

Prediction of Kidney Disease Progression in Patients with Diabetes

John Arthur, MD, PhD

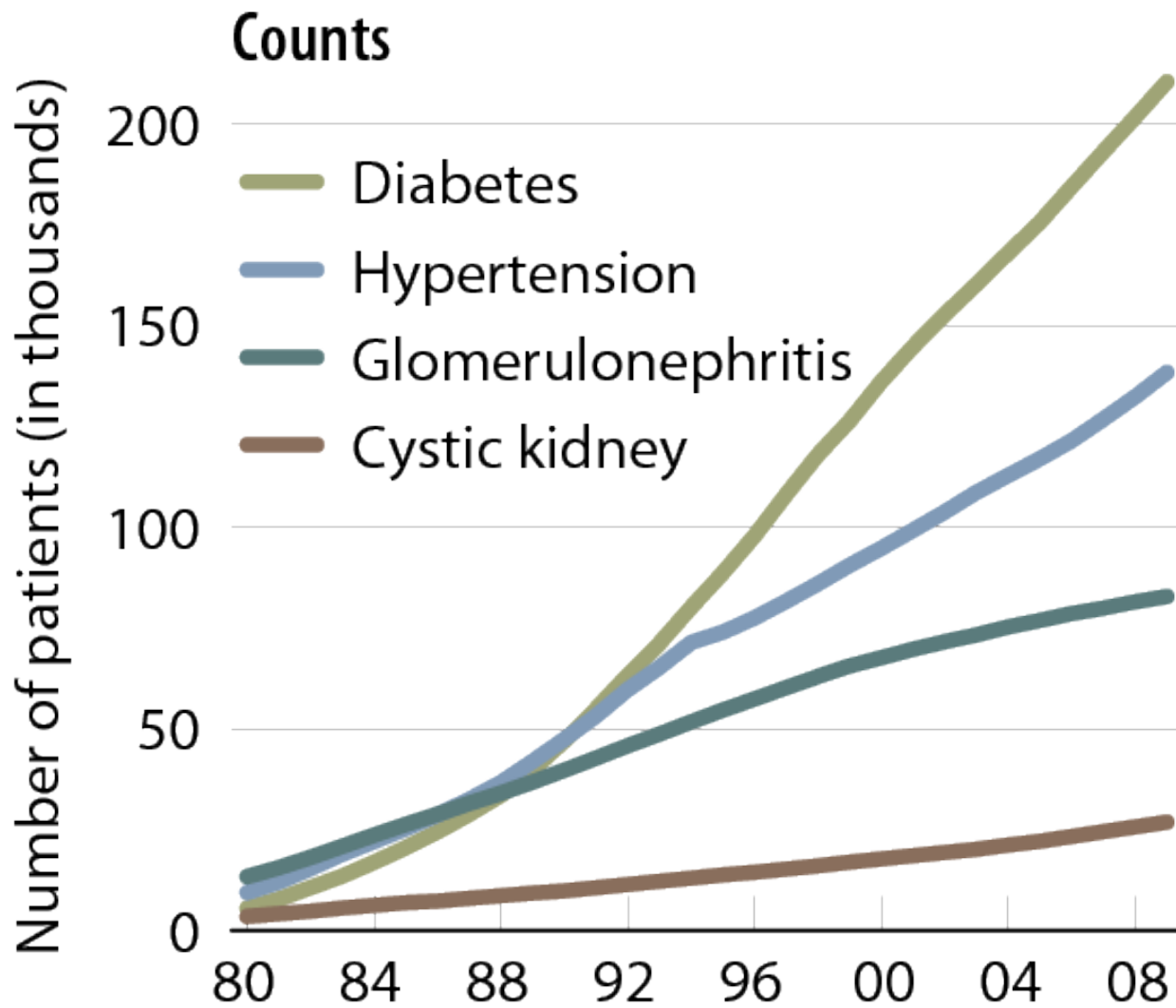
Medical University of South Carolina

SEKDC Meeting September 8, 2012

Objectives

- Understand the importance of predicting renal outcomes in patients with diabetes
- Understand the benefits and limitations of urinary albumin to predict the development of diabetic nephropathy
- Understand current and potential assays that can help predict renal function decline in patients with diabetes.

Diabetes is the leading cause of ESRD



December 31 point prevalent ESRD patients.
Adj: age/gender/race; ref: 2005 ESRD patients.

