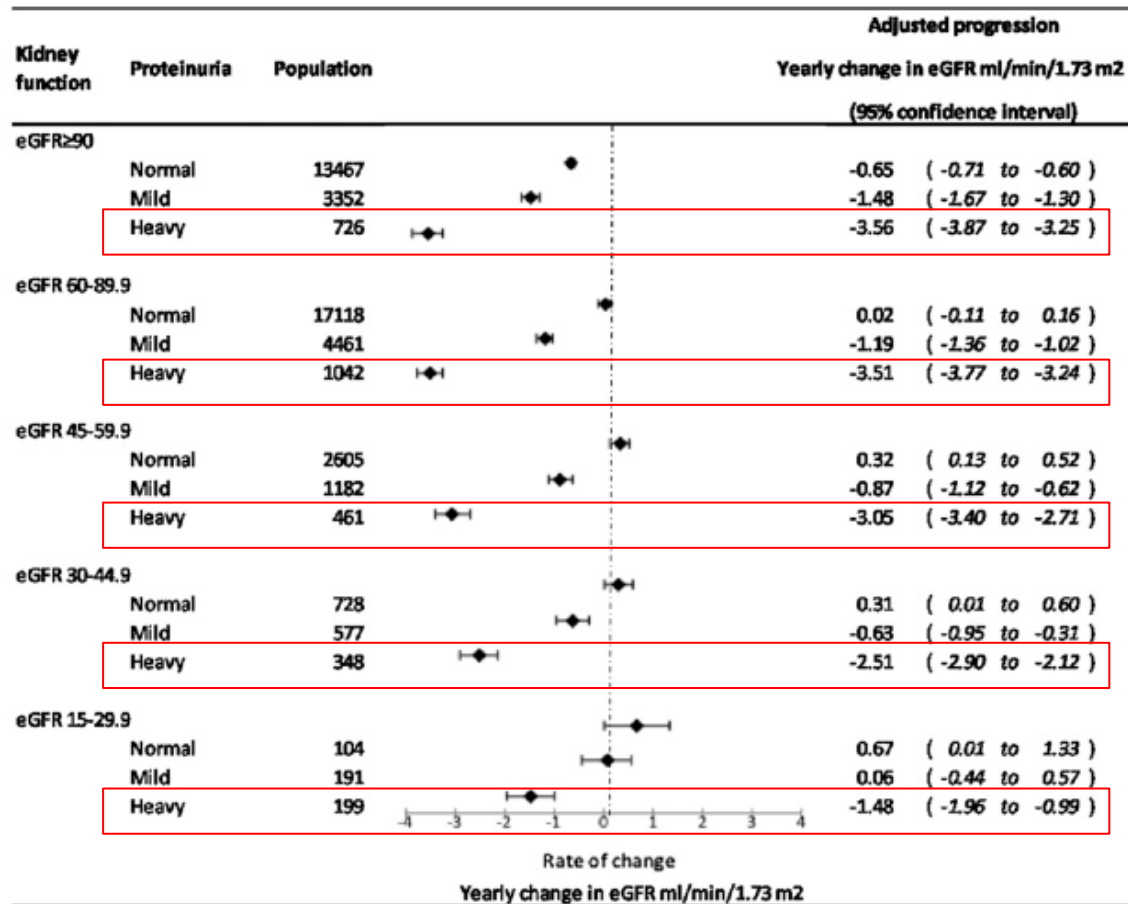
Loss of life expectancy due to CVD deaths with albuminuria



