

Forums des Savoirs
POURQUOI PRENDRE SOIN DE SES REINS ?

**Epidémiologie et diagnostic
de la maladie rénale chronique**

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BELGIQUE



- Pas de conflit d'intérêt pour cette présentation



Le rein: un organe original....

- Le seul organe que vous pouvez remplacer par une “machine” pendant des années
- Capable de se régénérer en cas d’insuffisance rénale aigue
- Le premier organe transplanté (reste le plus transplanté)

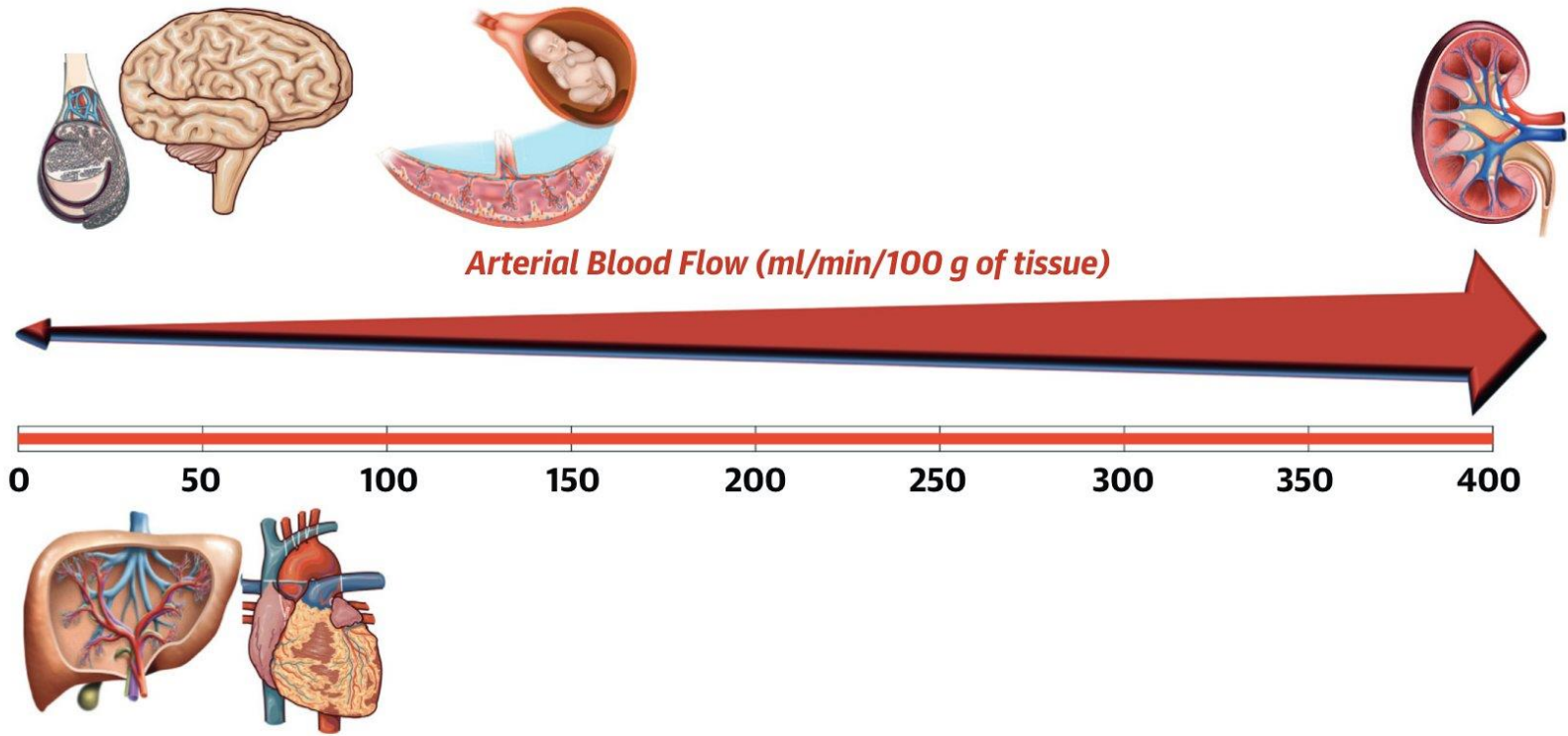


Rôles du rein

1. Régulation de l'eau, des électrolytes, du pH
2. Epuration des déchets organiques du sang vers les urines
3. Sécrétion hormonale
 - Erythropoïétine
 - Rénine
 - Vitamine D



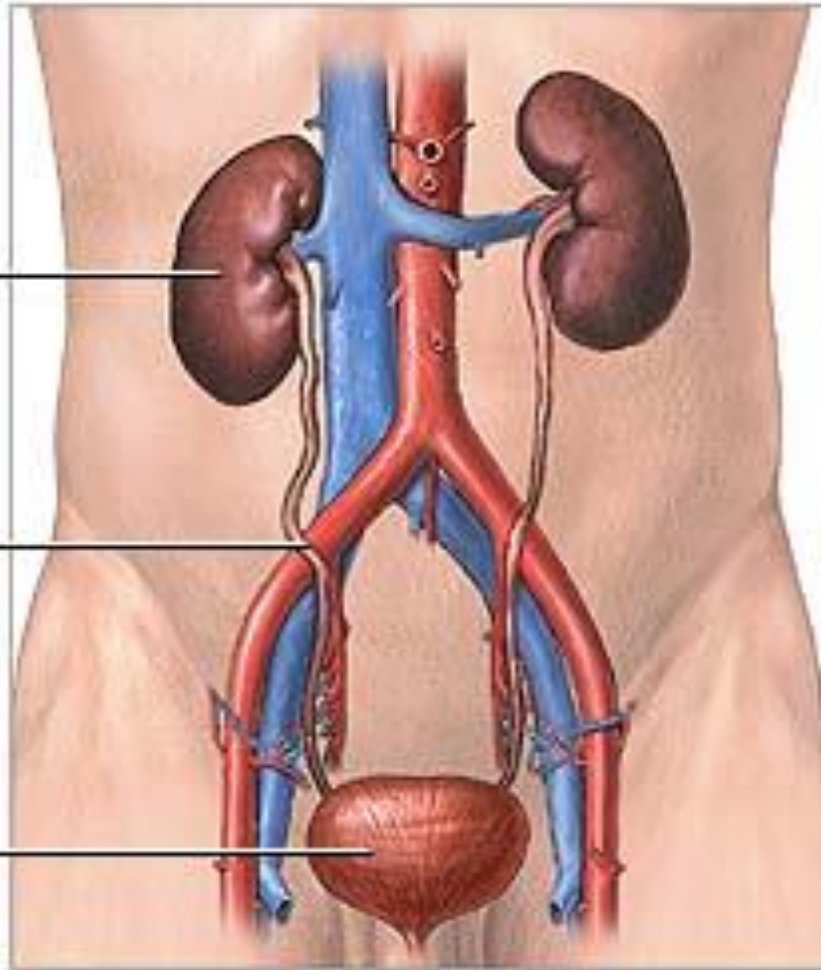
FIGURE 3 Arterial Blood Flow Per Unit of Tissue Mass in Various Organs