2011 USRDS

Screening for Kidney Disease

- US Preventive Services Task Force Statement (2012)
 - There is not enough evidence to determine the potential benefits and harms of screening all adults for CKD.
- KDOQI (2007) Patients with diabetes should be screened annually for DKD.
 - 5 years after the diagnosis of type 1 diabetes
 - From diagnosis of type 2 diabetes.
 - Measurements of urinary ACR in a spot urine sample
 - Measurement of serum creatinine and estimation of GFR
- Annual measurement of ACR is also recommended by the American Diabetes Association

Why Identify Patients at Risk for Progression?

- Treatment options to prevent or slow the progression of Diabetic Kidney Disease are limited.
- Lifestyle modification should be recommended to all diabetic patients.
- All diabetic patients should have good glycemic and blood pressure control.
- Most diabetic patients with hypertension should be on an agent to block the renin angiotensin system.
- There are no specific treatments for diabetic kidney disease.

Development of diabetic kidney disease drug

- Preclinical studies in animals to determine effectiveness.
Hampered by lack of good animal models of diabetic nephropathy.
- Phase I- Determination of safety and dosing.
- Phase II-Administration of drug to group of subjects with disease to determine preliminary information about efficacy and further assess safety.
- Phase III-Administration to large groups of subjects to determine efficacy and safety. Generally given in addition to standard of care medications.
- Effectiveness defined by FDA as a benefit to how patient “**feels, functions or survives**”.
- IDNT Phase III study enrollment over 2.5 years in 225 clinics worldwide. Endpoint was doubling of creatinine, ESRD or death. Not required to compare to ACE inhibitors (amlodipine in control group). Mean follow-up 2.6 years.

Hurdles to drug development

- Unclear if animal models will correlate with human disease.
- Long path to FDA approval.
- Current FDA approvable endpoints are difficult and time consuming to meet.
- Long clinical trials are costly.
- Difficult to predict patients at risk of progression in DKD.
- Recent high-profile failure of drug for DKD.

