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ICCN 2015 HONG KONG

Risk of progression of diabetic nephropathy

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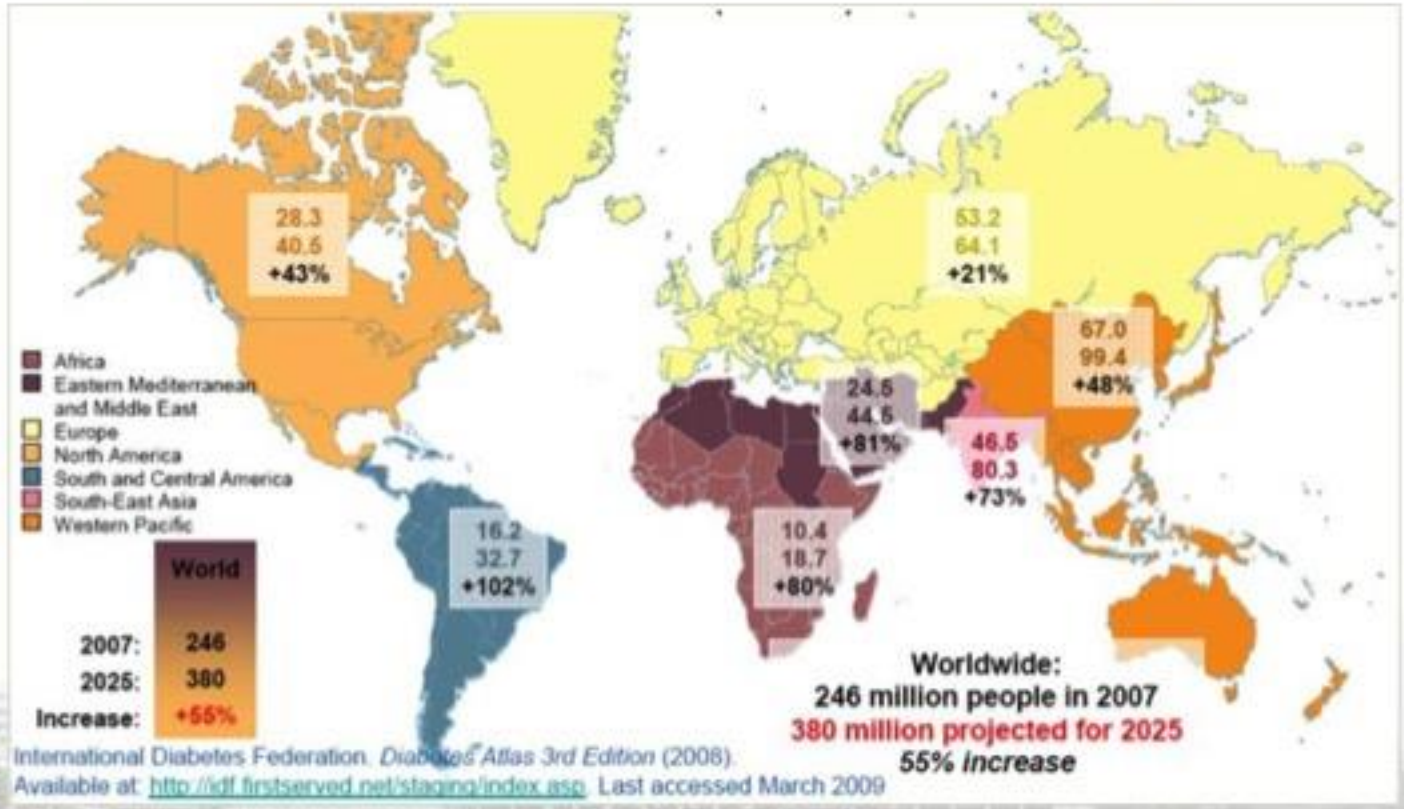
Hong Kong, 2015-12-12

World expansion of Diabetes Mellitus

* WHO states that 347 million people worldwide(9.5%) were suffering from diabetes in 2008. The incidence of diabetes is rapidly increasing, this number will almost double by 2030.



On the up. Nature 482: 276, 2012

Danaei G, Lancet 378: 31–40, 2011

China Faces Massive Wave of Diabetes-Linked Chronic Diseases

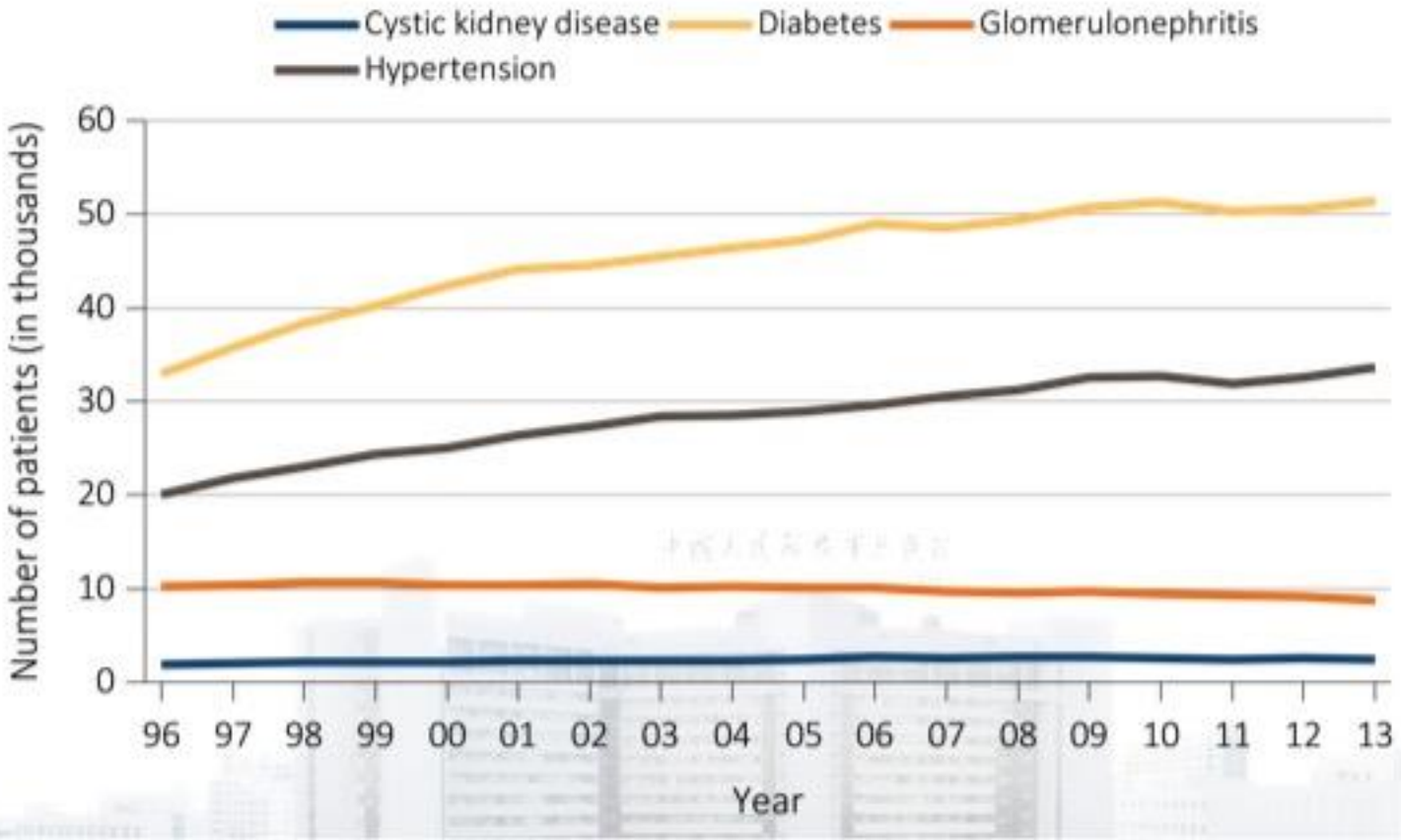
* In China, diabetes prevalence was 11.6%.
  - 12.1% in men, 11.0% in women.
* Two-thirds of diabetes cases were undiagnosed.
* Only 25.8% of diabetics were receiving treatment.
* Among those treated, fewer than 40% had adequate glycemic control.
* Over half of Chinese adults were prediabetic
  - no prior diagnosis, but fasting plasma glucose 100 to 125 mg/dL, 2-hour plasma glucose 140 to 199 mg /dL, or HbA_{1c} 5.7% to 6.4%.

JAMA. 2013;310(9):948-958

Kidney disease in diabetes

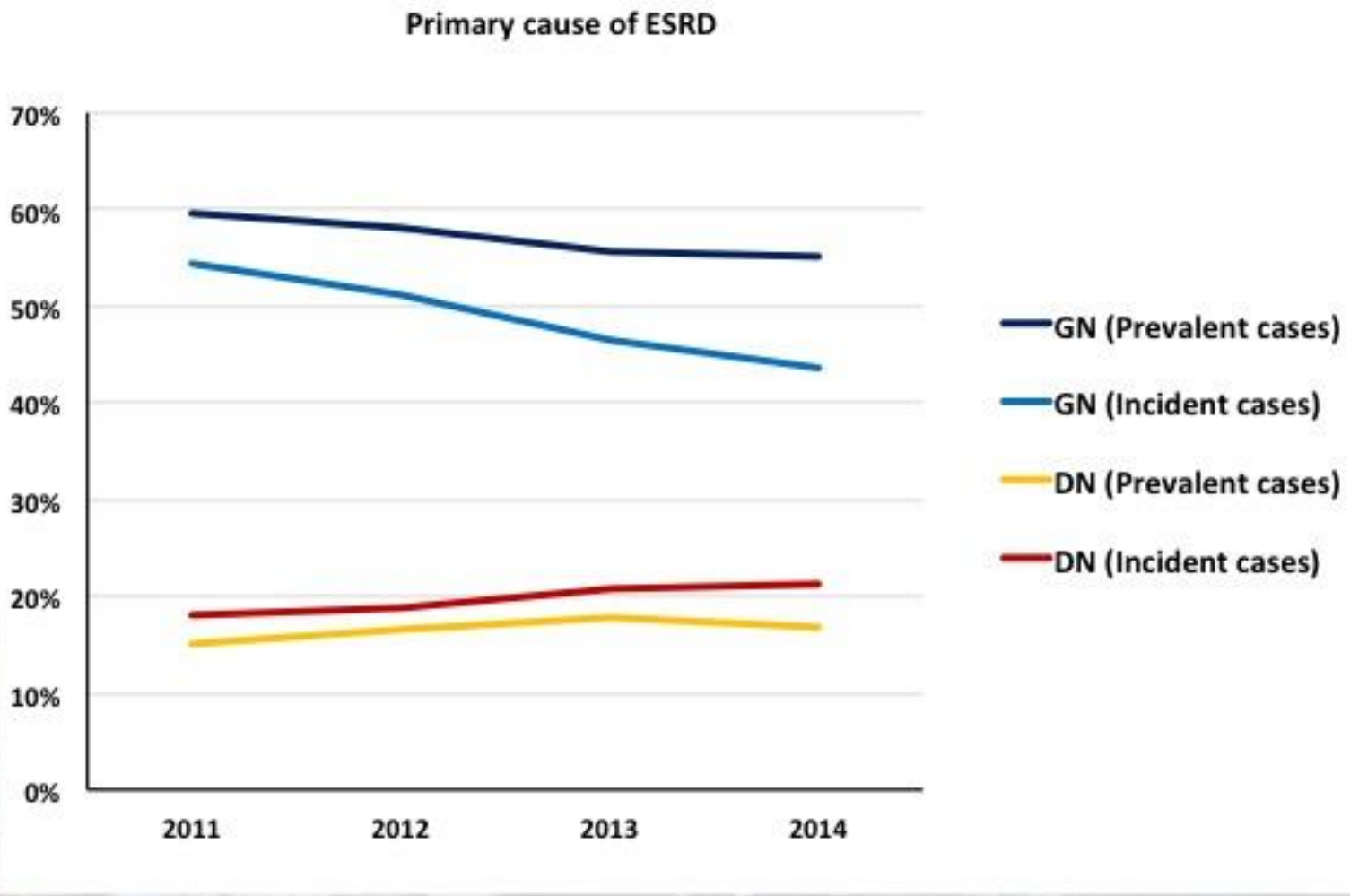
* Diabetic nephropathy develops in
  - 30–50% of patients with T1DM within 5–10 years after the onset of diabetes,
  - 20–30% of patients with T2DM, often after a considerable duration of undiagnosed diabetes.
* Asians have a higher prevalence of nephropathy
* Kidney disease in diabetes greatly diminishes quality and quantity of life, and is very expensive.
* Focused attention to the early stages of diabetic nephropathy is urgently needed, to define better therapies that may slow it down or even stop its progression, thus reducing its heavy burden.

Trends in annual number of ESRD incident cases (in thousands), by primary cause of ESRD, in the U.S. population, 1996-2013



Data Source: Reference Table A.1. Abbreviation: ESRD, end-stage renal disease.

Primary cause of ESRD in the Chinese population, 2011-2014



Data from CNRDS 2015

A Changing Concept: From Diabetic Nephropathy to Diabetic Kidney Disease (DKD)

Variety of non-diabetic renal diseases（1993-2003）

Pathological types	Case	Percentage (%)
IgA nephropathy	17	34.0
Membranous nephropathy	11	22.0
Mesangial proliferative GN[a]	7	14.0
HBV-associated GN	4	8.0
Minor glomerular abnormalities	3	6.0
Minimal change disease	2	4.0
Hypertensive nephrosclerosis	2	4.0
FSGS	2	4.0
Crescentic GN	1	2.0
Lupus glomerulonephritis	1	2.0

Zhou J, et al. Nephrol Dial Transplant. 2008,23(6):1940-5.

A Differential Diagnostic Model of DN and NDRD

$P_{DN} = ez/(1 + ez) = \exp(-13.5922 + 0.0371Dm + 0.0395Bp + 0.3224Gh - 4.4552Hu + 2.9613Dr)/[1+ \exp(-13.5922 + 0.0371Dm + 0.0395Bp + 0.3224Gh - 4.4552Hu + 2.9613Dr)]$.

- P_{DN}: the probability of DN diagnosis
- Dm: diabetes duration (month)
- Bp: systolic blood pressure(mmHg)
- Gh: HbA1c（%）;
- Hu: with haematuria (1 yes, 0 no)
- Dr: with diabetic retinopathy (1 yes, 0 no)

Predictive value	1993-2003 n=110
Sensitivity	90.0%
Specificity	92.0%
Positive predictive value	93.1%
Negative predictive value	88.5%
Total consistency	90.9%

$P_{DN} \geqslant 0.5$ the diagnosis should be DN, $P_{DN} < 0.5$ the diagnosis should be NDRD

Zhou J et al. Nephrol Dial Transplant. 2008,23(6):1940-5.

