Clinical characteristics of diabetic nephropathy

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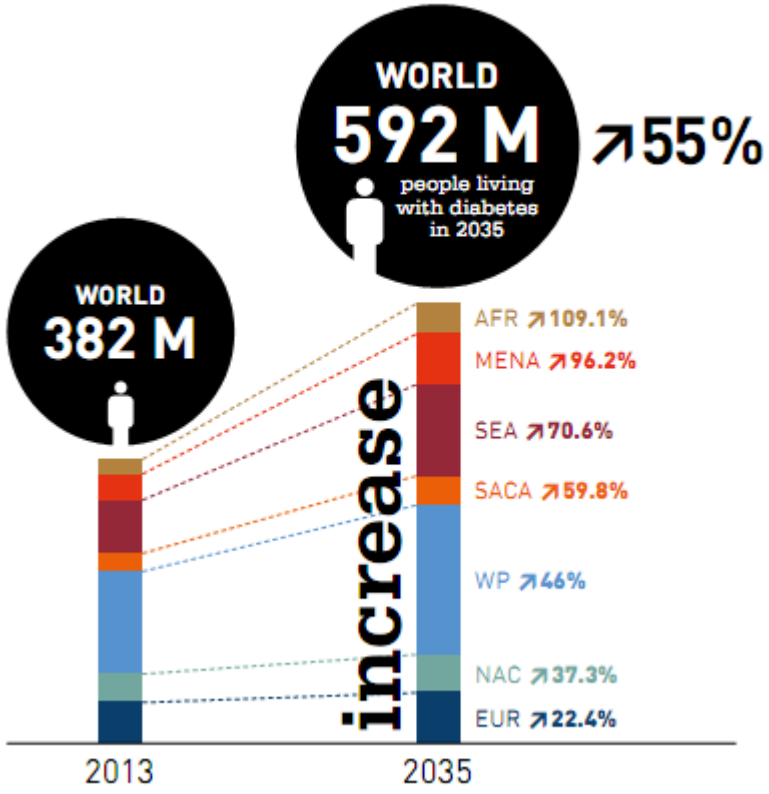
1. 당뇨성 신병증 역학

2. 당뇨성 신병증 진단
   : 신기능 저하가 있는 정상 알부민뇨 당뇨환자를
   당뇨병성 신병증으로 진단할 수 있는가

   : 단백뇨가 있는 당뇨환자는 모두 당뇨병성 신병증을
   가지고 있는가

3. 당뇨성 신병증 예후
   신기능 저하와 알부민뇨에 따른 사망, 말기신부전

Diabetes is a **huge and growing problem**, and the costs to society are **high and escalating**

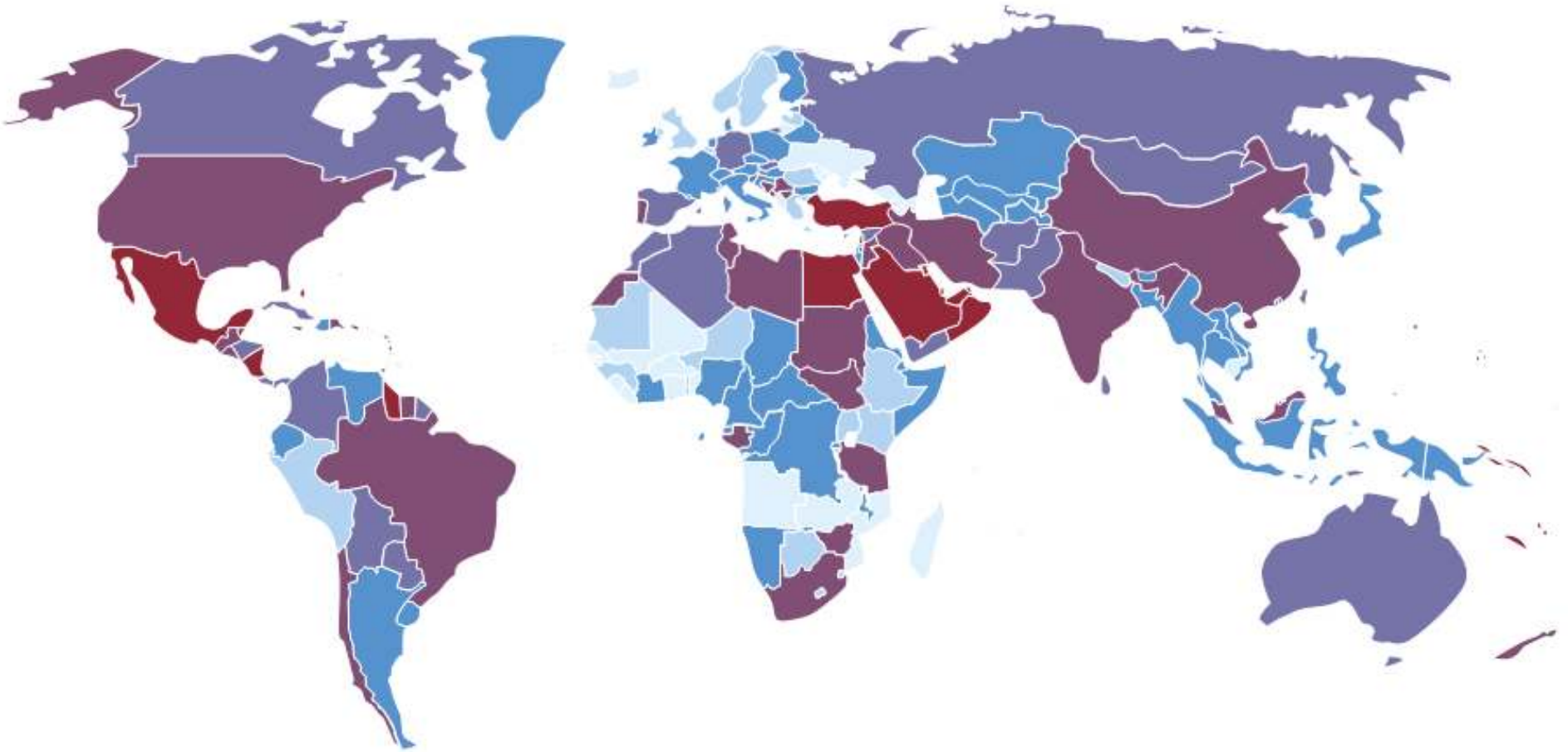


382 million people have diabetes

By **2035**, this number will rise to **592 million**

International Federation of Diabetes

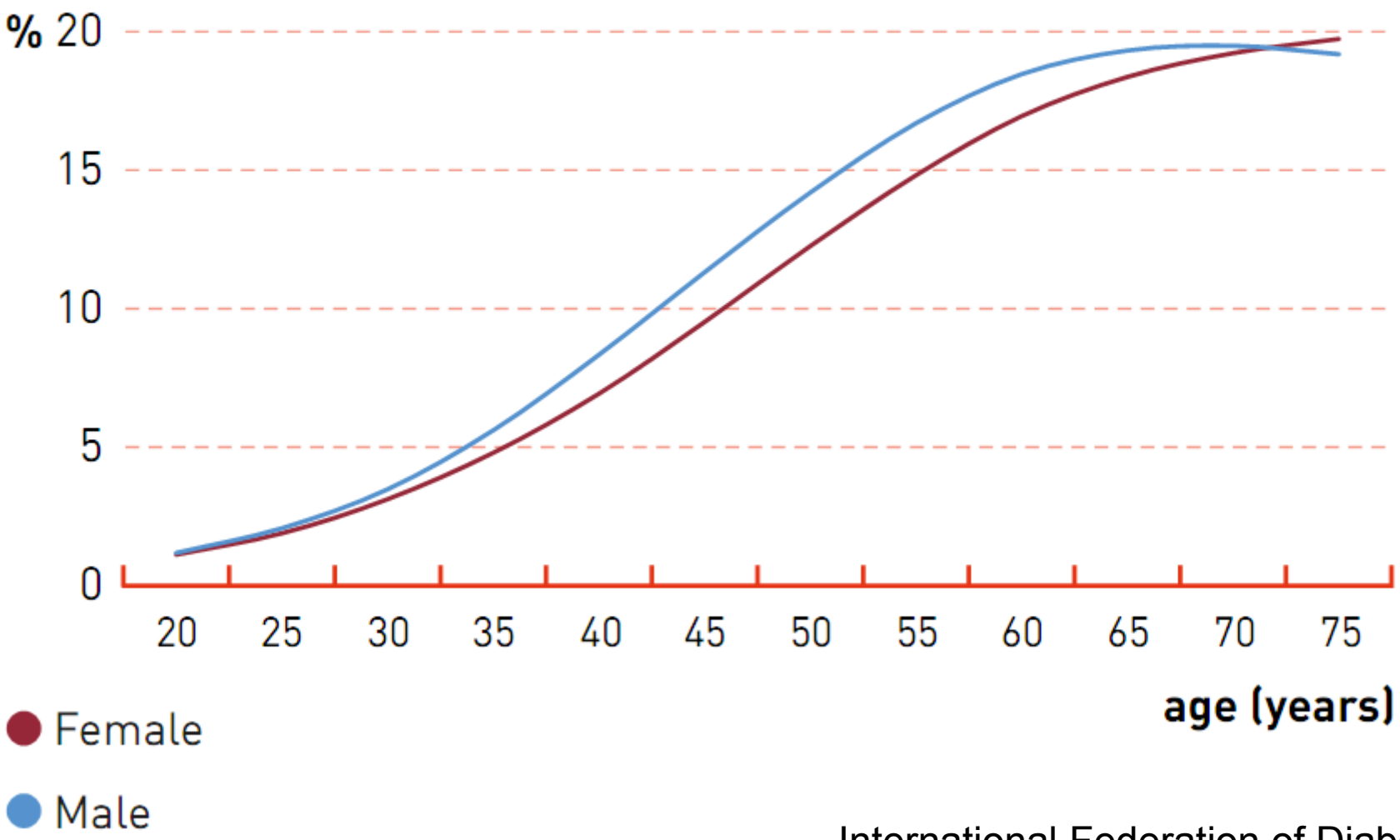
Prevalence* (%) of diabetes in adults (20-79 years), 2013



