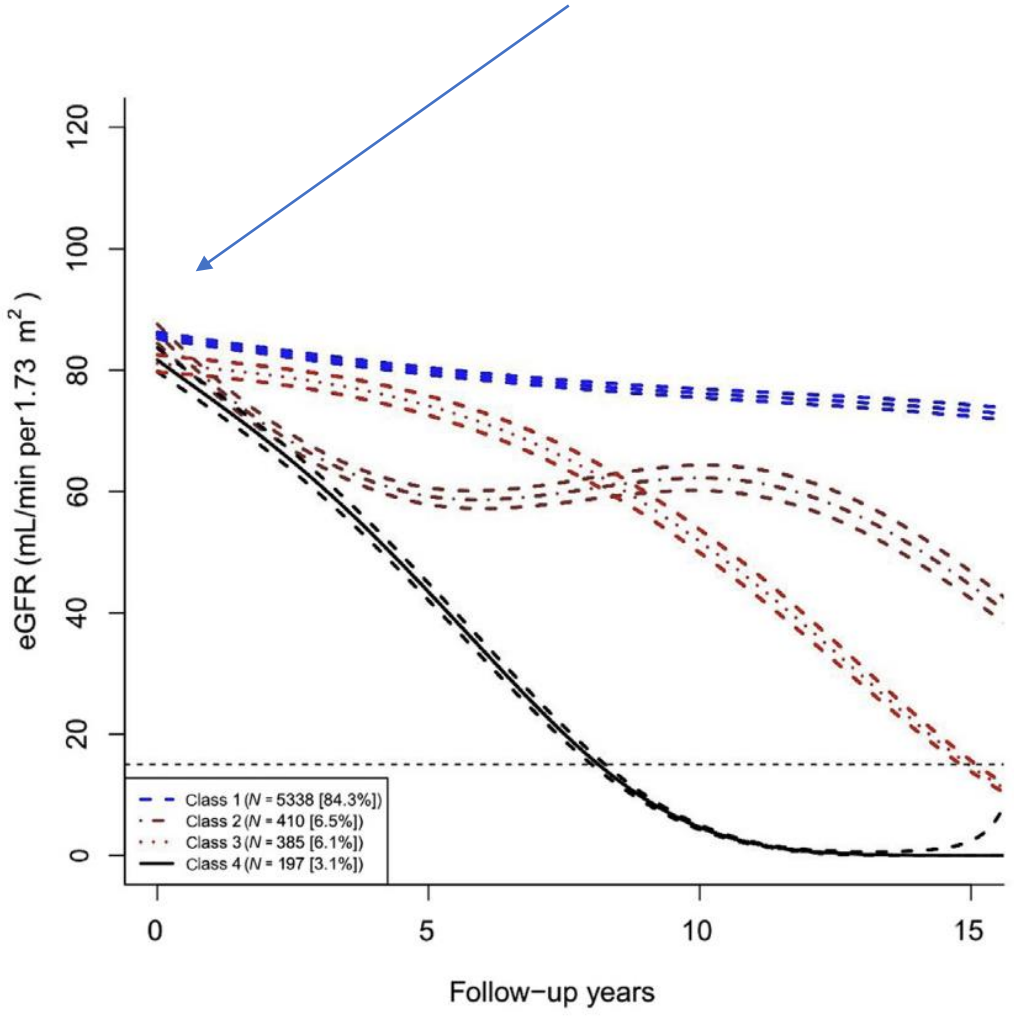
Les différentes formes cliniques et évolutives de la néphropathie diabétique que nous apprennent-elles ?

Pr Dominique JOLY

Paris

Peut on prédire qui est à risque de ND ?



84.3%

www.kidney-international.org clinical investigation

Progression of diabetic kidney disease and trajectory of kidney function decline in Chinese patients with Type 2 diabetes

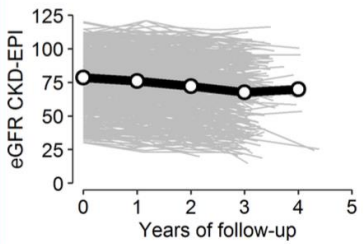
Guozhi Jiang[1,2,3,4], Andrea On Yan Luk[1,2,3,4], Claudia Ha Ting Tam[1,2,3,4], Fangying Xie[1], Bendix Carstensen[5], Eric Siu Him Lau[1,2], Cadmon King Poo Lim[1,2,3,4], Heung Man Lee[1,2,3,4], Alex Chi Wai Ng[1], Maggie Chor Yin Ng[6], Risa Ozaki[1,2], Alice Pik Shan Kong[1,2,3], Chun Chung Chow[1], Xilin Yang[7], Hui-yao Lan[1,3], Stephen Kwok Wing Tsui[8], Xiaodan Fan[9], Cheuk Chun Szeto[1], Wing Yee So[1,2,4], Juliana Chung Ngor Chan[1,2,3,4], and Ronald Ching Wan Ma[1,2,3,4]; for the Hong Kong Diabetes Register TRS Study Group[10]

Integrative analysis of prognostic biomarkers derived from multiomics panels helps discrimination of chronic kidney disease trajectories in people with type 2 diabetes

Study cohort

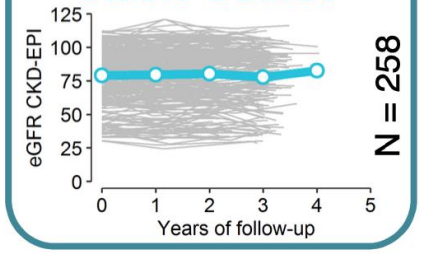
PROVALID

Prospective
Multinational
Type 2 diabetes
Maintained eGFR



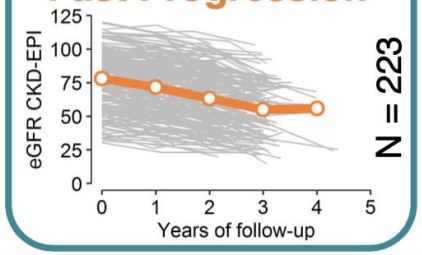
Course of Disease

Stable Course



N = 258

Fast Progression



N = 223

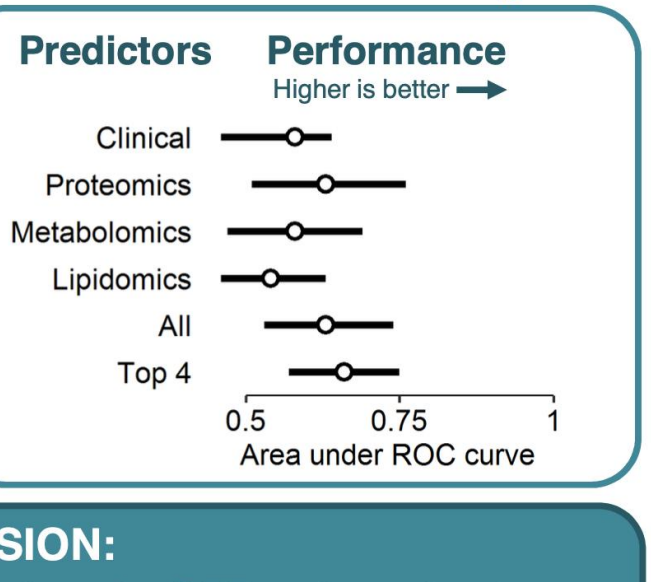
Multiomics at Baseline

Proteomics
Preselected (N = 17)

Metabolomics
Untargeted (N = 180)

Lipidomics
Untargeted (N = 637)

Prognostic Bayesian Model



CONCLUSION:

Discrimination of eGFR trajectories in incident early diabetic kidney disease with maintained eGFR was modest.

kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

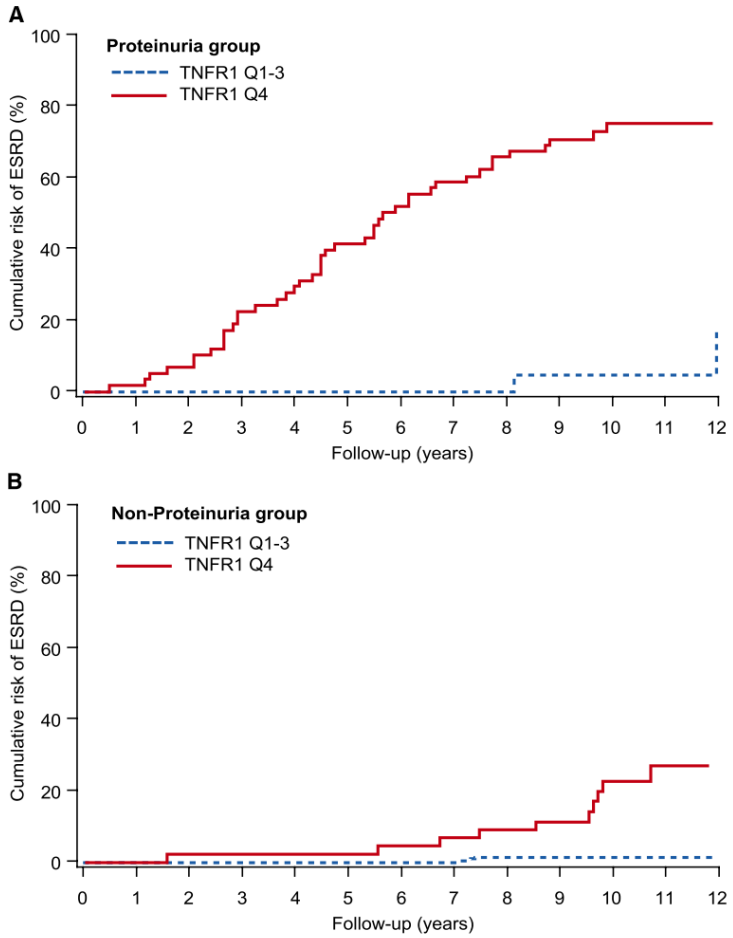
Kammer et al, 2019

- Joslin Diabetes Center, Boston
- 1990s : recruitement of 410 patients with type 2 diabetes
  - ✓ initial characteristics
  - ✓ plasma markers of systemic inflammation, endothelial dysfunction …
- 12 years of follow up : 84 deaths + 59 ESRD

Niewczas et al. JASN 2012

« Of the examined markers, TNF receptors 1 and 2 associated with risk for ESRD »