Changes Of Clinical Characteristics Reduced the Diagnostic Efficacy of the Model

Clinical Characteristics	DN		NDRD	
	1993-2003 *n*=60	2004-2012 *n*=93	1993-2003 *n*=50	2004-2012 *n*=107
Hematuria（Y,%）	10 (16.7)	30 (32.3)#	34 (68.0)	46 (43.0)#
Diabetes duration (month)	87.6±54.3	139.7±75.3#	26.3±18.8	52.3±29.6#
HbA1c（%）	8.4±2.0	7.3±1.6*	7.0±1.5	6.8±1.0*
Diabetic retinopathy（Y,%）	46 (76.6)	73 (78.5)	5 (10.0)	16 (15.0)*
SBP（mmHg）	149.2±22.3	152.1±19.0	133.7±17.9	136.3±20.5

*$P<0.05$, #$P<0.01$ versus 1993-2003 DN/NDRD

Predictive value	1993-2003 n=110	2004-2012 n=200
Sensitivity	90.0%	58.1%
Specificity	92.0%	94.4%
Positive predictive value	93.1%	90.0%
Negative predictive value	88.5%	72.1%
Total consistency	90.9%	77.5%

Liu MY, et al. J Diabetes. 2014, 519–26.

Development of New Differential Diagnostic Model

$$P_{DN} = \frac{\exp(0.846 + 0.022Dm + 0.033Bp + 2.050Gh - 0.078Hb - 2.664Hu + 2.942Dr)}{1 + \exp(0.846 + 0.022Dm + 0.033Bp + 2.050Gh - 0.078Hb - 2.664Hu + 2.942Dr)}$$

- Dm: diabetes duration (month)
- Bp: systolic blood pressure(mmHg)
- Dr: with diabetic retinopathy (1 yes, 0 no)
- Hb: hemoglobin(g/L)
- Hu: with hematuria(1 urine RBC>10/HP, 0 < 10/HP)
- Gh: HbA1c (1 HbA1c ≥ 7%, 0 < 7%)

Predictive value	2004-2012 n=200
Sensitivity	88.5%
Specificity	91.0%
Positive predictive value	88.5%
Negative predictive value	91.0%
Total consistency	89.9%

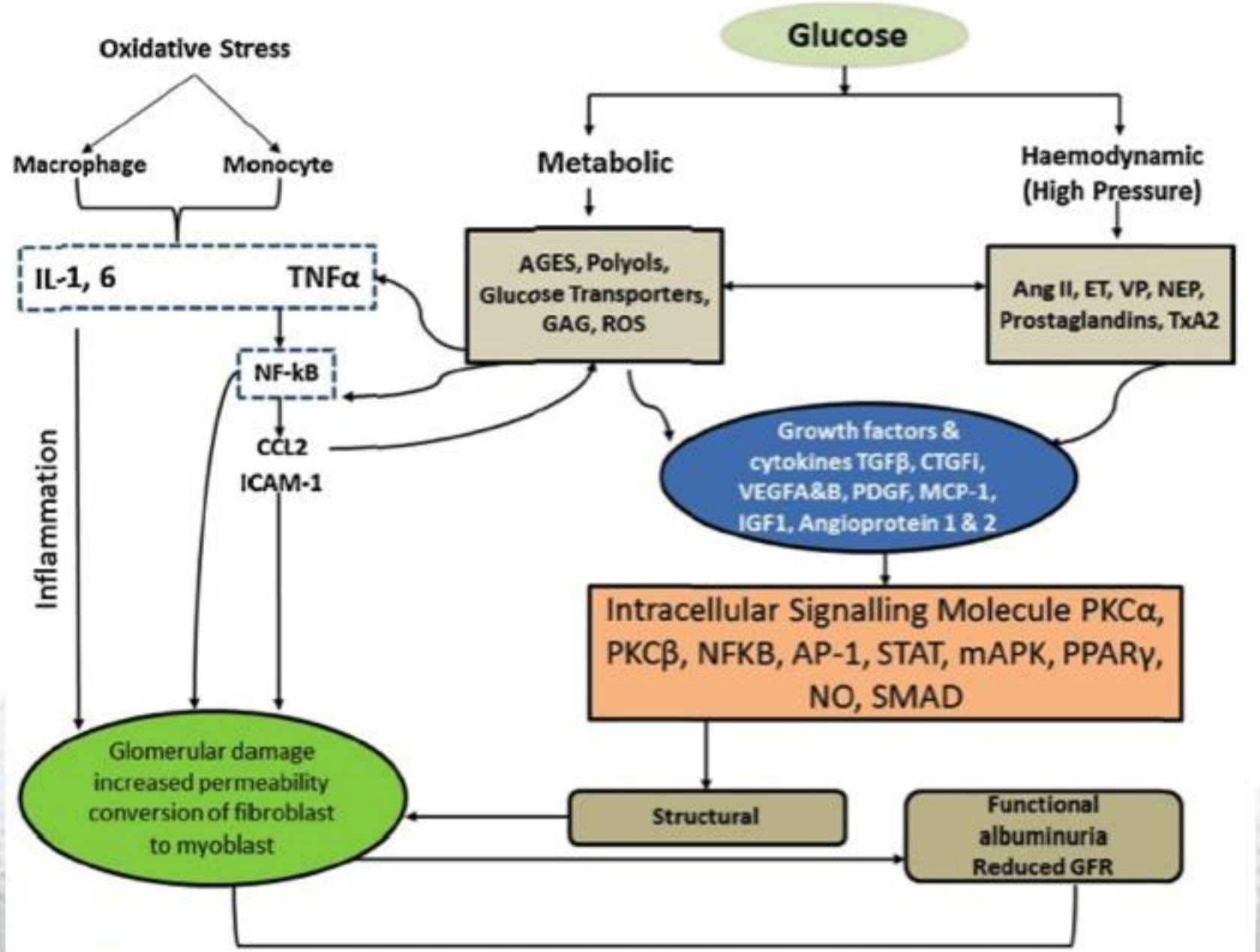
Liu MY, et al. J Diabetes. 2014, 519–26.

Predictive value of three different diagnostic criteria for hematuria

	>3 RBCs/hpf	>10 RBCs/hpf	Glomerular Hematuria
Sensitivity	0.44	0.17	0.25
Specificity	0.69	0.93	0.97
Positive predictive value	076	0.85	0.94
Negative predictive value	0.35	0.33	0.36
ROC AUC	0.57	0.56	0.61

Dysmorphic erythrocytes were superior to hematuria for indicating non-diabetic renal disease in type 2 diabetics.

Dong ZY, et al. J Diabetes Invest. 2015, doi:10.1111/jdi.12371.



Ahmad J Diabetes Metab Syndr. 2015 Oct-Dec;9(4):343-58

Initiators and Promoters of DKD

Initiators of DKD

Hyperglycemia

Predisposing genes

Promoters of DKD

Hyperglycemia

Albuminuria

Hypertension

Dyslipidemia

Insulin resistance

Smoking

Procoagulant state

Long duration of diabetes

Anemia

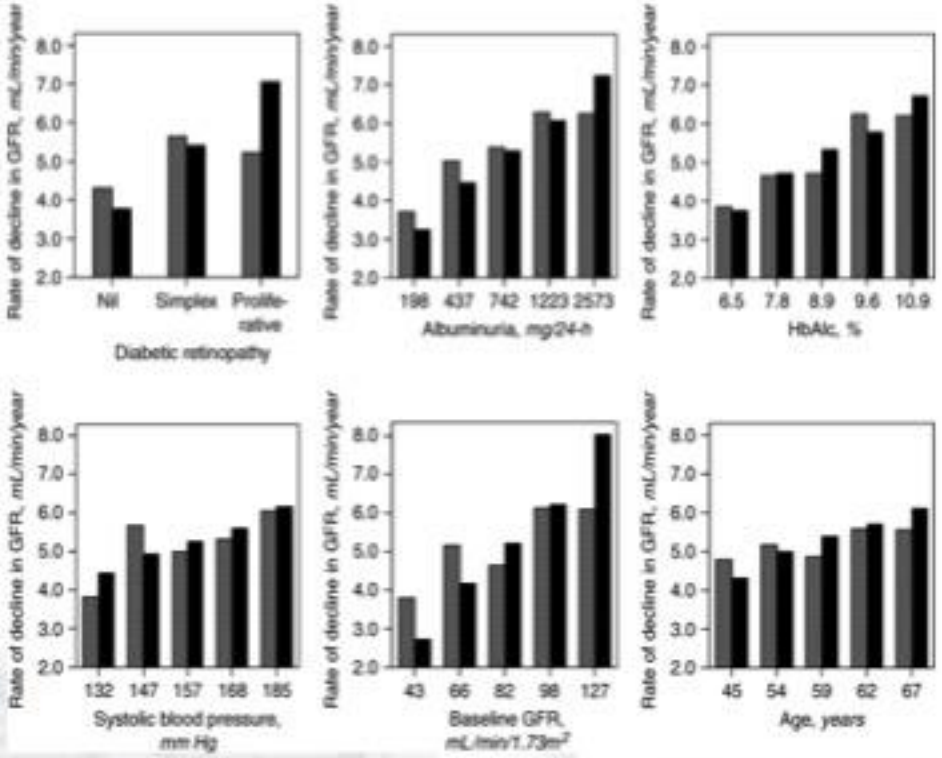
Ethnicity/westernization

Sex

Age

Impact of baseline parameters on the rate of decline in GFR

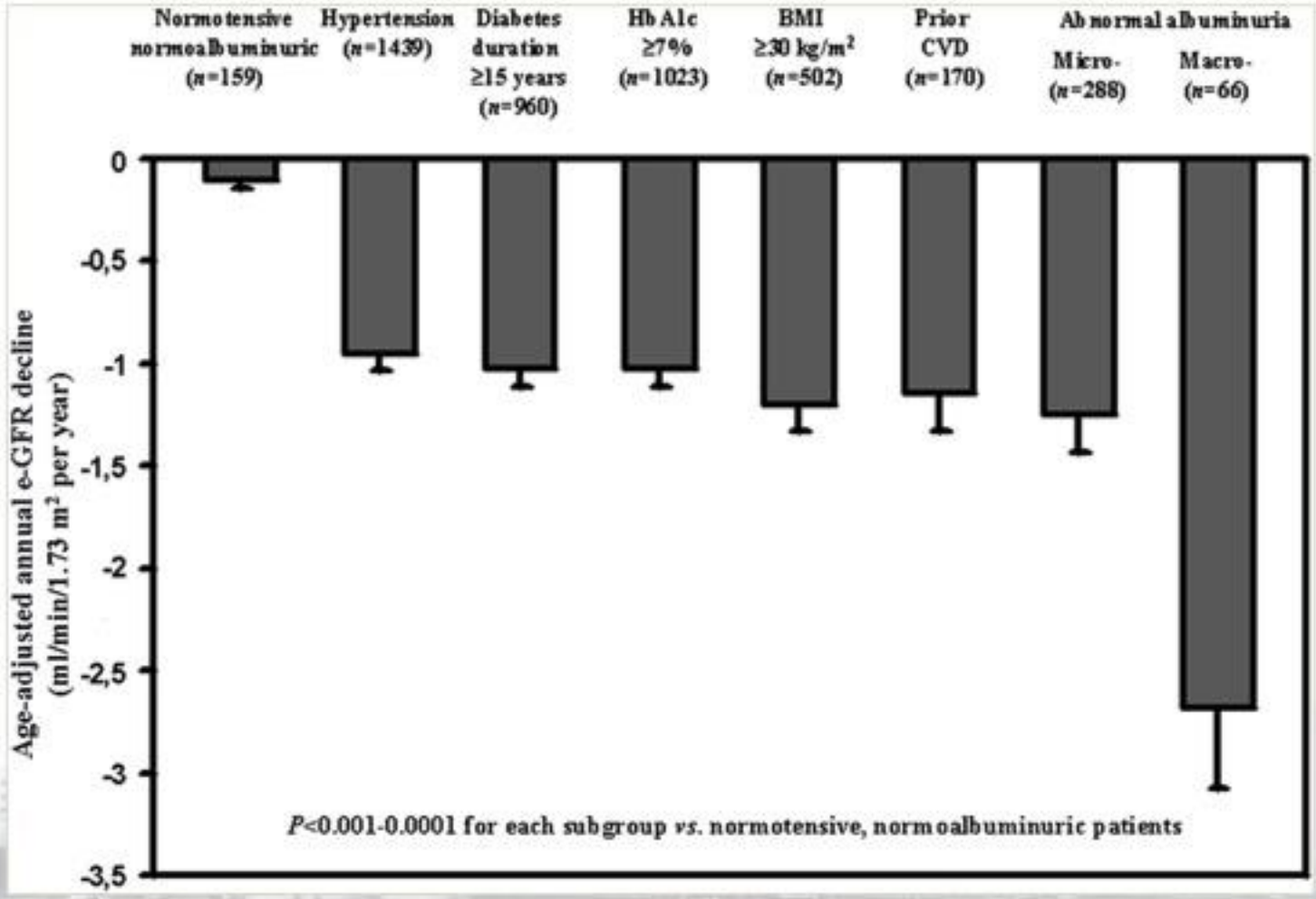
Variable	Slope (95% CI)	*P* value
Dependent variable		
Rate of decline in GFR *mL/min/year*		
Baseline model		
Independent variables at baseline		
Albuminuria $\log_{10}$	3.58 (2.22 to 4.9)	<0.001
Systolic blood pressure per 10 mm Hg	0.33 (0.03 to 0.63)	0.02
Hemoglobin A_{1c} per 1%	0.67 (0.32 to 1.02)	<0.001
Age per 10 years	0.82 (0.01 to 1.58)	0.03
GFR per 10 mL/min/1.73 m^2	0.60 (0.41 to 0.81)	<0.001
Level of diabetic retinopathy nil/simplex/proliferative	1.64 (0.80 to 2.48)	<0.001
R^2 adjusted 0.24		
Follow-up model		
Independent variables		
Mean albuminuria during follow-up $\log_{10}$	2.00 (0.92 to 3.10)	<0.001
Mean systolic blood pressure during follow-up per 10 mm Hg	0.51 (0.14 to 0.88)	0.010
Mean hemoglobin A_{1c} during follow-up per 1%	0.39 (0.01 to 0.77)	0.040
Mean hemoglobin during follow-up per mmol/L	-0.70 (-1.34 to -0.07)	0.030
Diabetic retinopathy at end of follow-up present/absent	2.13 (0.49 to 3.77)	0.011
Smoking ≥20 cigarettes a day during follow-up *yes/no*	1.33 (0.01 to 2.64)	0.048
Baseline age per 10 years	0.77 (0.05 to 1.48)	0.035
Baseline GFR per 10 mL/min/1.73 m^2	0.55 (0.33 to 0.75)	<0.001
R^2 adjusted 0.26		



Impact of baseline parameters: level of diabetic retinopathy, albuminuria, hemoglobin A1c, SBP, eGFR, and age on the rate of decline in GFR

Kasper Rossing . Ki (2004) 66, 1596–1605

Age-adjusted annual eGFR decline in 1682 patients with type 2 diabetes and preserved kidney function stratified by different clinical categories.