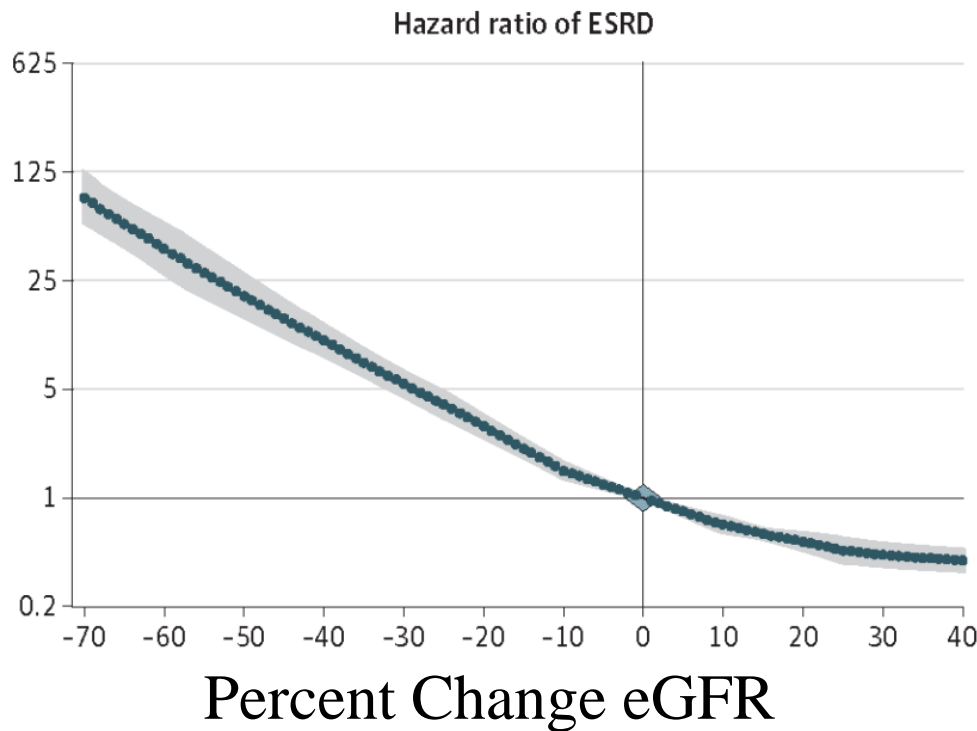
The After Clinic Blues



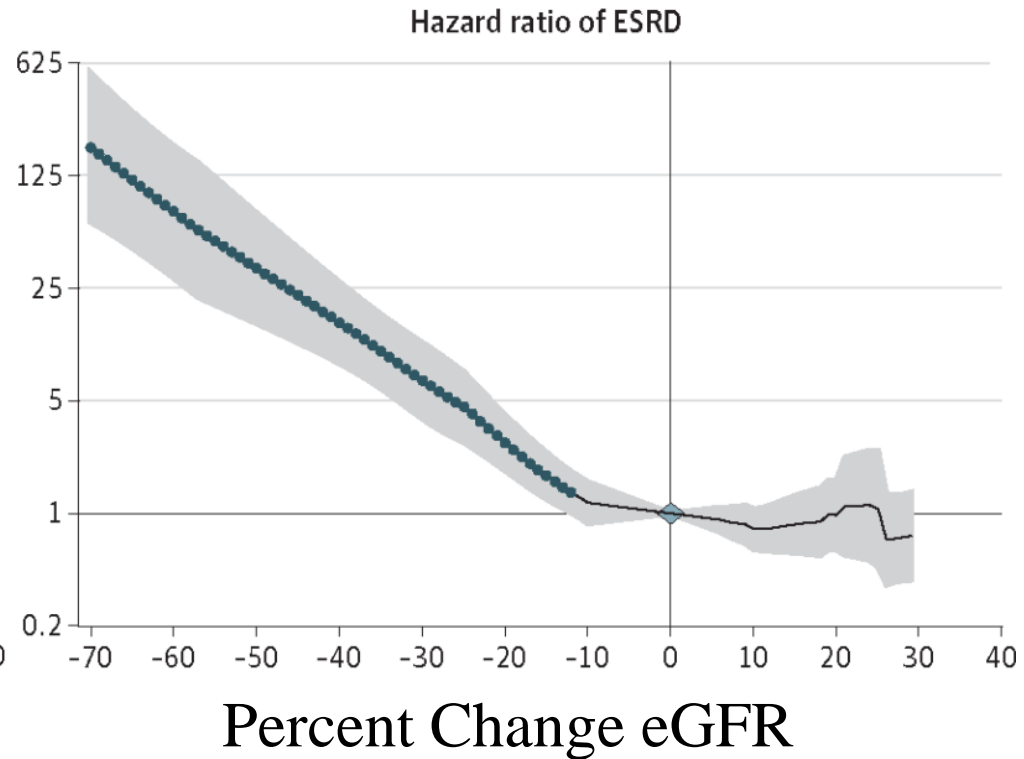
Wait! Help is on the way!

Changes in eGFR Over 2 Years Predict the Risk of ESRD

Adjusted Hazard Ratio of ESRD



eGFR < 60



eGFR ≥ 60

Drugs for Diabetic Nephropathy in Clinical Trials

Drug	Sponsor	Phase	Mechanism of action
MT-3995	Mitsubishi Tanabe	Phase 2	Aldosterone receptor blocker
Acthar	Questcor	Phase 2	Melanocortin receptor agonist (ACTH)
LY3016859	Eli Lilly	Phase 2	Binds TGF alpha (an EGF-R ligand)
GS-4997	Gilead Sciences	Phase 2	Apoptosis signal-regulating kinase 1 inhibitor
Probucol	Otsuka	Phase 2	Antioxidant
BMS-813160	Bristol-Myers Squibb	Phase 2	CCR2/CCR5 antagonist
PF-04634817	Pfizer	Phase 2	CCR2/CCR5 antagonist
GKT137831	Genkyotex Innovation	Phase 2	NOX1/4 inhibitor
Pyridorin (pyridoxamine)	NephroGenex	Phase 3	Inhibits formation of advanced glycation end products
Atrasentan	AbbVie	Phase 3	Endothelin receptor antagonist