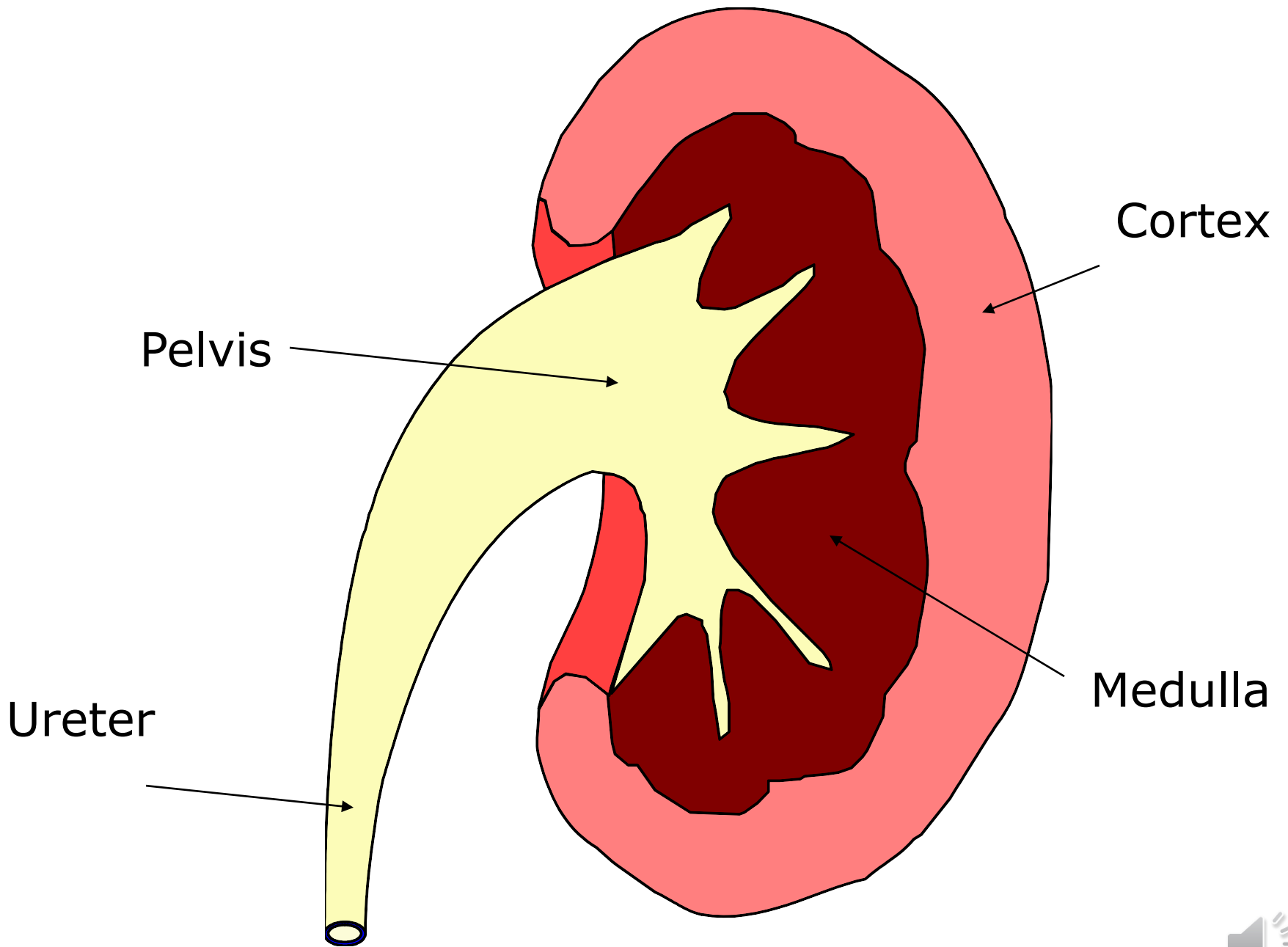


Kidney

Ureter

Bladder





Cortex

Pelvis

Medulla

Ureter



Chaque REIN contient 1 million de NEPHRONS

↳ Chaque NEPHRON consiste en :

GLOMERULE (cortex)

barrière au passage des protéines

TUBULE (médullaire)

Absorption et sécrétion

↳ Chaque TUBULE a différents segments:

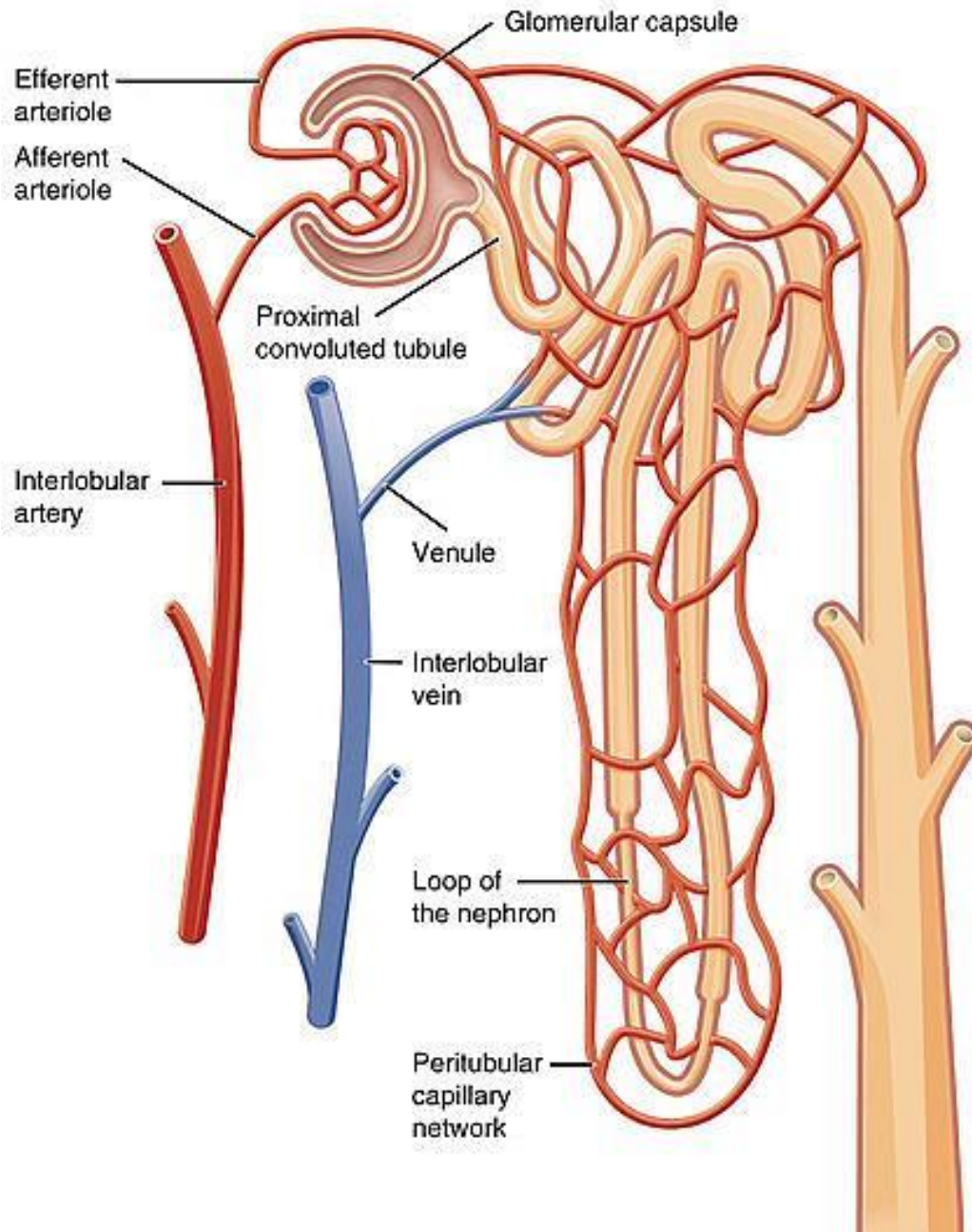
Proximal

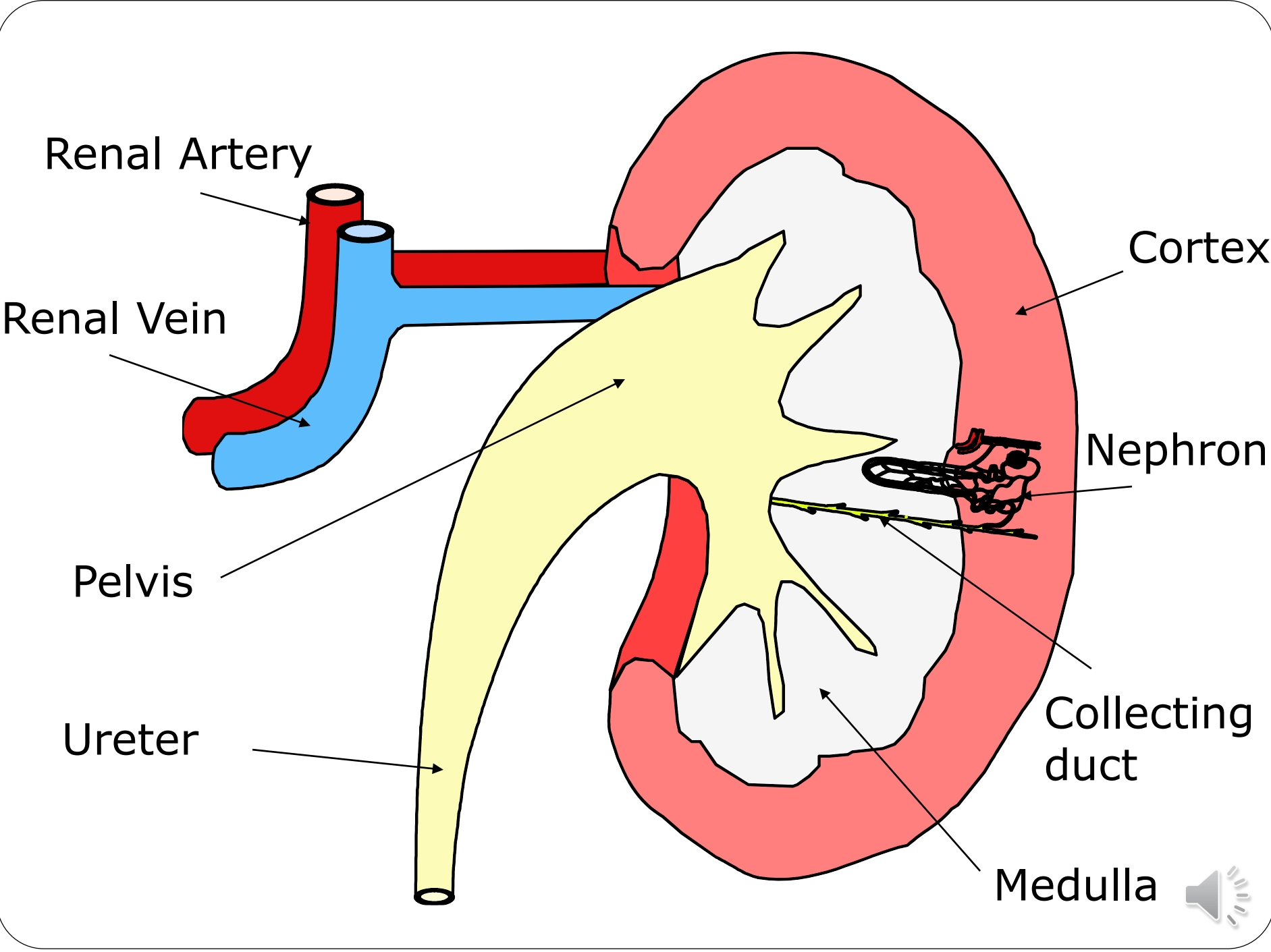
Anse de Henlé

Distal

Tubes collecteurs







Renal Artery

Renal Vein

Cortex

Nephron

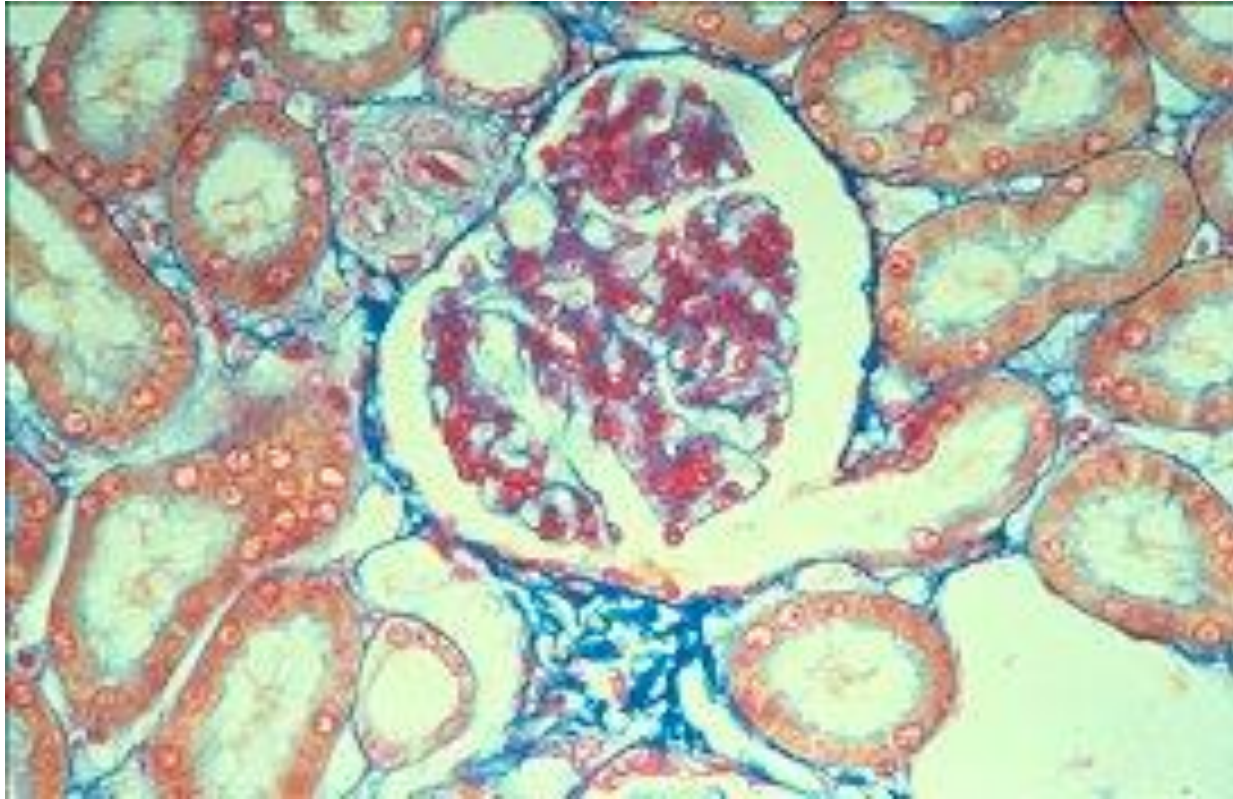
Pelvis

Collecting duct

Ureter

Medulla





La mesure du débit de filtration
glomérulaire (DFG) est le meilleur
moyen d'estimer la fonction globale du
rein



Le concept de clairance

- Clairance d'un soluté (ml/min):

volume de plasma épuré de cette substance par unite de temps

$$Cl = [U] \times [V] / [P]$$

- Marqueur "idéal" du DFG (endogène/exogène):

- Production constante
- Pas d'effets sur le DFG, non toxique
- Non lié aux protéines, librement filtré au niveau glomérulaire
- Pas de sécrétion, ni de réabsorption au niveau tubulaire
- Pas de clairance extra rénale
- Facile à mesurer



Disponibles sur le marché...