Giacomo Zoppini et al. CJASN 2012;7:401-408

Risk of Progression of DKD

* HbA1C Level
* Albuminuria
* Hypertension
* Obesity, Hyperuricemia, Dyslipidemia
* Histological Damage
* Others
  - Genetics & Demographics: Ethnic, Age, Sex
  - Life style: Diet, Smoking

Risk of Progression of DKD

* HbA1C Level
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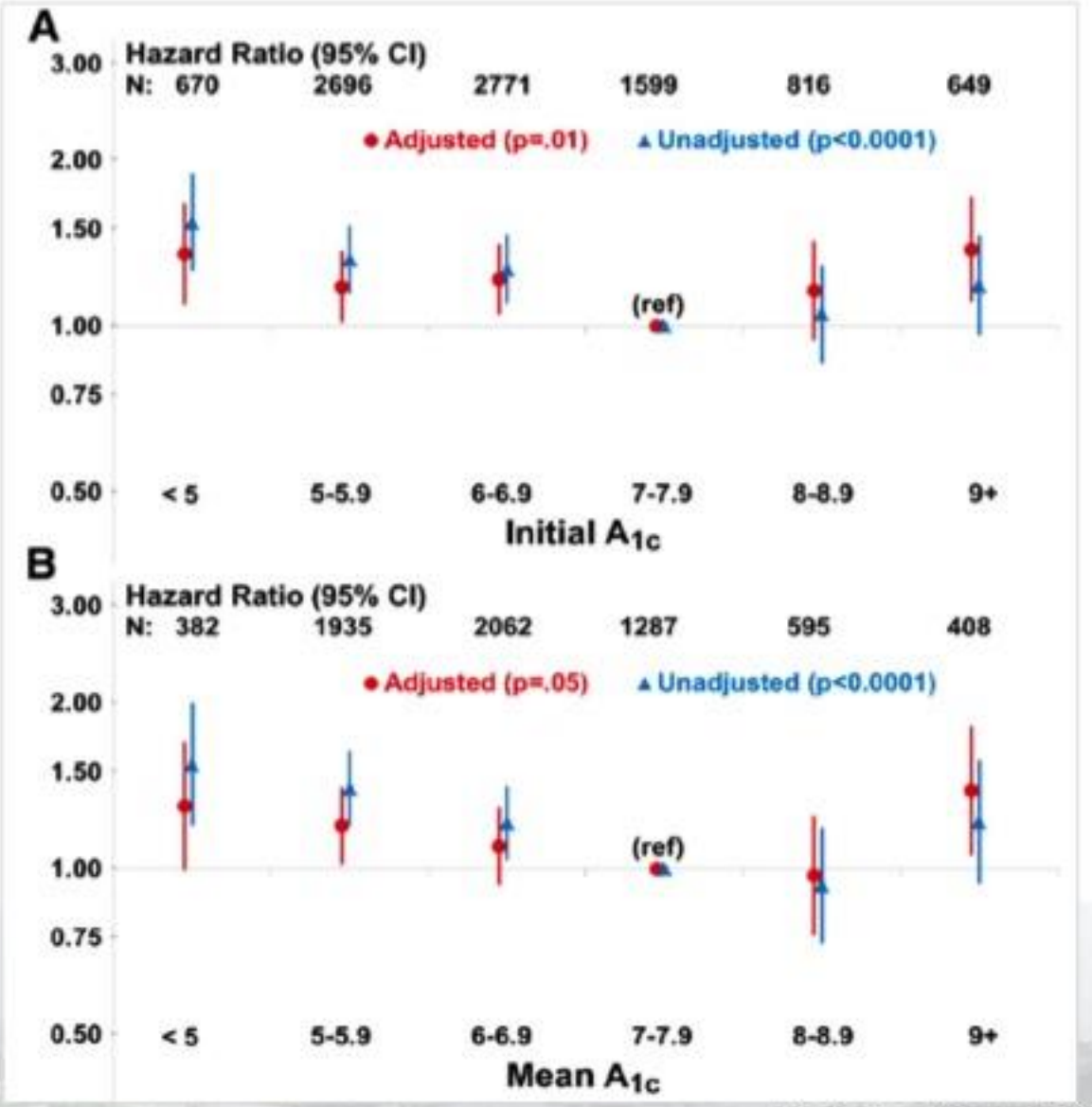
* Others
  - Genetics & Demographics: Ethnic, Age, Sex
  - Life style: Diet, Smoking

HbA1C Level

* Uncontrolled hyperglycemia is the prime cause of vascular complications including kidney disease.
* RCTs have demonstrated that intensive glycemic control reduces albuminuria;
* Whether intensive glycemic control prevents clinical renal endpoints in type 2 diabetics is less clear;
* Studies, including ACCORD, ADVANCE, and VADT demonstrated that compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels (HbA1C＜6-6.5 %) did not significantly reduce major CV events

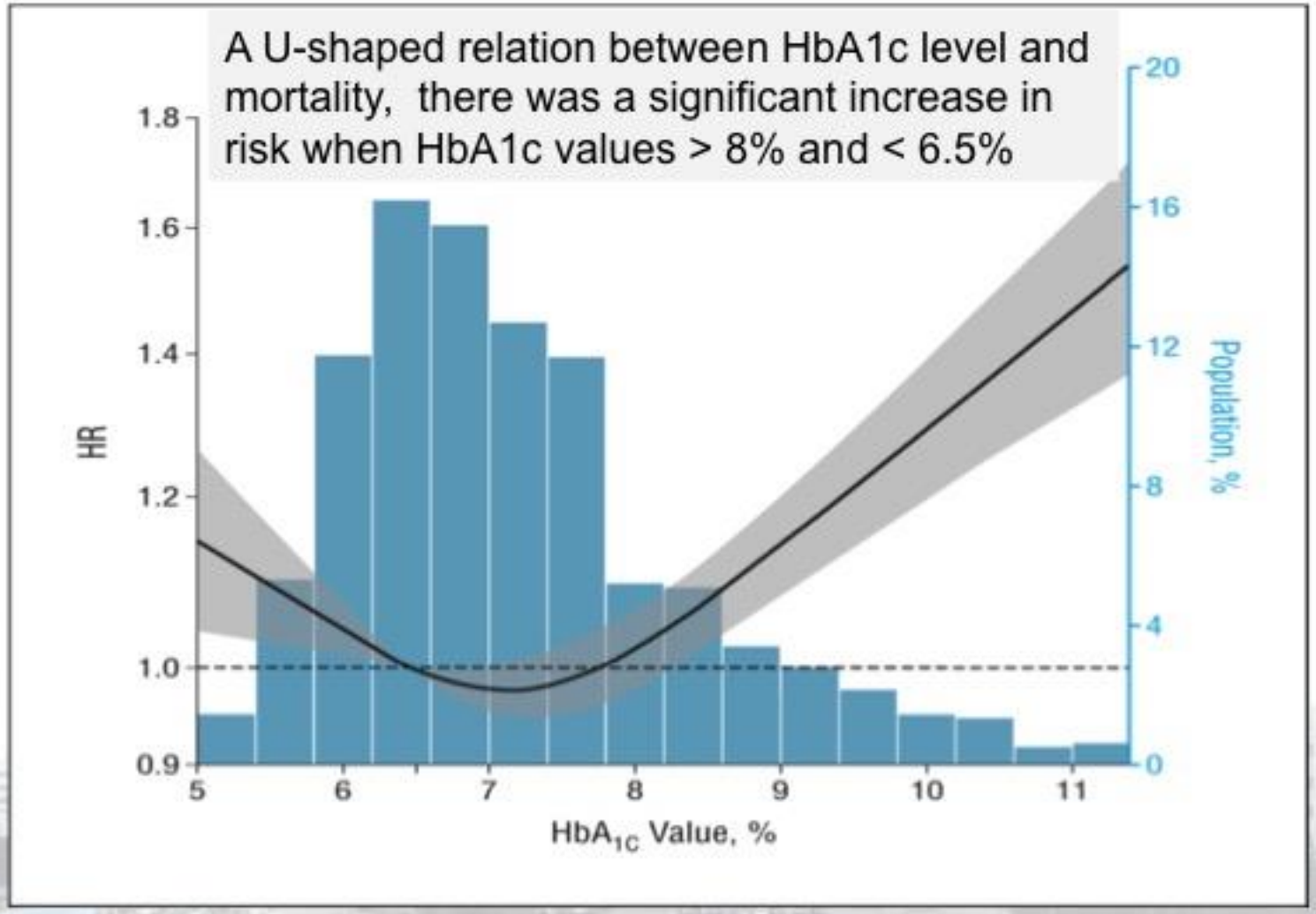
Gerstein, H. C et al. 2008 NEJM, 358, 2545–2559

Risk of mortality in patients with diabetes and ESRD



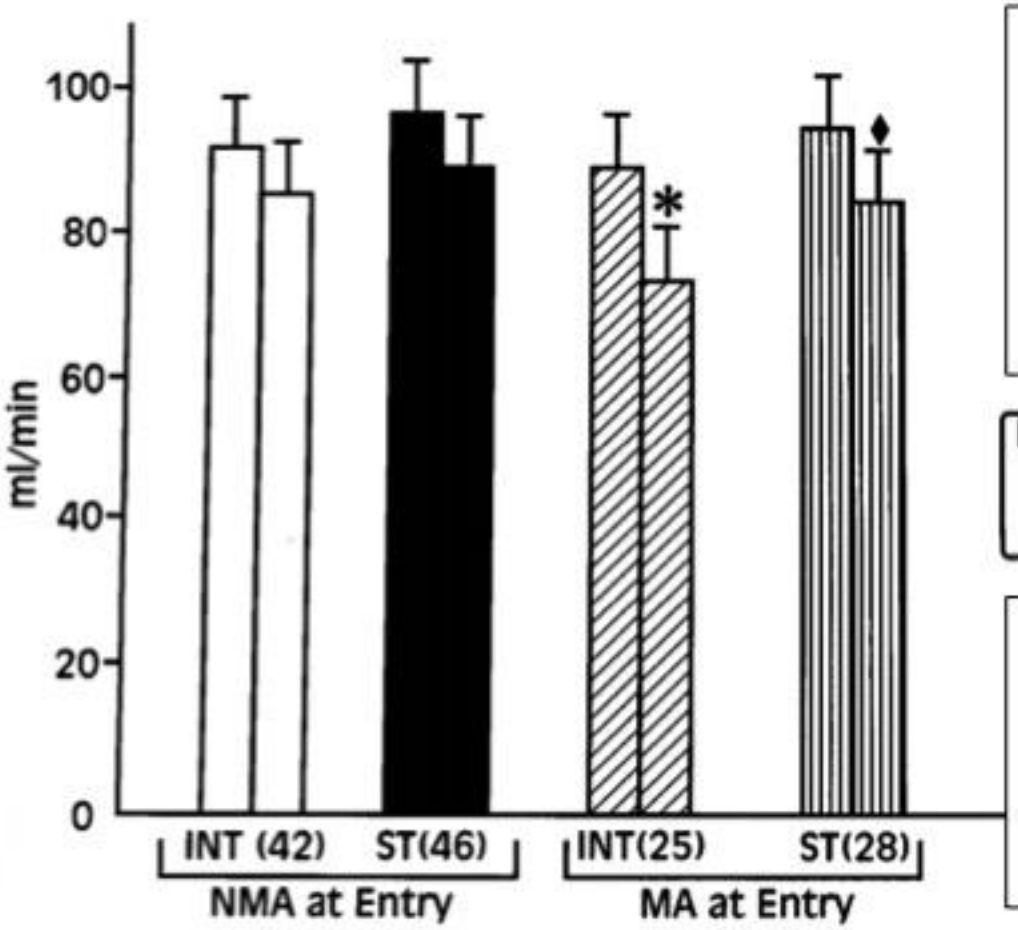
Diabetes Care 2012;35: 2527–2532

Association Between Glycemic Control and Adverse Outcomes in People With Diabetes Mellitus and Chronic Kidney Disease: A Population-Based Cohort Study



Arch Intern Med. 2011;171(21):1920-1927.

Patients entering with microalbuminuria had a deterioration in Ccr at 2 yrs regardless of the intensity of glycemic control



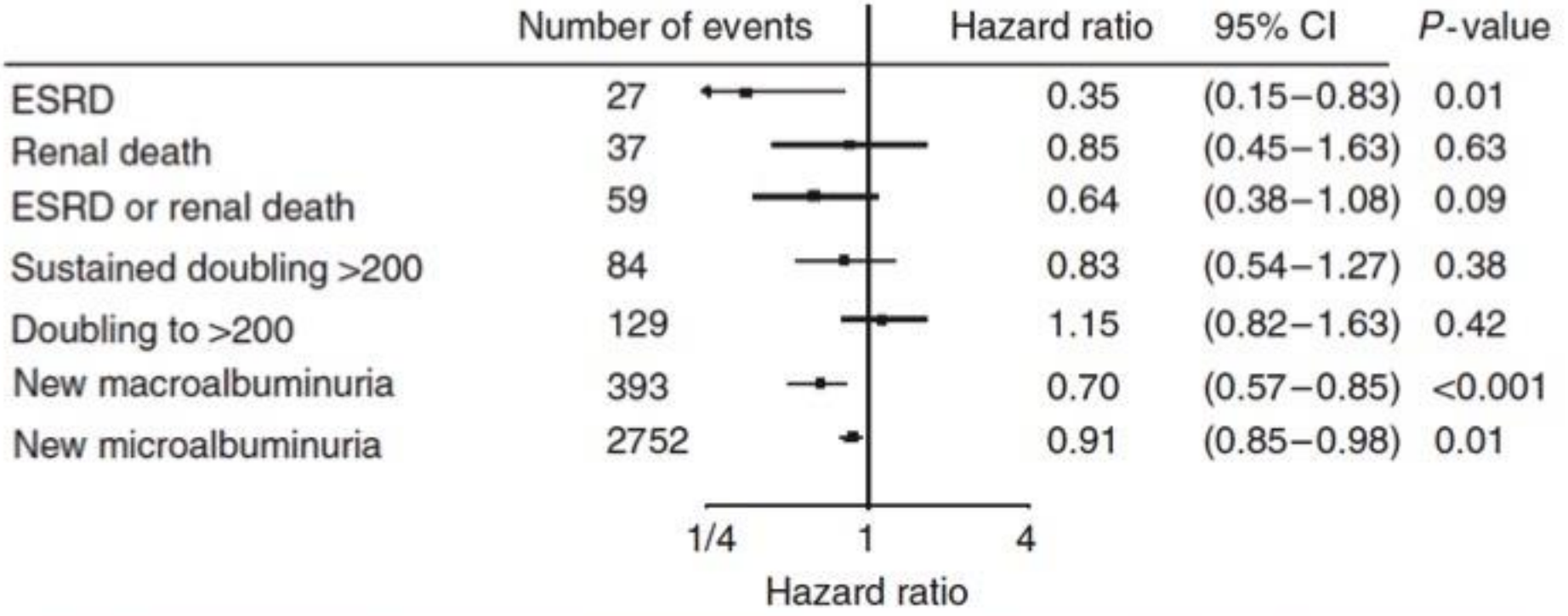
INT : intensive treatment
goal HbA1c 7.1%
ST : standard treatment
goal HbA1c 9.1 %
MA: microalbuminuria at entry,
NMA : no microalbuminuria at entry

Paired analysis
* p = 0.0001
♦ p = 0.009

INT retards microalbuminuria in patients who have had type 2 diabetes for several years but may not lessen the progressive deterioration of glomerular function

Levin, S. R.2000 Diabetes Care, 23, 1478–1485

Summary plot showing the effects of intensive glucose lowering compared with standard glucose lowering on renal outcomes.