*comparative prevalence

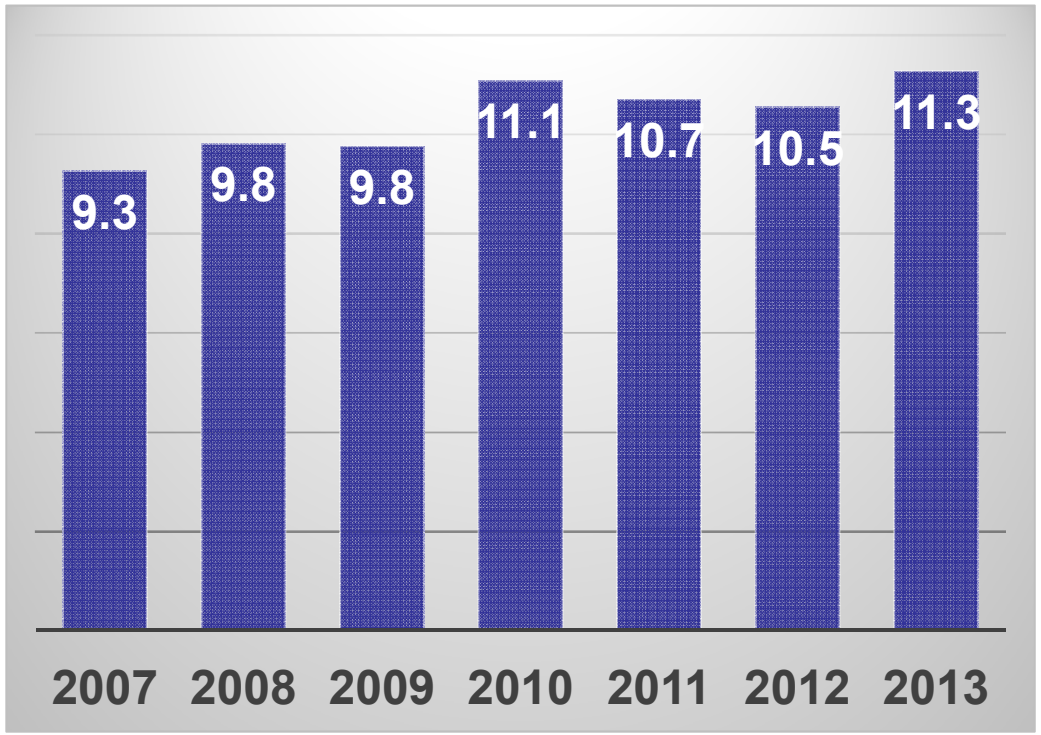
International Federation of Diabetes

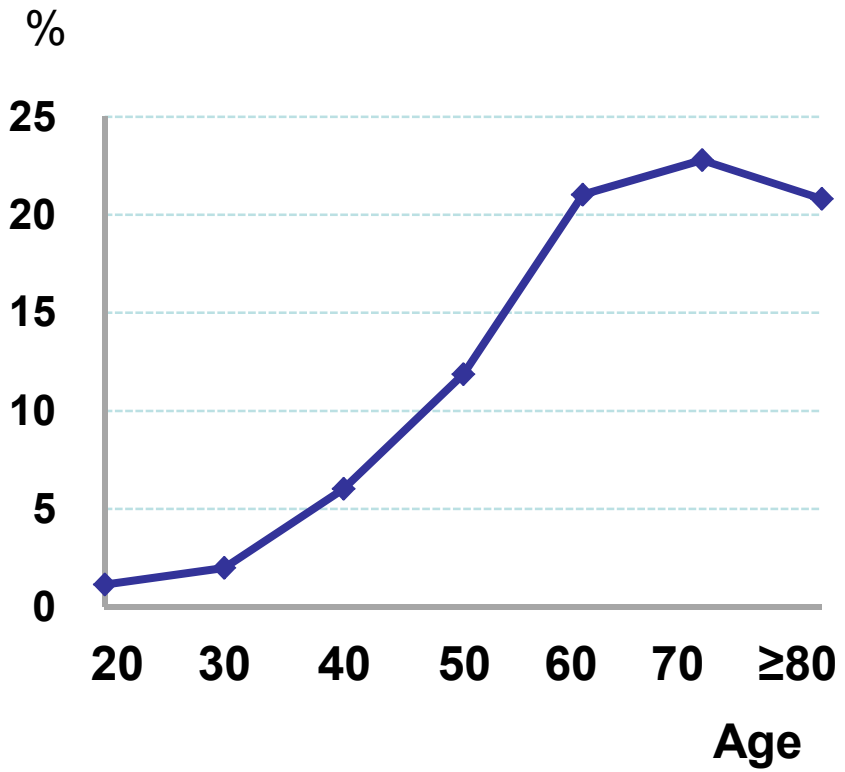
Figure 2.2 **Prevalence (%) of people with diabetes by age and sex, 2013**



International Federation of Diabetes

Prevalence of diabetes in Korea

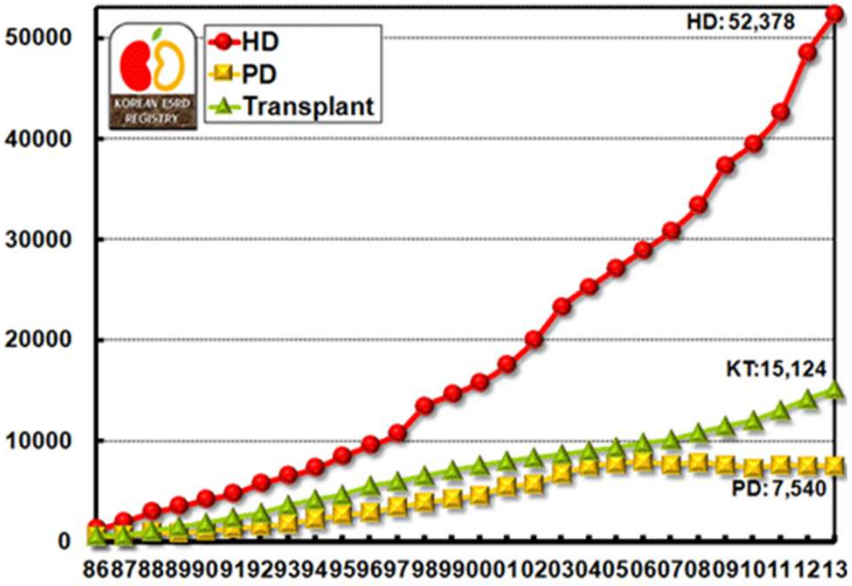




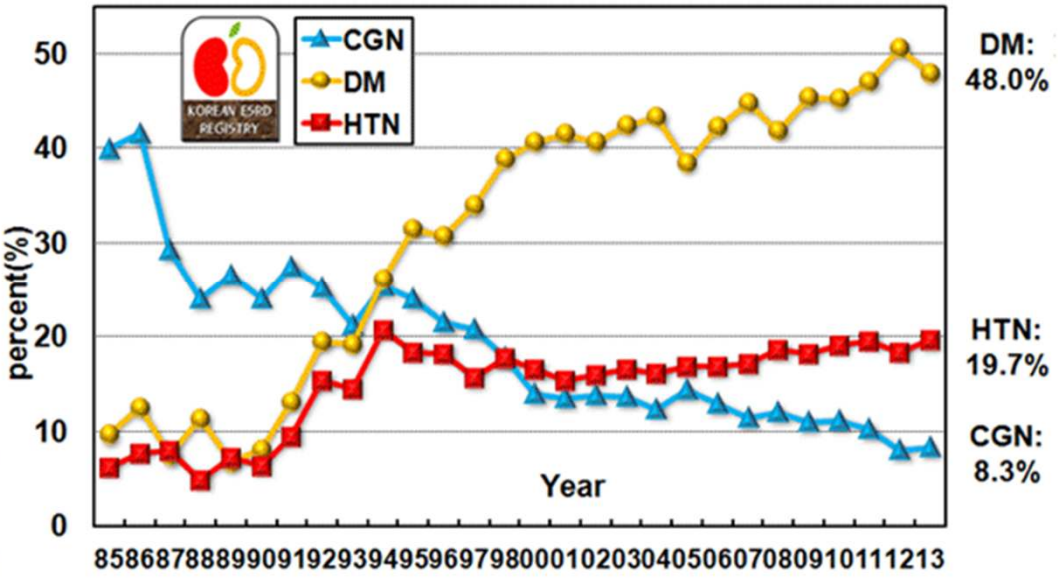
국민영양조사 (Korea National Health and Nutrition Examination Survey)
Age≥19 years

End stage renal disease in Korea

1446.4 patients per million population



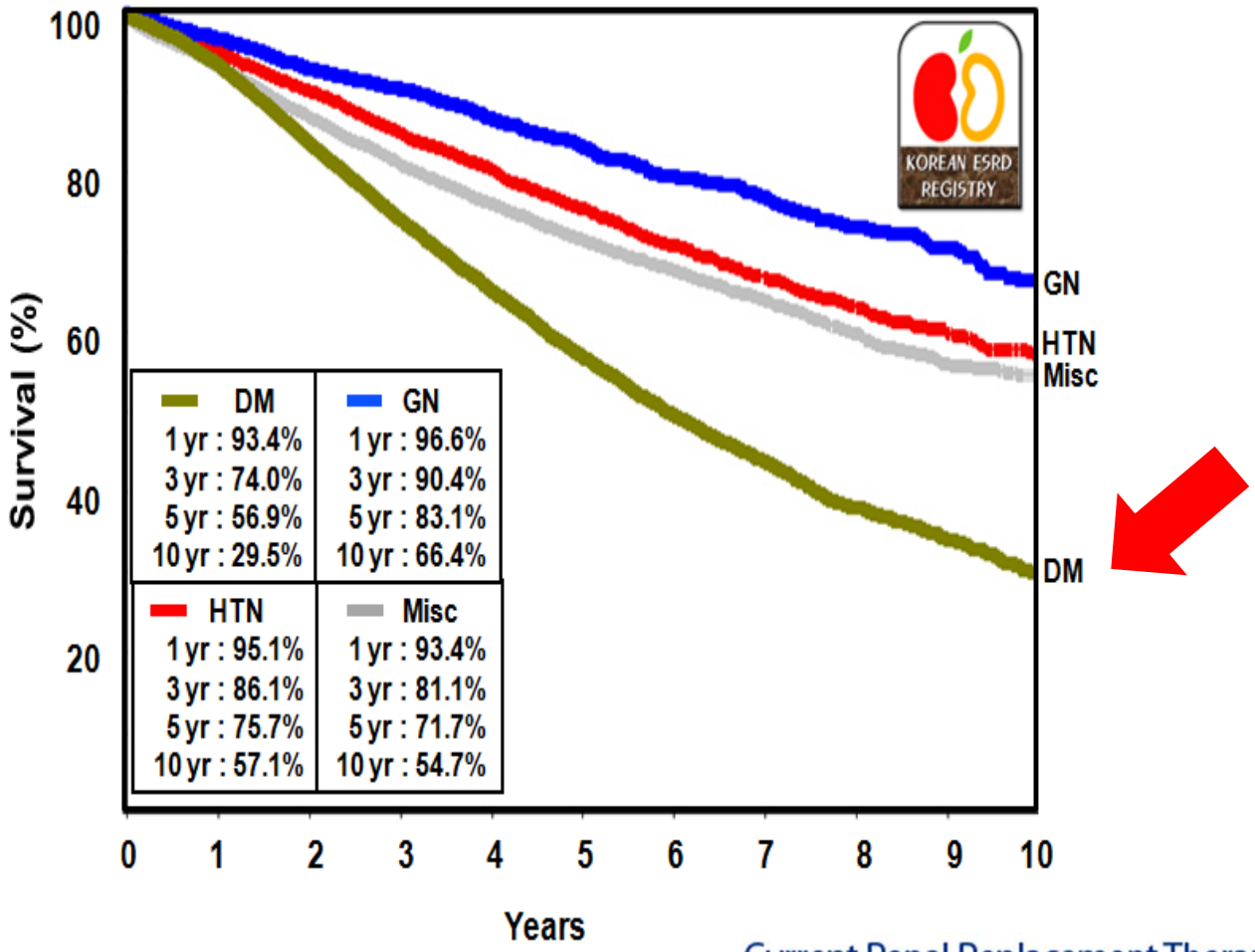
국내 말기 신부전 빈도



국내 말기 신부전 원인 질환

Current Renal Replacement Therapy in Korea
- Insan Memorial Dialysis Registry, 2013 -
ESRD Registry Committee, Korean Society of Nephrology

Survival of ESRD patients



Current Renal Replacement Therapy in Korea
- Insan Memorial Dialysis Registry, 2013 -
ESRD Registry Committee, Korean Society of Nephrology

Clinical diabetic nephropathy

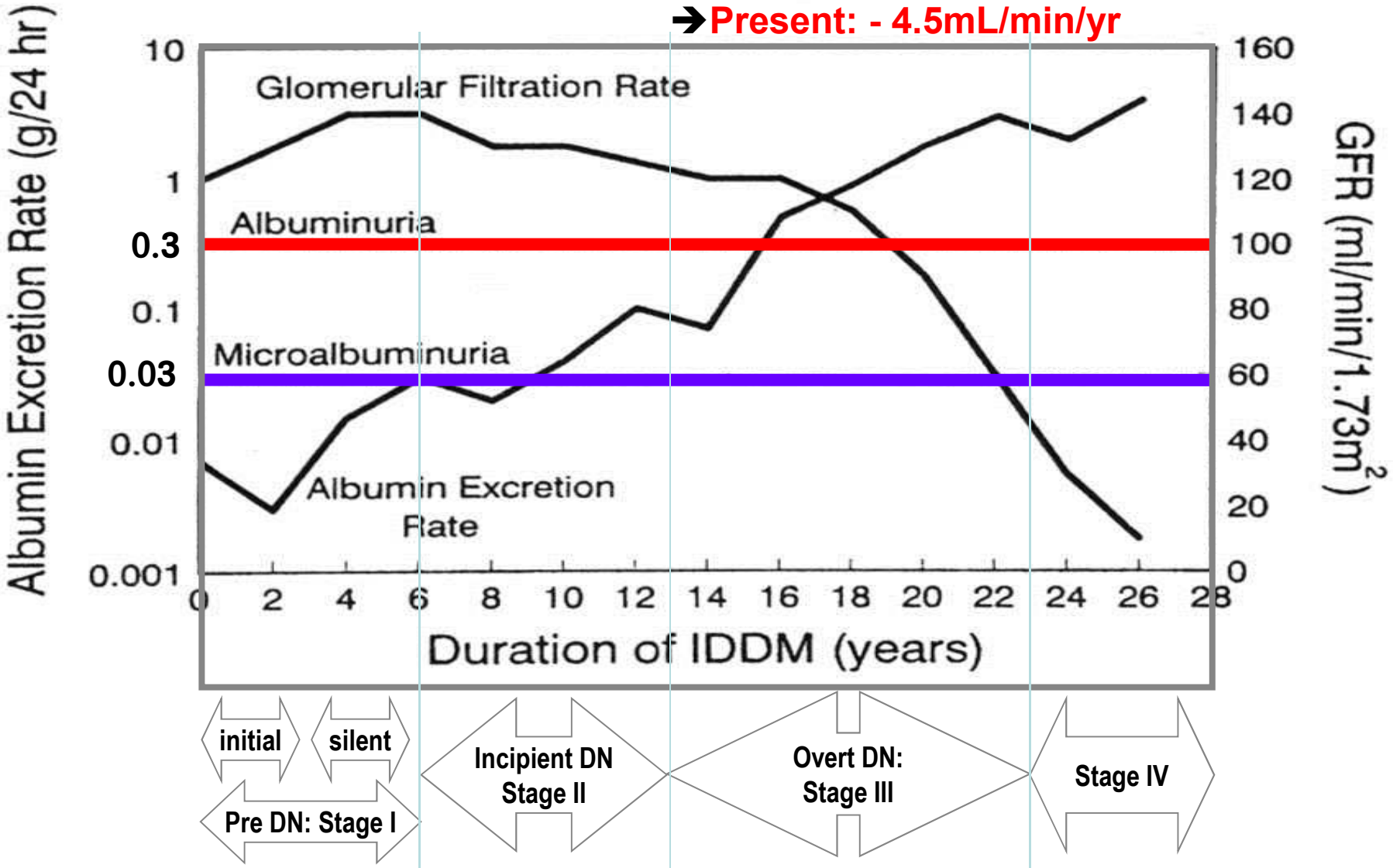
DM with albuminuria or more

Diabetic retinopathy
Long duration (≥ 10 years, 특히 제 1형)
Slowly progressive proteinuria