Cumulative incidence of ESRD



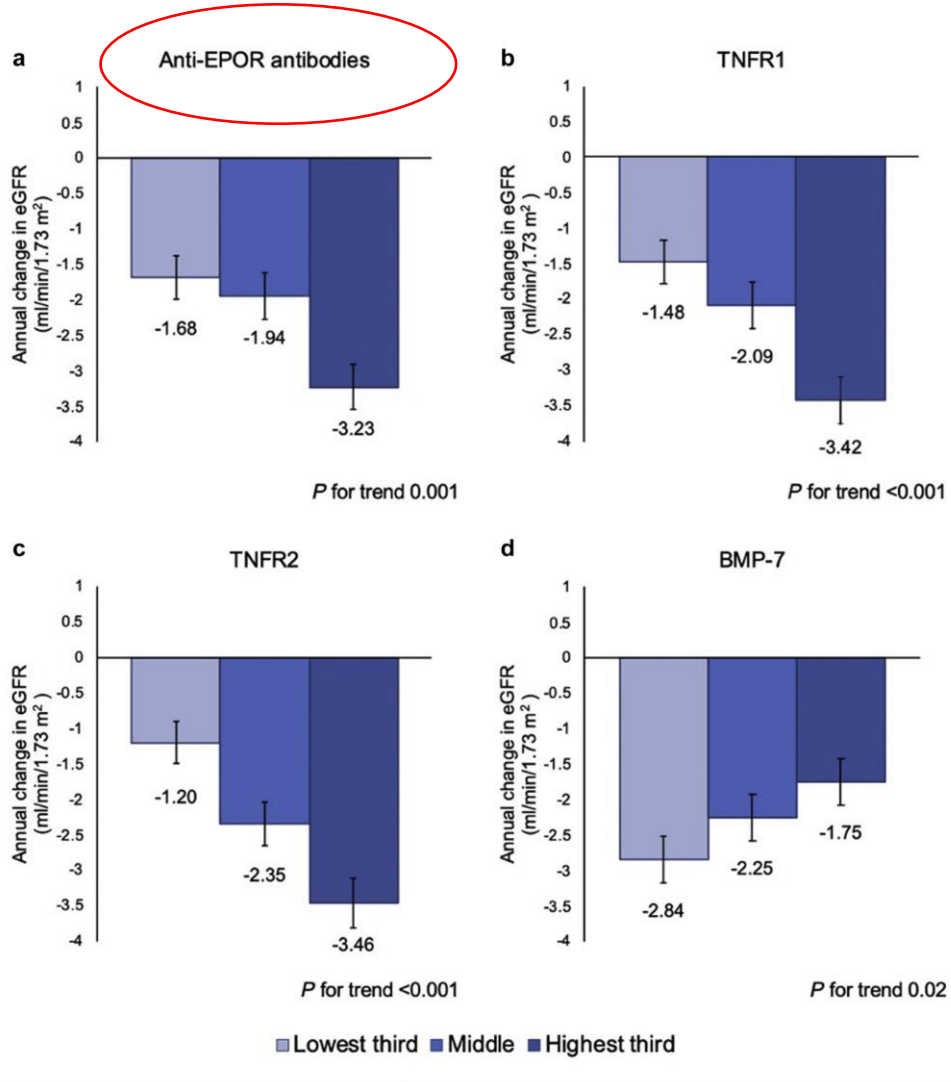
54% (highest TNFR1 quartile)

3% (other quartiles)

TNFR1 predicted risk for ESRD even better than urinary albumin excretion

	Nonproteinuria		Proteinuria	
	HR[a] (95% CI)	*P* Value	HR[a] (95% CI)	*P* Value
Clinical predictor[b]				
HbA1c	1.56 (0.86, 2.82)	0.14	1.24 (0.96, 1.61)	0.10
AER	2.23 (1.11, 4.48)	0.02	2.52 (1.14, 5.56)	0.02
eGFR	1.10 (0.72, 1.67)	0.67	1.37 (1.11, 1.69)	0.004
Individual marker[c]				
free TNFα	2.22 (1.20, 4.12)	0.01	1.21 (0.81, 1.81)	0.34
total TNFα	2.53 (1.25, 5.13)	0.01	2.61 (1.42, 4.81)	0.002
TNFR1	7.11 (2.13, 23.69)	0.0004	7.05 (2.23, 22.30)	0.0018
TNFR2	3.82 (1.59, 9.20)	0.0008	5.88 (2.10, 16.43)	0.0013

Niewczas et al. JASN 2012



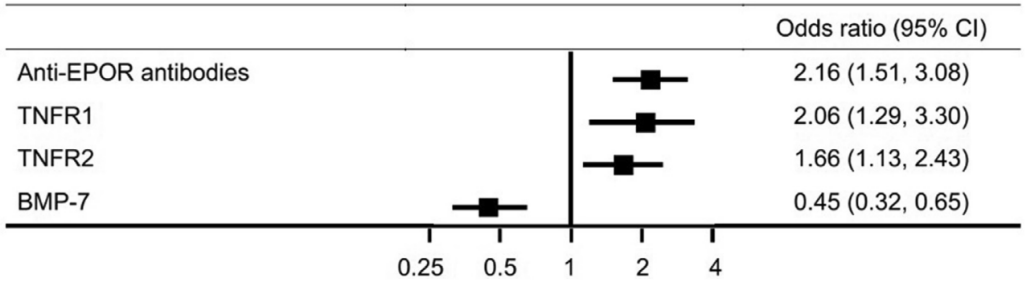


Table 3. Discrimination statistics for models including circulating biomarkers

Model	C-statistic (95% CI)		NRI (95% CI)	IDI (95% CI)	AIC	BIC
eGFR and UACR	0.673 (0.618, 0.728)				209.0	217.1
Base model	0.711 (0.659, 0.762)				200.7	261.7
Additional markers into base model						
+Anti-EPOR antibodies	0.746 (0.698, 0.795)[a]		+0.596 (0.400, 0.792)[a]	+0.105 (0.074, 0.136)[a]	180.7	245.8
+TNFR1	0.733 (0.684, 0.783)[a]	$P = 0.003$	+0.504 (0.308, 0.698)[a]	+0.073 (0.025, 0.076)[a]	191.5	256.5
+TNFR2	0.722 (0.672, 0.773)[a]		+0.411 (0.215, 0.607)[a]	+0.041 (0.022, 0.060)[a]	194.4	259.4
+BMP-7	0.742 (0.694, 0.790)[a]		+0.628 (0.432, 0.824)[a]	+0.074 (0.049, 0.100)[a]	179.1	244.2

Base model included age, sex, duration of diabetes, history of macrovascular and microvascular disease, smoking habit, systolic blood pressure, HbA1c, eGFR, log-transformed UACR, body mass index, and randomized treatment allocation (blood pressure and glucose lowering). AIC, Akaike information criterion; BIC, Schwarz Bayesian information criterion; BMP, bone morphogenetic protein; eGFR, estimated glomerular filtration rate; EPOR, erythropoietin receptor; IDI, integrated discrimination improvement; NRI, net reclassification improvement; TNFR, tumor necrosis factor receptor; UACR, urinary albumin/creatinine ratio.
[a]Values indicate significant improvement ($P < 0.001$) compared with base model.

Comparison of Circulating Biomarkers in Predicting Diabetic Kidney Disease Progression With Autoantibodies to Erythropoietin Receptor

Megumi Oshima[1,2,3], Akinori Hara[2], Tadashi Toyama[2], Min Jun[1], Carol Pollock[3], Meg Jardine[1,4], Stephen Harrap[5], Neil Poulter[6], Mark E. Cooper[7], Mark Woodward[1,8,9], John Chalmers[1], Vlado Perkovic[1], Muh Geot Wong[1,3] and Takashi Wada[2]

[1]Department of Renal and Metabolic, The George Institute for Global Health, University of New South Wales, Sydney, New South Wales, Australia; [2]Department of Nephrology and Laboratory Medicine, Kanazawa University, Kanazawa, Japan; [3]Renal Department, Kolling Institute of Medical Research, Sydney Medical School, University of Sydney, Royal North Shore Hospital, Sydney, New South Wales, Australia; [4]Nephrology Unit, Concord Repatriation General Hospital, Sydney, New South Wales, Australia; [5]Department of Physiology, Royal Melbourne Hospital, University of Melbourne, Melbourne, Victoria, Australia; [6]International Center for Circulatory Health, Imperial College, London, UK; [7]Department of Diabetes, Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, Australia; [8]The George Institute for Global Health, University of Oxford, Oxford, UK; and [9]Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland, USA

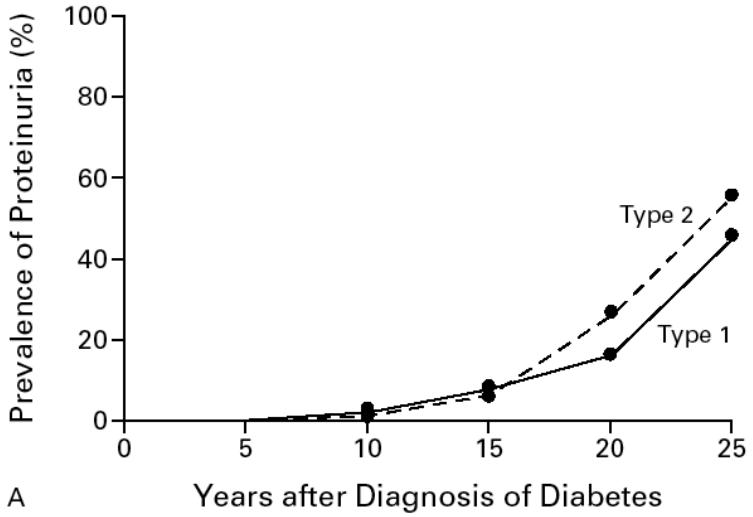
Kidney Int Rep (2021) 6, 284–295

Les différentes formes cliniques et évolutives de la néphropathie diabétique

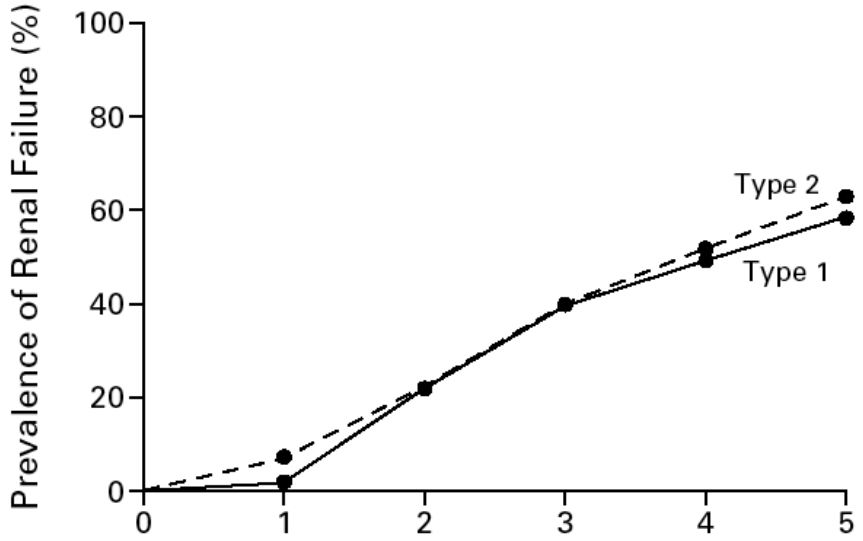
DT1 vs DT2	Db rares	Histoire naturelle classique	Histoire naturelle moderne	Δ DFG rapide	Hématurie	Histologie	Remission	Regression