In ADVANCE trial, median follow-up 5 years, compared with the standard group(7.3%), intensive glucose control(HbA1c 6.5%) significantly reduced the risk of ESRD by 65%, microalbuminuria by 9%, and macroalbuminuria by 30%.

Perkovic V. Kidney Int (2013) 83, 517–523

The controversies related to glycemic control

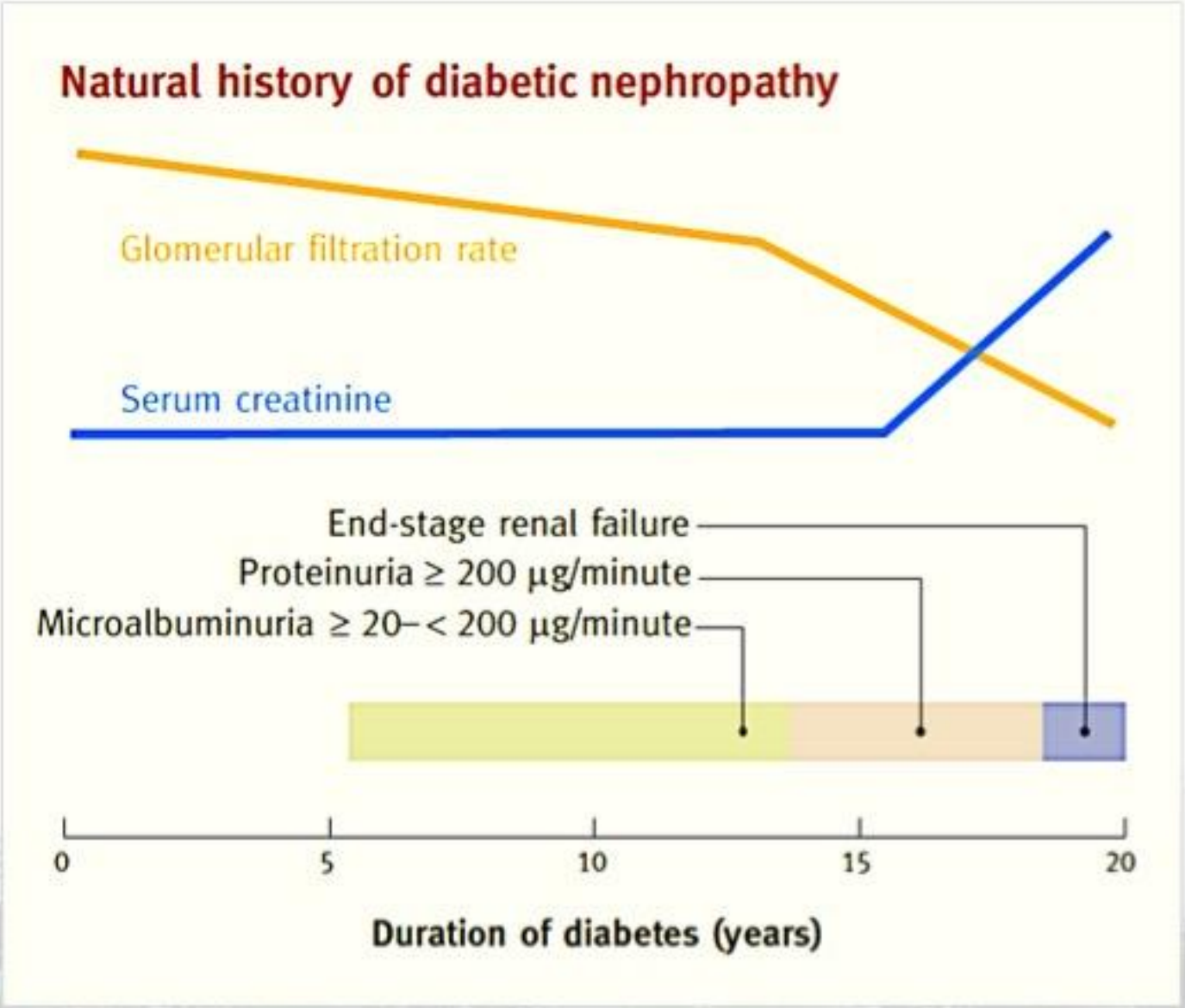
* How can durable glycemic control be achieved?
* What is the HbA1c target for DKD vs CVD?
* Should the HbA1c target or the antidiabetic medicines used to achieve this target vary by severity of CKD or duration of diabetes?
* What is the HbA1c target in patients receiving dialysis and which antidiabetic medicines should be used to achieve these targets?
* What is the HbA1c target in kidney transplant recipients with diabetes and which antidiabetic medicines should be used to achieve these targets?

Mark E. Molitch et al. Kidney Int. 2015; 87(1): 20–30

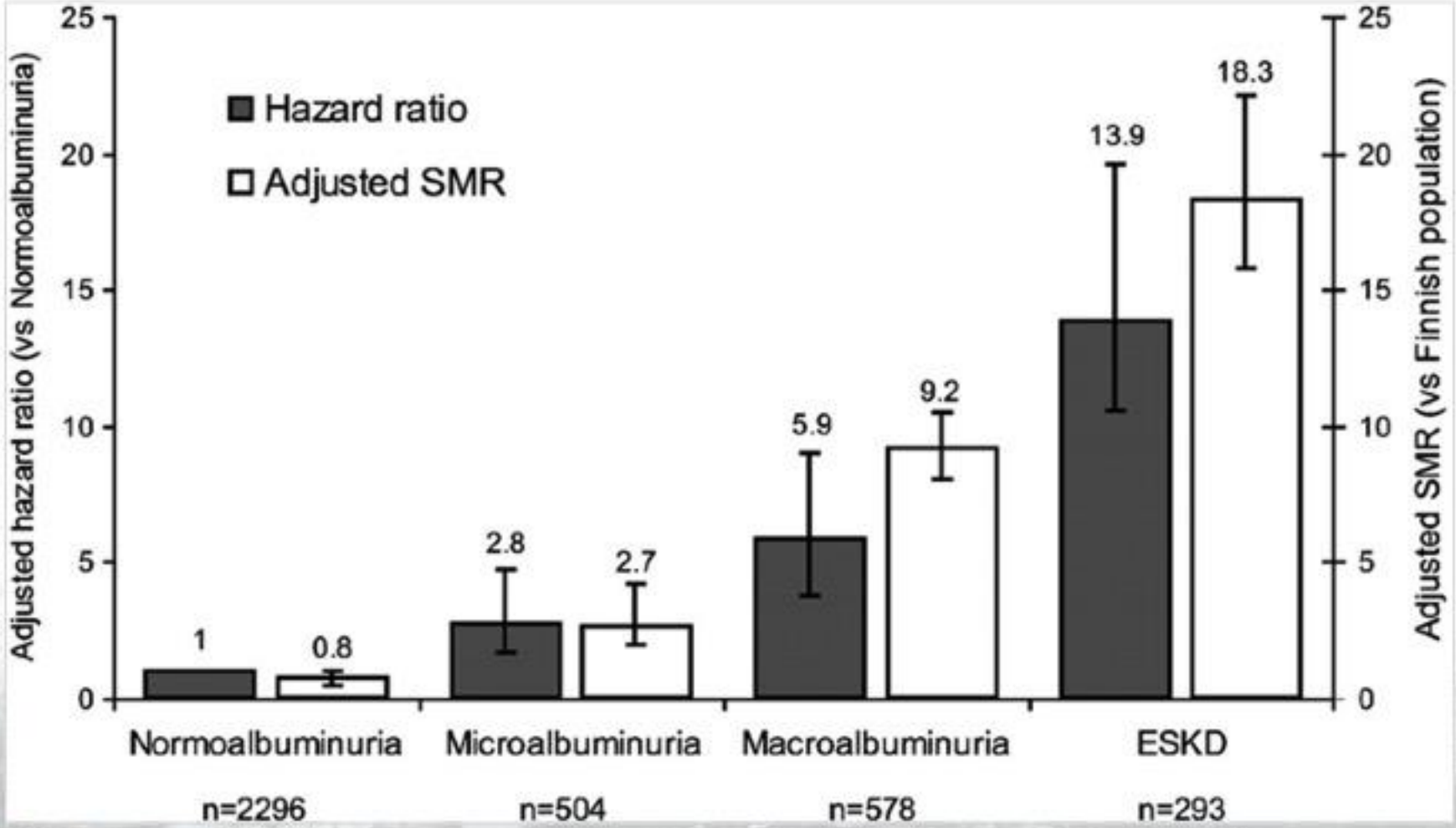
Risk of Progression of DKD

* HbA1C Level
* Albuminuria
* Hypertension
* Obesity, Hyperuricemia, Dyslipidemia
* Histological Damage
* Others
  - Genetics & Demographics: Ethnic, Age, Sex
  - Life style: Diet, Smoking

Classical, five-stage natural history of DN

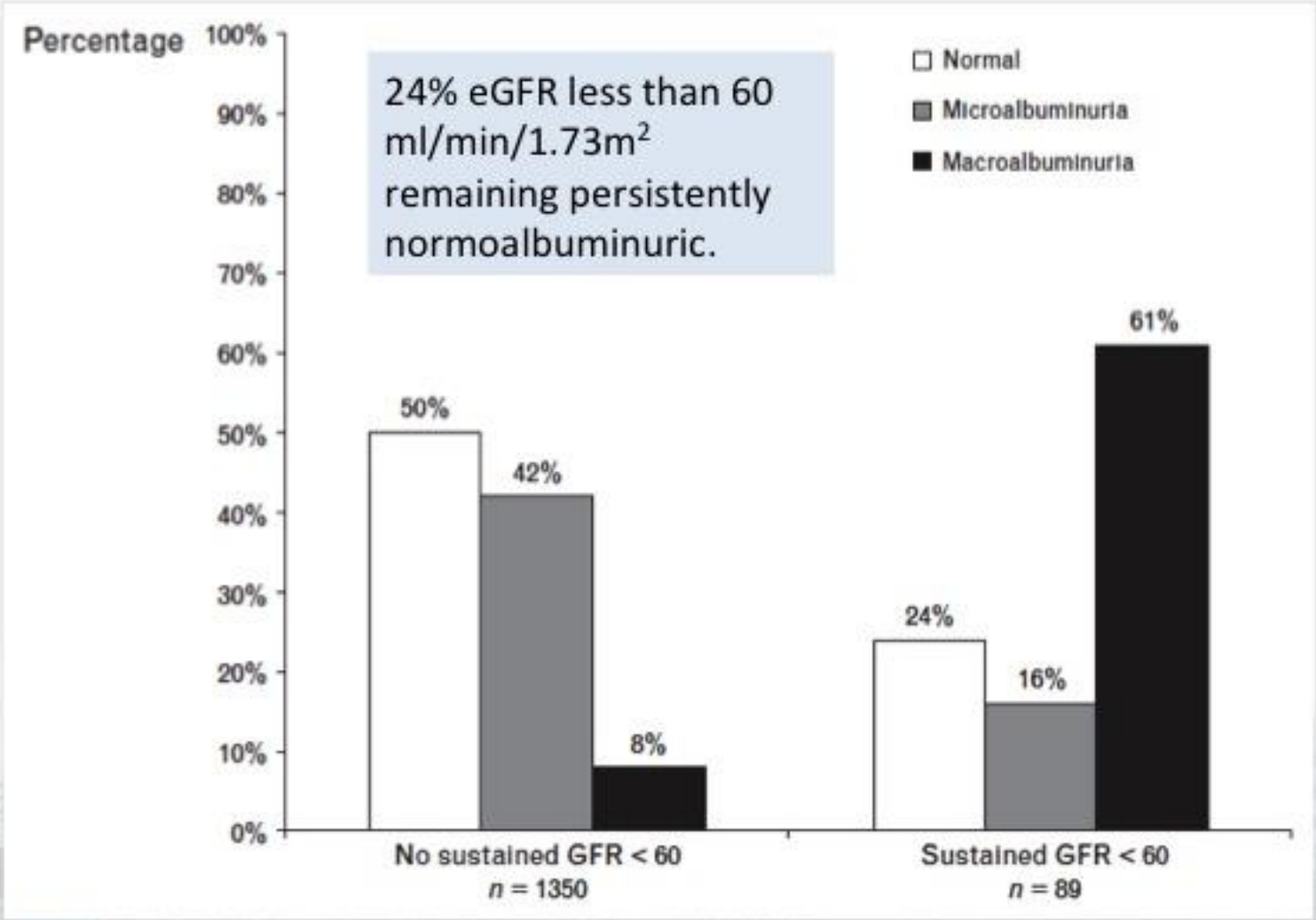


Risk of mortality in individuals with T1DM from the FinnDiane study associated with each level of albuminuria and ESKD