Higher albuminuria associated with higher risk of ESKD

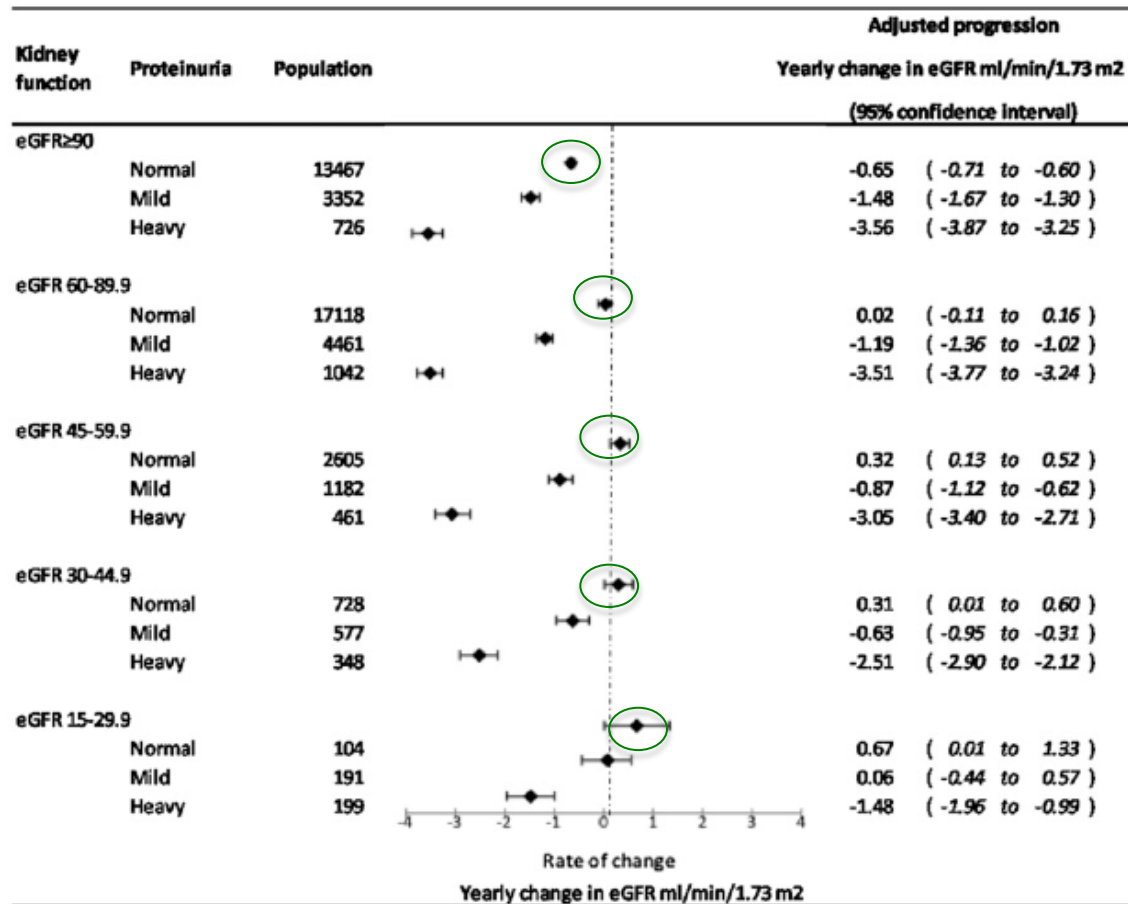


Higher albuminuria is associated with **FASTER RATE** of CKD Progression



Heavy =
ACR > 30

Higher albuminuria is associated with **FASTER RATE** of CKD Progression



Normal =
ACR < 3

What's more likely: Death or ESKD?

Age has an important effect on Risk

Age	ESRD Rate/1000 P-Yrs			Mortality Rate/1000 P-Yrs	
	ACR			ACR	
	Normal	High		Normal	High
18 - 54	0.5	5.2		4.0	11.6
55 - 64	0.8	5.1		10.3	22.5
65 - 74	0.8	6.2		22.0	44.7
≥ 75	0.6	2.3		49.6	84.0

Most patients with CKD are more likely to **DIE from CVD** than get kidney failure

CKD Definition: KDIGO 2012

Includes Assessment of Albuminuria

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

				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
GFR categories (ml/min/1.73 m ²) Description and range	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.

Proteinuria

Treatment Considerations

General Treatment Principles

- Identify and treat the underlying cause
- Cardiovascular risk factor modification
- Blood pressure control
- Antiproteinuric agents: ACE inhibitors, ARBs
- Considerations in the nephrotic syndrome

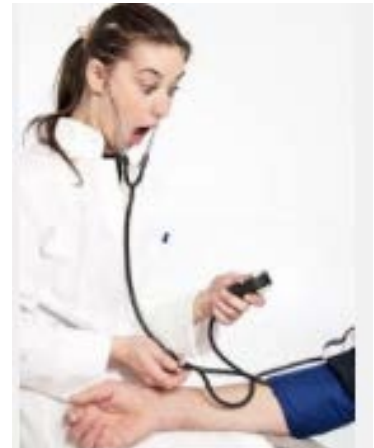
Manage cardiovascular risk factors

- Lifestyle
 - Quit smoking
 - Exercise
 - Weight (BMI 20 – 25)
- Diet
 - Salt restrict
- Pharmacologic
 - Lipids
 - Diabetes
 - Blood pressure