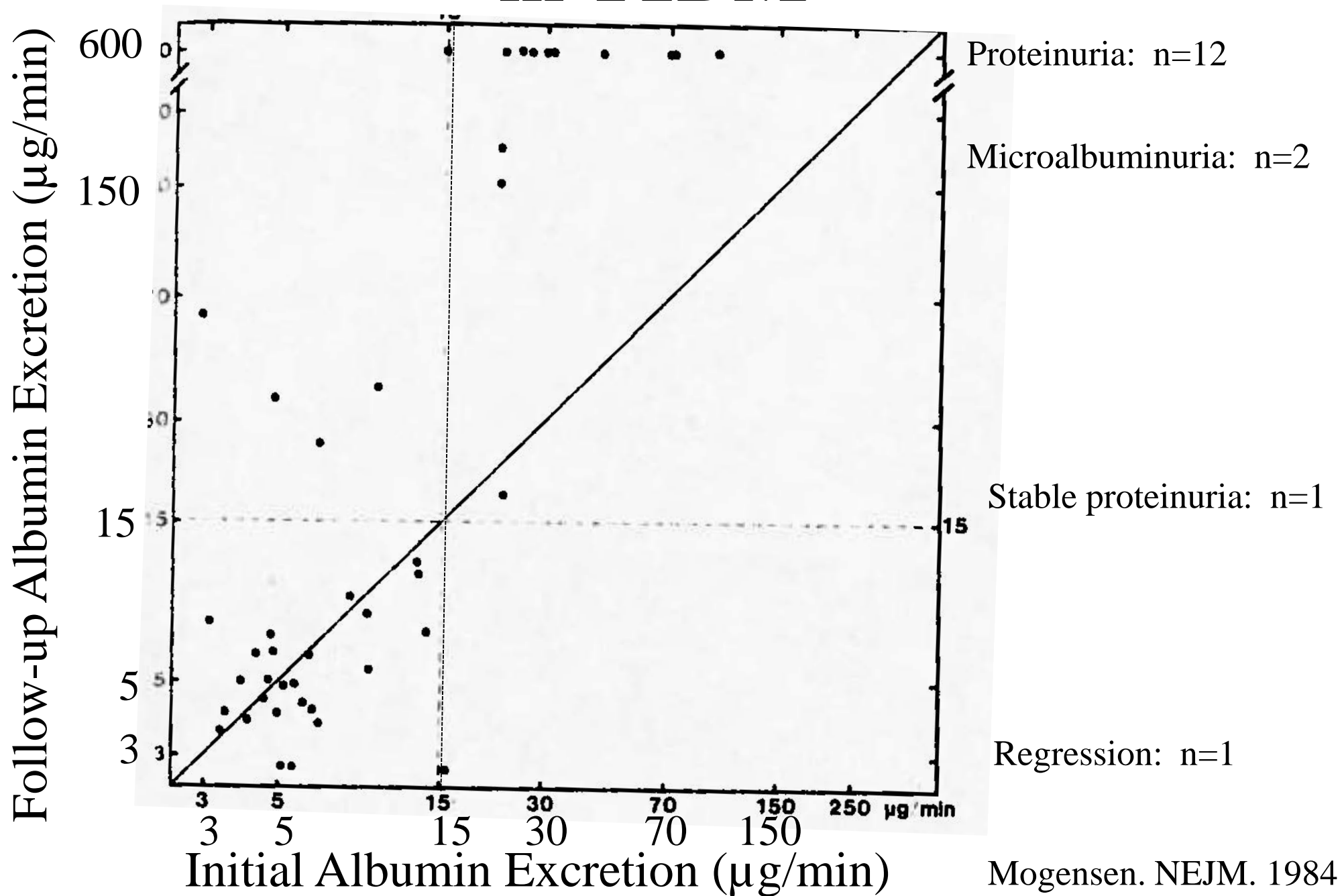
Biomarkers for Identification of Patients at Risk for Renal Function Loss

- Can be used to reinforce importance of blood pressure and glycemic control and lifestyle modifications to patients.
- Will help guide enrollment in clinical trials.
- When new treatments available, they can predict which patients may benefit from them.
- Other potential uses.
 - Guide dosing
 - Indicate potential of successful treatment

Albuminuria

- 2-4 grams per day of albumin are filtered normally.
- Filtered proteins are reabsorbed and catabolized in the proximal tubule.
- Typically 40-80 mg protein excreted per day of which 4-7 mg is intact albumin.
- <30 mg/day is termed normoalbuminuria (ACR <30)
- 30-300 mg/day is termed microalbuminuria (ACR 30-300)
 - 20-200 μ g/minute
- >300 mg/day is termed macroalbuminuria (ACR >300)
 - Macroalbuminuria is used to define diabetic nephropathy