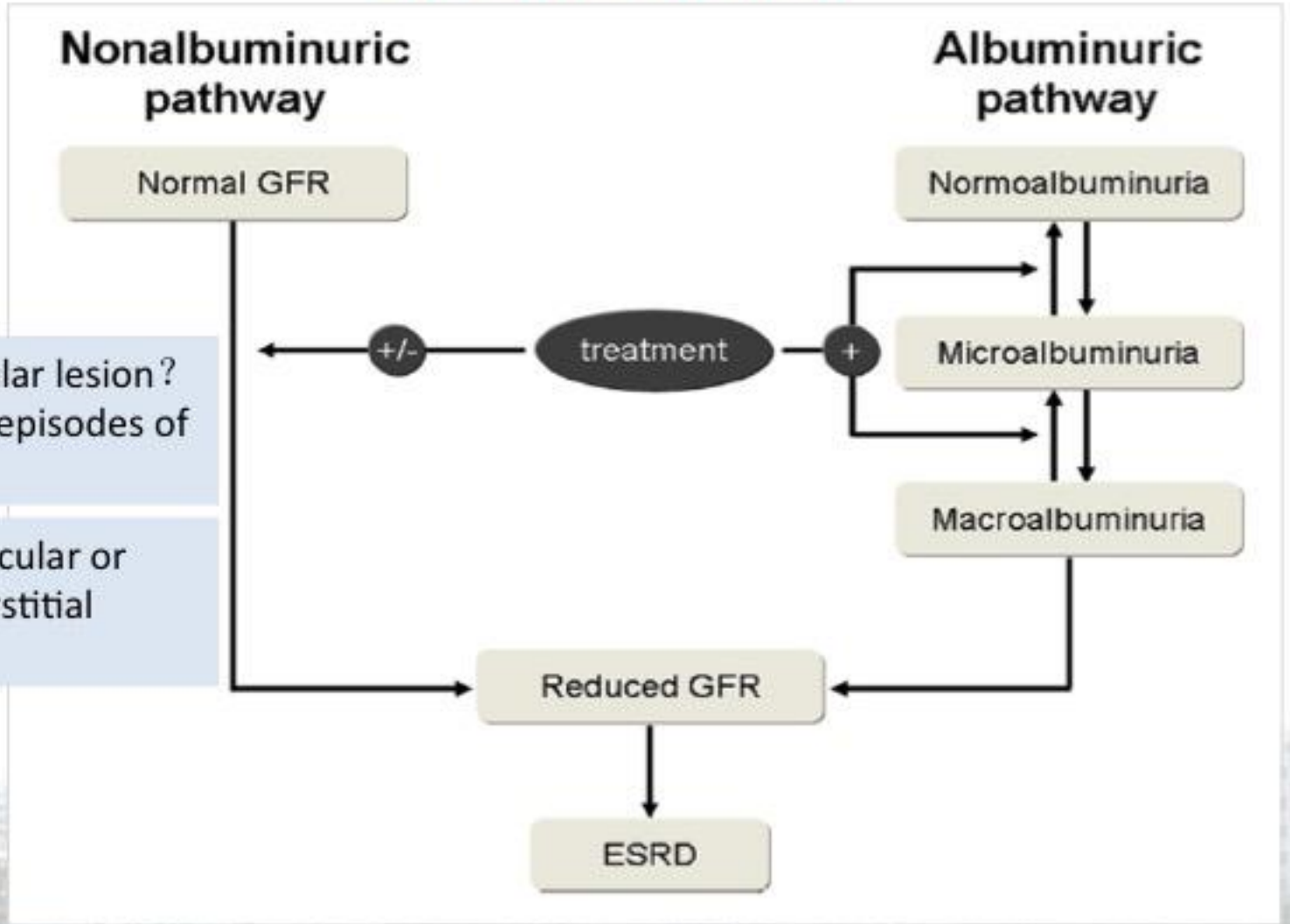
Groop PH et al. Diabetes 2009 Jul;58(7):1651–1658

Is albuminuria an acceptable surrogate marker for diabetic CKD?



Diabetes Care 2010; 33: 1536–1543

Nonalbuminuric and albuminuric pathways to loss of renal function



Macrovascular lesion? unresolved episodes of AKI

Atypical vascular or tubulo-interstitial lesions

Acta Diabetol (2014) 51:905–915

Albuminuria: biomarker use and major limitations

Biomarker use	Major limitations
DKD Higher albuminuria levels associate with faster eGFR decline Discordance between lowering albuminuria by treatment and clinical events	Not sensitive • Low eGFR present in half or more without increased albuminuria
CVD Independently predicts events and mortality	Nonstandardized measurement and reporting • Assays vary by ~40% • Variably reported as concentration, ratio to creatinine, or timed excretion Individual variability is large • Day-to-day variability ~40% • Episodic increases with fever, urinary tract infection, exercise, congestive heart failure, hypertension, hyperglycemia, high-protein diet Categorical nomenclature does not reflect continuous nature of association with DKD and CVD risks • Moderately increased albuminuria ("microalbuminuria") • Severely increased albuminuria ("macroalbuminuria")

Risk of Progression of DKD

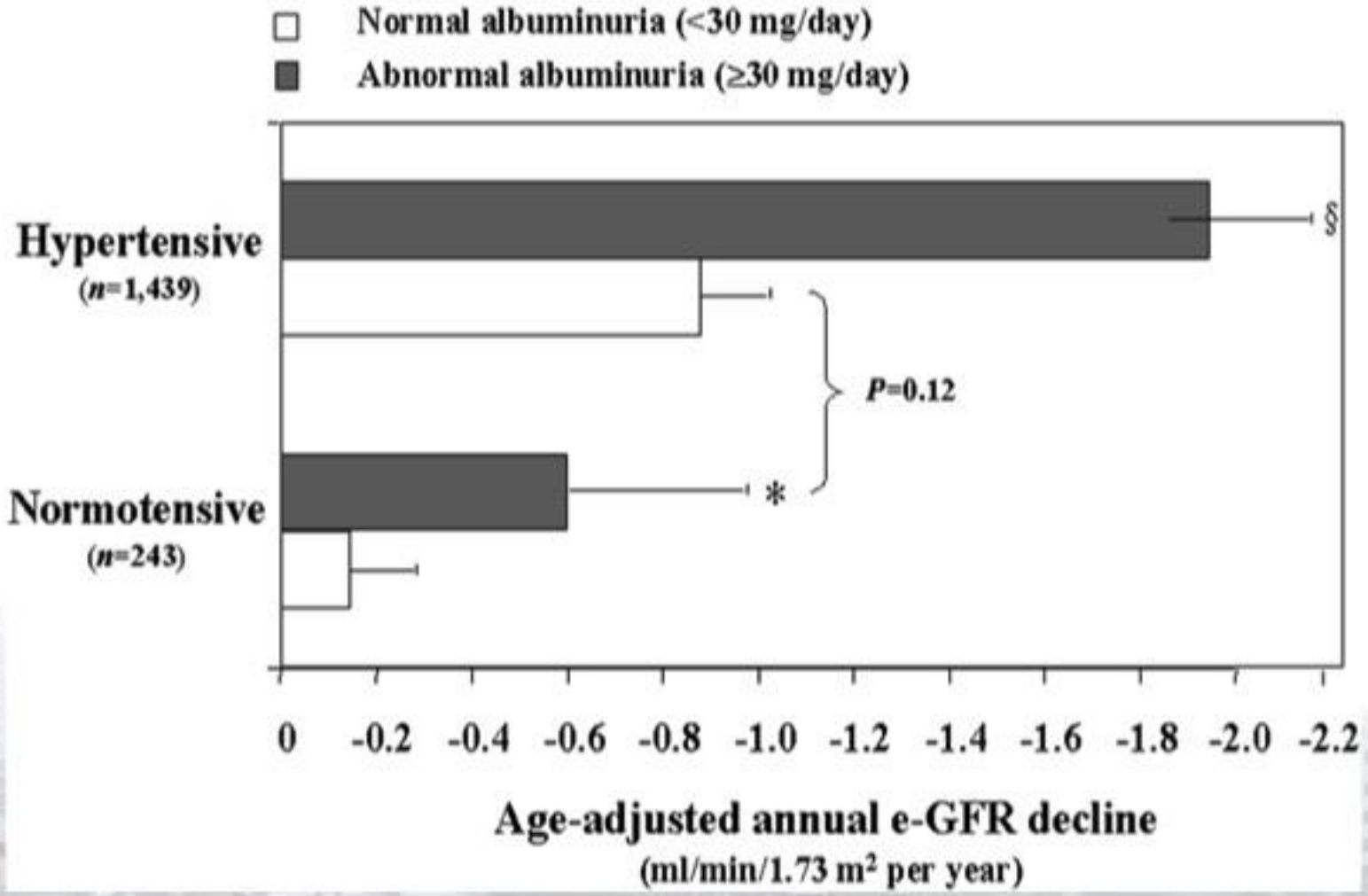
* HbA1C Level
* Albuminuria
* Hypertension
* Obesity, Hyperuricemia, Dyslipidemia
* Histological Damage
* Others
  - Genetics & Demographics: Ethnic, Age, Sex
  - Life style: Diet, Smoking

Hypertension in Diabetic Nephropathy

* A strong risk factor for progression of kidney disease and increased incidence of CV in diabetes.
* The prevalence of hypertension in DN increases at each stage of CKD, approaching 90 % for ESRD patients
* Multivariate logistic regression analysis of some studies showed that baseline SBP is a main predictor for GFR decline.
* Major benefits in retarding the progression of kidney disease, and sometimes even preventing or delaying the onset of end-stage renal disease.

Rossing, K (2004) Kidney Int, 66, 1596–1605.

Age-adjusted annual eGFR decline in 1682 patients with type 2 diabetes and preserved kidney function stratified by different clinical categories.



Giacomo Zoppini et al. CJASN 2012;7:401-408

BP management in DN

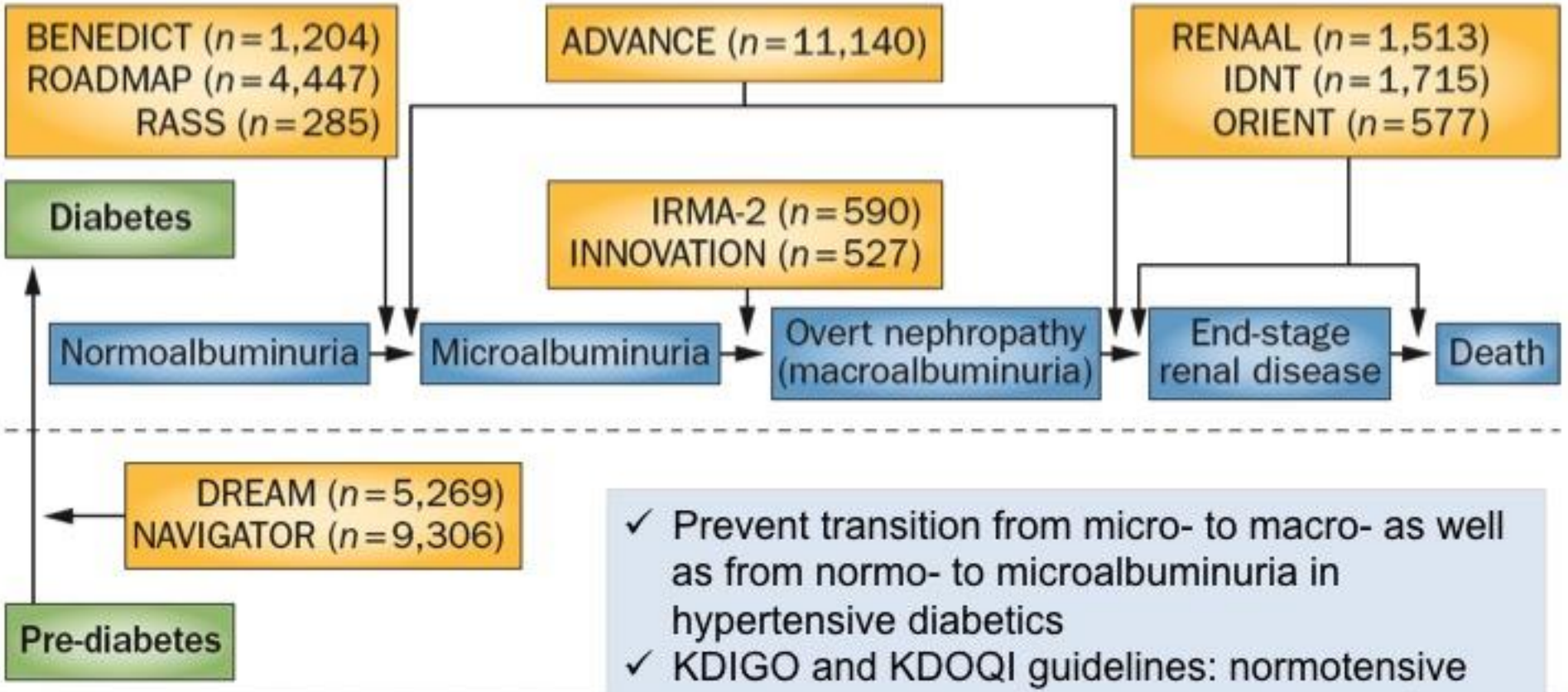
* Optimal BP level
* Drug choice
* Treating early CKD
* Sodium restriction

Optimal BP level in DN

* KDIGO & JNC 8 $\leqslant$ 140/90 mmHg
* Patients with stage 3 or later CKD demonstrate that DBP $<$60mmHg is associated with higher incidence of ESR
* Whether low BPs are actually beneficial?
* The SPRINT trial on this issue is to examine the effect of the ambitious low target of 120 vs 140 mmHg, although it is not specifically aimed at patients with diabetes

Wheeler DC et al. Kidney Int 2013;83:377–383
James PA et al. JAMA 2014;311: 507–520

Randomized controlled trials investigated the effects of RAAS blockade at the various stages of progression of DN



- ✓ Prevent transition from micro- to macro- as well as from normo- to microalbuminuria in hypertensive diabetics
- ✓ KDIGO and KDOQI guidelines: normotensive diabetic patients with albuminuria >30 mg/day

Roscioni, S. S. *et al. Nat. Rev. Nephrol.*10,77–87 (2014)