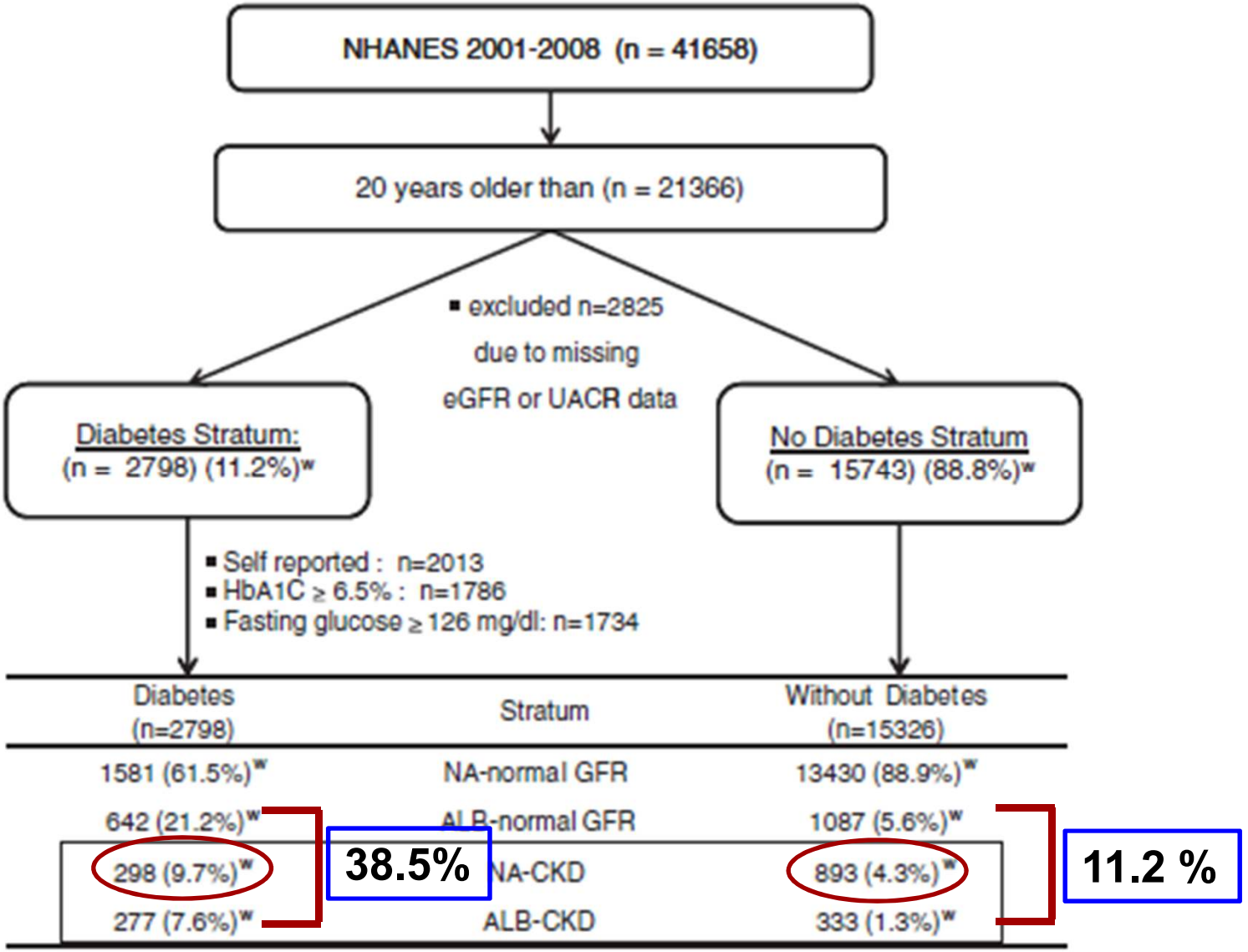
Rare glomerular hematuria

Natural history of type 1 DM

Rate of dec. GFR:
Past: -10~15mL/min/yr
➔**Present: - 4.5mL/min/yr**



Prevalence of diabetic kidney disease in US



Journal of Diabetes and Its Complications 27 (2013) 123–127

Normoalbuminuric CKD with type 2 DM would have DMN?

Pathologic finding of diabetic nephropathy

1. Mesangial expansion with increased mesangial matrix

   → Diffuse glomerulosclerosis

   Nodular glomerulosclerosis (Kimmelstiel-Wilson lesion)

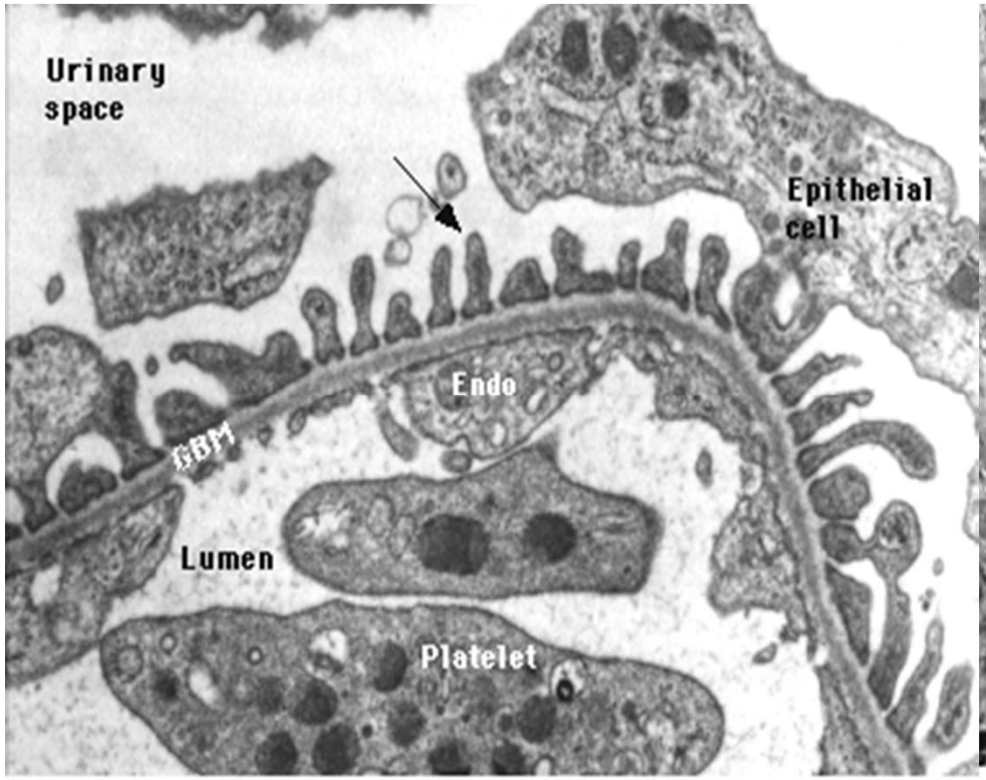
2. Thickened Glomerular Basement Membrane

3. Hyalinosis of afferent and efferent arteriole

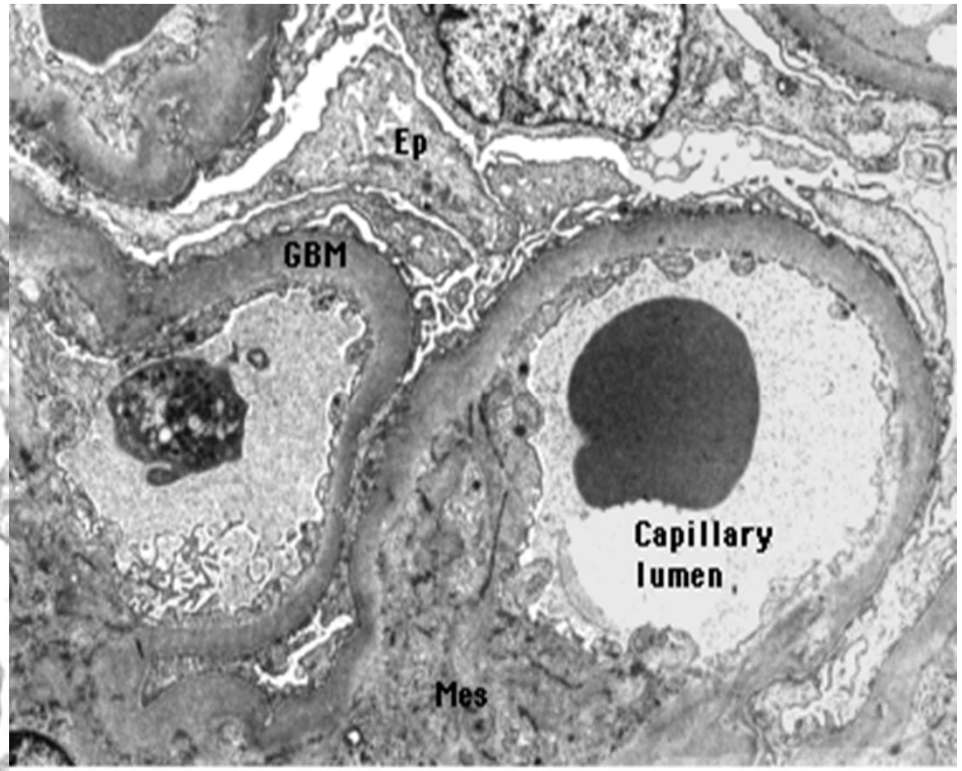
* Hyalinosis: insudative lesions as consisting of intramural accumulations of presumably imbibed plasma proteins and lipids within renal arterioles, glomerular capillaries, Bowman's capsule, or proximal convoluted tubules.

J Am Soc Nephrol 21: 556–563, 2010

Pathologic finding of diabetic nephropathy

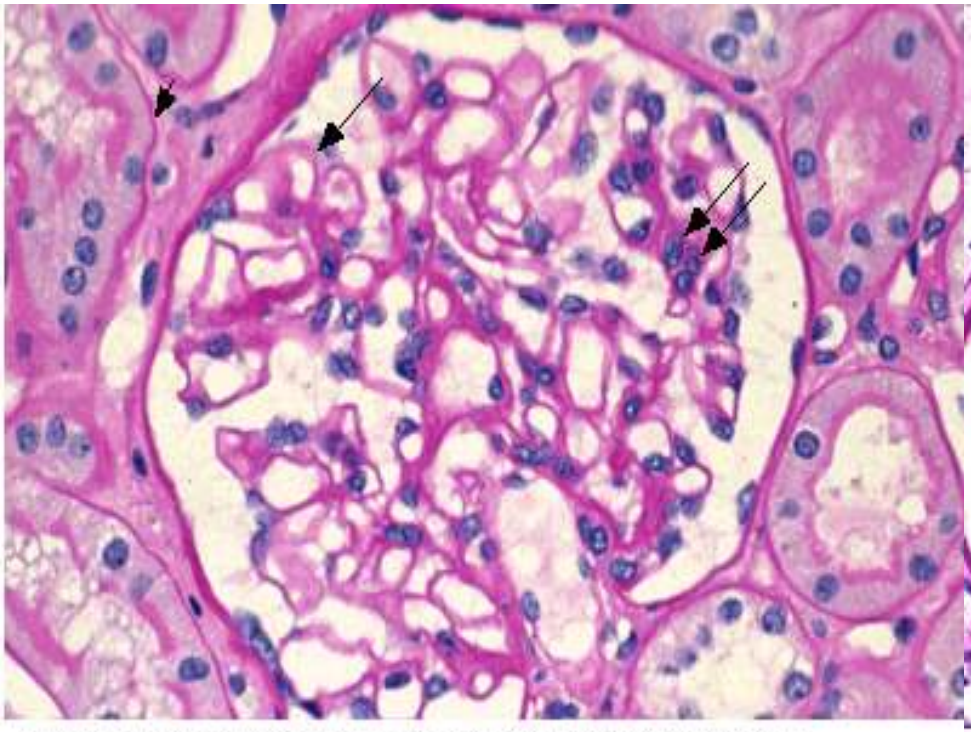


Normal glomerulus Electron micrograph of a normal glomerular capillar loop showing the fenestrated endothelial cell (Endo), the glomerular basement membrane (GBM), and the epithelial cells with its interdigitating foot processes (arrow). The GBM is thin and no electron dense deposits are present. Two normal platelets are seen in the capillary lumen. Courtesy of Helmut Rennke, MD.