Marqueurs	Forces	Limites
<i>Inuline</i>	“Gold standard” (ou historique)	Coûteux Dosage ni facile ni standardisé Impossible en clairance plasmatique
<i>Iothalamate</i>	Le plus populaire aux USA Isotopique ou “froide”	Sécrétion tubulaire Allergie Iode
<i>Iohexol</i>	Populaire en Europe Froide	Allergie Iode
<i>EDTA</i>	Facile à mesurer	Seulement isotopique Pas disponible aux USA...et plus en Europe!!
<i>DTPA</i>	Facile à mesurer	Seulement isotopique Liaison aux protéines

Stevens LA, *J Am Soc Nephrol*, 2009, 20, 2305

Cavalier E, *Clin Chim Acta*, 2008, 396, 80

Delanaye P, *Clin Kidney J*, 2016, 9, 700



Biomarqueur sérique: créatinine



Max Jaffe



Otto Folin



Créatinine sérique

Une des analyses les plus prescrites

...mais important d'en connaître les limitations

Limitations physiologiques

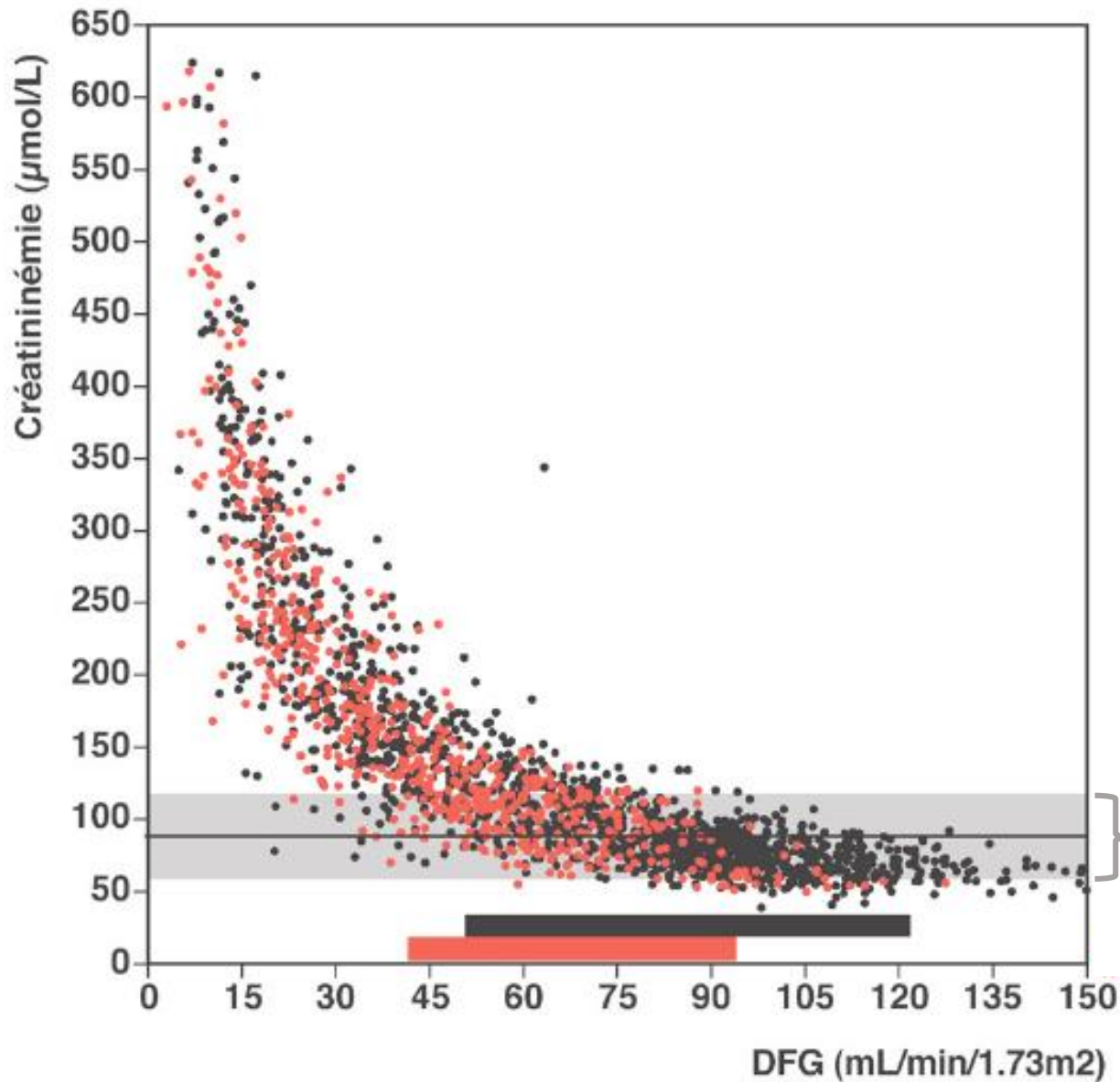
Limitations analytiques

Limitations “mathématiques”

Perrone RD, Clin Chem, 1992, 38, 1933

Delanaye P, Ann Biol Clin (Paris), 2010, 68, 531





Cohorte NephroTest (France)
 Quel DFG correspond à une
 concentration de créatinine
 mesurée à 0.9 mg/dL (80
 µmol/L) ?

IC 95% pour sujets <65 ans
 IC 95% pour sujets >65 ans

Valeurs normales
 de créatinine

Avec la permission de Marc Froissart



Equation CKD-EPI

ARTICLE

Annals of Internal Medicine

A New Equation to Estimate Glomerular Filtration Rate

Andrew S. Levey, MD; Lesley A. Stevens, MD, MS; Christopher H. Schmid, PhD; Yaping (Lucy) Zhang, MS; Alejandro F. Castro III, MPH; Harold I. Feldman, MD, MSCE; John W. Kusek, PhD; Paul Eggers, PhD; Frederick Van Lente, PhD; Tom Greene, PhD; and Josef Coresh, MD, PhD, MHS, for the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)*

Ann Intern Med. 2009;150:604-612.

Table 2. The CKD-EPI Equation for Estimating GFR on the Natural Scale*

Race and Sex	Serum Creatinine Level, $\mu\text{mol/L}$ (mg/dL)	Equation
Black		
Female	≤ 62 (≤ 0.7)	$\text{GFR} = 166 \times (\text{Scr}/0.7)^{-0.329} \times (0.993)^{\text{Age}}$
	> 62 (> 0.7)	$\text{GFR} = 166 \times (\text{Scr}/0.7)^{-1.209} \times (0.993)^{\text{Age}}$
Male	≤ 80 (≤ 0.9)	$\text{GFR} = 163 \times (\text{Scr}/0.9)^{-0.411} \times (0.993)^{\text{Age}}$
	> 80 (> 0.9)	$\text{GFR} = 163 \times (\text{Scr}/0.9)^{-1.209} \times (0.993)^{\text{Age}}$
White or other		
Female	≤ 62 (≤ 0.7)	$\text{GFR} = 144 \times (\text{Scr}/0.7)^{-0.329} \times (0.993)^{\text{Age}}$
	> 62 (> 0.7)	$\text{GFR} = 144 \times (\text{Scr}/0.7)^{-1.209} \times (0.993)^{\text{Age}}$
Male	≤ 80 (≤ 0.9)	$\text{GFR} = 141 \times (\text{Scr}/0.9)^{-0.411} \times (0.993)^{\text{Age}}$
	> 80 (> 0.9)	$\text{GFR} = 141 \times (\text{Scr}/0.9)^{-1.209} \times (0.993)^{\text{Age}}$



EXAMEN DES URINES



PROTEINURIE PHYSIOLOGIQUE

Protéinurie physiologique :

< 150 mg/24h constituée de:

□ 50% des protéines ultrafiltrées

➤ 20 à 30 mg d'albumine

➤ 10 à 20 mg de protéines de bas PM

(lysozyme :15kD, β 2-microglobuline :12 kD, CL κ et λ d'Ig : 22 kD, ...)

□ 50 % (40 à 60 mg) de protéines secrétées

➤ **Uromoduline** ou Protéine de **Tamm-Horsfall** secrétée par la branche ascendante de l'anse de Henlé



DÉFINITIONS DE LA PROTÉINURIE

Tableau I. Stades de gravité en fonction des valeurs de protéinurie ou d'albuminurie obtenues selon les différentes méthodes de récolte et de dosage (inspiré des KDIGO) (1).