Formes cliniques : diabète de type 1 vs type 2

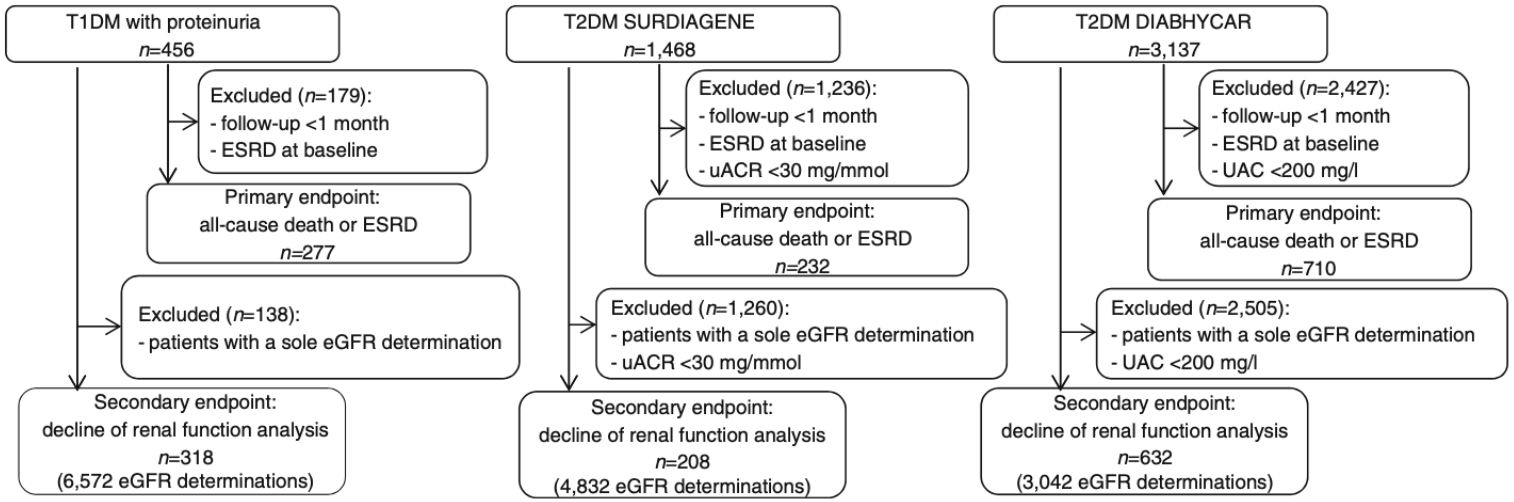
Protéinurie



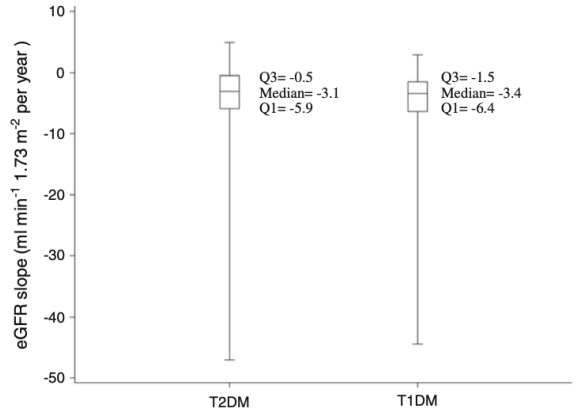
Créat > 125 µM



Ritz E, NEJM 1999 341:1127



=> once baseline risk factors were taken into account, the risk for **death**, **ESRD** and **renal function decline** did not significantly differ between type 1 diabetes and type 2 diabetes.



Hadjadj S et al, Diabetologia 2016

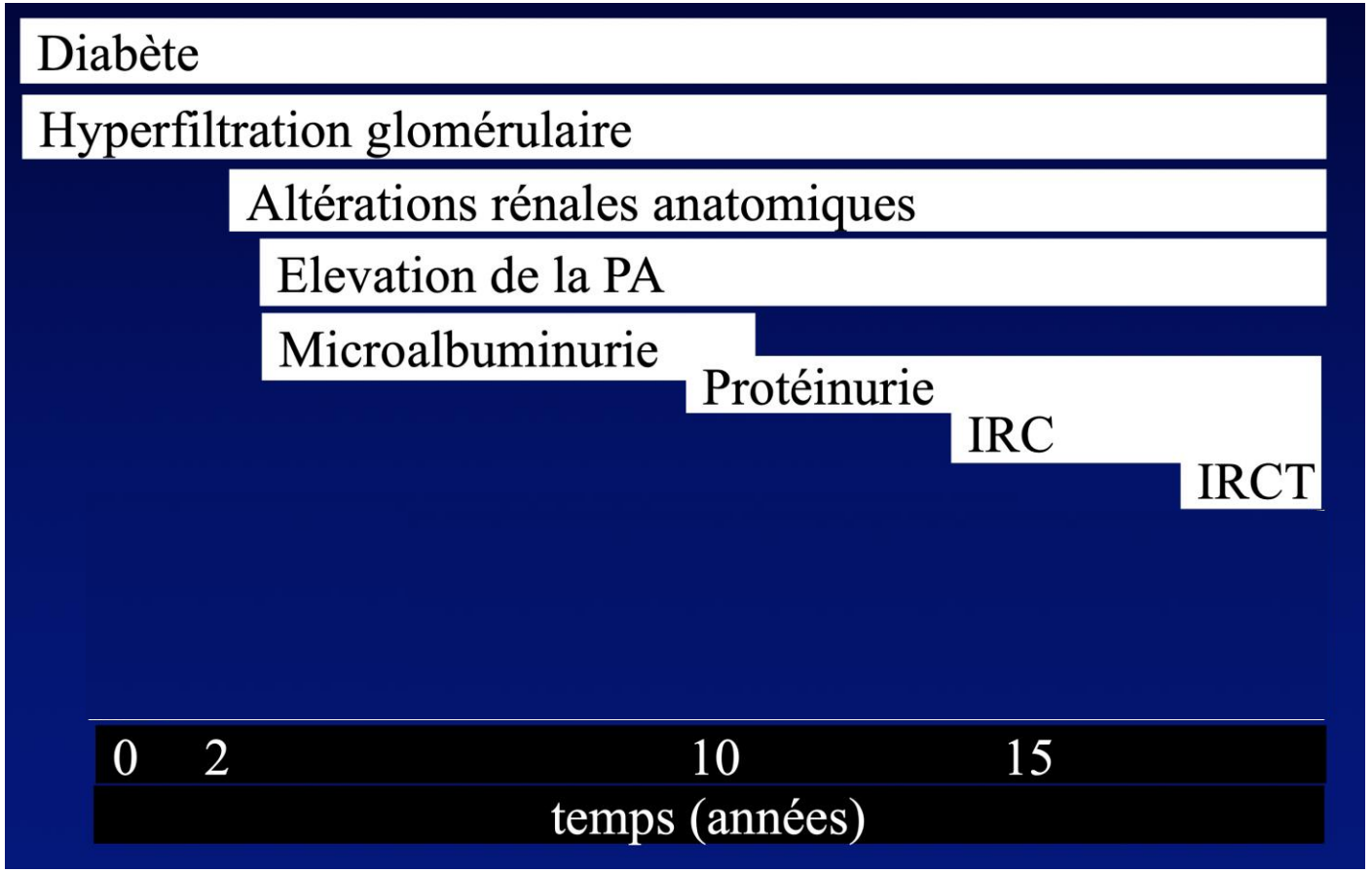
Formes cliniques : diabètes de cause rare

Tableau 1. – **Principaux diabètes monogéniques et syndromiques susceptibles de se présenter avec un phénotype de diabète de type 2.**

• ***DIABÈTES SYNDROMIQUES***
Hémochromatose (HFE)
Mucoviscidose (CFTR)
• ***DIABÈTES DE TYPE MODY***
MODY 2 (GCK)
MODY 3 (HNF-1α)
MODY 5 (HNF-1β)
MODY 1 (HNF-4α)
Mutations du gène de l'insuline (INS)
Formes exceptionnelles de MODY : MODY4 (PDX1), MODY 6 (NeuroD1), MODY 7 (CEL)
• ***CYTOPATHIES MITOCHONDRIALES***
MIDD, MELAS (3243 A > G)
Autres formes, Syndrome de Kearn-Sayre, Syndrome de Pearson
• ***AUTRES DIABÈTES MONOGÉNIQUES***
Pancréatite calcifiante familiale
Hyperinsulinémie de l'enfance (KIR 6.2, ABCC8)

Pierre-Jean GUILLAUSSEAU, 2011

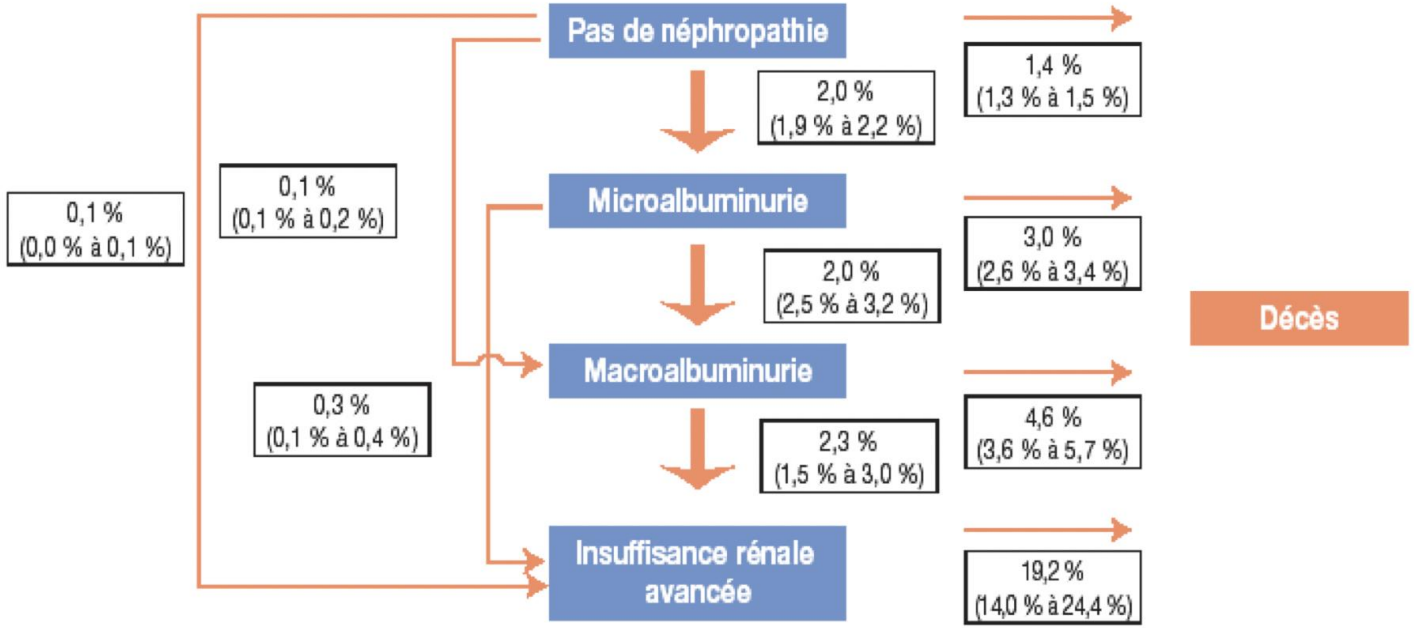
Histoire naturelle classique (DT1)



Mogensen CE *et al*. *Diabetes* 1983 ; 32 : 64-78.