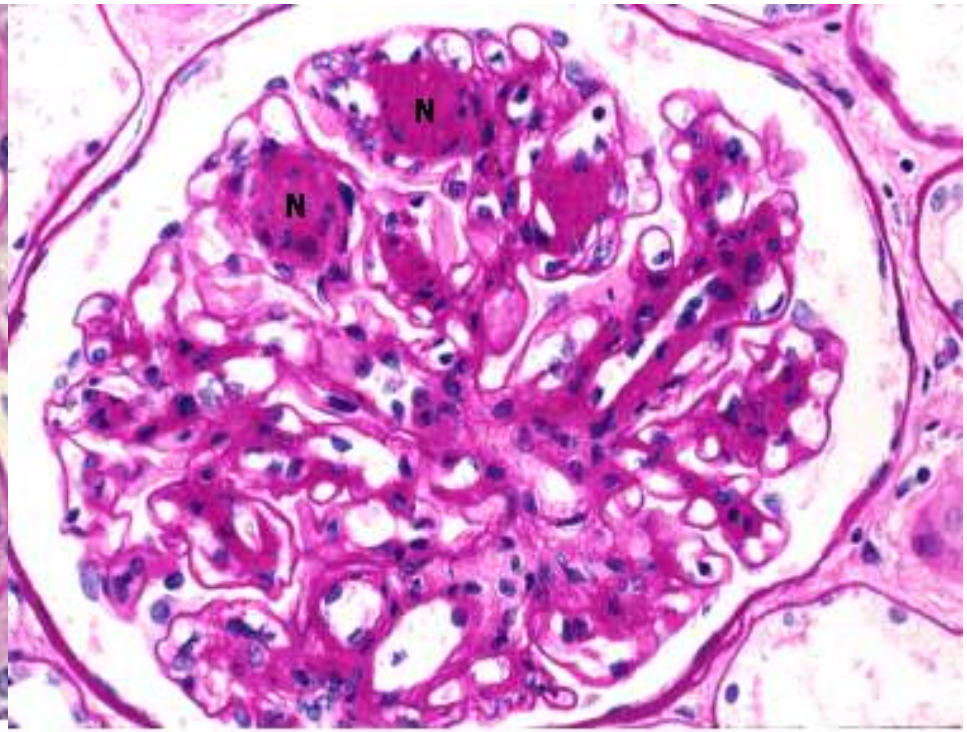


Basement membrane thickening in diabetic nephropathy Electron micrograph in diabetic nephropathy shows a 2 to 3 fold increase in the thickness of the glomerular basement membrane (GBM). Mes = mesangium; Ep = epithelial cell. Although not seen, the mesangium is also expanded by basement membrane-like material, a process that contributes to nodule formation and glomerulosclerosis. Courtesy of Helmut Rennke, MD.

Pathologic finding of diabetic nephropathy



Normal glomerulus Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows). Courtesy of Helmut G Rennke.



Diabetic nephropathy Light micrograph showing diffuse and nodular (N) glomerulosclerosis in diabetic nephropathy. Note the dense appearance of the deposits and the rim of cells around the nodules, which distinguish this disorder on light microscopy from fibrillary glomerulonephritis or amyloidosis. Courtesy of Helmut Rennke, MD.

Heterogenous renal biopsy findings in type 2 DM

Type 1 DM: Classical glomerular changes

Type 2 DM: Heterogenous

※ Study by Fioretto et al.

Subjects: Type 2 DM + Microalbuminuria + normal GFR

→ Renal biopsy showed heterogenous changes

C1: Normal renal structure (29.4%)

C2: Typical DN, predominantly glomerular changes (29.4)

C3: Severe interstitial, vascular damage, minimal glomerular change (41.2%)

Diabetologia 1996; 39: 1569-1576

Diabetes care, July 8, 2013

Renal Structure in Normoalbuminuric and Albuminuric Patients With Type 2 Diabetes and Impaired Renal Function

Ekinci El, Jerums G, Skene A, Crammer P, Power D, Cheong KY, Panagiotopoulos S, McNeil K, Baker ST, Fioretto P, Macisaac RJ.

Endocrine Centre, Austin Health, Melborune, Victoria, **Australia**

Subjects

Patients attending the Diabetes clinic of Austin Health

January 2005 ~ December 2010 :

= GFR <60 & various albuminuric status =

Biopsy type	Research	Research	Clinical
GFR (mL/min/1.73 m^2)	<60	<60	<60
AER category	Normo	Micro	Macro
Pre biopsy (*n*)	10	4	17
At biopsy (*n*)	8	2 + 4	17

Diabetes care, July 8, 2013

Renal structure patterns in patients with type 2 DM

Albuminuria category	Normo	Micro	Macro
Fioretto et al. (11)	**Previous study in type 2 DM, preserved GFR -Typical glomerular changes of DN was less common (10/34)**		
GFR >60 mL/min/1.73 m^2 (mean GFR 101 ± 27 mL/min/1.73 m^2)			
Number of subjects per category	*n* = 34 C1: 10 C2: 10 C3: 14		
Current study			
GFR <60 mL/min/1.73 m^2	*n* = 8	*n* = 6	*n* = 17
Mean MDRD eGFR (mL/min/1.73 m^2)	41 ± 3.0	48 ± 4	31 ± 3
Number of subjects per category	C1: 2 C2: 3 C3: 3	C1: 0 C2: 5 C3: 1	C1: 0 C2: 17 C3: 0

C1, defined by normal or near-normal histology; C2, defined by histology reflecting typical DN with predominantly glomerular changes; C3, defined by atypical histology, with disproportionately severe interstitial, tubular, or vascular damage and few or no glomerular changes; MDRD, Modification of Diet in Renal Disease.

C1 : Normal of near-normal
C2 : Typical DN
C3 : Atypical patterns of renal injury

Diabetes care, July 8, 2013

Biopsy findings in participants with normoalbuminuria

	Category	Mesangial expansion	Arterial Hyalinosis	Summary
1	C1	0	0	Not DN, mild IgA nephropathy, no cause for renal impairment found
2	C1	0	1	Mild nonspecific changes, not DN
3	C2	3	3	Typical advanced DN
4	C2	1	1	Typical early DN
5	C2	1	1	Typical early DN
6	C3	0	2	Renovascular, not DN
7	C3	0	0	Renovascular, not DN
8	C3	1	1	Atypical DN, mild glomerular changes + Severe vascular and tubulointerstitial disease

Diabetes care, July 8, 2013

Patients with type 2 DM, renal insufficiency :

1) Micro- or macroalbuminuric DMCKD

→ Nearly all (22/23) typical glomerular changes of DN

2) Normoalbuminuric DMCKD

→ 3/8 : interstitial or vascular changes

3/8 : typical changes of DN

7/8 : arteriosclerosis

3) Normoalbuminuric DMCKD

→ multifactorial pathogenesis

such as age, HTN, arteriosclerosis

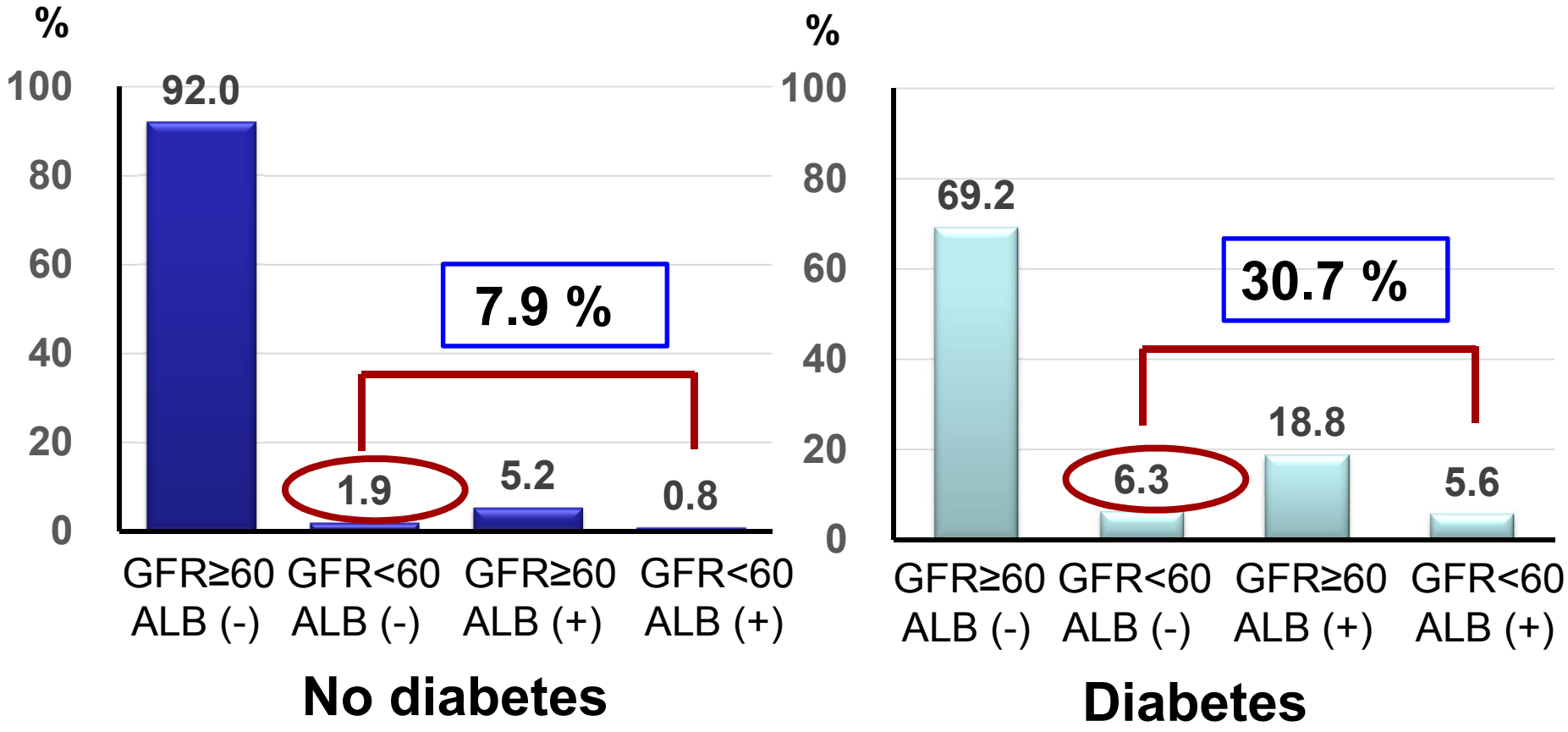
Nonalbuminuric Renal Insufficiency in Type 2 Diabetes

	Normo-albuminuria	Micro-albuminuria	Macro-albuminuria	*P*
n	43	38	28	
AER (μg/min)	9.3 ×/÷ 1.1	61 ×/÷ 1.2	671 ×/÷ 1.2	<0.0001
Age (years)	73 ± 1	72 ± 2	67 ± 2	<0.01
Females (%)	56	45	18	<0.01
Duration of diabetes (years)	14 ± 1	16 ± 1	15 ± 2	0.64
BMI (kg/m^2)	30.8 ± 1.0	29.3 ± 0.7	31.6 ± 1.4	0.26
Retinopathy (%)	26	50	41	0.11
HbA_{1c} (%)	7.3 ± 0.3	7.9 ± 0.2	7.9 ± 0.3	0.23
SBP (mmHg)	138 ± 3	147 ± 3	147 ± 3	0.02*
DBP (mmHg)	75 ± 2	78 ± 1	77 ± 1	0.37
GFR ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)	47 ± 2	47 ± 2	39 ± 2	0.01