Méthodologie	Mesures	Catégories			
		A1	A2	A3	
		Normale à légèrement ↑	Modérément ↑ «(Microalbuminurie)»	Sévèrement ↑	Néphrotique ↑↑↑
Echantillon urinaire	Bandelette urinaire	Négatif à traces	Traces à +	+ ou supérieur	
Echantillon urinaire	PCR (mg/mmol)	<15	15-50	>50	>350
	(mg/g)	<150	150-500	>500	>3500
Echantillon urinaire	ACR (mg/mmol)	<3	3-30	>30	>220
	(mg/g)	<30	30-300	>300	> 2200
Urines de 24h	AER (mg/24h)	<30	30-300	>300	>2200
	PER (mg/24h)	<150	150-500	>500	>3500

PCR : ratio protéine sur créatinine; ACR : ratio albumine sur créatinine; PER : excrétion protéique (ou perte protéique);
AER : excrétion d'albumine (ou perte d'albumine).



Mortalité cardiovasculaire en fonction du DFG et de l'albuminurie

Cardiovascular mortality

	ACR <10	ACR 10–29	ACR 30–299	ACR ≥300
eGFR > 105	0.9	1.3	2.3	2.1
eGFR 90–105	Ref	1.5	1.7	3.7
eGFR 75–90	1.0	1.3	1.6	3.7
eGFR 60–75	1.1	1.4	2.0	4.1
eGFR 45–60	1.5	2.2	2.8	4.3
eGFR 30–45	2.2	2.7	3.4	5.2
eGFR 15–30	14	7.9	4.8	8.1

ACR: Albuminurie/Creatininurie Ratio, eGFR: estimated Glomerular Filtration Rate



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rénale chronique**

10% de la population

Diabète

HTA

Maladie familiale

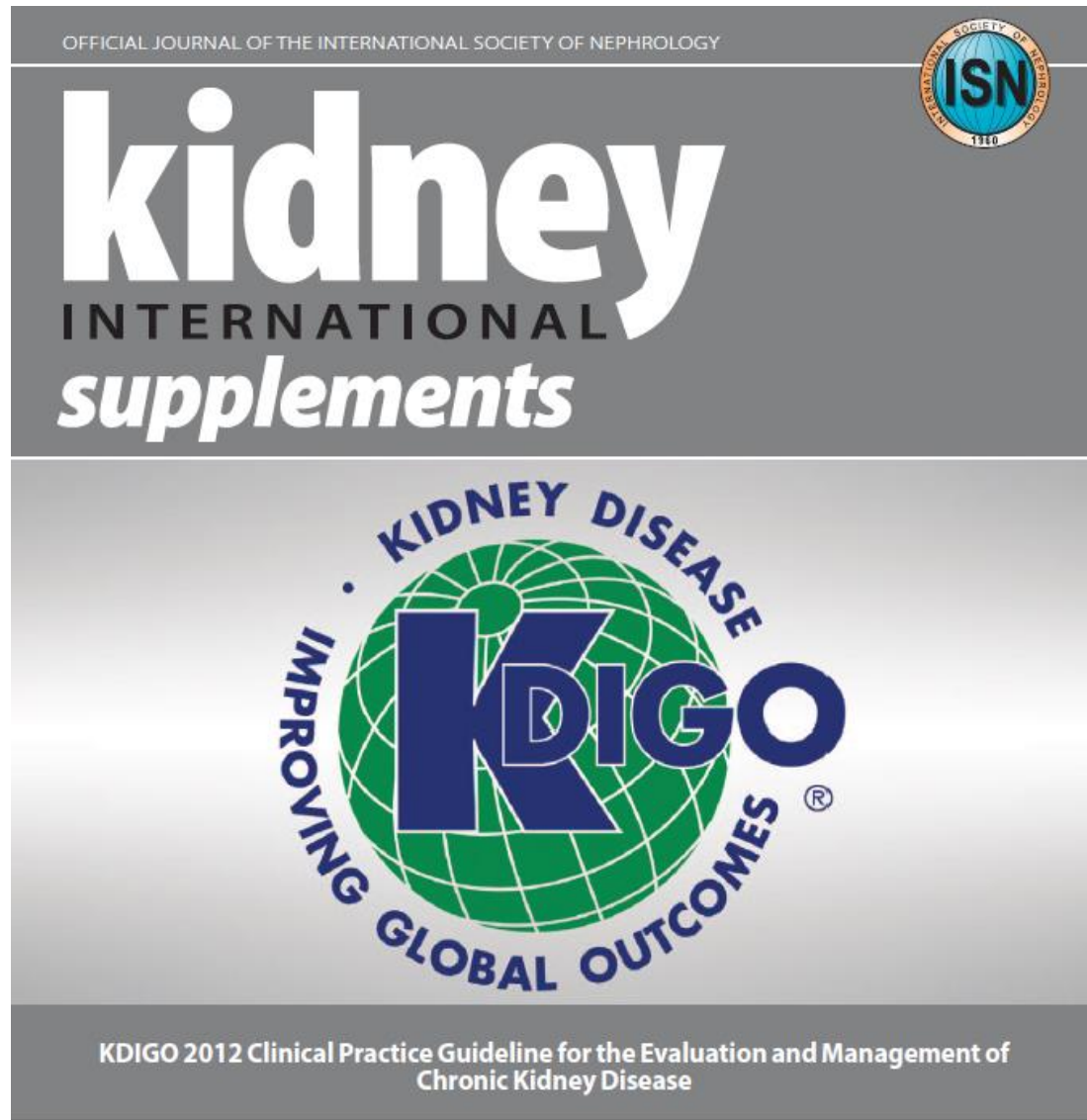


Définition de la maladie rénale chronique: Focus sur le DFG

- Age et définition de la MRC
- Chronicité



International guidelines in Nephrology



VOLUME 3 | ISSUE 1 | JANUARY 2013

<http://www.kidney-international.org>



GFR categories in CKD Chronic Kidney Disease

GFR category	GFR (ml/min/1.73 m ²)	Terms
G1	≥ 90	Normal or high
G2	60-89	Mildly decreased*
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	< 15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

*Relative to young adult level

In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

1.4.1: Evaluation of chronicity

1.4.1.1: In people with GFR < 60 ml/min/1.73 m² (GFR categories G3a-G5) or markers of kidney damage, review past history and previous measurements to determine duration of kidney disease. (*Not Graded*)

- If duration is > 3 months, CKD is confirmed. Follow recommendations for CKD.
- If duration is not > 3 months or unclear, CKD is not confirmed. Patients may have CKD or acute kidney diseases (including AKI) or both and tests should be repeated accordingly.

60 mL/min/1.73 m²



Deux sujets

- Age et définition de la MRC
- Chronicité



Justification de ce “cut-off” unique

- Simplicité
- Moitié de la valeur normale de DFG chez le jeune adulte mais arbitraire (et peut-être pas si correct)
- Parce qu'un $DFG < 60 \text{ mL/min/1.73 m}^2$ est associé à un risque relatif plus élevé d'évènements cliniques péjoratifs



**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/1.73m 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			



Prévalence de la MRC $\approx 10\%$

11,1% (σ : 10,4% ♀ : 11,8%) **Mills KT, Kidney Int, 2015, p950**

Stage 3-5 : 5,3%

13,4% (σ : 12,8% ♀ : 14,6%) **Hill NR, PlosOne, 2016, e0158765**

Stage 3-5: 8,1%

Stage 3-5= sur base d'un DFG estimé seul $<60 \text{ mL/min/173m}^2$)



Comment définir une maladie?