Blood Pressure Treatment

- Objectives:
 - Protect against cardiovascular risks of high BP
 - Delay progressive loss of kidney function
- Lifestyle intervention is important
 - Weight optimization, exercise, reduce alcohol intake, salt restriction



Blood Pressure Targets in CKD



Blood Pressure Targets in CKD

CHEP 2014

- **Nondiabetics**, regardless of urine protein level, target: **<140/<90** mmHg
 - Post hoc analysis of some trials suggest lower target MAY benefit proteinuria – evidence insufficient to recommend lower target
- **Diabetics**, regardless of urine protein level, target: **<130/<80** mmHg
 - Lower target is recommended mainly for STROKE risk reduction, but may also assist ESKD risk reduction

First line antihypertensives for people with proteinuria

- ACE inhibitors
- Angiotensin receptor blockers

Blood Pressure Targets in CKD

Not everyone can tolerate their “target”

- Individualize BP targets if necessary:
 - Inquire about medication side effects such as postural dizziness, check for postural hypotension
 - Use caution in the elderly



Antiproteinuric Medications: ACE inhibitors and ARBs

Consider various individuals with albuminuria:

	Diabetes	**No Diabetes
Normal BP	Treat	Individualize
High BP	Treat	Treat

** Treatment may also include specific interventions directed against the disease process e.g. Immunosuppressives for glomerulonephritis

Practical Tips for ACE inhibitor and ARB use

- **CHECK** creatinine and potassium at baseline and within 1 – 2 weeks of starting or uptitrating an ACEi or ARB
- If hyperkalemia develops or creatinine rises >30% therapy may need to be **STOPPED** and labwork should be repeated
- **HOLD** during episodes of acute kidney injury and during acute illness (“sick days”)

Practical Tips for ACE inhibitor and ARB use

- Mild to moderate hyperkalemia may be manageable without permanent discontinuation with: low potassium diet, diuretics, potassium binders
- In general, there is no “eGFR cutoff” below which patients do not benefit from these medications but stage 4 and 5 CKD are at higher risk of complications – closer monitoring required

ACE inhibitor + ARB?

Two are not better than one!

- Use of an ACE inhibitor and ARB together is **not** recommended
 - No reduction in CKD progression
 - Increased risk of adverse events



N Engl J Med 2013;369:1892-903.
Lancet 2008;372:547-53.

Is there a specific “target” level for proteinuria during treatment?

- The cause is an important determinant of the answer to this question
 - In some cases, disappearance of proteinuria is an indicator that the disease has been adequately treated, e.g. minimal change disease, other glomerular diseases
- Observational studies, post hoc analysis of trials: the lower the level of urine protein achieved, the lower the risk of CKD progression
 - This is not the same as having a trial where proteinuria level is the target of treatment

Complications of Nephrotic Syndrome

- Edema
- Malnutrition
- Hypercoagulability
- Hyperlipidemia
- Increased risk of infection

Summary

- The most commonly used measure of urine protein is the urine ACR
 - Transient proteinuria can occur – confirmatory testing is needed
 - Be careful not to “overinterpret” small changes in ACR
- Proteinuria is associated with an increased risk of kidney failure and death from cardiovascular disease
- The mainstays of proteinuria management include: cardiovascular risk factor modification, blood pressure control and ACE inhibitors/ARBs



Kidney Failure Risk Equation

- <http://www.qxmd.com/calculate-online/nephrology/kidney-failure-risk-equation>

By clicking on the "Submit" button below, you acknowledge that you have read, understand, and agree to be bound by the terms of the [QxMD Online Calculator End User Agreement](#).

Use the Kidney Failure Risk Equation to determine 2 and 5 year probability of treated kidney failure (dialysis or transplantation) for a patient with CKD Stage 3 to 5.

Age (yrs)	<input type="text"/>	
Sex	<input type="button" value="Male"/> ▾	
GFR (ml/min/1.73m ²)	<input type="text"/>	
Urine Albumin:Creatinine Ratio	<input type="text"/>	<input type="radio"/> mg/g <input checked="" type="radio"/> mg/mmol
Calcium	<input type="text"/>	<input type="radio"/> mg/dL <input checked="" type="radio"/> mmol/L
Phosphorus	<input type="text"/>	<input type="radio"/> mg/dL <input checked="" type="radio"/> mmol/L
Albumin	<input type="text"/>	<input type="radio"/> g/dL <input checked="" type="radio"/> g/L
Bicarbonate (mmol/L)	<input type="text"/>	
	<input type="button" value="Submit"/>	

Proteinuria is not just a disease marker, it influences disease progression