Histoire naturelle classique (DT2)

Cohorte UKPDS (5097 DT2 incidents)



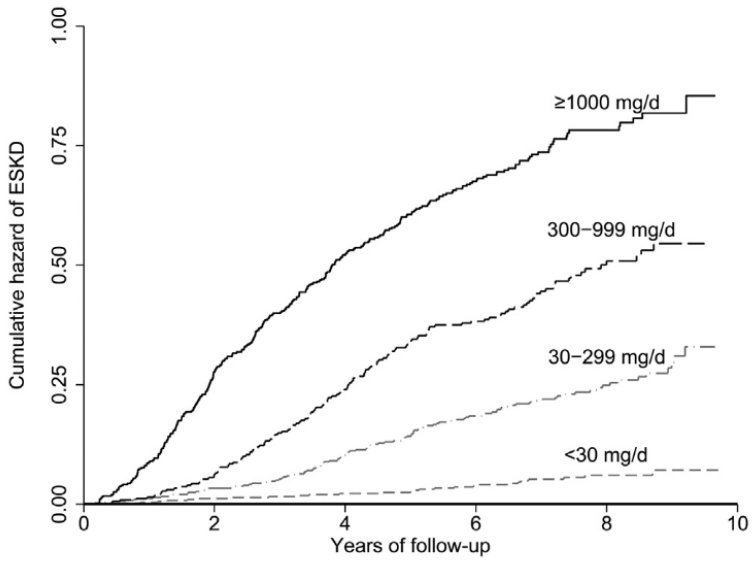
- **néphropathie = augmentation du risque de décès cardiovasculaire**
- **a tous les stades de néphropathie, le risque de décès surpasse celui de passer au stade de néphropathie suivant.**

UKPDS 64. Adler AI *et al. Kidney Int* 2003 ; 63 : 225-32.

Histoire naturelle moderne

Histoire naturelle moderne

IRCT



CRIC (post hoc : diabète et IRC)

→ **1. Normoalbuminurie**

28% des patients DB/IRC

5% de ceux qui progressent vers l'IRCT

→ Femmes
Blancs
PA et glycémie bien contrôlés

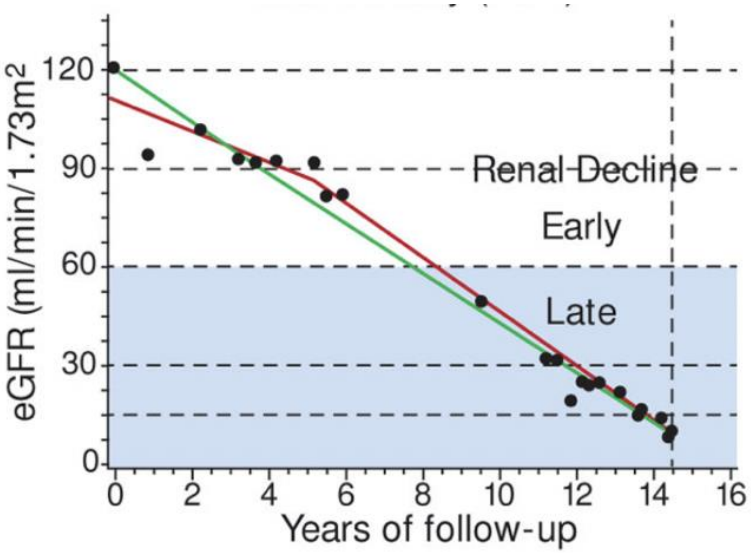
Koye AJKD 2018
J Diabetes Complications. 2013

Histoire naturelle moderne

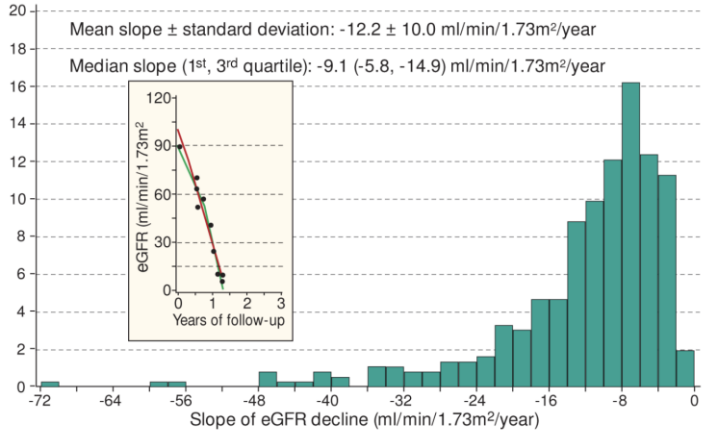
2. déclin du DFG

Joslin Clinic patients (DT1)

Déclin linéaire = 87%

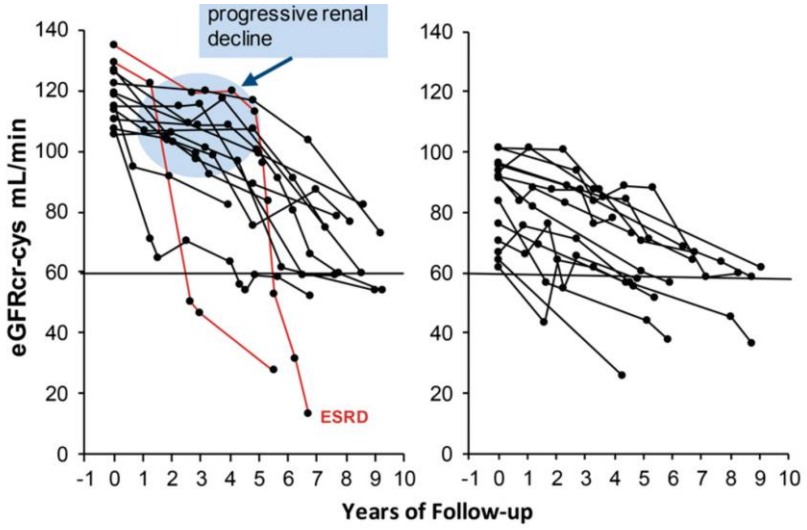


Pente variable



	Categories of progressive renal decline			
	Very fast	Fast	Moderate	Slow
eGFR slope (ml/min/1.73m²/year)	< -15	< -10	< -5	≤ -5
Time to onset of ESRD in years	2-6	6-10	10-20	20-45