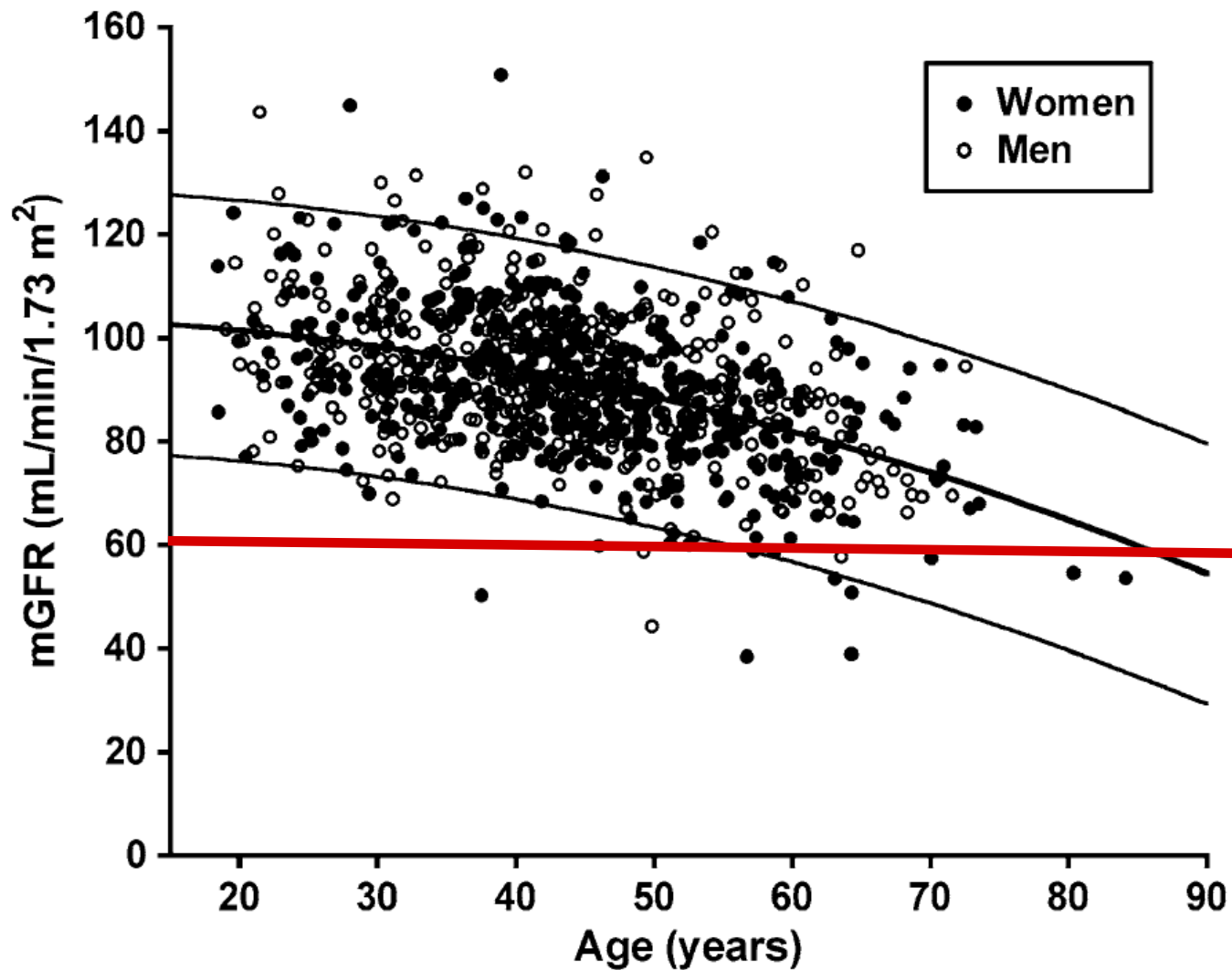
- Comme un résultat, un état statistiquement différent de la normalité
- Comme une condition qui est associée (association/ cause) à un risque augmenté de maladie, d'événement ou de mortalité



Comment définir une maladie?

- Comme un résultat, un état statistiquement différent de la normalité
- Comme une condition qui est associée (association/ cause) à un risque augmenté de maladie, d'événement ou de mortalité





DFG mesuré par ⁵¹Cr-EDTA chez 904 donneurs vivant potentiels



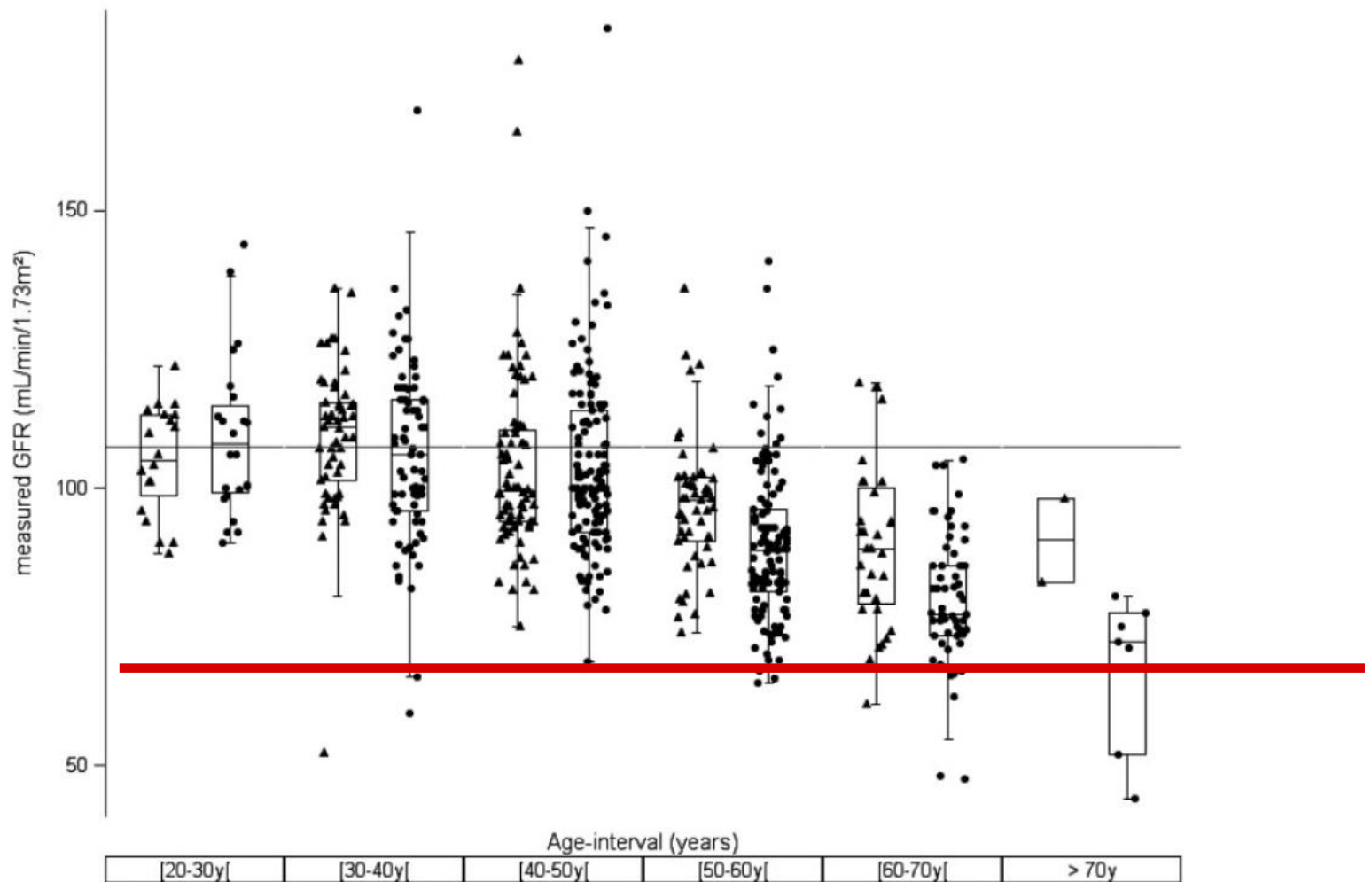
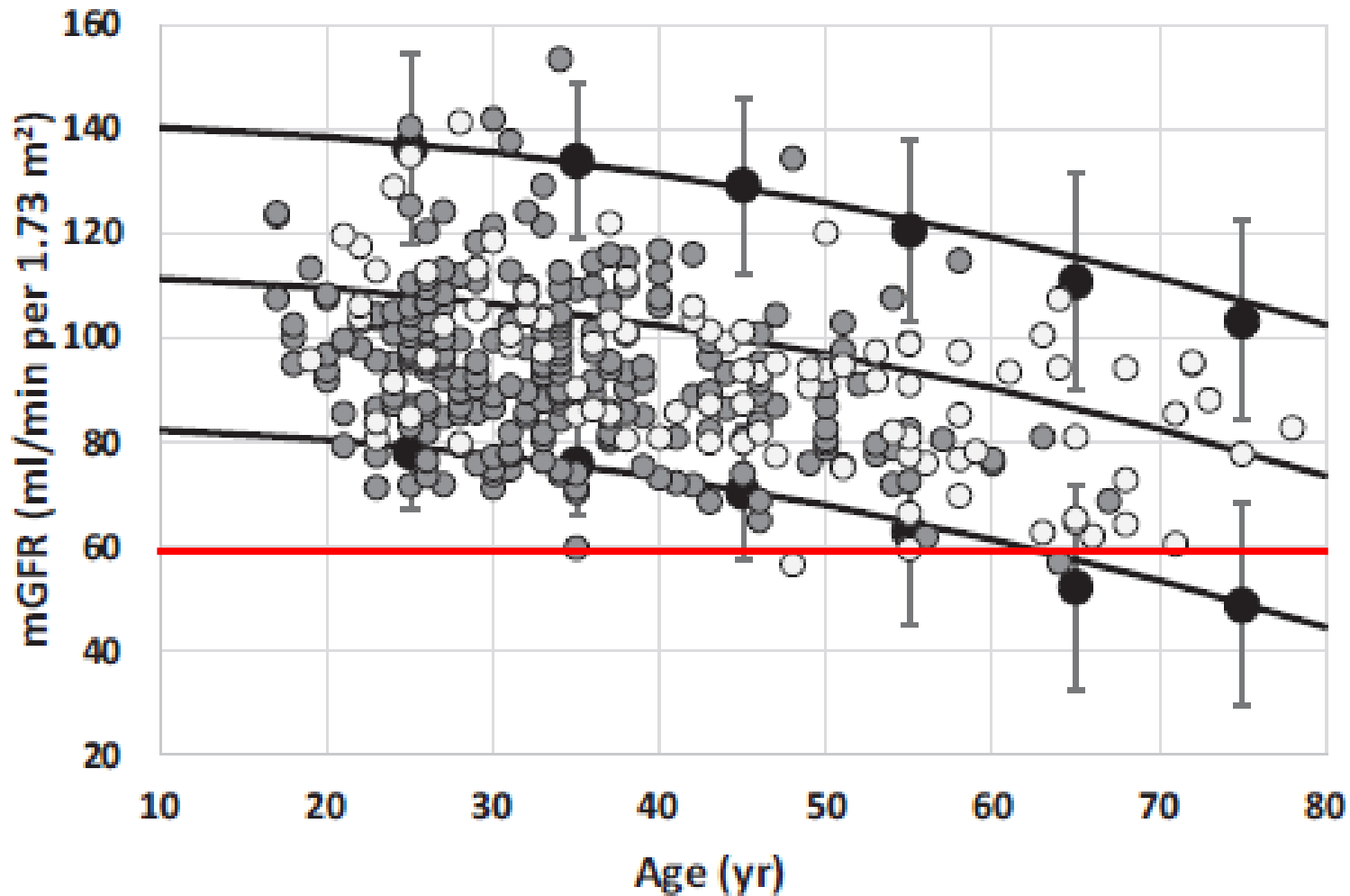