Diabetes Care 27:195–200, 2004

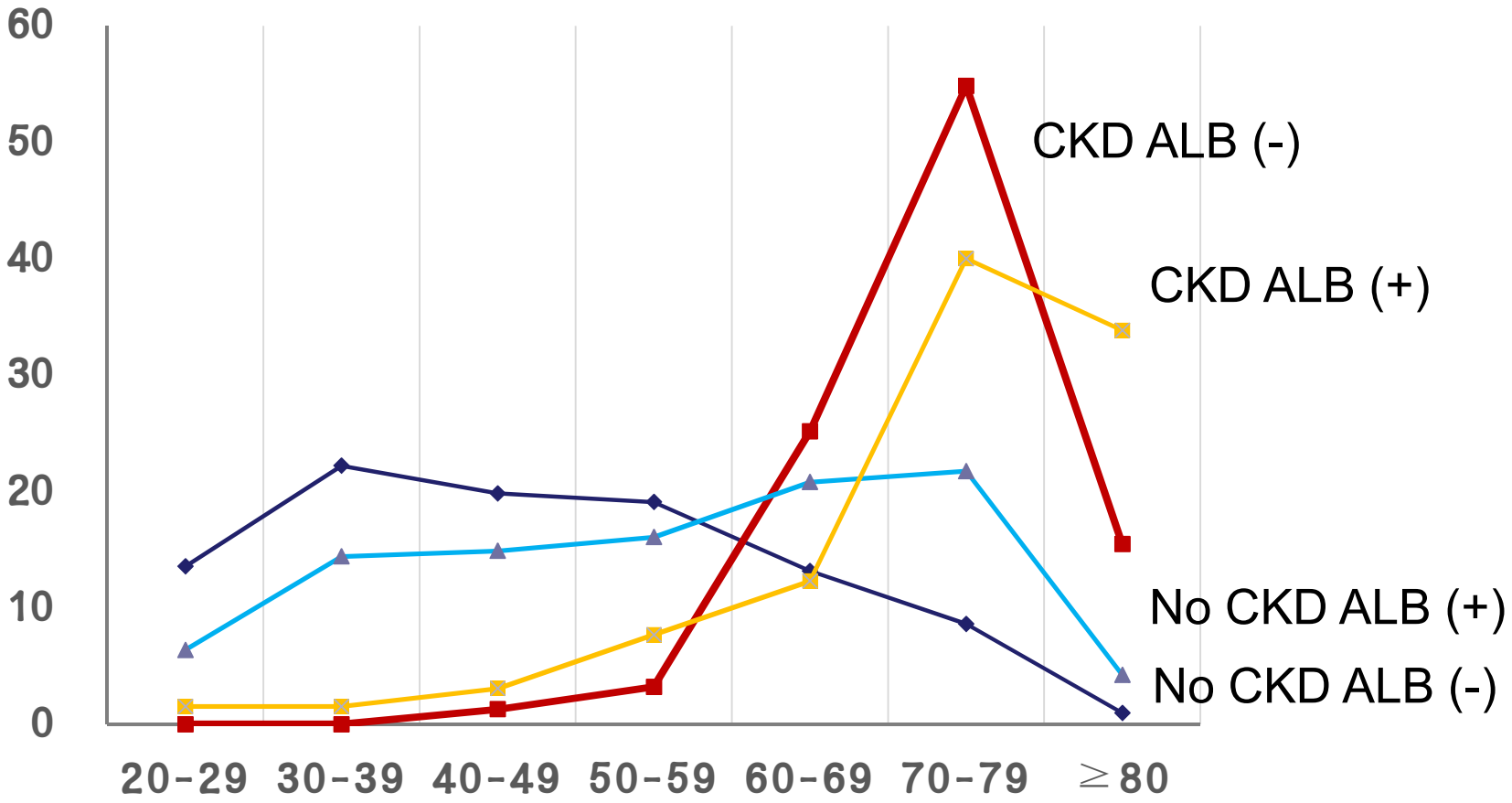
Prevalence of diabetic kidney disease in Korea

KNHANES 2011-2013
Total 15,482 patients aged≥19 years
Albuminuria: UACR≥30 mg/g · Cr



Age distribution according to presence of CKD and albuminuria in DM patients

KNHANES 2011-2013, 1692 DM patients aged≥19 years



Clinical characteristics according to presence of CKD and albuminuria in DM patients

KNHANES 2011-2013, 1692 DM patients aged≥19 years

	No CKD ALB (-) (N=1128)	**CKD ALB(-)** (N=102)	No CKD ALB (+) (N=307)	CKD ALB(+) (N=92)
Age (years)	60.7±11.6*	71.5±7.0	62.2±11.5*	69.6±9.9
Male (%)	558 (49.5)	56 (54.9)	170 (55.4)	46 (50.0)
DM duration (years)	8.0±7.6*	11.2±10.1	10.0±7.7	14.2±9.5*
DM retinopathy (%)*	106 (14.0)	11 (16.7)	57 (25.7)	20 (32.8)
SBP (mmHg)	125±16	124±16	134±18*	131±33*
DBP (mmHg)	76±10*	69±10	78±12*	70±13
HTN (%)*	633 (56.3)	80 (78.4)	218 (71.0)	70 (78.7)
BMI (kg/m^2)	25.1±3.5	24.8±3.3	25.5±4.1	25.0±4.1

* $P<0.05$, vs. CKD ALB (-) group

Clinical characteristics according to presence of CKD and albuminuria in DM patients

KNHANES 2011-2013, 1692 DM patients aged≥19 years

	No CKD ALB (-) (N=1128)	**CKD ALB(-)** (N=102)	No CKD ALB (+) (N=307)	CKD ALB(+) (N=92)
Cholesterol (mg/dl)	186±42*	172±38	191±42*	176±39
TG (mg/dl)	169±137	171±117	198±187**	166±114
HDL (mg/dl)	47.5±11.5*	42.7±11.2	47.6±11.7*	44.0±12.0
Glucose (mg/dl)	139±40*	124±35	149±42*	137±52
Hb (g/dl)	14.2±1.5*	13.4±1.6	14.3±1.7*	12.8±2.1
HbA1c (%)	7.3±1.4	7.1±1.3	7.7±1.5*	7.8±1.6*
ALT (IU/L)	26.8±18.8*	21.5±14.8	29.1±23.8*	20.4±10.3
AST (IU/L)	25.6±22.1	24.4±10.6	27.6±17.2	23.5±9.3

* $P<0.05$, vs. CKD ALB (-) group

Korean patients with type 2 DM, normoalbuminuric renal insufficiency :

1) 6.3% among all DM patients,
   53.4% among DM patients with renal insufficiency

2) Nearly all (94.1%) patients: older than 60 years of age.

3) Low prevalence of DM retinopathy

4) High prevalence of HTN but low BP

5) Better glycemic control, cholesterol

→ **multifactorial pathogenesis such as age, HTN**
than obesity, dyslipidemia, poor glycemic control

All type II DM with albuminuria would have DMN ?

DIABETES RESEARCH AND CLINICAL PRACTICE 97 (2012) 418–424

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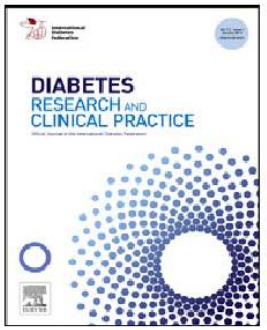
Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres



Clinical implications of pathologic diagnosis and classification for diabetic nephropathy

Se Won Oh [a], *Sejoong Kim* [b], *Ki Young Na* [b,c], *Dong-Wan Chae* [b,c], *Suhnggwon Kim* [c,d], *Dong Chan Jin* [e], *Ho Jun Chin* [b,c,d,*]

Inclusion criteria of renal biopsy

- proteinuria more than 1 g/day,
- renal involvement without retinopathy,
- renal involvement within 5 years,
- unexplained hematuria or azotemia.

126 DM with proteinuria ≥ 1g/day

Table 1 – Clinical characteristics of the diabetes patients.

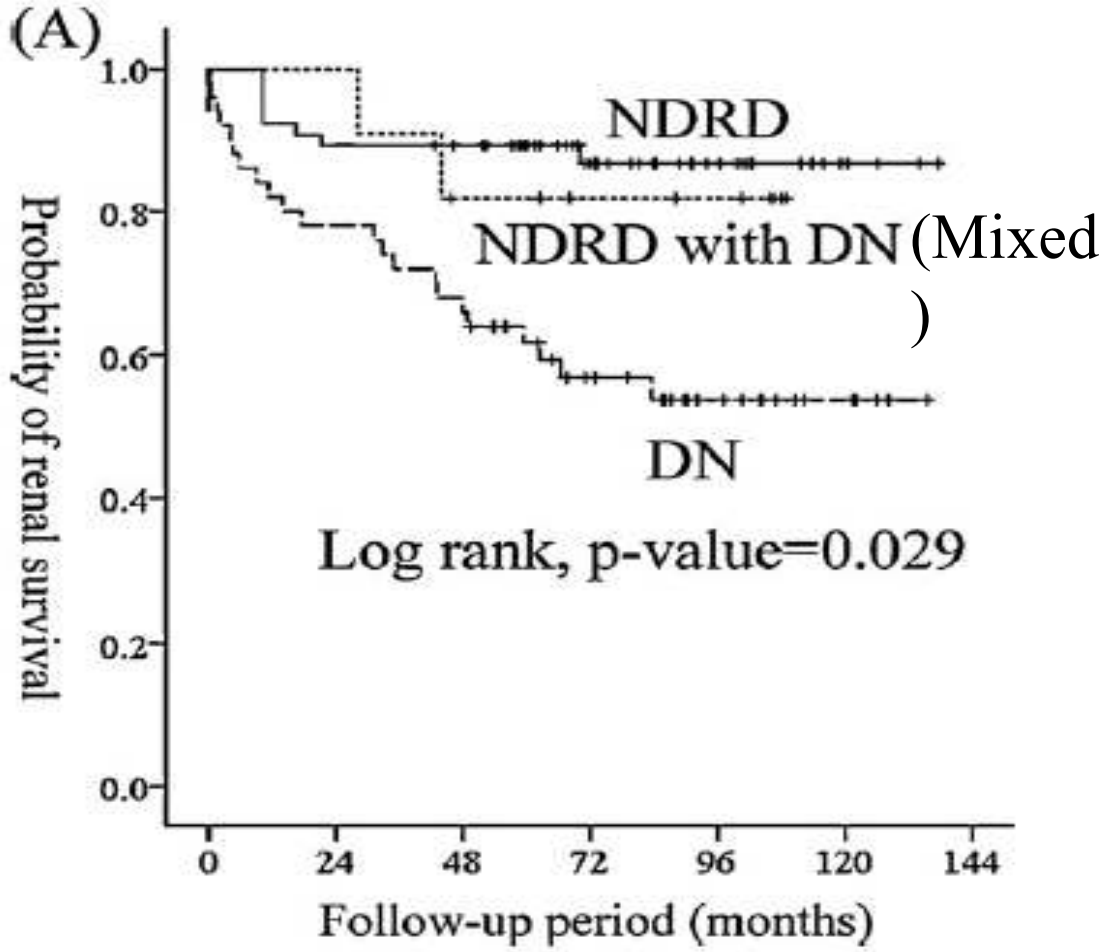
	Data* (%)	NDRD* (n = 65)	DN* (n = 50)	Mixed* (n = 11)	p-value
Age (years)	100.0	61.9 ± 11.4	58.0 ± 10.1	57.0 ± 8.8	0.102
Male (%)	100.0	66.2	72.0	63.6	0.754
Duration of DM (years)	100.0	6.2 ± 6.4[1]	11.1 ± 7.3[2]	7.7 ± 7.3[1,2]	0.001
HbA1c (%)	96.8	6.99 ± 1.54	7.16 ± 1.37	7.44 ± 1.33	0.616
Glucose (mg/dL)	93.0	160 ± 75	156 ± 58	168 ± 63	0.863
Creatinine (mg/dL)	99.2	2.28 ± 1.86	2.72 ± 2.00	1.46 ± 0.69	0.104
eGFR (ml/min/1.73 m²)*	99.2	49.8 ± 31.3[1,2]	37.5 ± 25.3[1]	55.4 ± 18.0[2]	0.034
UPCR (g/g Cr)*	95.3	5.4 ± 5.8	6.1 ± 5.9	5.9 ± 4.5	0.823
Hematuria (%)*	97.6	74.2	78	81.8	0.812
Proteinuria ≥2+ (%)*	98.4	69.8	82	81.8	0.289
Kidney length (cm)*	92.9	11.0 ± 1.0[1]	10.7 ± 1.0[1]	11.7 ± 1.5[2]	0.034
Diabetic retinopathy (%)	100.0				<0.001
None		81.5	15.3	72.7	
NPDR*		13.8	34.0	9.1	
PDR*		4.6	44.0	18.2	

Table 2 – Clinical findings at renal biopsy related to the presence of DN.