Y compris normoalbuminuriques

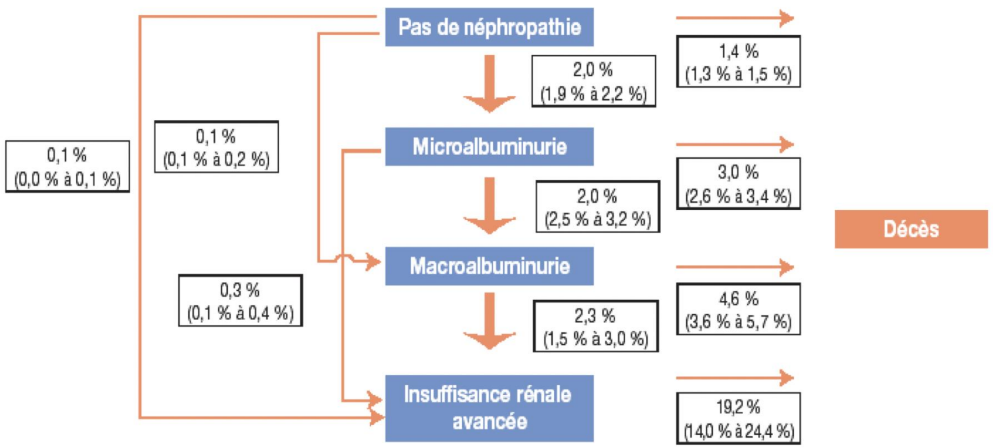


Krolevski et al. Kidney Int. 2017

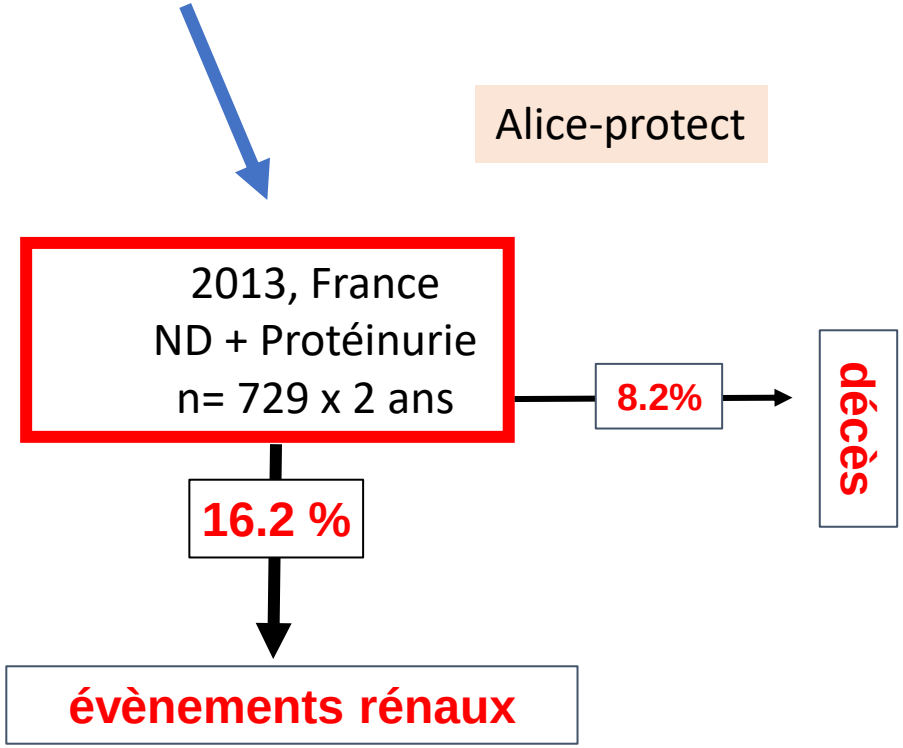
Histoire naturelle moderne

3. risques compétitifs

UKPDS



Alice-protect

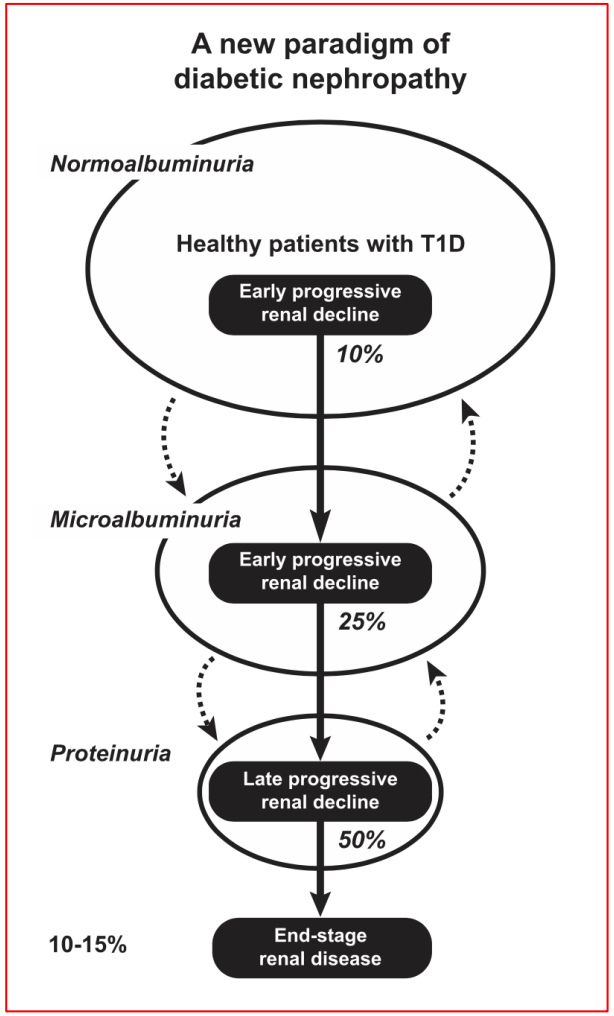


Halimi et al. BMC nephrol 2016

Histoire naturelle moderne

Nouveau paragidme

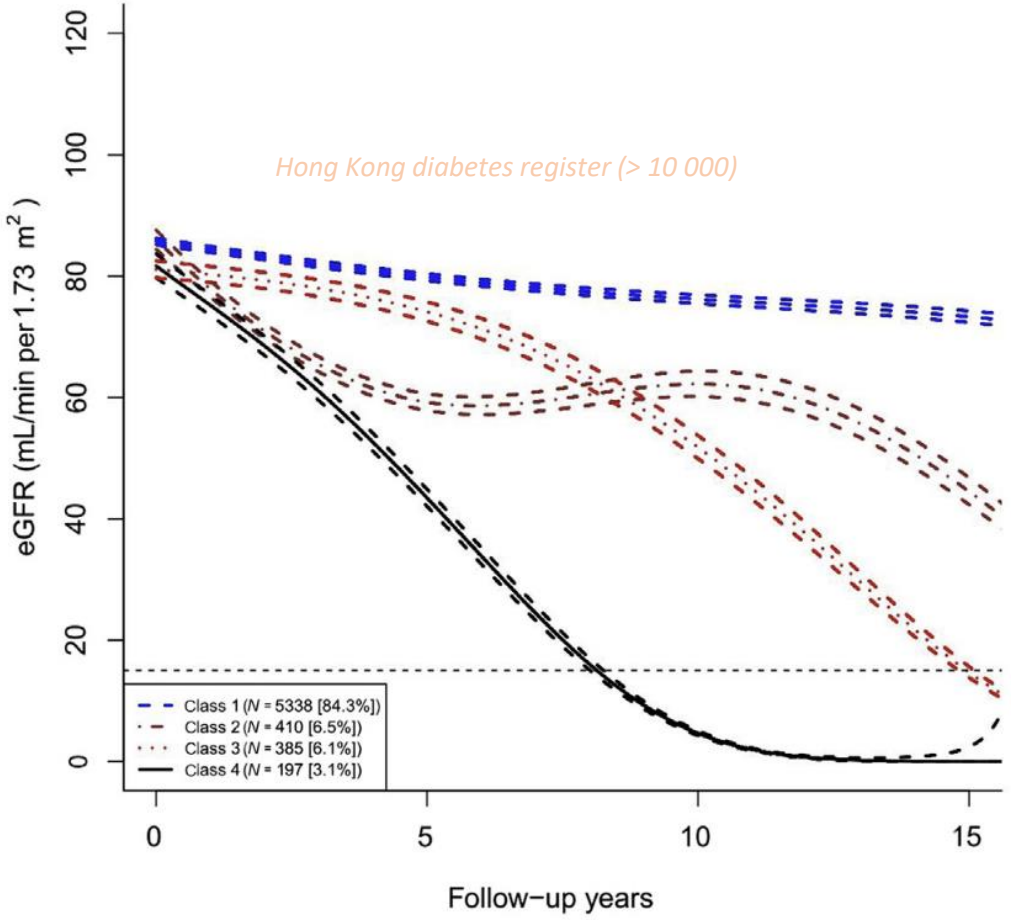
Délin précoce du DFG >> albuminurie



Krolevski et al. Kidney Int. 2017

Formes avec déclin rapide du DFG

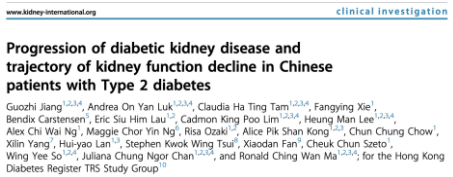
Formes avec déclin rapide du DFG



curvilinear decline (6.5%)

progressive decline (6.1%)

accelerated decline (3.1%) ⟷ albuminuria retinopathy ⟷ mortality



www.kidney-international.org clinical investigation

Progression of diabetic kidney disease and trajectory of kidney function decline in Chinese patients with Type 2 diabetes

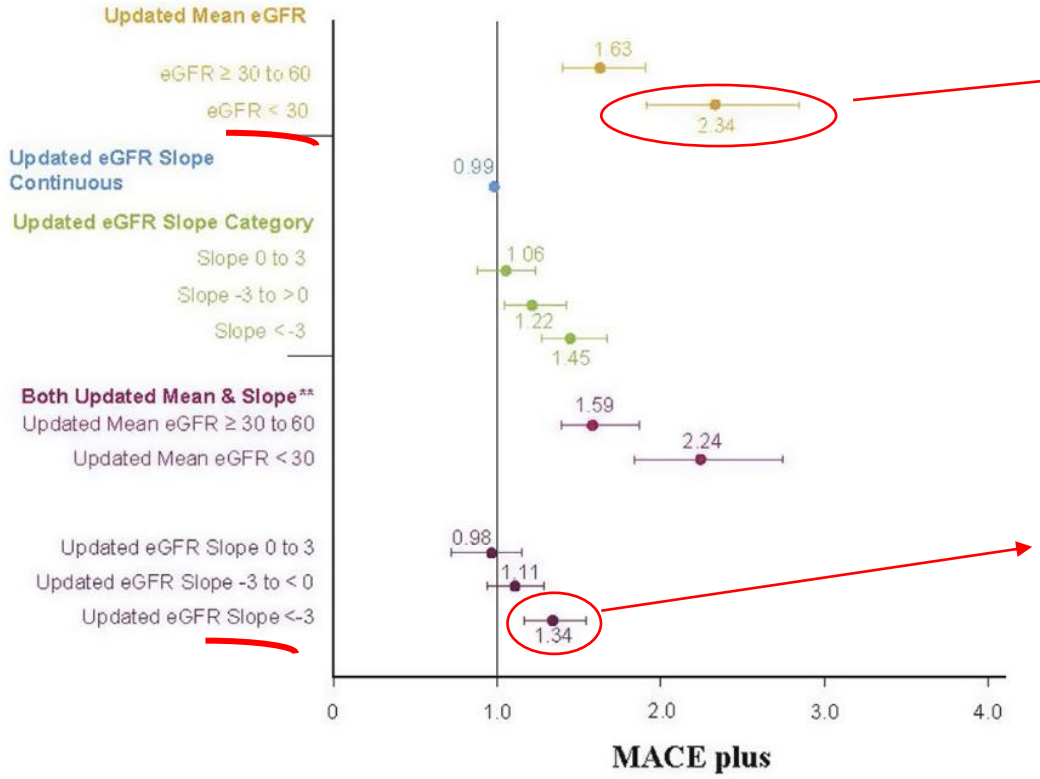
Guozhi Jiang[1,2,3,4], Andrea On Yan Luk[1,2,3,4], Claudia Ha Ting Tam[1,2,3,4], Fangying Xie[1], Bendix Carstensen[5], Eric Siu Him Lau[1,2], Cadmon King Poo Lim[1,2,3,4], Heung Man Lee[1,2,3,4], Alex Chi Wai Ng[1], Maggie Chor Yin Ng[6], Risa Ozaki[1,2], Alice Pik Shan Kong[1,2,7], Chun Chung Chow[1], Xilin Yang[1], Hui-yao Lan[1,3], Stephen Kwok Wing Tsui[8], Xiaodan Fan[9], Cheuk Chun Szeto[1], Wing Yee So[1,2,4], Juliana Chung Ngor Chan[1,2,3,4], and Ronald Ching Wan Ma[1,2,3,4]; for the Hong Kong Diabetes Register TRS Study Group[10]

Guozhi et al. Kidney International (2018)

Formes avec déclin rapide du DFG

UK Clinical Practice Research Data Link GOLD (CPRD) were followed from CKD diagnosis (n = 30,222)

Proportional hazards regression models in 30,222 patients with associated diabetic nephropathy estimating time to cardiovascular
disease outcomes by updated mean and updated estimated glomerular filtration (eGFR) slope



CKD stage predicts cardiorenal risk

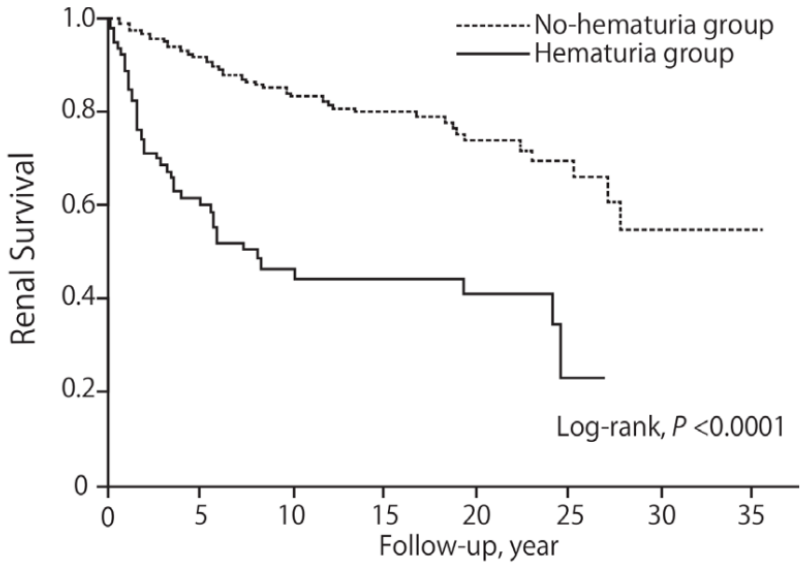
rate of progression of CKD **predicts cardiorenal risk**

Kidney Int Rep (2020) 5, 1651–1660

Formes avec hématurie

Table 1 Baseline characteristics of the patients with/without hematuria

	Hematuria	No-hematuria	
	N=91	N=306	P value
Age, years	59.1±10.8	57.3±11.5	0.2
Men, n (%)	65 (60)	184 (71)	0.05
BMI, kg/m^2	24.7±4.0	23.9±3.7	0.08
Blood pressure, mm Hg			
Systole	145±27	132±22	<0.0001
Diastole	78±15	75±13	0.04
Smoking, n (%)			0.4
Never	30 (33)	124 (41)	
Past	14 (15)	47 (15)	
Current	47 (52)	135 (44)	
Diabetic retinopathy, n (%)	58 (65)	117 (39)	<0.0001
Laboratory findings			
Serum creatinine, mg/dL	1.23 (0.80–1.80)	0.90 (0.70–1.20)	<0.0001
Serum creatinine, µmol/L	108.7 (70.7–159.1)	79.6 (61.9–106.1)	<0.0001
eGFR, mL/min/1.73m^2	45.4 (29.0–65.7)	61.2 (43.4–82.0)	<0.0001
Proteinuria, g/day	3.1 (0.5–6.8)	0.3 (0.1–1.0)	<0.0001
HbA1c, %	7.9±2.2	8.4±2.4	0.1
HbA1c, mmol/mol	63±24	68±26	0.1
Pathological findings			
Glomerular lesion class, n (%)			<0.0001
IIa	12 (13)	115 (38)	
IIb	25 (27)	123 (40)	
III	40 (44)	59 (19)	
IV	14 (15)	9 (3)	
IFTA score, n (%)			<0.0001
0	4 (4)	28 (9)	
1	31 (34)	189 (62)	
2	22 (24)	44 (14)	
3	34 (37)	45 (15)	
Arteriolar hyalinosis score, n (%)			<0.02
0	7 (8)	48 (16)	
1	22 (24)	98 (32)	
2	62 (68)	160 (52)	
Arteriosclerosis score, n (%)			0.9
0	17 (20)	61 (22)	
1	30 (36)	93 (33)	
2	36 (43)	129 (46)	