Fig. 1. Box plot for mGFR versus age decades for female (filled circles) and male (filled triangles) potential kidney donors ($n = 633$). A horizontal reference line is drawn at $GFR = 107.3 \text{ mL/min/1.73 m}^2$.

DFG chez 633 donneurs vivant potentiels (Belgique, France)





DFG mesuré en Afrique (iohexol)

Percentiles (lignes et cercles noirs) pour donneurs vivant européens

Cercles gris = 237 sujets sains ivoiriens

Cercles blancs = 95 sujets sains congolais

Bukabau J, Delanaye P *Kidney Int*, 2019, p1181

Yayo E, Delanaye P, *Nephrol Dial Transplant*, 2018, p1176



- DFG mesuré diminue avec l'âge
- ...mais peu de données après 65 ans
- Cependant, il y a des raisons de penser que certains sujets sains de plus de 65 ans ont un DFG mesuré sous $60 \text{ mL/min/1.73m}^2$

=> Quid du DFG estimé?



- Population saine aux Pays-Bas
- Estimation du DFG par CKD-EPI
- Pas de diabète, pas d'hypertension, pas de traitement spécifique
- 1663 hommes 2073 femmes

Nephrol Dial Transplant (2011) 26: 3176–3181

doi: 10.1093/ndt/gfr003

Advance Access publication 16 February 2011

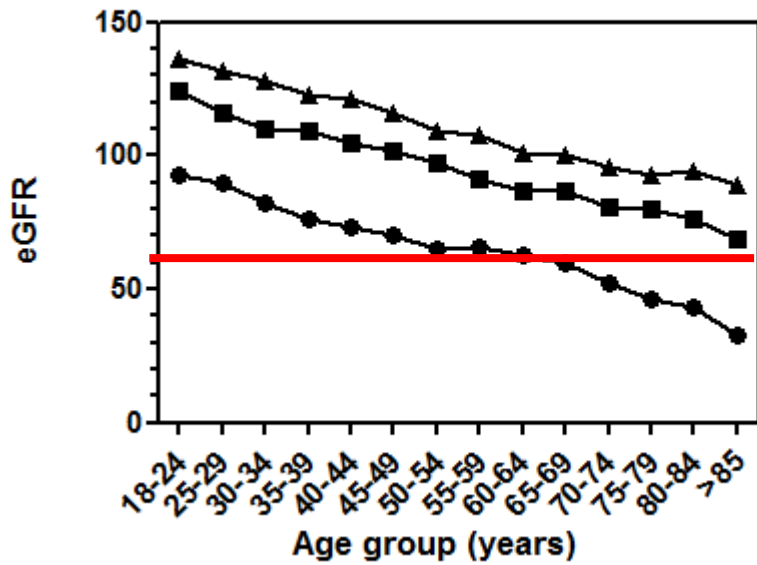
Introduction of the CKD-EPI equation to estimate glomerular filtration rate in a Caucasian population

Jan A.J.G. van den Brand¹, Gerben A.J. van Boekel¹, Hans L. Willems², Lambertus A.L.M. Kiemeny³, Martin den Heijer^{3,4} and Jack F.M. Wetzels¹

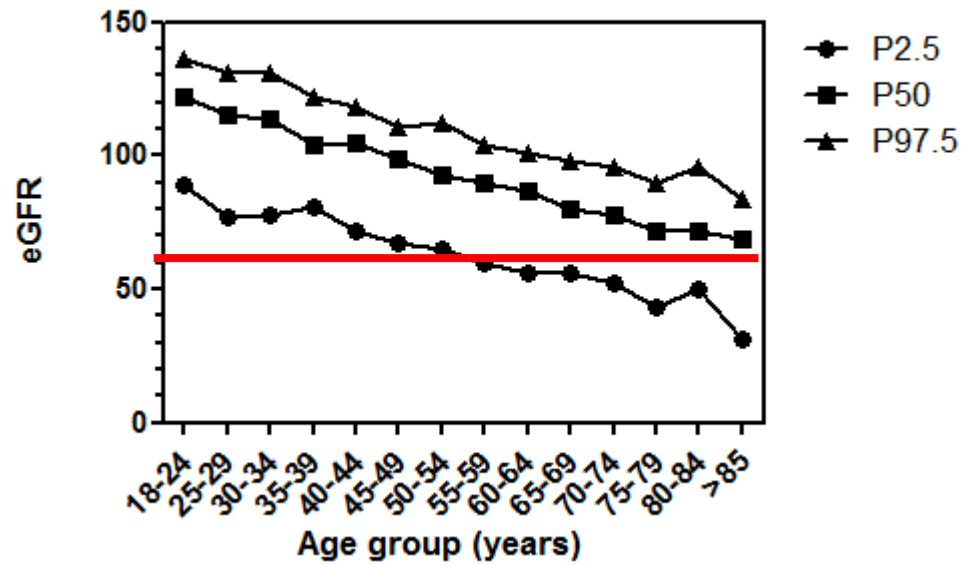
¹Department of Nephrology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, ²Department of Laboratory Medicine, Radboud University Medical Centre, Nijmegen, The Netherlands, ³Department of Epidemiology, Biostatistics and Health Technology Assessment, Radboud University Medical Centre, Nijmegen, The Netherlands and ⁴Department of Endocrinology, Radboud University Medical Centre, Nijmegen, The Netherlands