	B	Wald	OR	95% C.I. for OR		p-value
Age (years)	−0.054	5.020	0.947	0.904	0.993	0.025
Duration of DM (years)	0.137	11.345	1.146	1.059	1.241	0.001
Retinopathy (compared to absence)		15.192				0.001
NPDR	1.602	8.661	4.965	1.708	14.435	0.003
PDR	2.269	9.646	9.668	2.310	40.472	0.002

Diab Res Clin Pract (2012) 97: 418-424

Renal survival in patients with and without DN



Diab Res Clin Pract (2012) 97: 418-424

Prevalence of complicating renal disease in NIDDM

Table 3. Reports in the literature of complicating renal disease in NIDDM

	Amoah et al. [12] 1988	Suzuki et al. [13] 1991	Richards et al. [11] 1992	Parving et al. [14] 1992	Klein-knecht et al. [15] 1992	Gambara et al. [16] 1992	John et al. [17] 1994	Olsen and Mogensen 1995	Pinel et al. [19] 1995	Fioretto et al. [18] 1996
n	60	128	46	35	35	52	80	33	30	34
Nodular glomerulopathy	47	25	24	8				20	4	24[c]
Diffuse diabetic glomerulopathy		83		20				13	21	
No diabetic glomerulopathy	13	20	22	7					5	10
Glomerulonephritis	16 (27%)	20 (16%)	8 (17%)	8 (20%)	11 (31%)	16 (31%)	53 (66%)	3 (9%)[b]	0	0
Other renal complications	1 (2%)	0	9 (20%)	0	3 (9%)	1 (2%)[a]	10 (12%)	1 (3%)	0[a]	0[c]

Complicating renal disease in NIDDM
: 27–79% in studies with selected inclusion criteria.

However, a randomized controlled study indicated a prevalence of only 15% and a study with protocol biopsy presented 23%.

Diabetologia (1996) 39: 1638–1645

Proteinuria with DM patients
Had non-typical features of DMN
Selected biopsy, Hospital setting :

1) 48% : DMN, 52% : non diabetic renal disease (NDRD)

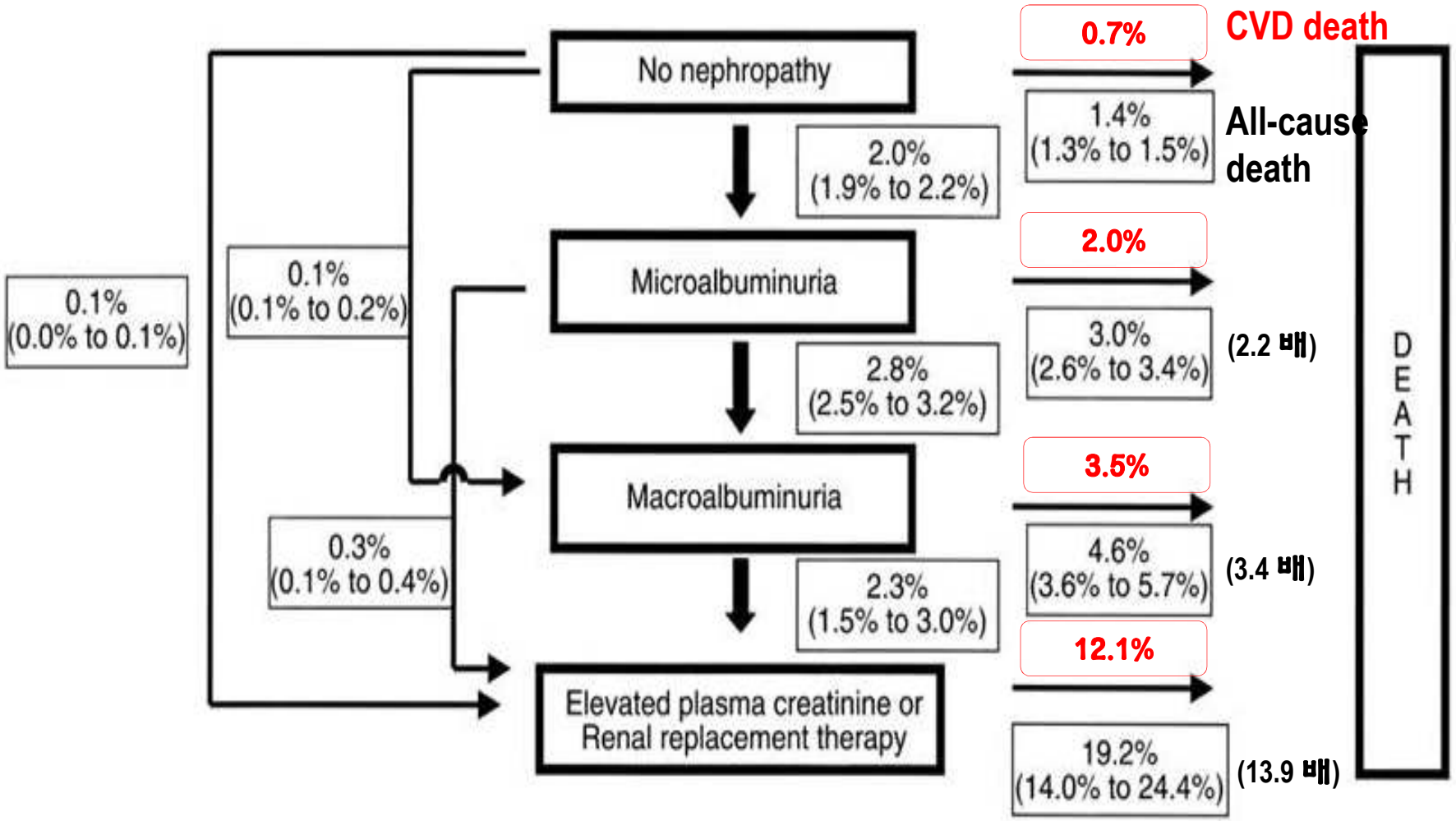
2) NDRD had shorter diabetic duration
and lower prevalence of DM retinopathy

3) NDRD had better renal survival in DM patients

4) Prevalence of complicating renal disease in NIDDM
: heterogenous according to the biopsy criteria

Prognosis of DM patients:

normoalbuminuria, albuminuria, and renal insufficency?



Annual transition rate through the stages of nephropathy and to death in type 2 DM. -KI 2003;225-232, UKPDS 64-

KDIGO Controversy conference

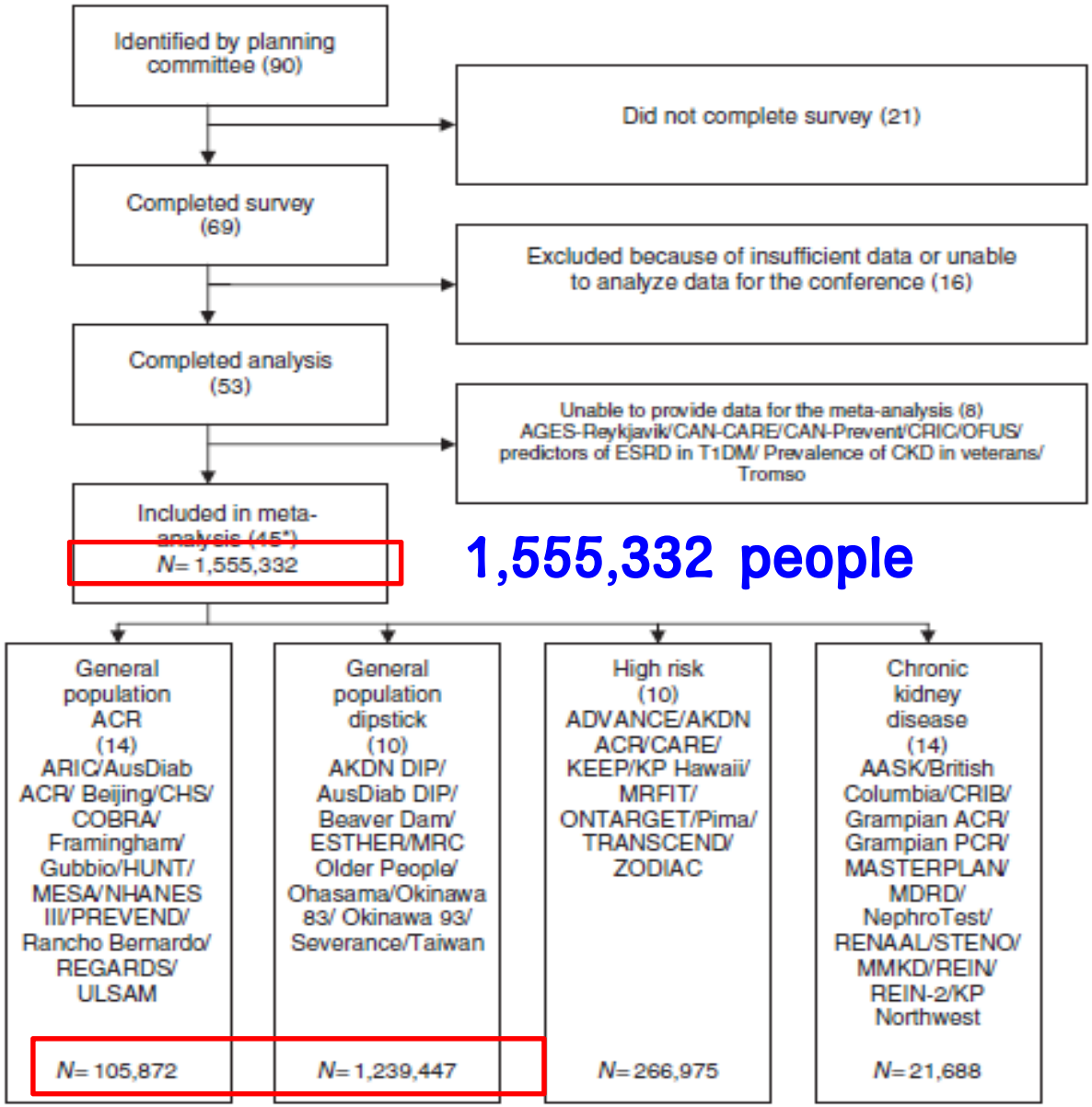
The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report

Andrew S. Levey[1], Paul E. de Jong[2], Josef Coresh[3], Meguid El Nahas[4], Brad C. Astor[3], Kunihiro Matsushita[3], Ron T. Gansevoort[2], Bertram L. Kasiske[5] and Kai-Uwe Eckardt[6]

[1]Division of Nephrology, Department of Medicine, Tufts Medical Center, Boston, Massachusetts, USA; [2]Department of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [3]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; [4]Sheffield Kidney Institute, University of Sheffield, Sheffield, UK; [5]Hennepin County Medical Center, Minneapolis, Minnesota, USA and [6]Department of Nephrology and Hypertension, University of Erlangen-Nuremberg, Erlangen, Germany