No. at risk

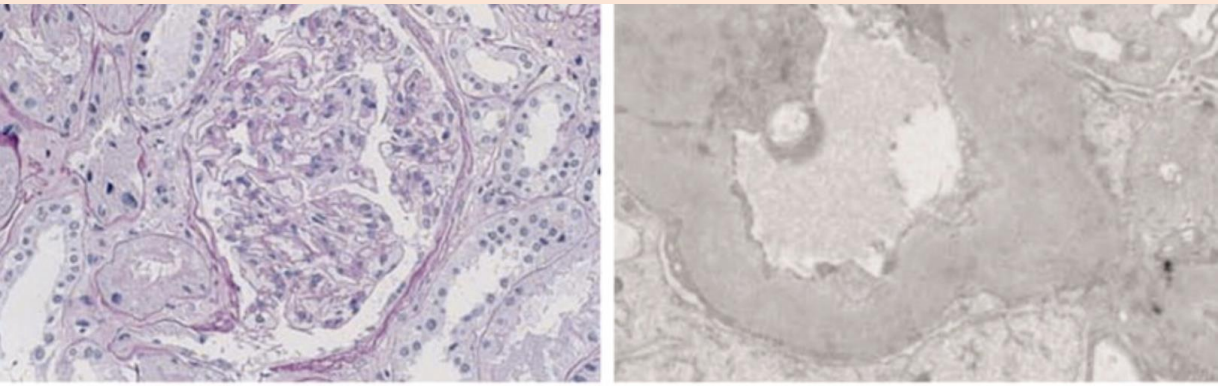
No-hematuria group	306	197	128	87	51	21	9	1
Hematuria group	91	41	21	15	11	1		

Crude HR (95% CI) : 4.11 (2.73-6.18), P <0.0001
Adjusted HR (95% CI)
Model 1: 4.08 (2.70-6.16), P <0.0001
Model 2: 2.07 (1.29-3.34), P = 0.03
Model 3: 1.64 (1.03-2.60), P = 0.04

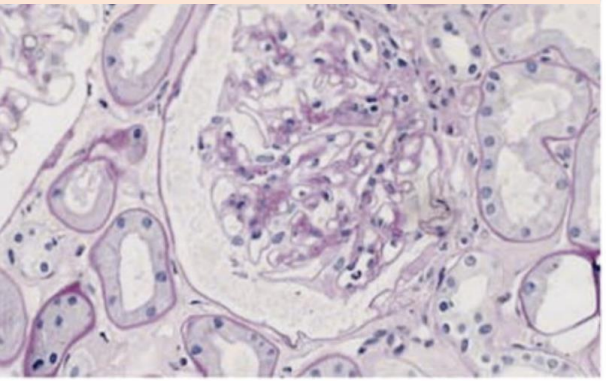
Okada, BMJ Open Diab Res Care 202

Formes histologiques : classification

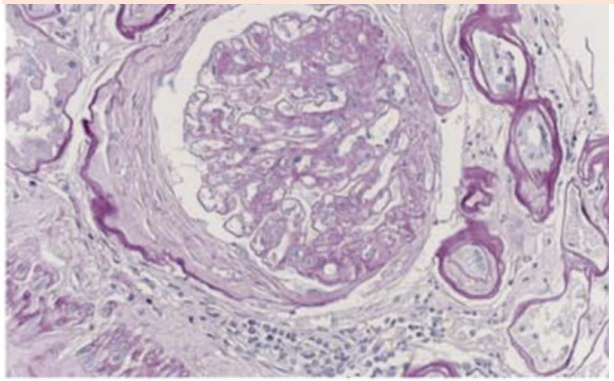
Stade I MBG > 395 nm /430 nm



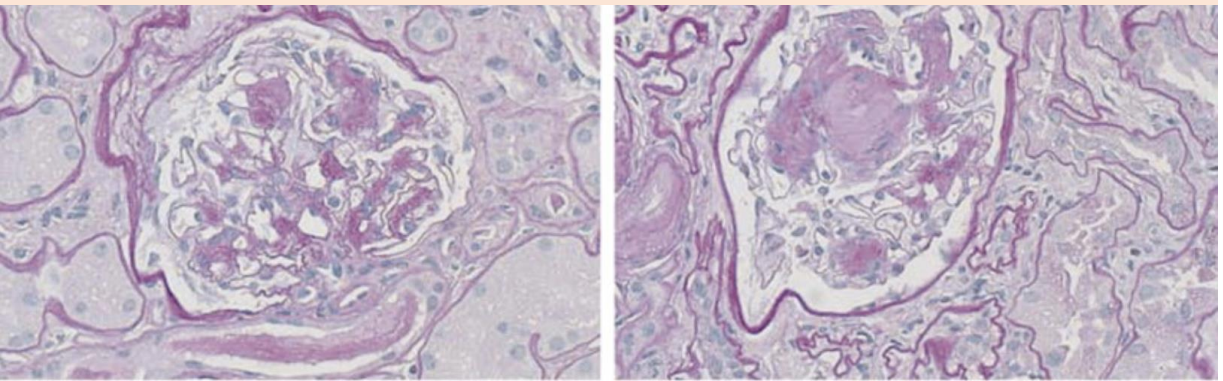
Stade II A



Stade II B



Stade III



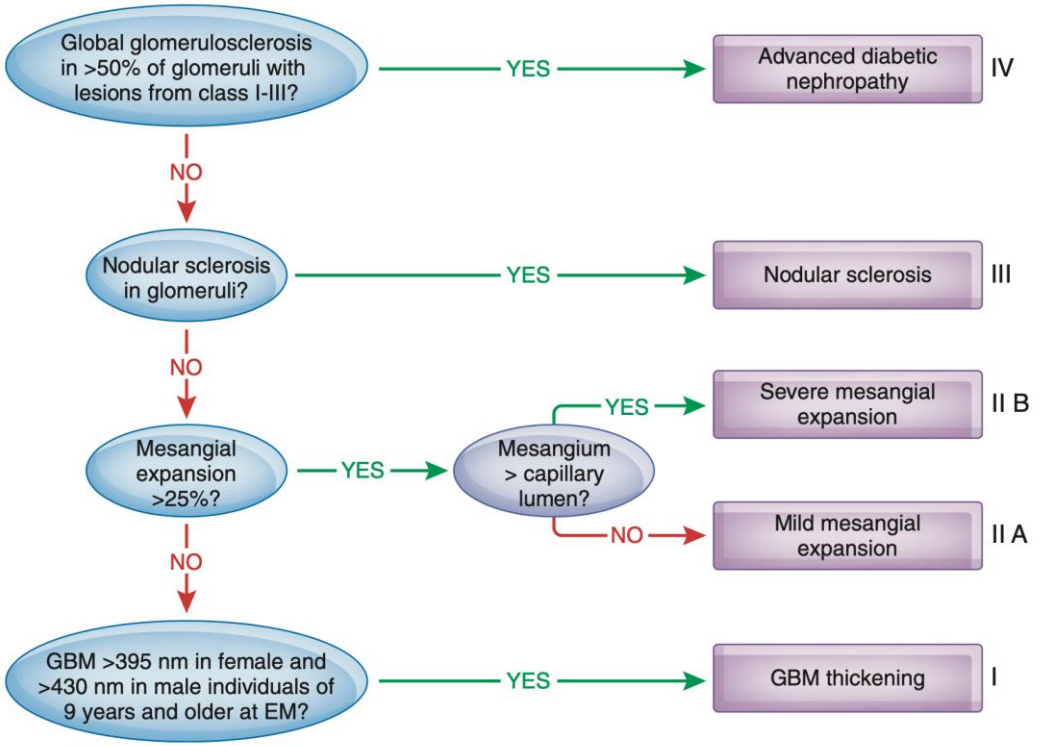


Figure 2. Flow chart for classifying DN.

J Am Soc Nephrol **21:** 556–563, 2010

Table 2—*Renal structure patterns in patients with type 2 diabetes*

Albuminuria category	Normoalbuminuria			Microalbuminuria			Macroalbuminuria		
Fioretto et al. (11)									
GFR >60 mL/min/1.73 m^2 (mean GFR 101 ± 27 mL/min/1.73 m^2)					*n* = 34				
Number of subjects per category				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.