Risk of Progression of DKD

* HbA1C Level
* Albuminuria
* Hypertension
* Obesity, Hyperuricemia, Dyslipidemia
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* Others
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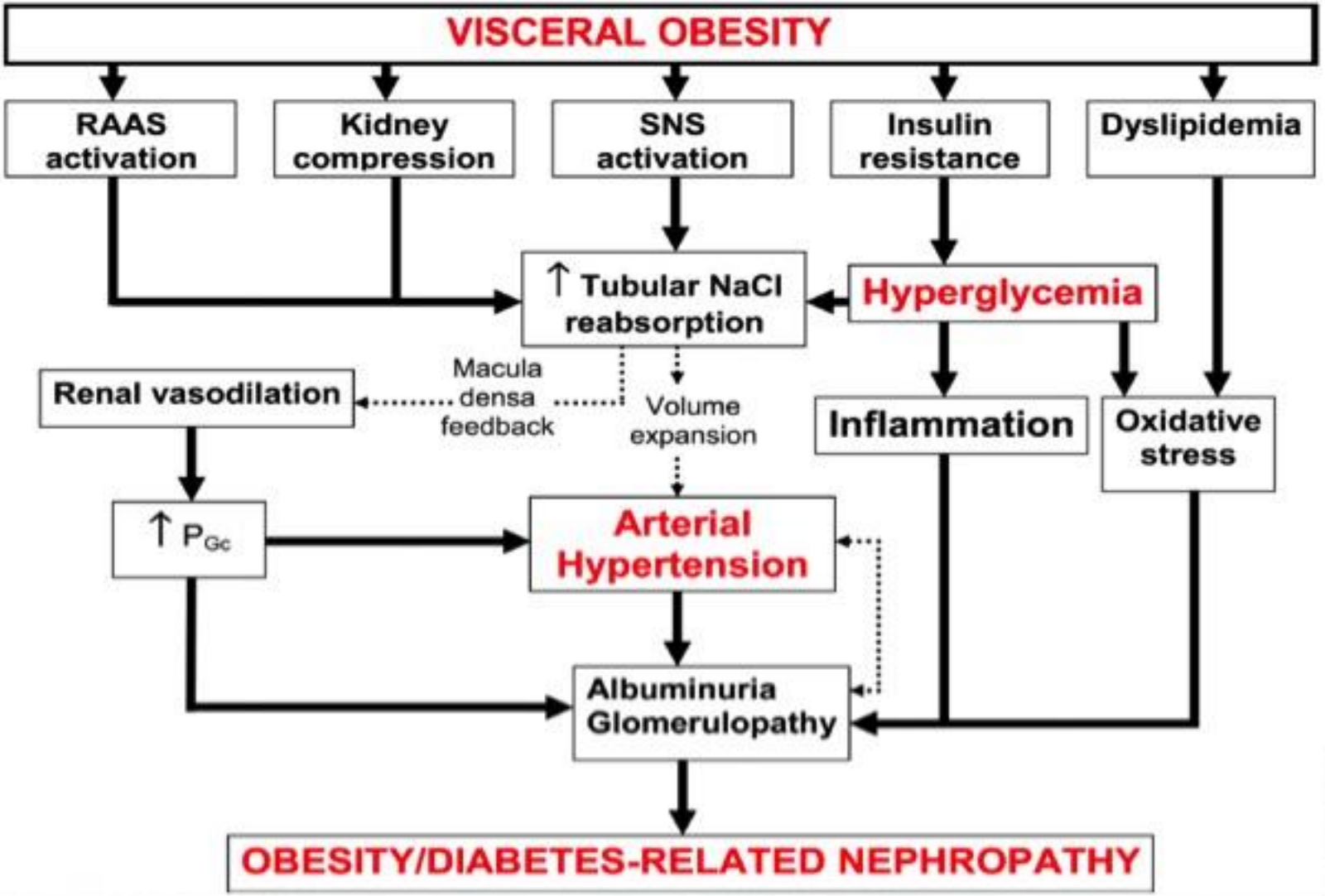
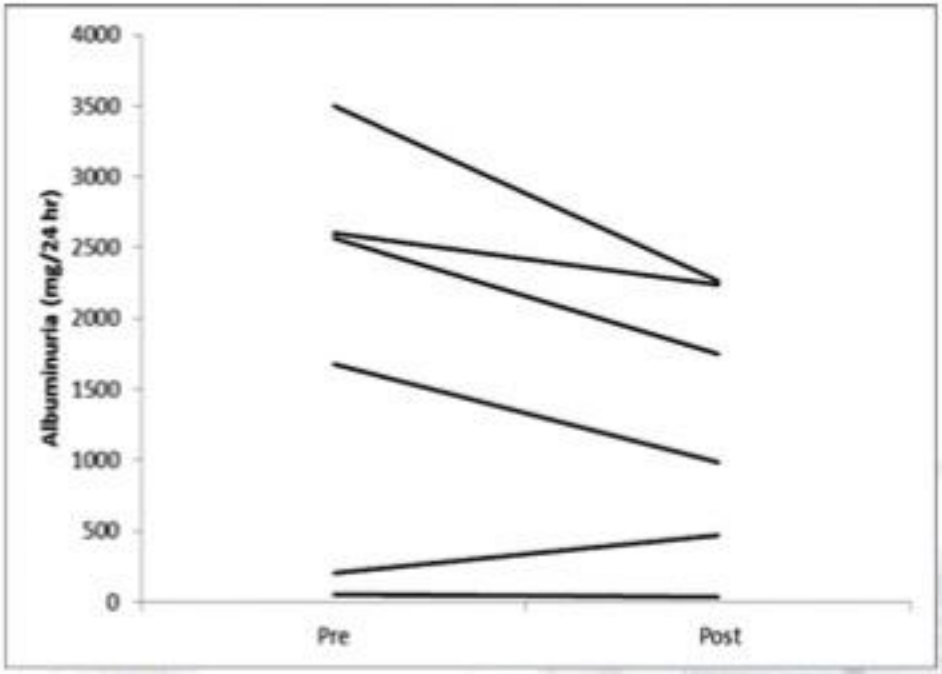
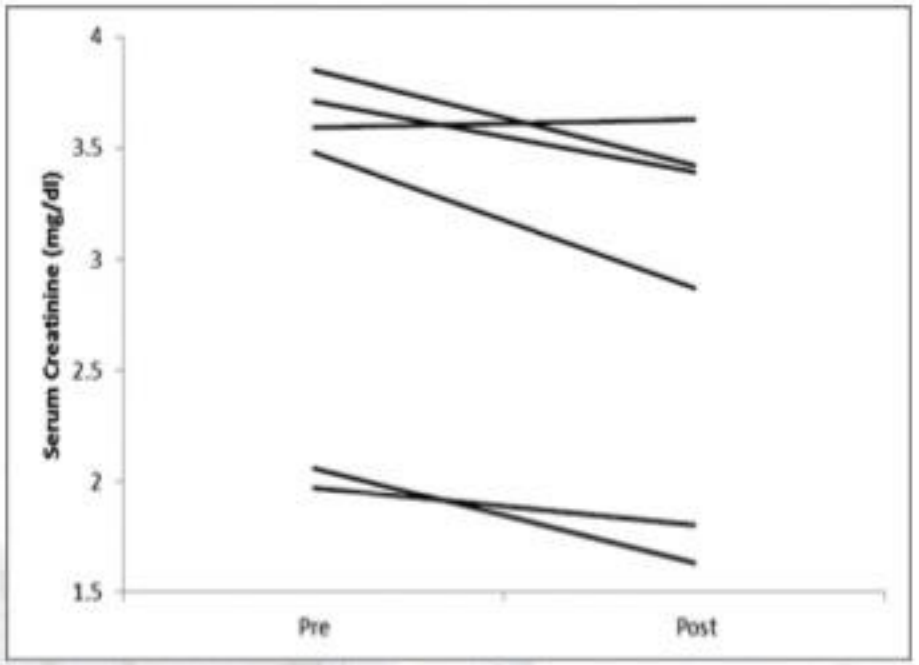
Interaction between metabolic and hemodynamic pathways in the pathophysiology of obesity -and diabetes-related renal disease



Med Clin North Am . 2013 January ; 97(1): 59–74

Short-Term Changes after a Weight Reduction Intervention in Advanced Diabetic Nephropathy

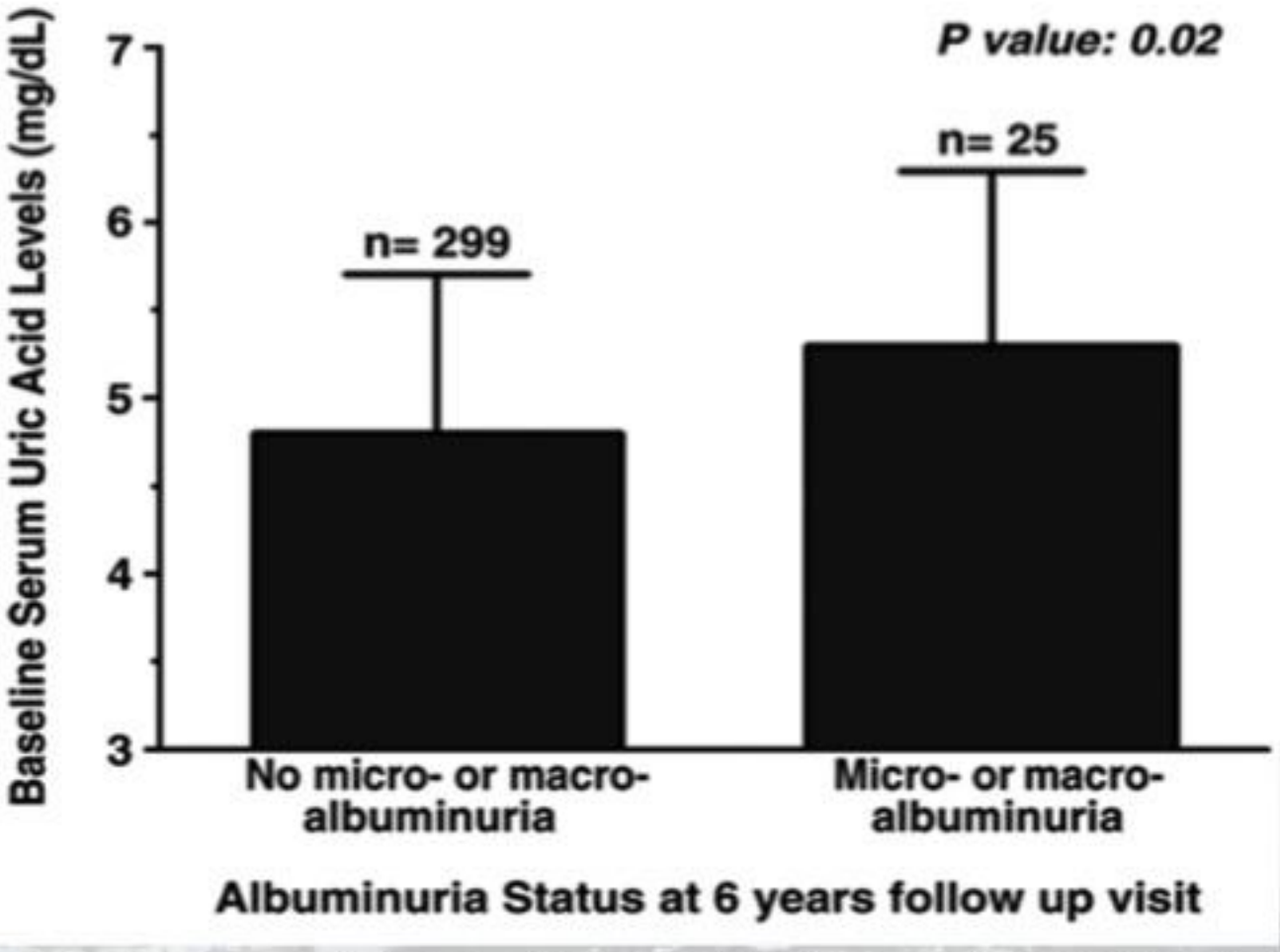




- 12-week very low calorie ketogenic weight reduction diet with encouragement of exercise
- 800 kcal/d with at least 75 g of protein and all essential vitamins and nutrients
- 12% reduction in weight

Friedman A. Clin J Am Soc Nephrol 8: 1892–1898, 2013

Mean baseline serum uric acid levels according to albuminuria status at the 6-year follow-up visit in a cohort of type 1 diabetics



Jalal et al. Nephrol Dial Transplant 25:1865–1869, 2010

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* Albuminuria
* Hypertension
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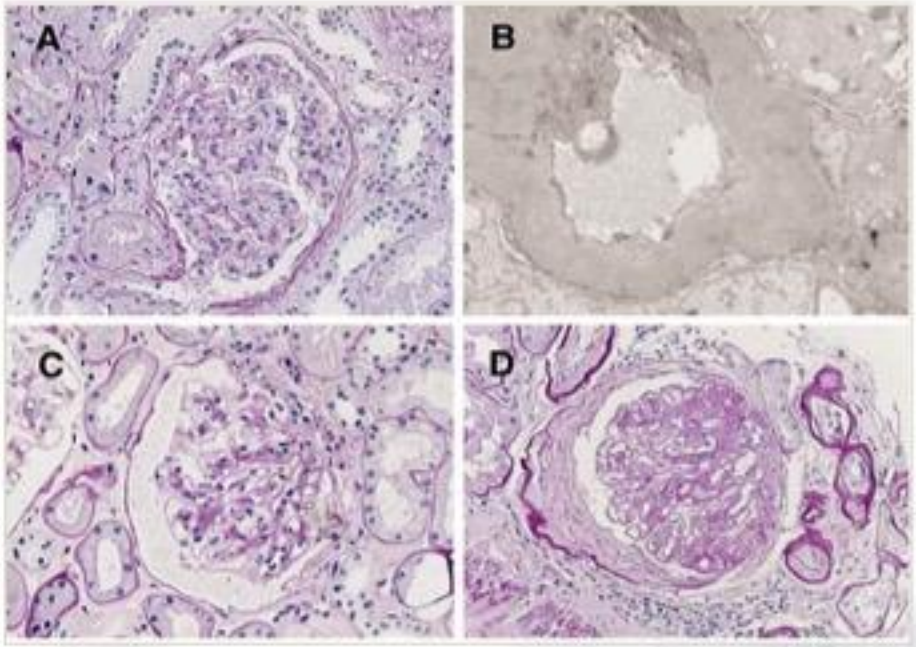
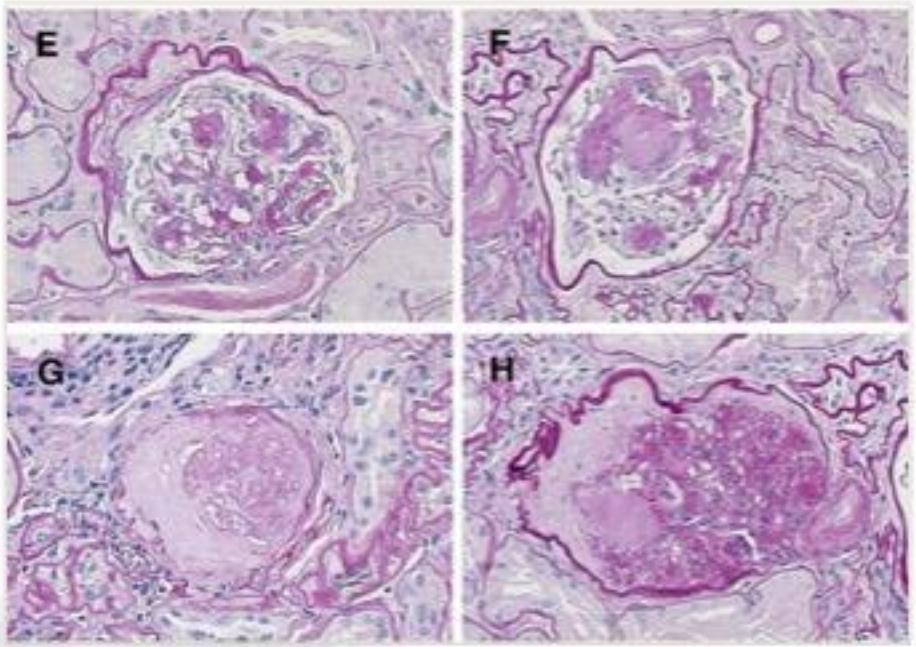
Pathologic classification of diabetic nephropathy





Class I (A, B)
Class II (C, D) (IIa, IIb).