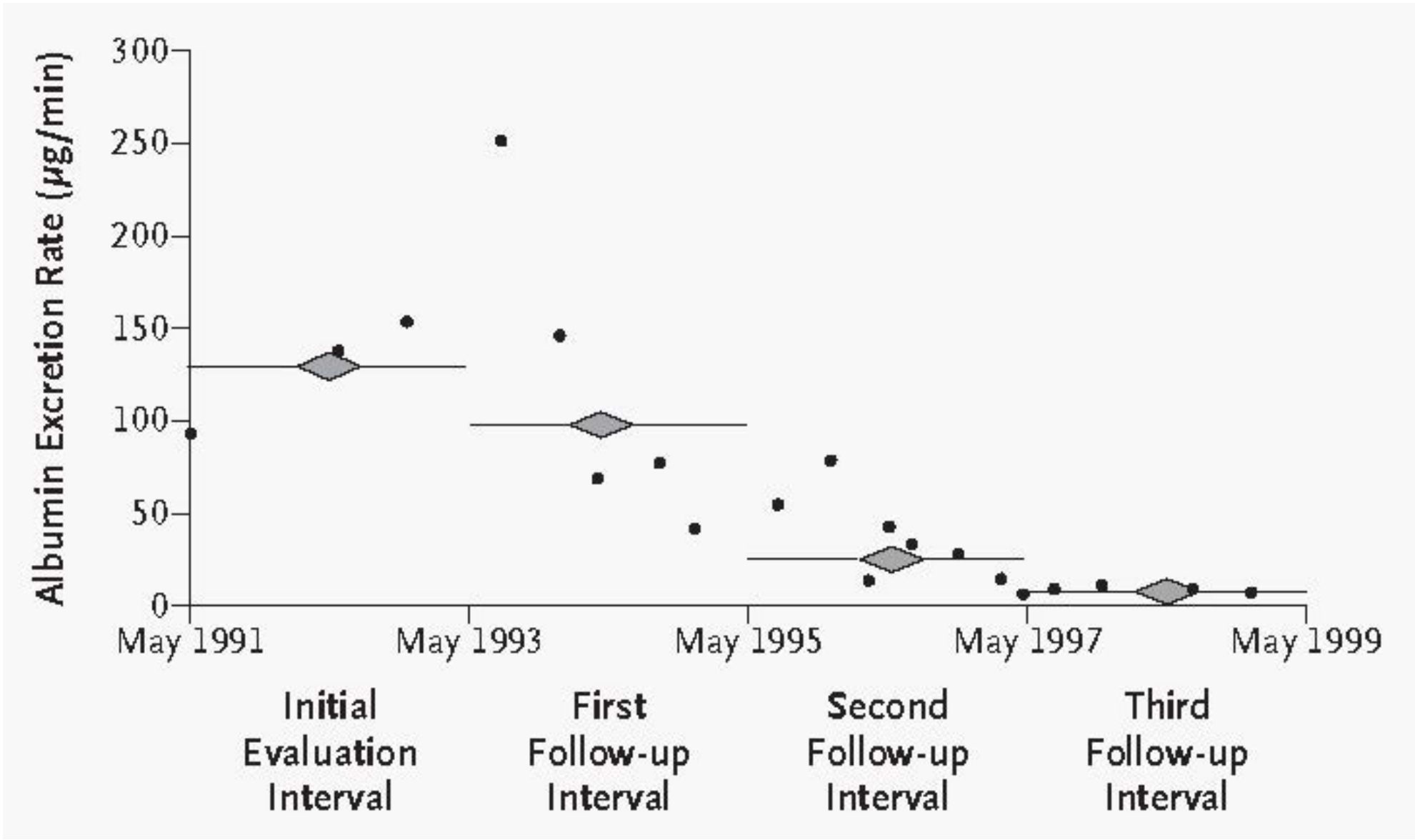
Albuminuria predicts renal disease in T1DM



The five stages of 'conventional' diabetic nephropathy as defined in the 1980's

Stage 1	Reversible glomerular hyperfiltration
Stage 2	Normal glomerular filtration rate and normoalbuminuria
Stage 3	Microalbuminuria and normal GFR (5-10 years after diabetes mellitus discovery)
Stage 4	Proteinuria appears and may reach nephrotic range levels (after 10-20 years)
Stage 5	Chronic kidney disease which leads to terminal kidney disease (usual slope <10 ml/min/year)

Regression of microalbuminuria



Regression of albuminuria

1 st Author	Journal	Type	# with micro-albuminuria	Follow-up (years)	Regression	Progression
Tabaei	Diabetes Care (2001)	1/2	16	7	56%	11%
Perkins	NEJM 2003	1	386	8	58%	19%
Hovind	BMJ (2004)	1	79	7,5	35%	34%
Gaede	NDT (2004)	2	151	7,8	31%	31%
Araki	Diabetes (2005)	2	216	8	51	28%
Steinke	Diabetes (2005)	1	22	5	64%	NA
Yamada	Diabetes Care (2005)	2	94	8	21%	17%
Perkins	KI (2010)	1	79	12,4	39%	27%

Progression of Nephropathy Without Macroalbuminuria

- 79 patients with type 1 diabetes and new onset microalbuminuria followed for 12 years.
- Advanced CKD ($\text{GFR}_{\text{MDRD}} < 60$ or ESRD) developed in 29% (23 subjects).
- Remaining 71% maintained eGFR > 60 .
- Only 12 of the 23 progressing patients developed proteinuria which generally did not precede the progression to advanced kidney disease.