Age
HTA
NAS

Néphropathie diabétique

Ekinci Diabetes Care 36:3620–3626, 2013

Classe de ND

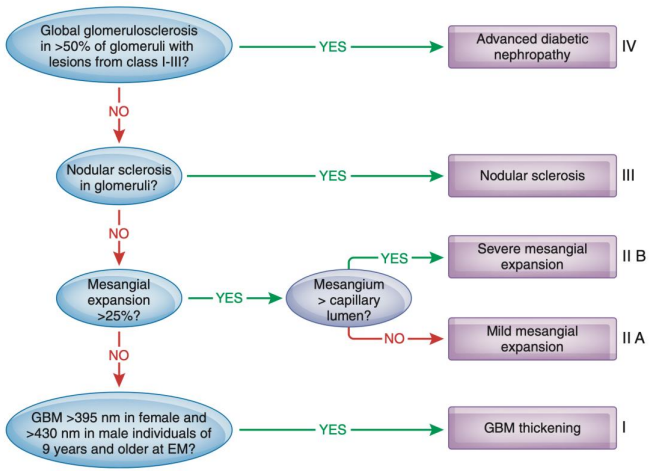
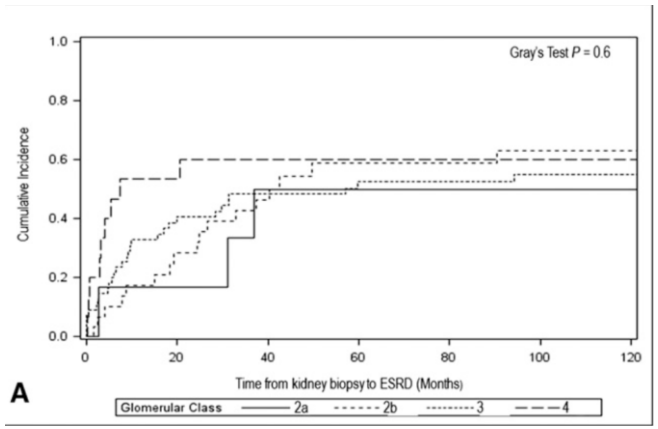
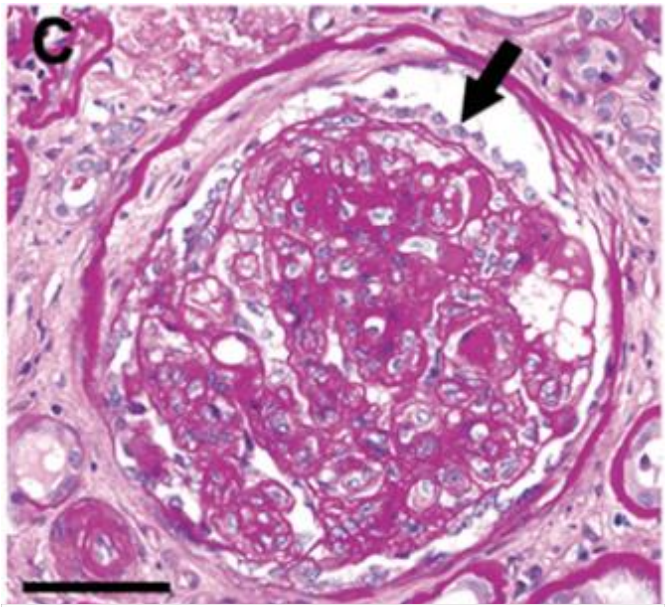
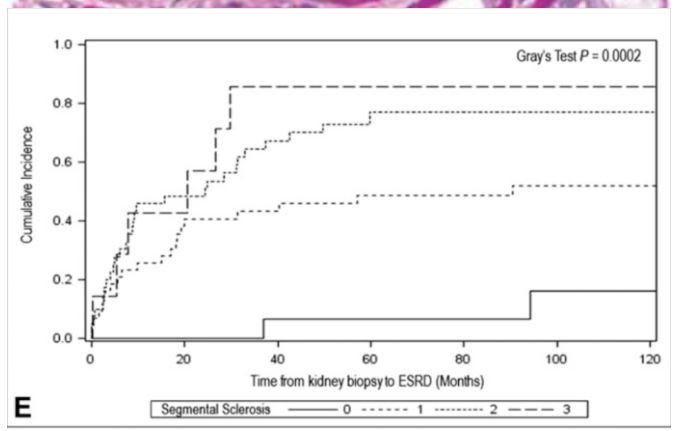


Figure 2. Flow chart for classifying DN.

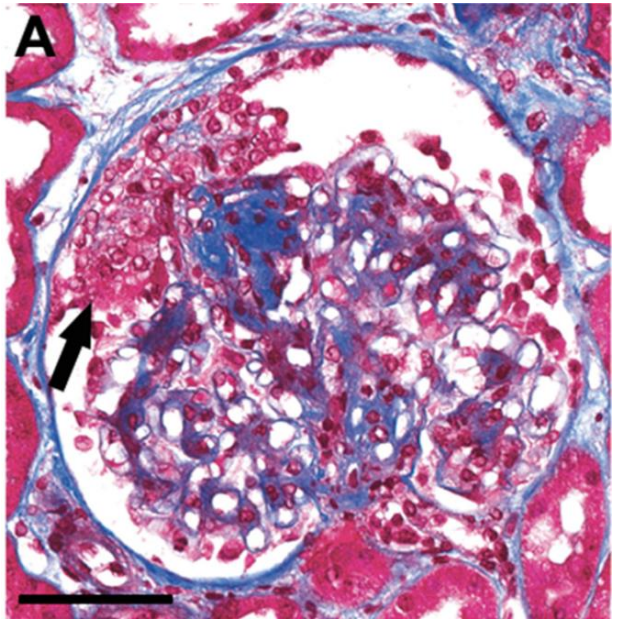


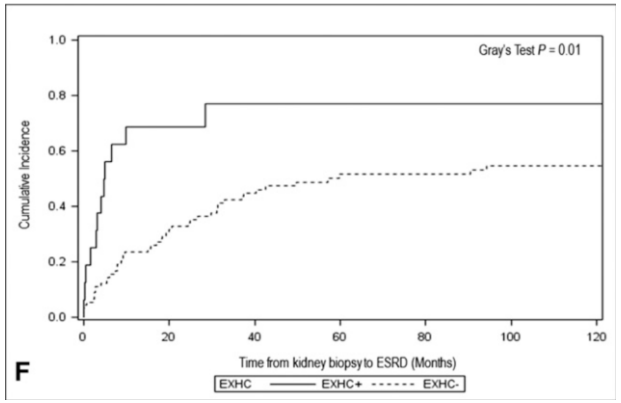
HSF (34%)



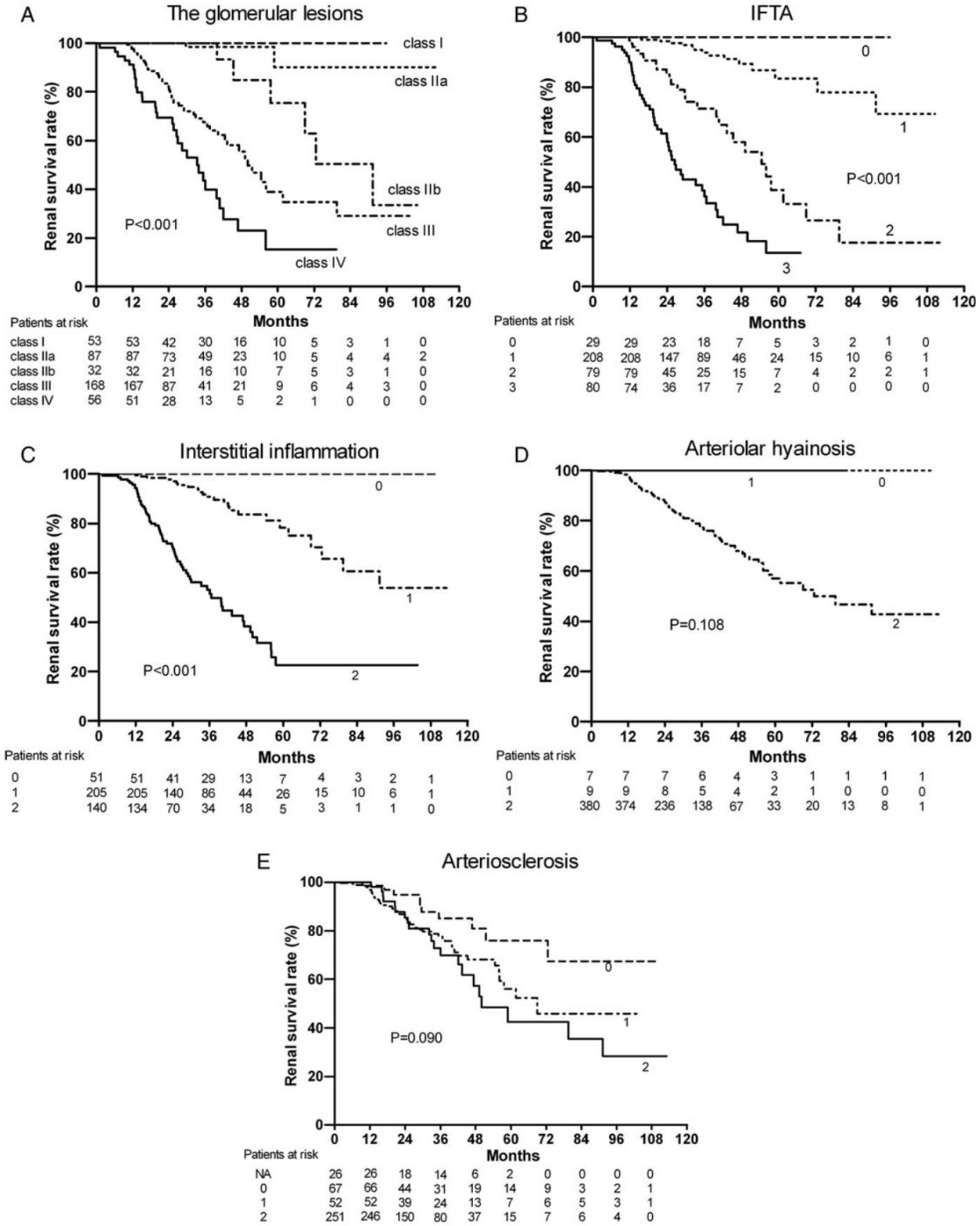


HC extra capillaire (16%)





Mottl, J Am Soc Nephrol 29: 694–703, 2018



Renal histologic changes and the outcome in patients with diabetic nephropathy

Yu An*, Feng Xu*, Weibo Le, Yongchun Ge, Minlin Zhou, Hao Chen, Caihong Zeng, Haitao Zhang and Zhihong Liu

National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China

Correspondence and offprint requests to: Zhihong Liu; E-mail: liuzhihong@nju.edu.cn; zhihong–liu@hotmail.com
*Yu An and Feng Xu contributed equally to the work; both are first authors.

Yu, Nephrol Dial Transplant 2015; 30: 155–157.