Class III (E, F)
Class IV (H, G)

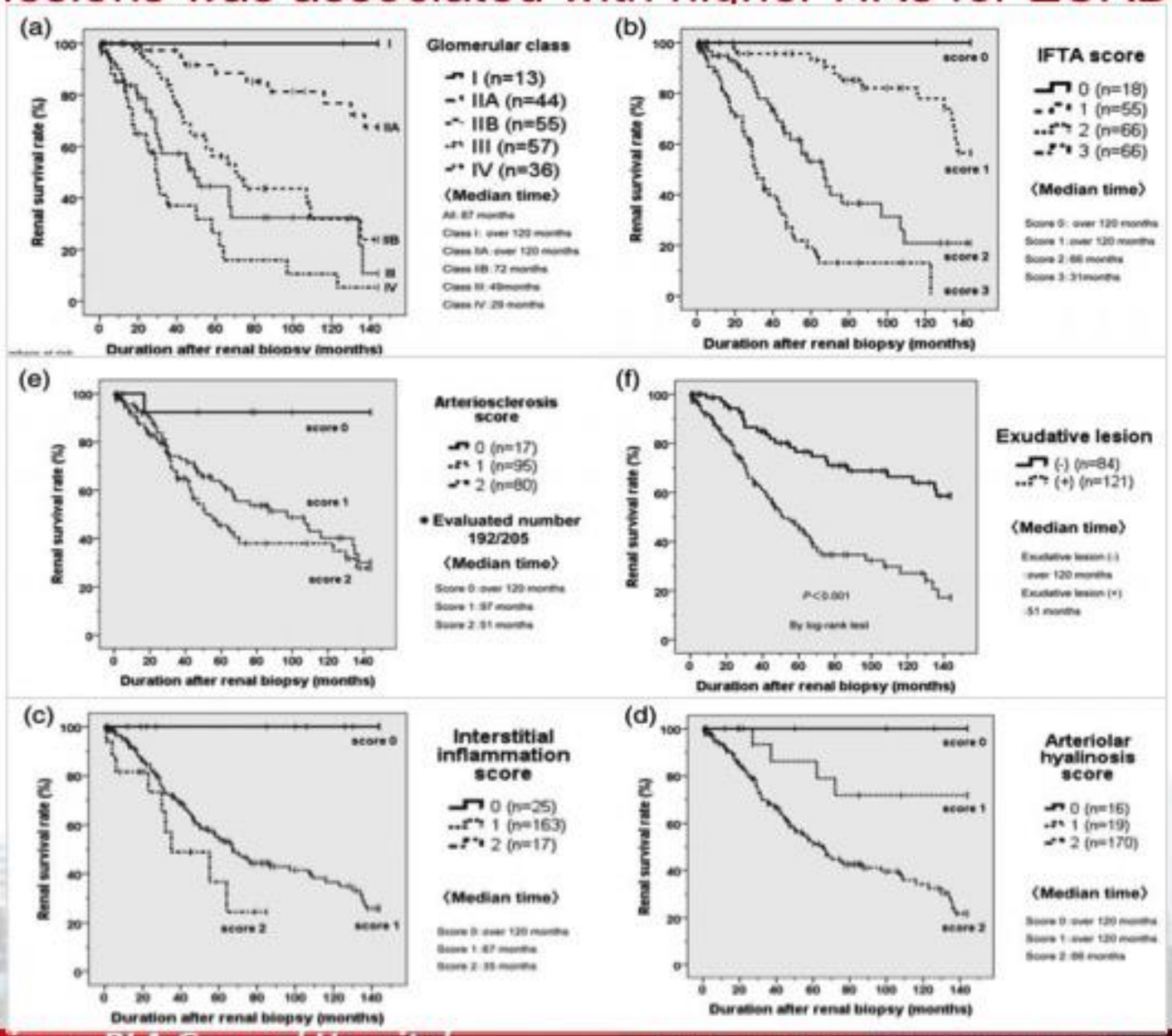
Thijs W. JASN 2010;21:556-563

Interstitial and vascular lesions of DN

Lesion	Criteria	Score
Interstitial lesions		
IFTA	No IFTA	0
	<25%	1
	25% to 50%	2
	>50%	3
interstitial	Absent	0
inflammation	Infiltration only in relation to IFTA	1
	Infiltration in areas without IFTA	2
Vascular lesions		
arteriolar hyalinosis	Absent	0
	At least one area of arteriolar hyalinosis	1
	More than one area of arteriolar hyalinosis	2
presence of large vessels	–	Yes/no
arteriosclerosis (score worst artery)	No intimal thickening	0
	Intimal thickening less than thickness of media	1
	Intimal thickening greater than thickness of media	2

Tervaert el al JASN.2010;21:556–563

The progression of glomerular, tubulointerstitial and vascular lesions was associated with higher HRs for ESRD

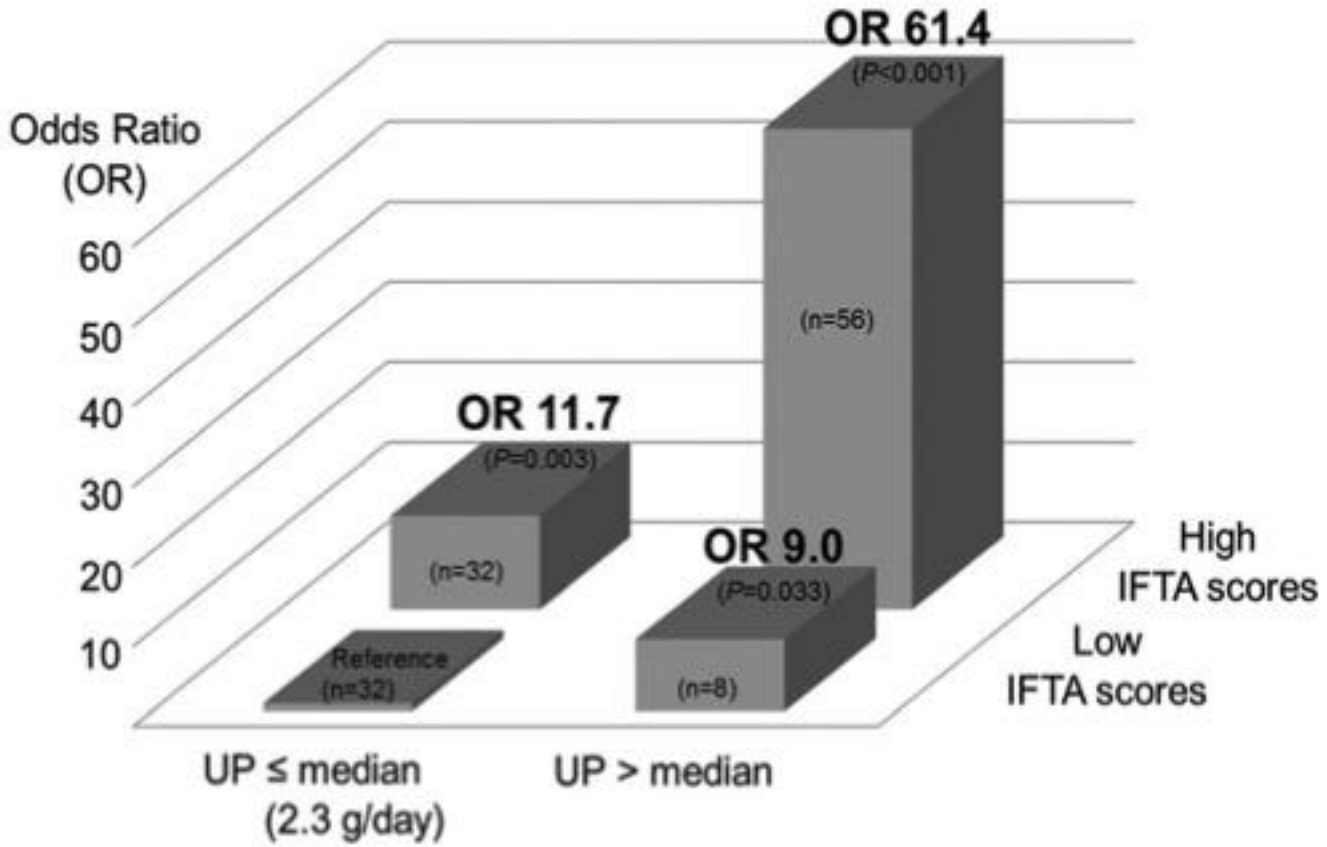


Severity of glomerular and interstitial lesions were associated with renal outcomes in DN

	Rate of renal survival			
	Univariate		Multivariate[a]	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Glomerular lesions	2.99 (2.32–3.87)	<0.001	1.49 (1.10–2.02)	0.011
IFTA	3.93 (3.01–5.12)	<0.001	1.51 (1.05–2.17)	0.028
Interstitial inflammation	6.71 (4.27–10.53)	<0.001	1.31 (0.76–2.28)	0.332
Arteriolar hyalinosis	7.95 (0.64–99.48)	0.108		
Arteriosclerosis	1.28 (0.96–1.70)	0.090		

An Y et al. NDT. 2015;30:257–266

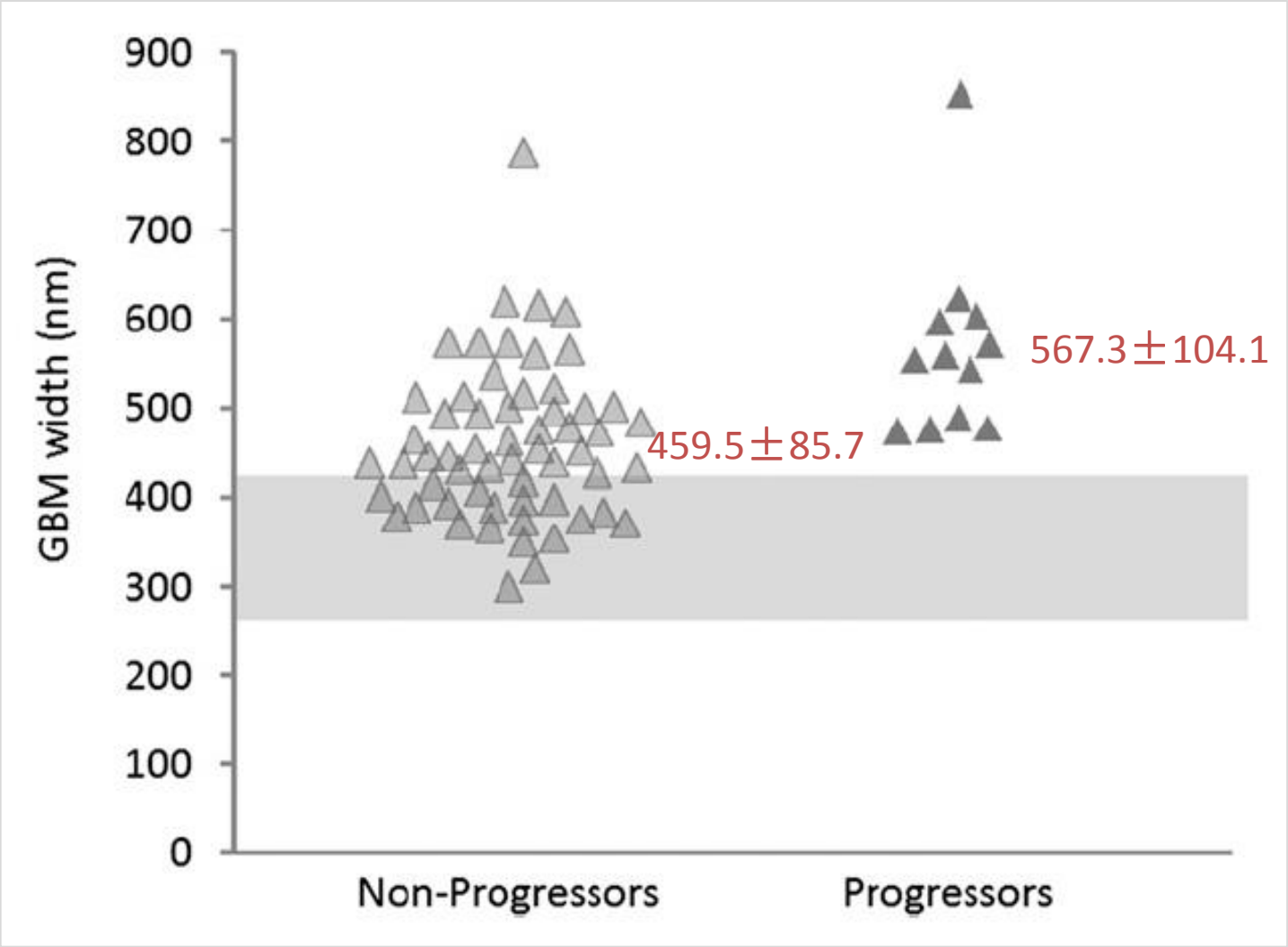
Tubulointerstitial lesions should be assessed to predict rapid eGFR decline in DN



The risk of rapid eGFR decline in groups stratified according to urinary protein excretion (UP) and interstitial fibrosis and tubular atrophy (IFTA) scores

Mise K et al. Diabetes Metab Res Rev. 2015 Sep;31(6):572-81

GBM width in normoalbuminuric T1D patients who remained normoalbuminuric or progressed to proteinuria and/or ESRD