Loss of GFR Precedes Albuminuria

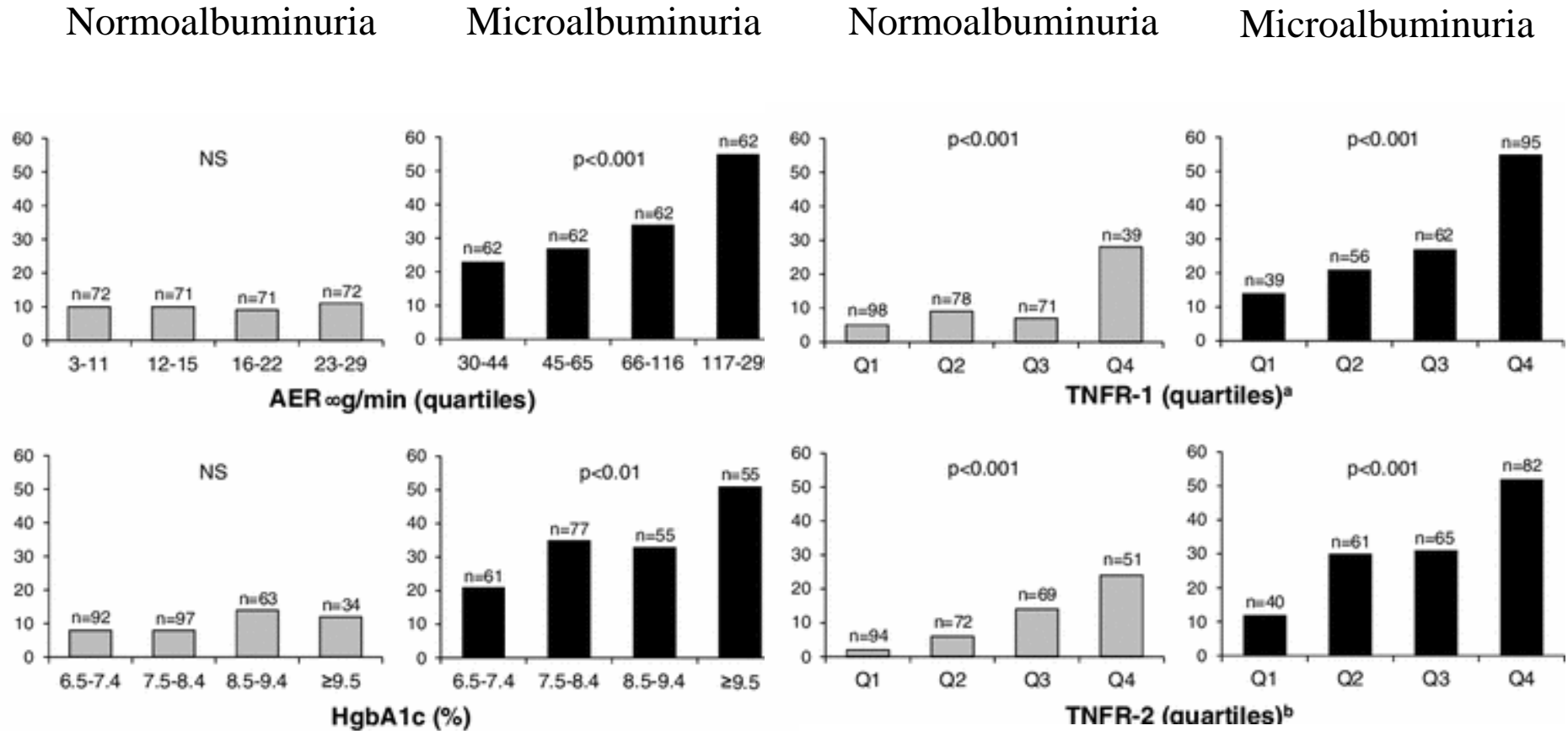
1 st Author	Journal	Type	Patients with GFR <60	Normo-albuminuric	Micro-albuminuric
Kramer	JAMA (2003)	2	171	35%	37%
Caramori	Diabetes (2003)	1	23	22%	NA
MacIsaac	Diabetes Care (2004)	2	109	39%	35%
Retnakaran	Diabetes (2006)	2	1132	51%	49%
Parving	Kidney Int (2006)	2	2546	38%	48%
Rigalleau	Diabetes Care (2007)	1 / 2	79	17%	40%
Yokoyama	NDT (2009)	2	506	73%	21%
Perkins	Kidney Int (2010)	1	23	13%	35%
Molitch	Diabetes Care (2010)	1	89	24%	16%
Afghahi	NDT (2011)	2	407	71%	21%
Penno	J Hypertension (2011)	2	2659	57%	31%
			Mean	50%	31%

Summary: ACR as a Predictor of Renal Functional Decline and ESRD

- ACR is correlated with diabetic nephropathy, loss of renal function, ESRD and death in patients with diabetes.
- Annual measurement of ACR is recommended by the ADA.
- Glomerular structural changes occur prior to the development of microalbuminuria.
- Many patients with microalbuminuria regress to normoalbuminuria (25-50%) or do not progress.
- Loss of renal function occurs in the absence of macroalbuminuria or microalbuminuria.