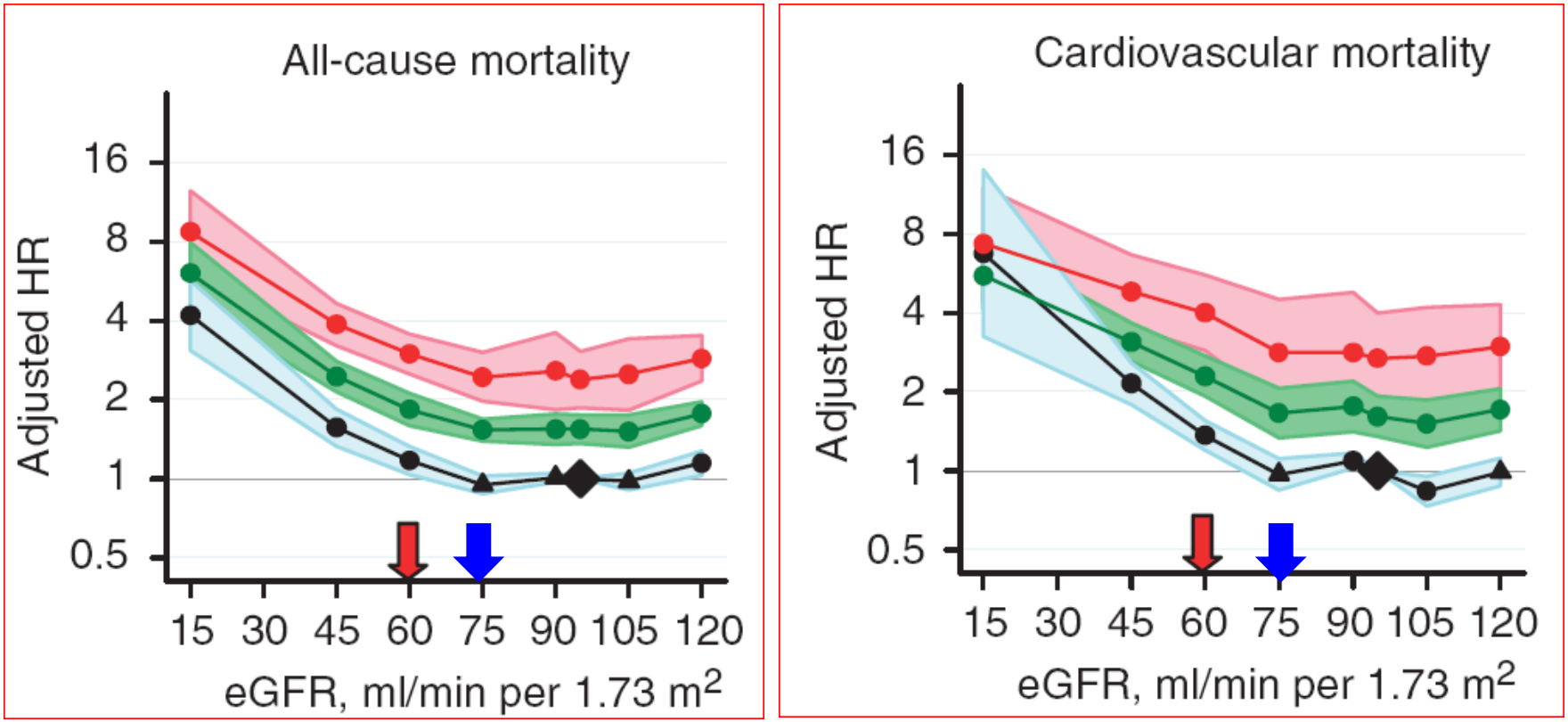
Kidney International (2011) **80**, 17–28

KDIGO Controversy conference



KDIGO Controversy conference

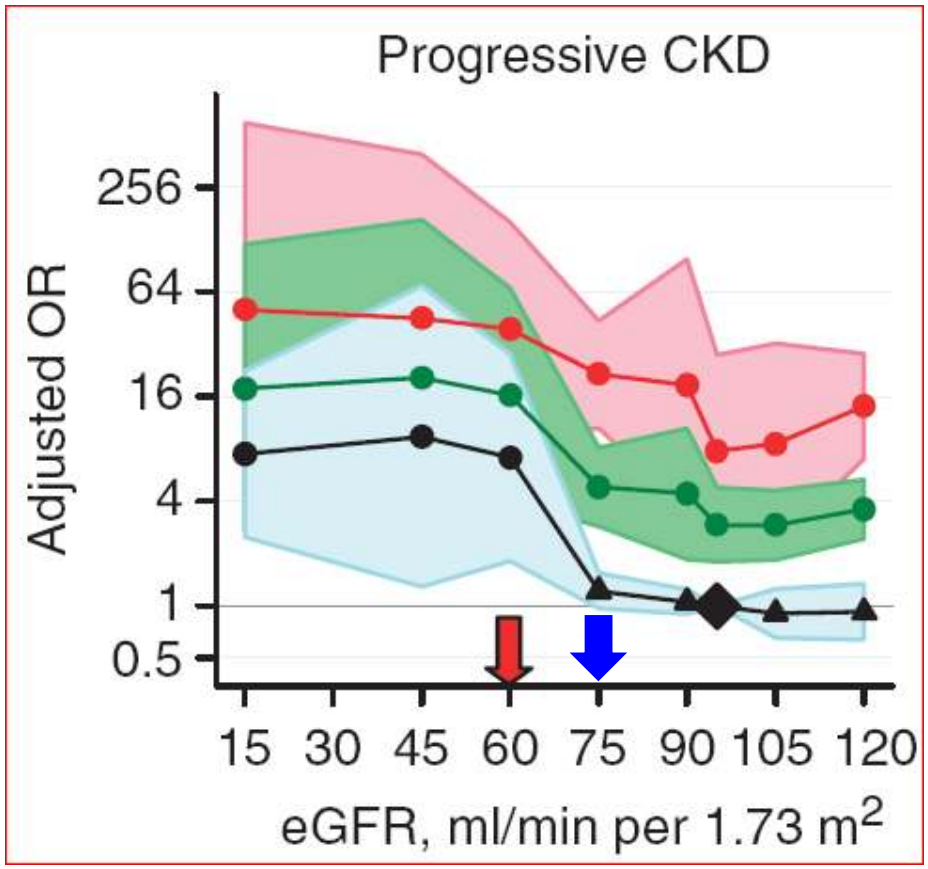
Blue: urine ACR of <30 mg/g
Green: urine ACR 30–299 mg/g
Red: urine ACR ≥300 mg/g

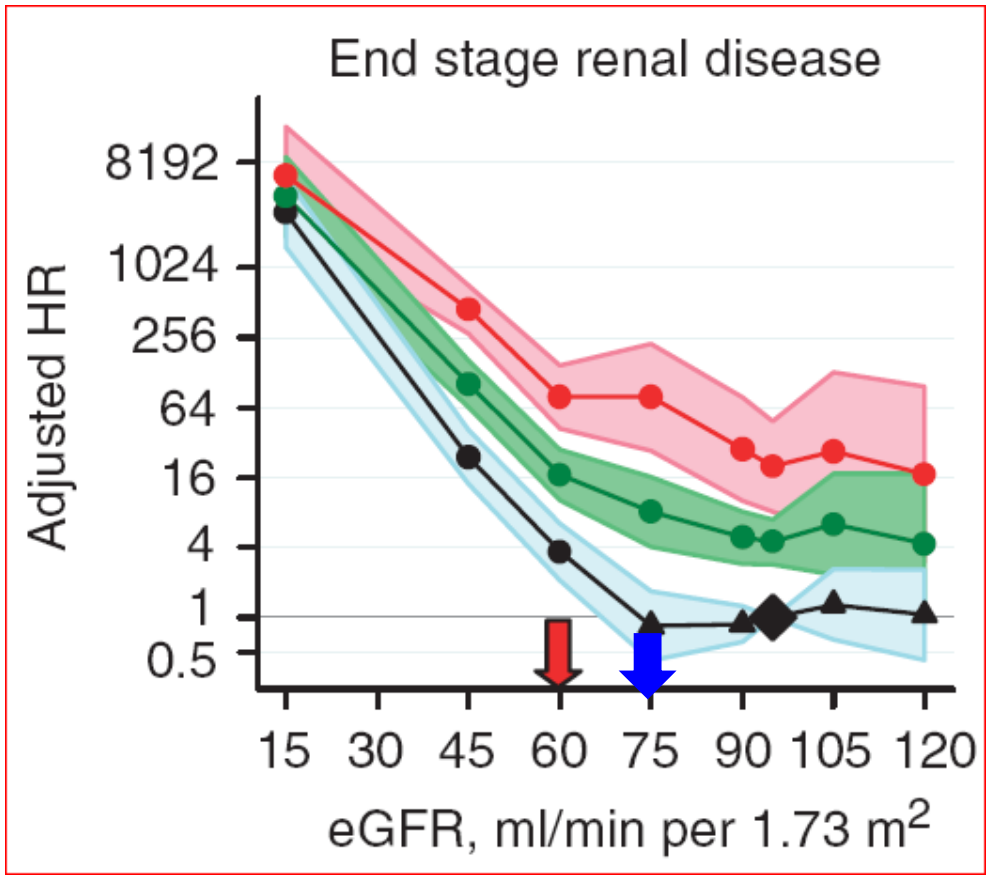


Summary of continuous meta-analysis (adjusted relative risk (RR)) for general population cohorts with albumin-tocreatinine ratio (ACR).

KDIGO Controversy conference

Blue: urine ACR of <30 mg/g or dipstick negative and trace
Green: urine ACR 30–299 mg/g or dipstick 1 positive
Red: urine ACR ≥300 mg/g or dipstick ≥2 positive





Summary of continuous meta-analysis (adjusted relative risk (RR)) for general population cohorts with albumin-tocreatinine ratio (ACR) or urinalysis.

Mild decrease in estimated glomerular filtration rate and proteinuria are associated with all-cause and cardiovascular mortality in the general population

Se Won Oh[1], Seon Ha Baek[2], Yong Chul Kim[2], Ho Suk Goo[3], Nam Ju Heo[2,4], Ki Young Na[1,2], Dong Wan Chae[1,2], Suhnggwon Kim[2,5] and Ho Jun Chin[1,2,5]

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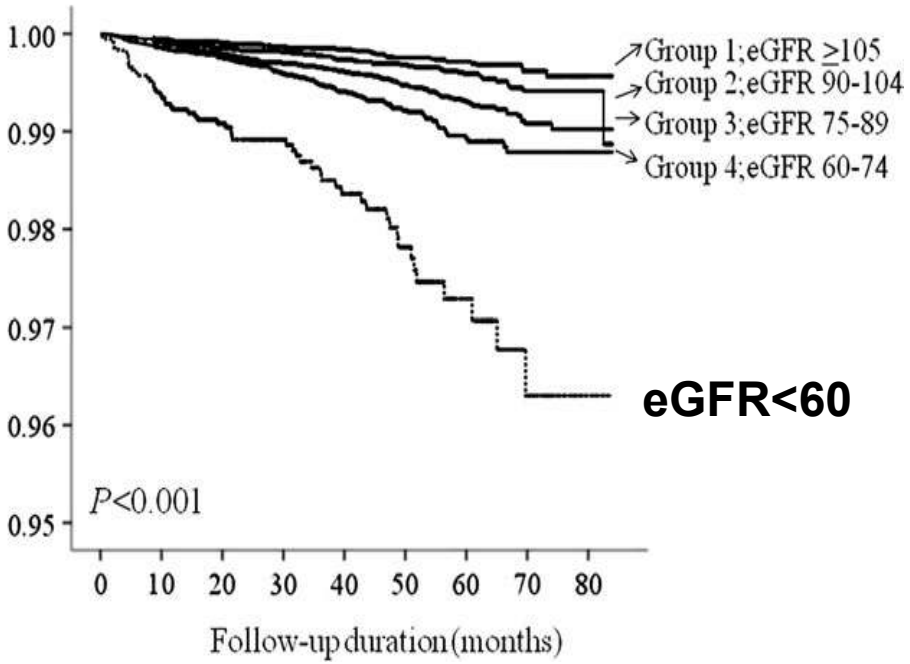
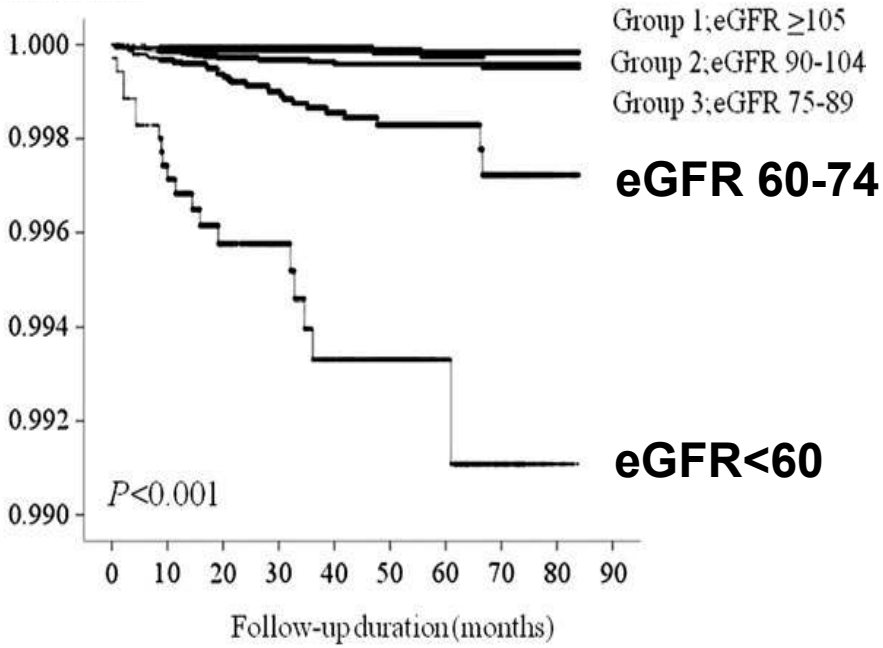
건강검진: 112,115**명** (2003.1~2009.2)
사망까지 평균 추적기간: 40 **개월**