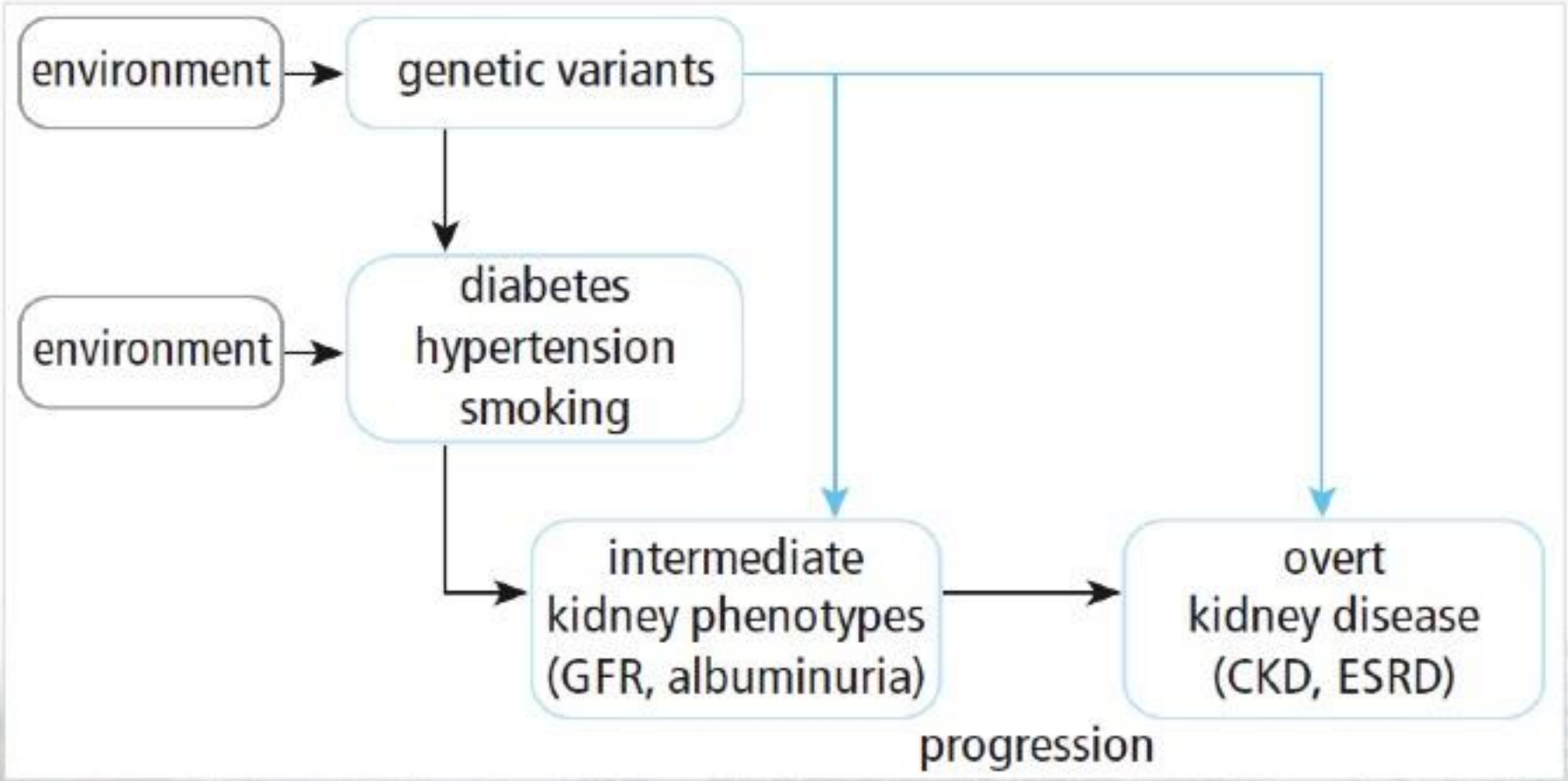


Luiza Caramori M. J Am Soc Nephrol 24: 1175–1181, 2013

Risk of Progression of DKD

* HbA1C Level
* Albuminuria
* Hypertension
* Obesity, Hyperuricemia, Dyslipidemia
* Histological Damage
* Others
  - Genetics & Demographics: Ethnic, Age, Sex
  - Life style: Diet, Smoking

Genes involved in the progression of DN

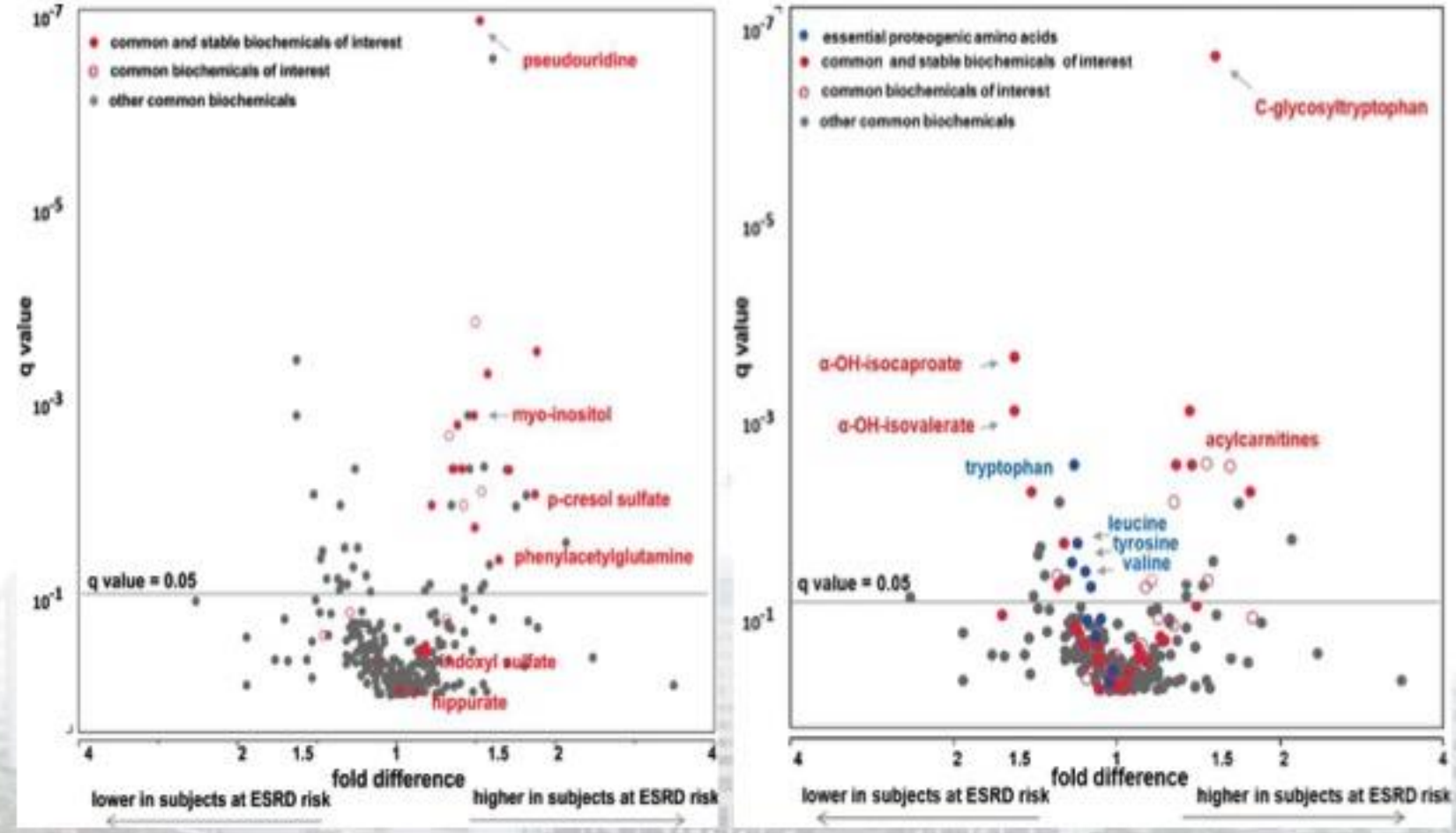


Candidate Genes Implicated in the Susceptibility for the development of DKD

- Angiotensin-converting enzyme (ACE)
- Angiotensinogen
- Angiotensin II receptor (type 1)
- Aldose reductase
- Apolipoprotein E
- Atrial natriuretic peptide
- Heparin sulfate
- Intercellular adhesion molecule 1 (ICAM)
- Matrix metalloproteinase
- Methylene metalloproteinase 9 (MM-9)
- Na/H exchanger
- Nitric oxide synthase
- Plasminogen activator inhibitor 1 (PAI-1)
- Peroxisome proliferator-activated receptor (PPAR)
- Type 4 collagen
- 3-Adrenergic receptor
- Vascular endothelial growth factor (VEGF)
- Engulfment and cell motility 1 (ELMO1)

MacIsaac R.J. Am J Kidney Dis. 2014;63(2)(suppl 2):S39-S62

Establish metabolomic profiles associated with progression to ESRD in T2D



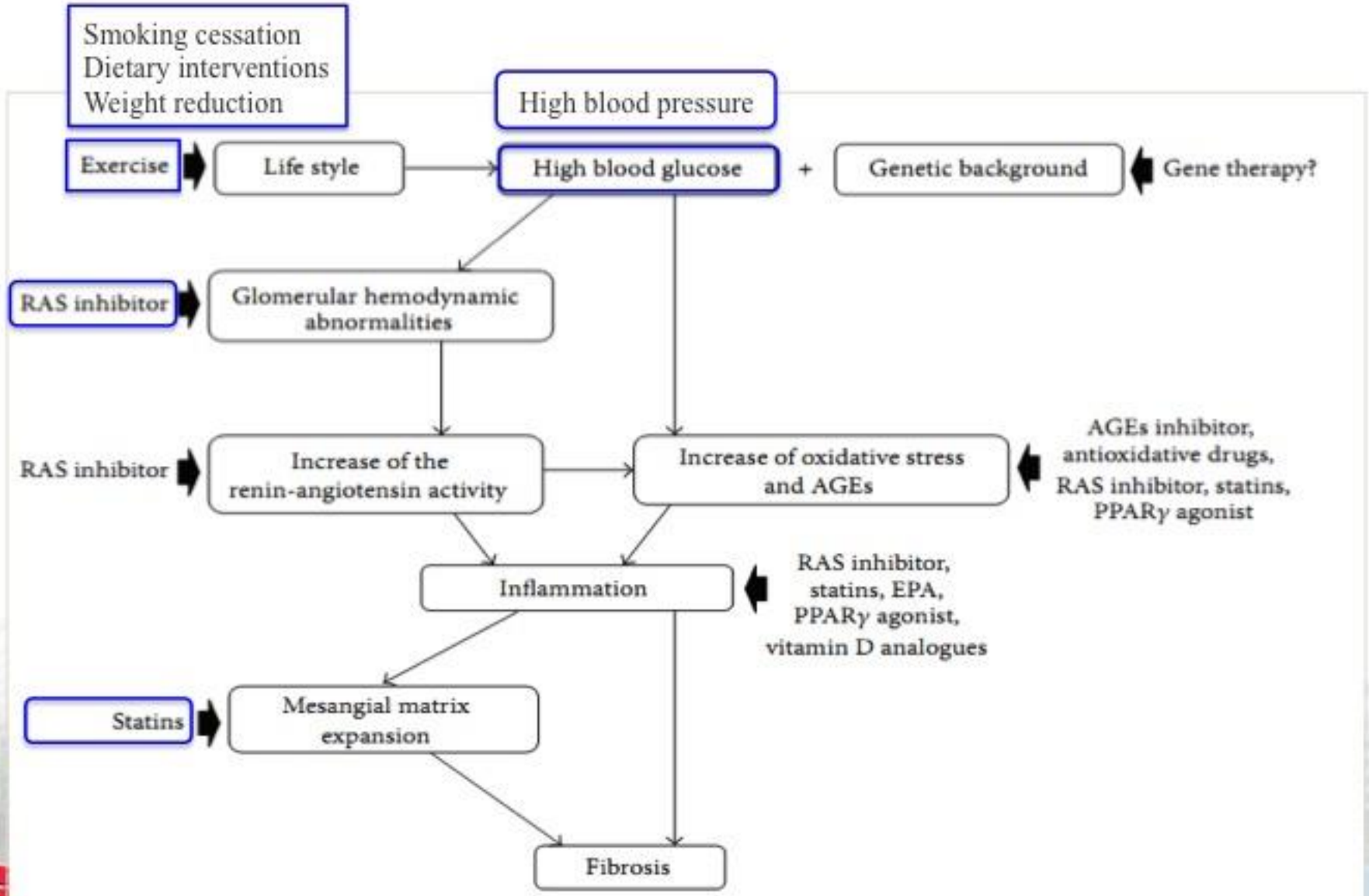
Dylan Burger JASN. : 1401–1407, 2014

Usefulness of Various Markers for the Development and Progression of DKD

Marker for DKD	Advantages	Disadvantages
Albuminuria	Urinary albumin levels within the microalbuminuric range predict ESRD	High variability, low specificity for DKD; spontaneous regression and ΔAER within the microalbuminuric range ≠ ΔGFR
GFR	Best measure of kidney function	Routine methods for accurately estimating GFR in the normal-high range are still lacking
Glucose	An important marker because hyperglycemia is the initiator of DKD	Targets still to be optimally defined; evidence documenting that intensive glycemic control prevents ESRD is sparse
Blood pressure	An important promoter of DKD; also important in CV risk reduction	Targets are still to be optimally defined
Lipids	Important in CV risk reduction; lipid-modifying agents may have renal-protective effects independent of changes in lipid profile	The relationship between components of the lipid profile and risk for DKD progression is not optimally defined
Soluble TNF receptors	Circulating levels of TNF receptors have been shown to predict ESRD and possibly have a more powerful predictive ability than proteinuria	The relationship between TNF receptors and ESRD remains to be confirmed in various patient populations attending different centers
Uric acid	Easy to measure; levels also may relate to CV risk	Kidney disease outcome intervention studies to target uric acid levels are still required
Tubular markers	Easy to measure in urine sample	The prognostic significance of their measurement over and above established risk factors remains to be fully defined
Urinary proteome	The appearance of the CKD273 biomarker classifier is an earlier marker for the risk of the development of proteinuria, even prior to the onset of microalbuminuria	Clinical assays are lacking
Serum cystatin C	Predicts ESRD better than creatinine-based eGFR methods and possibly directly measured GFR	Expensive and the standardization of assays is not yet universal

MacIsaac R.J. Am J Kidney Dis. 2014;63(2)(suppl 2):S39-S62

Multiple interventions to slow the progression of DKD



Medical management of diabetic kidney disease

Proven benefit	Probable benefit	Benefit to be proven[a]
Blood glucose control	Control of hyperlipidemia	Aldose reductase inhibitors
Blood pressure control	Smoking cessation	Inhibitors of AGE
Low protein diet	Low salt diet	Antiplatelet and related therapy
		Antioxidants
		PKC inhibitors
		Sulodexide
		Growth factor inhibitors
		Gene therapy

AGE advanced glycation end products, *PKC* protein kinase C, *GAG* glycosaminoglycans

感谢聆听！

Thank you for your attention