Formes traitées intensivement

Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes

Patienter

Steno-2

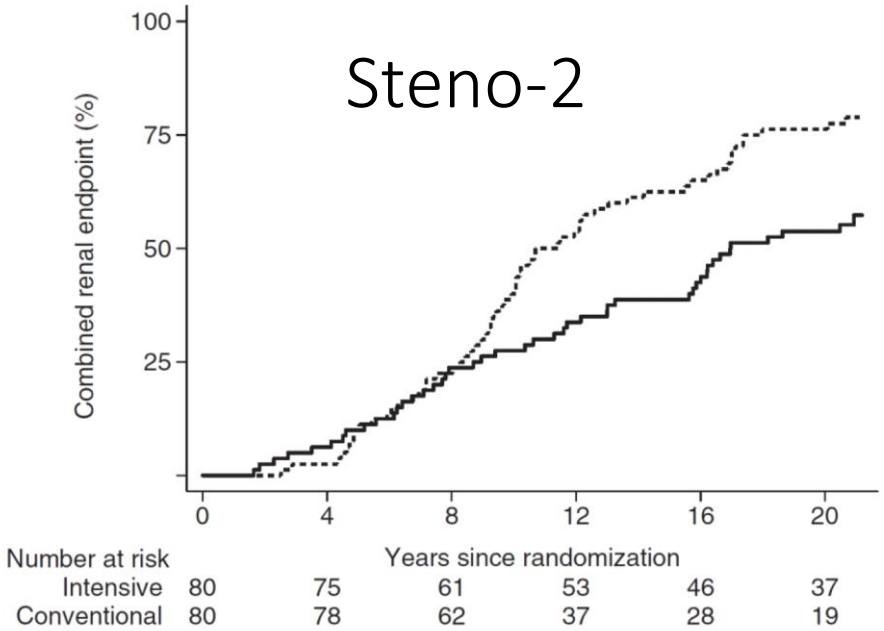
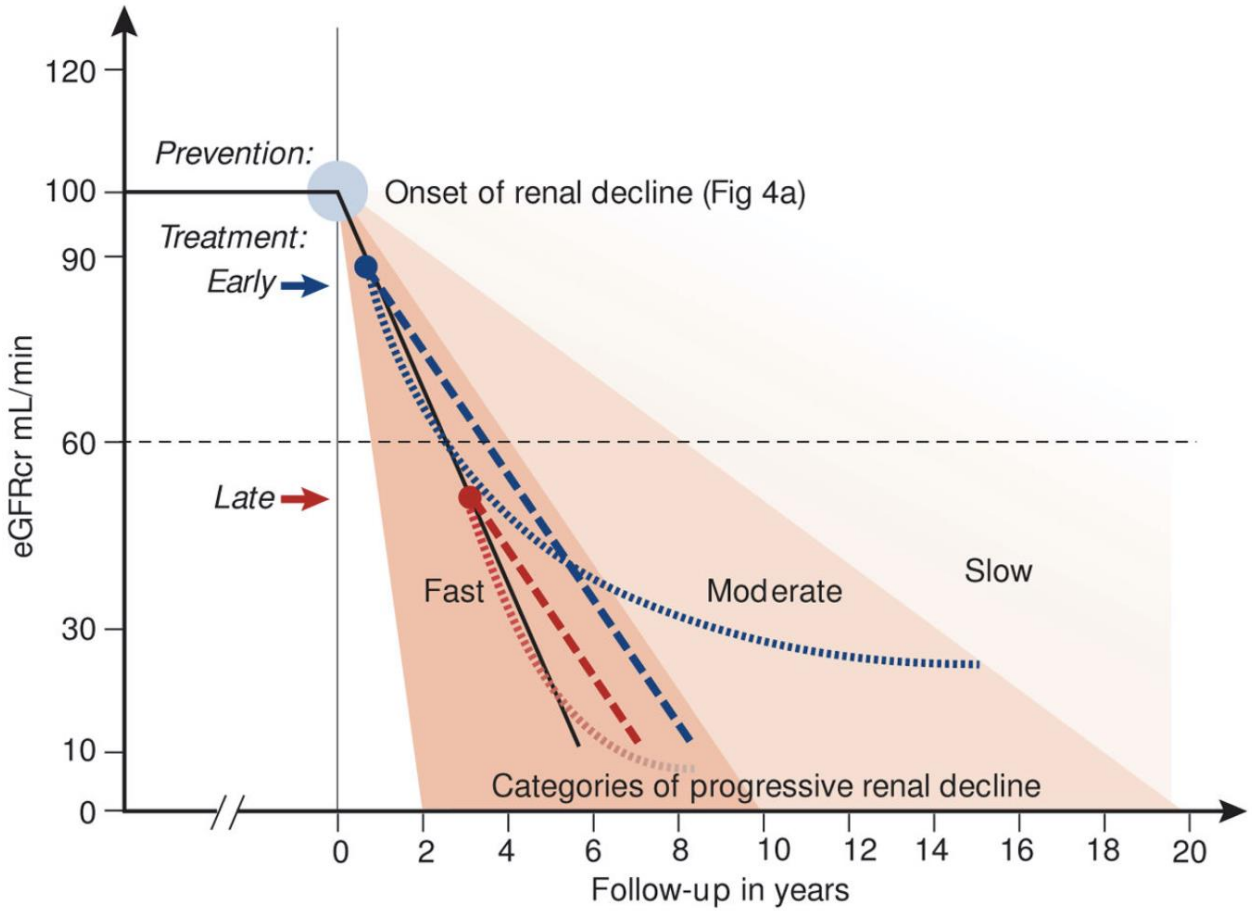


Figure 5 | Kaplan-Meier estimates of the combined renal endpoint of progression to glomerular filtration rate <45, end-stage renal disease, or death. Solid line: intensive therapy group. Dashed line: conventional therapy group. Adjusted hazard ratio of 0.55 (95% confidence interval: 0.37–0.81; $P = 0.003$; model 2).

The NEW ENGLAND JOURNAL of MEDICINE

Gaede *et al*. *New Eng J Med* 2008;358:580–91

Intervenir précocément



Skupien et al. JASN 2014

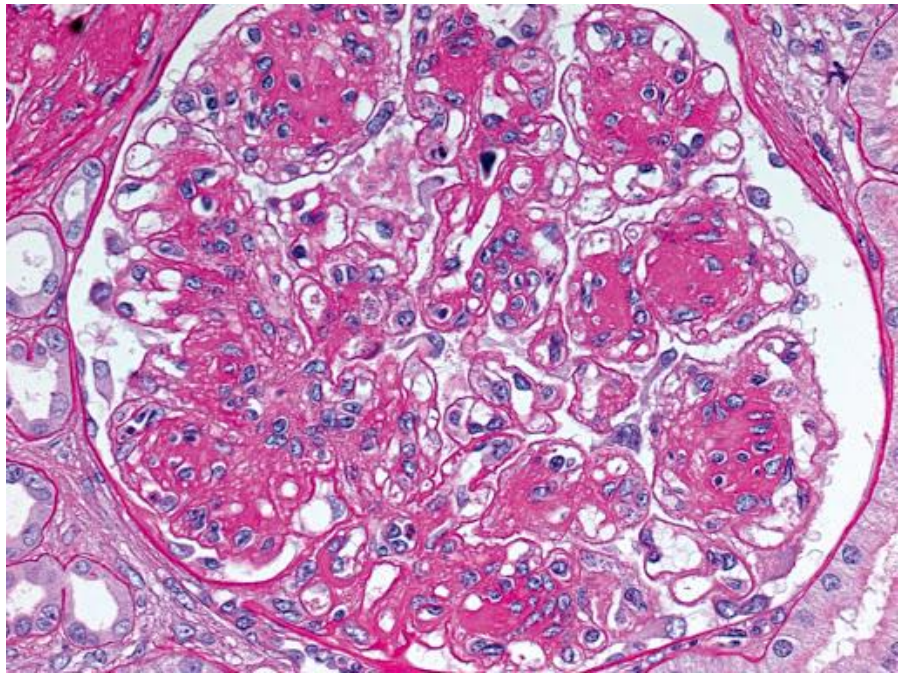
Formes régressives

Diabète de type 1

Peut on elle faire **régresser** les lésions de Nx diabétique ???

A. Oui => Oui, si on obtient une **normoglycémie prolongée**

B. Non

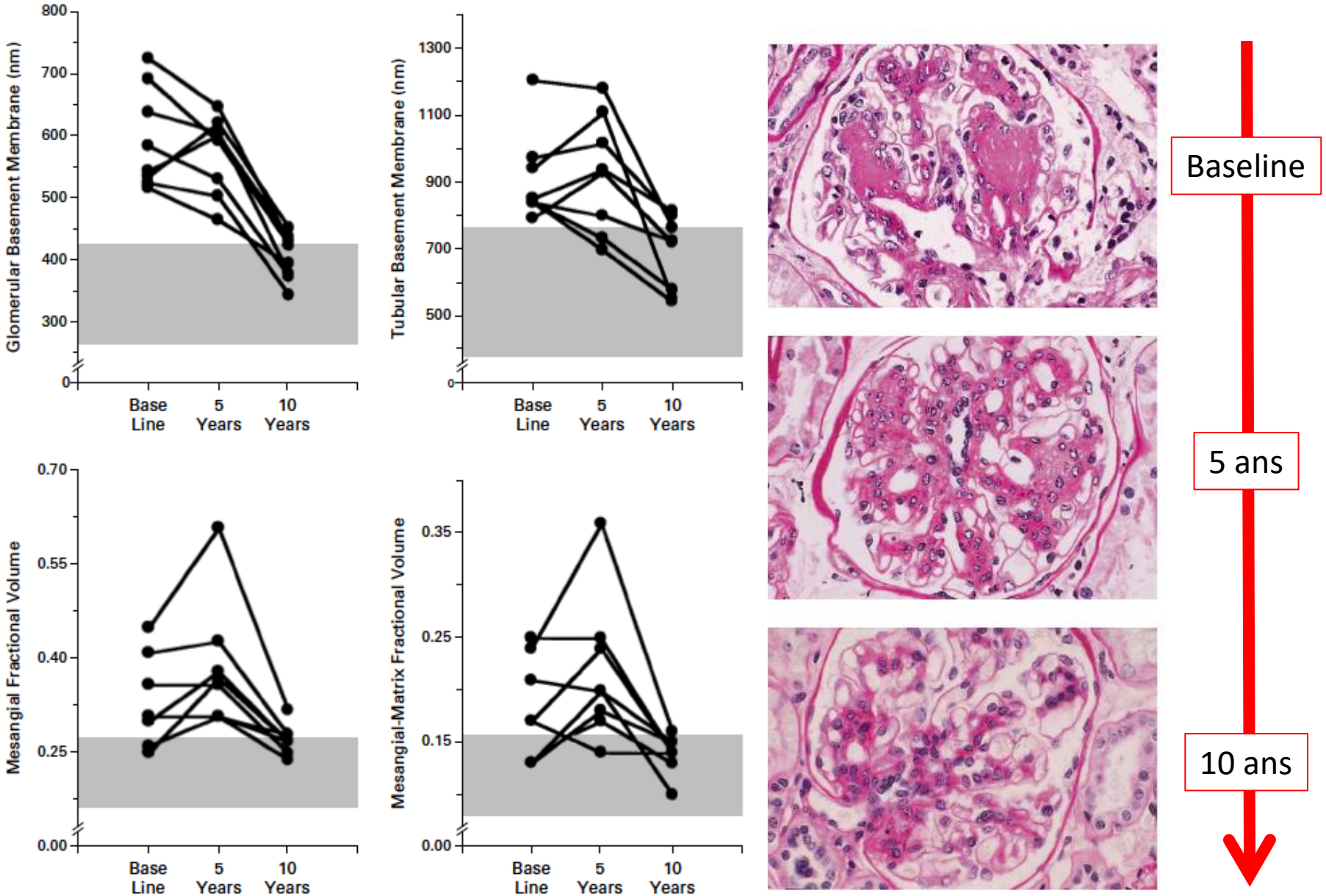


« non »
(13 patients)
5 ans

Fioretto P, Effects of pancreas transplantation on glomerular structure in insulin-dependent diabetic patients with their own kidneys. **Lancet. 1993 ; 342(8881):1193-6**.

« oui »
(10 patients)
10 ans

Fioretto P et coll. H. REVERSAL OF LESIONS OF DIABETIC NEPHROPATHY AFTER PANCREAS TRANSPLANTATION
NEJM 1998 339 p6


Glomerular Basement Membrane (nm)
800
700
600
500
400
300
0
Base Line
5 Years
10 Years
Tubular Basement Membrane (nm)
1300
1100
900
700
500
0
Base Line
5 Years
10 Years
Mesangial Fractional Volume
0.70
0.55
0.40
0.25
0.00
Base Line
5 Years
10 Years
Mesangial-Matrix Fractional Volume
0.35
0.25
0.15
0.00
Base Line
5 Years
10 Years
Baseline
5 ans
10 ans

Formes cliniques de néphropathie diabétique

- Inconstante
- Prévisible
- Pièges diagnostiques
- Histologie perfectible = indications, informations
- Formes normoalbuminuriques
- Déclin précoce du DFG
- Déclin rapide du DFG = marqueur de risque CV fort
- Rémission : traitement intensif et précoce
- Régression !