Mortality and cardiovascular mortality according to eGFR

Survival



CVD death free survival



Oh SW, Chin HJ et al. Nephrol Dial Transplant (2012)

Adjusted risk of mortality and CV mortality

Table 3. Adjusted HR (95% CI) for ACM[b] and CVM[c] according to eGFR and dipstick urine analysis for proteinuria[a]

	Negative	Trace or more	All
ACM			
≥105 mL/min/1.73m^2	0.99 (0.63–1.56)	0.99 (0.46–2.13)	0.89 (0.60–1.32)
90–104 mL/min/1.73m^2	Reference	1.57 (0.93–2.66)	Reference
75–89 mL/min/1.73m^2	1.33 (0.94–1.86)	2.10 (1.41–3.12)	1.33 (1.00–1.77)
60–74 mL/min/1.73m^2	1.60 (1.12–2.30)	2.30 (1.50–3.53)	1.56 (1.15–2.12)
<60 mL/min/1.73m^2	3.54 (2.20–5.68)	3.77 (2.15–6.38)	3.02 (2.04–4.47)
All	Reference	1.46 (1.19–1.80)	
CVM			
≥105 mL/min/1.73m^2	0.89 (0.16–4.86)	NA	0.70 (0.14–3.66)
90–104 mL/min/1.73m^2	Reference	1.02 (0.11–9.18)	Reference
75–89 mL/min/1.73m^2	1.18 (0.36–3.83)	2.34 (0.62–8.76)	1.40 (0.50–3.91)
60–74 ml/min/1.73m^2	3.19 (1.05–9.67)	7.04 (2.20–22.57)	3.96 (1.50–10.46)
<60 mL/min/1.73m^2	10.87 (3.16–37.41)	14.60 (4.06–52.53)	10.91 (3.74–31.83)
All	Reference	1.72 (1.02–2.90)	

[a]NA, not applicable.
[b]HRs and 95% CIs of ACM adjusted for age, gender, SBP, DBP, BMI, DM, HTN, HBsAg, anti-HCV antibody, ALT, AST, fasting glucose, uric acid, total cholesterol and HDL cholesterol.
[c]HRs and 95% CIs of CVM adjusted for age, gender, SBP, DBP, BMI, DM, HTN, HBsAg, anti-HCV antibody, ALT, AST, fasting glucose, uric acid, total cholesterol, albumin and HDL cholesterol.

Oh SW, Chin HJ et al. Nephrol Dial Transplant (2012)

Kidney Disease and Increased Mortality Risk in Type 2 Diabetes

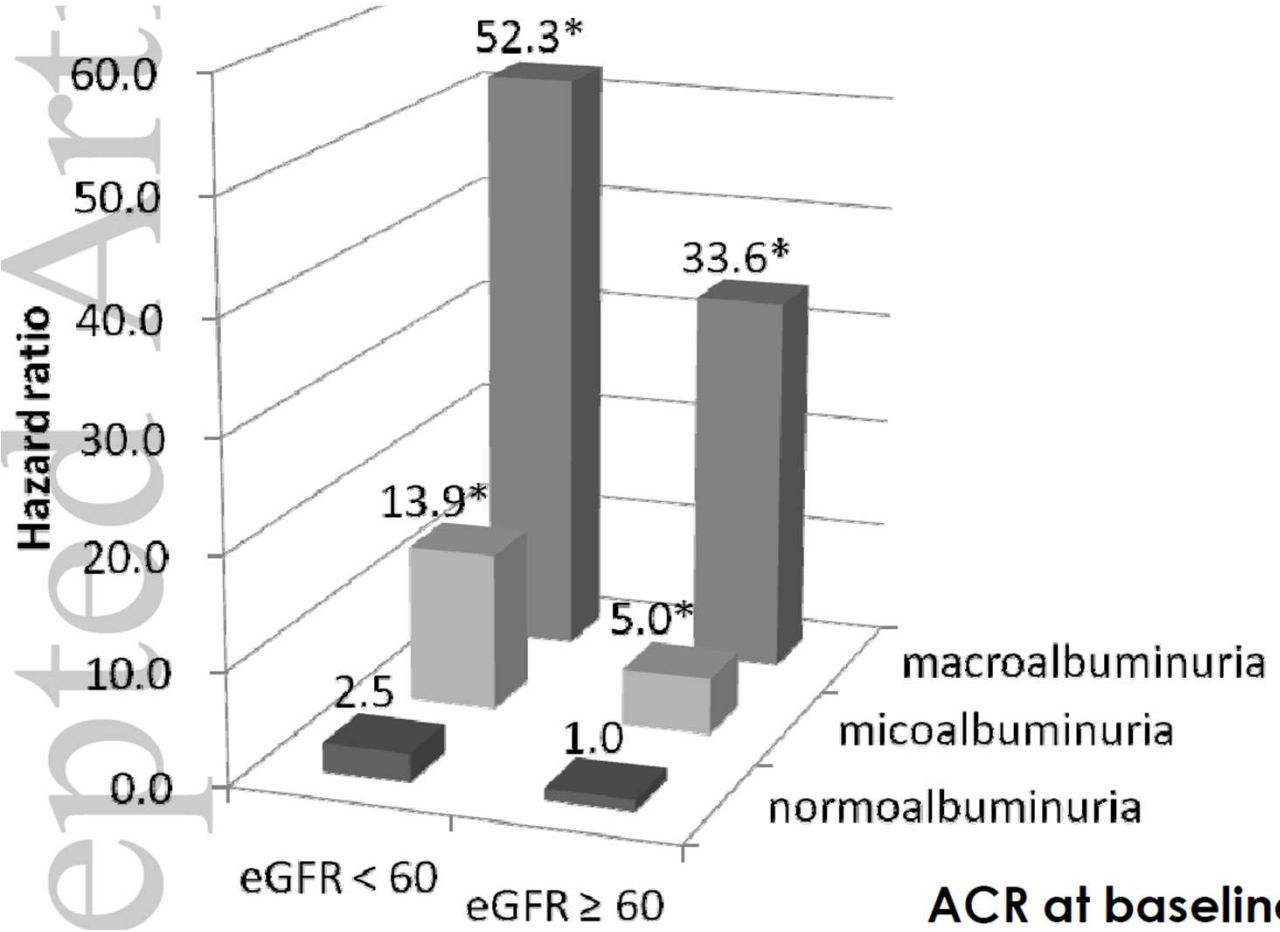
NHANES III, 10-year cumulative mortality for 15,046 participants

	Standardized Cumulative Incidence (%, 95% CI)
No Diabetes	
No Kidney Disease	7.6 (7.0 to 8.2)
Albuminuria	14.3 (11.8 to 16.8)
Impaired GFR	16.3 (11.5 to 21.1)
Albuminuria and Impaired GFR	40.9 (31.7 to 50.0)
Diabetes	
No Kidney Disease	11.7 (8.1 to 15.3)
Albuminuria	25.4 (19.2 to 31.5)
Impaired GFR	31.5 (19.0 to 43.9)
Albuminuria and Impaired GFR	54.6 (41.4 to 67.8)

J Am Soc Nephrol 2013;24(2):302-8

Renal outcome according to the albuminuria and renal insufficiency

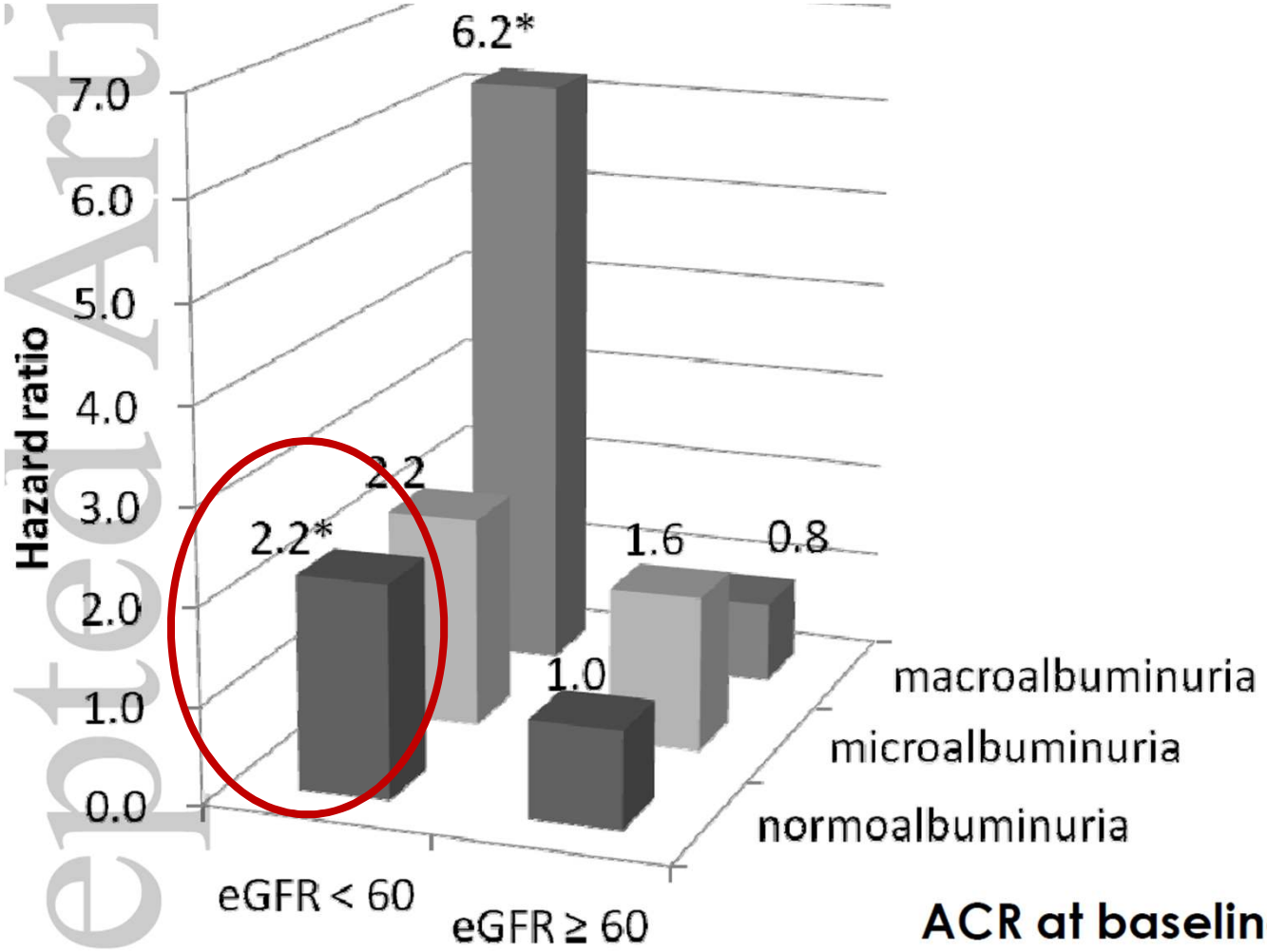
A total of 3,231 type 2 diabetic patients, 2003-2005
Renal outcome: RRT or 50% reduction of GFR



Nephrology (Carlton). 2015 Mar 16.

Mortality according to the albuminuria and renal insufficiency

A total of 3,231 type 2 diabetic patients, 2003-2005



Nephrology (Carlton). 2015 Mar 16.

Summary

1. 우리나라 성인의 11.3% 가 당뇨, 증가 추세
   - 30.7%에서 알부민뇨가 있거나 신기능저하
   - 6.3%에서 알부민뇨가 없이 신기능 저하

2. 알부민뇨가 없이 신기능 저하가 있는 당뇨병
   - 당뇨병성 신병증인 경우와 그렇지 않은 경우가 혼재
   - 고령, 고혈압 등이 관련된 multifactorial pathology

3. 단백뇨가 있는 당뇨병, 비전형적 특징을 가진 환자
   - 반 수에서 당뇨병성 신증
   - 비당뇨병성 신증일 가능성: 당뇨병성 망막증 없음,
     당뇨 유병기간이 짧음

4. 알부민뇨와 GFR: 사망, 말기신부전, 신기능감소 예측 인자
   - renal outcome: 알부민뇨 정도에 따라 결정
   - 사망: 정상 알부민뇨 신부전 환자 > 알부민뇨 정상 신기능