Predictors of Progressive Renal Decline in Type 1 Diabetes

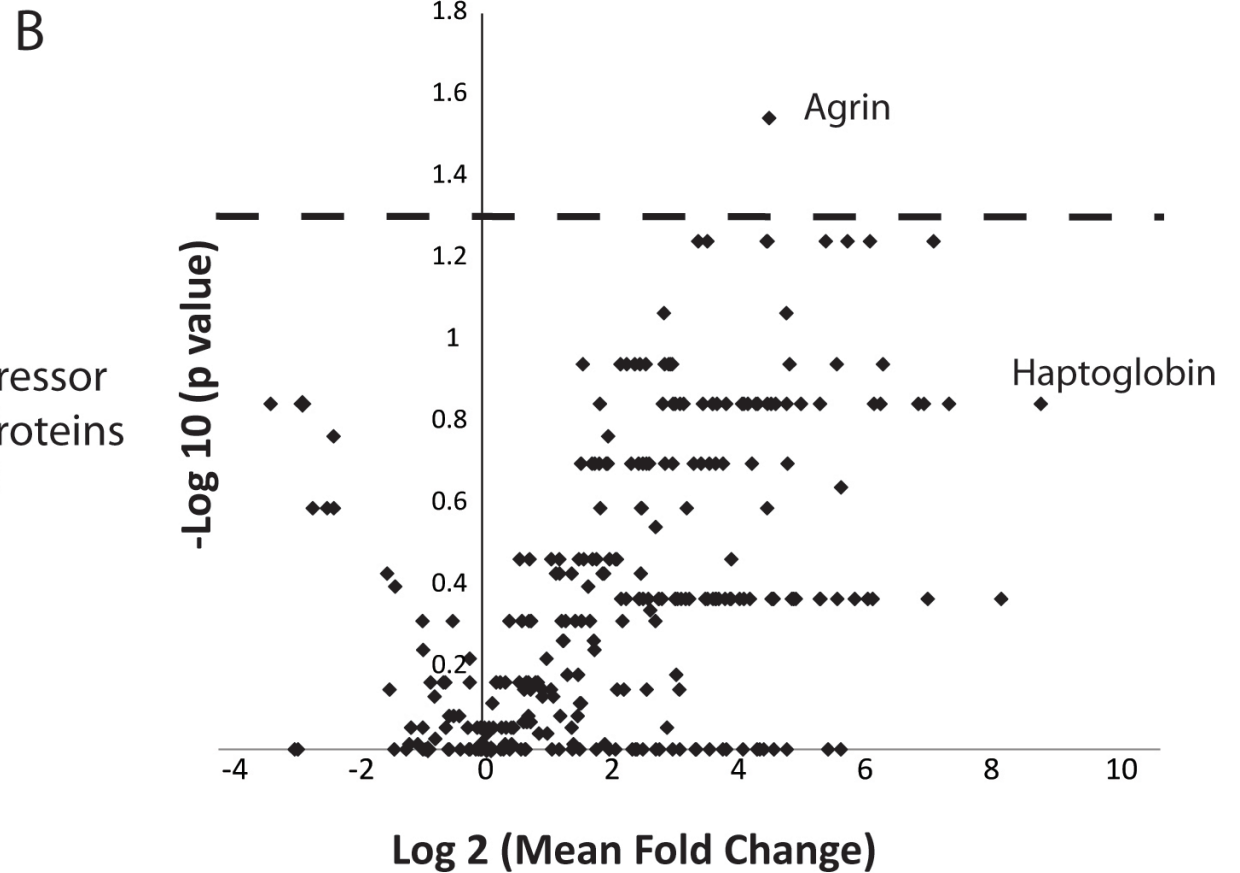
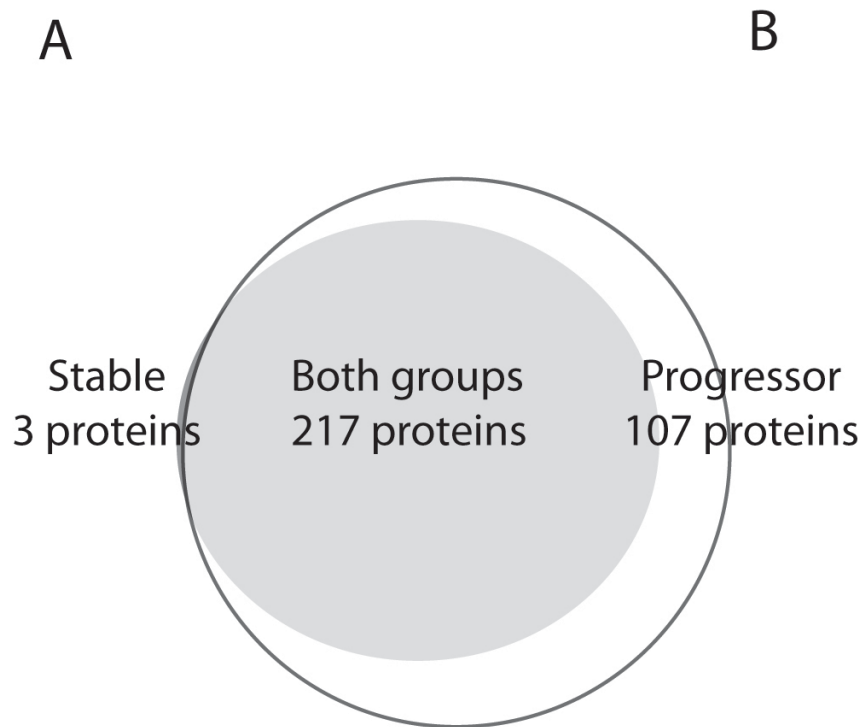
Risk of Progressive renal decline in %



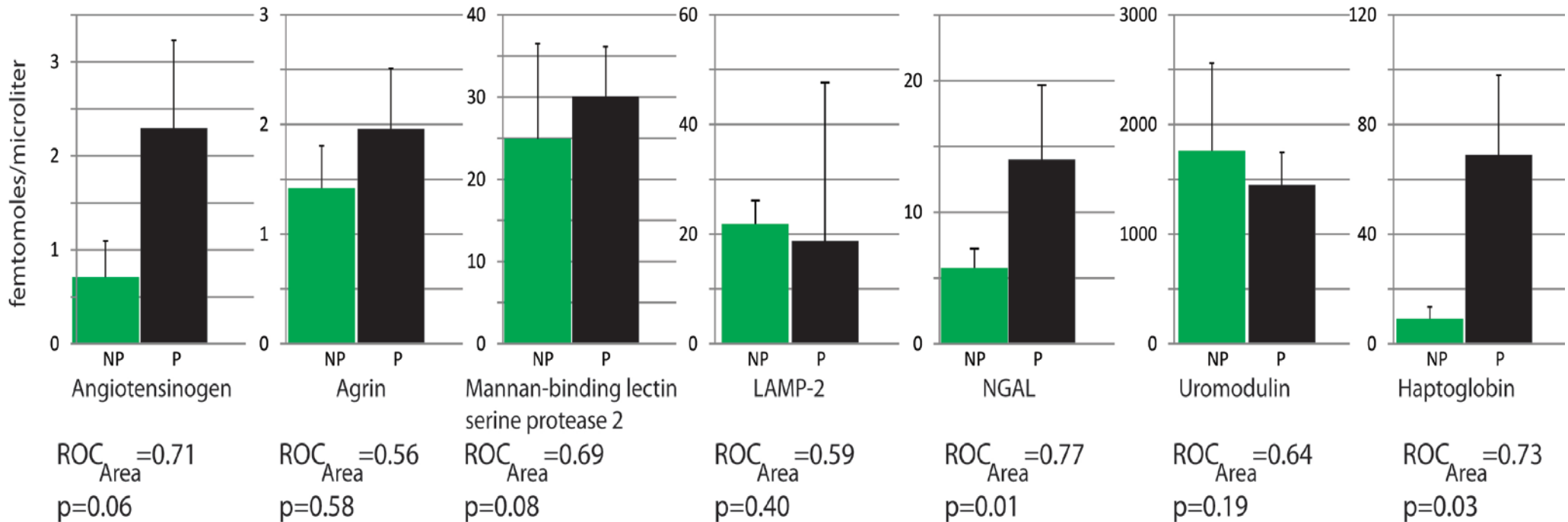
Biomarker Discovery Analysis

- Comparison of proteins in urine by proteomics.
- Samples obtained from VADT trial.
- Urine from 4 patients that had an increase in serum creatinine of at least 60% over 6 years compared to 4 patients that did not.

Discovery Analysis



Verification by MRM



Summary

- Biomarkers could potentially help to predict risk of progression to guide therapy and help with development of new treatments.
- ACR is commonly used to predict risk of renal disease in patients with diabetes but it is neither sensitive nor specific. However, it is currently the best option.
- New biomarkers are currently being tested which may showed improved prognostic characteristics compared to albumin.