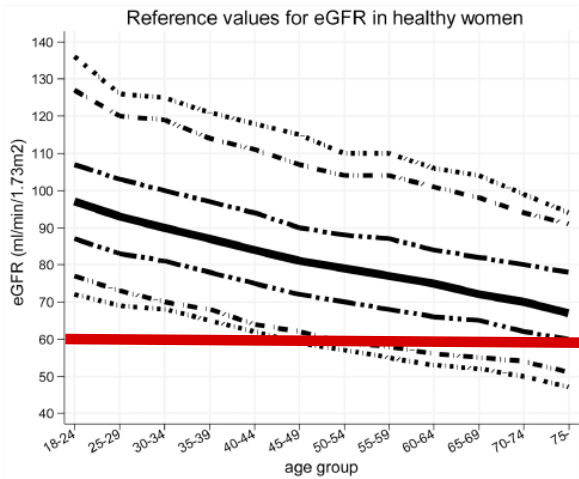
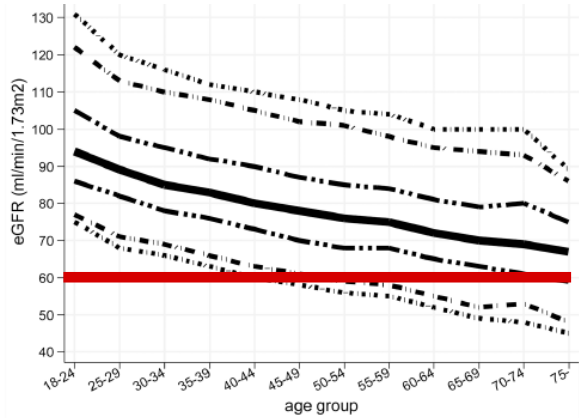


Men



Women





- - - 2.5 percentile - - - 5 percentile - - - 25 percentile - - - 50 percentile
 - - - 75 percentile - - - 95 percentile - - - 97.5 percentile

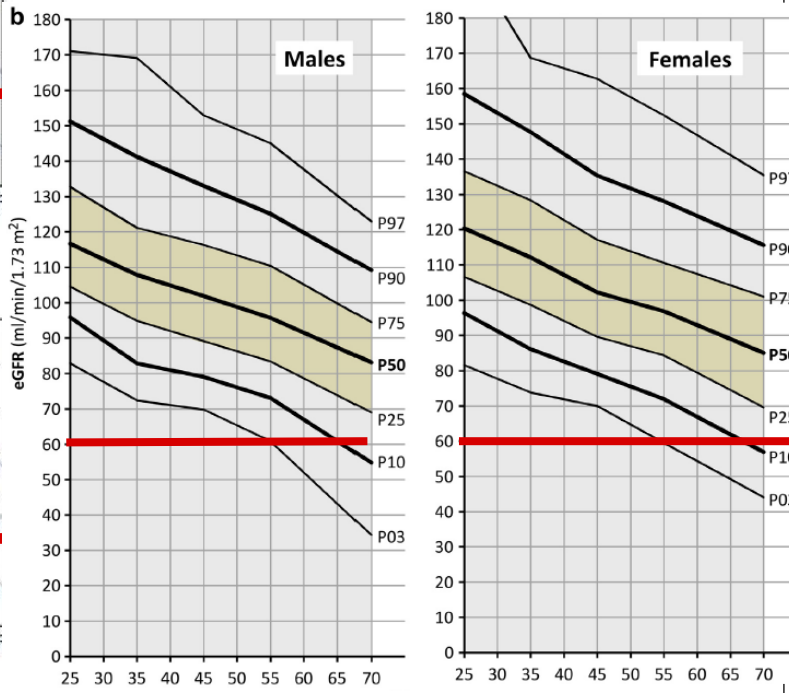
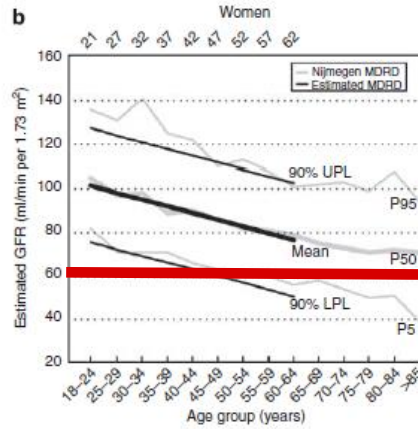
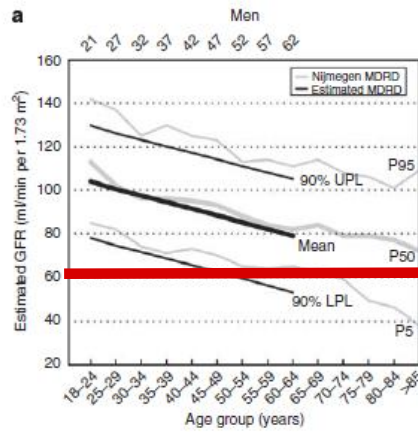


Figure 5 | Comparison of estimated GFR in two different cohorts. Mean, 5th, and 95th percentiles for expected eGFR by the re-expressed MDRD equation in living kidney donors (black lines) and eGFR by the re-expressed MDRD equation in subjects participating in the Nijmegen study²⁸ (gray lines) among different age groups for (a) men and (b) women.

Pareil au Japon...

Baba M, PlosOne, 2015

Pareil aux USA...

Poggio ED, Kidney Int, 2009

Pareil au Maroc...

Benghanem Gharbi M, Kidney Int, 2015



- Données concordantes sur tous les continents
- Le DFG estimé diminue avec l'âge
- Une part significative des sujets sains de plus de 65 ans ont un DFG estimé $<60\text{mL}/\text{min}/1.73\text{m}^2$



Comment définir une maladie?

- Comme un résultat, un état statistiquement différent de la normalité

=> argument pour une définition de la MRC adaptée à l'âge




Comment définir une maladie?

- Comme un résultat, un état statistiquement différent de la normalité
- Comme une condition qui est associée (association/cause) à un risque augmenté de maladie, d'événement ou de mortalité

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/1.73m ²) Description and range	G1	Normal or high	≥90		
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	G3a	Mildly to moderately decreased	45-59		
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	G4	Severely decreased	15-29		
	G5	Kidney failure	<15		



Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis

Caroline S Fox, Kunihiro Matsushita, Mark Woodward, Henk J G Bilo, John Chalmers, Hidde J Lambers Heerspink, Brian J Lee, Robert M Perkins, Peter Rossing, Toshimi Sairenchi, Marcello Tonelli, Joseph A Vassalotti, Kazumasa Yamagishi, Josef Coresh, Paul E de Jong, Chi-Pang Wen, Robert G Nelson, for the Chronic Kidney Disease Prognosis Consortium

Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: a meta-analysis

Bakhtawar K Mahmoodi, Kunihiro Matsushita, Mark Woodward, Peter J Blankestijn, Massimo Cirillo, Takayoshi Ohkubo, Peter Rossing, Mark J Sarnak, Bénédicte Stengel, Kazumasa Yamagishi, Kentaro Yamashita, Luxia Zhang, Josef Coresh, Paul E de Jong, Brad C Astor, for the Chronic Kidney Disease Prognosis Consortium

ONLINE FIRST

Age and Association of Kidney Measures With Mortality and End-stage Renal Disease

BMJ 2013;346:f324 doi: 10.1136/bmj.f324 (Published 29 January 2013)

Page 1 of 14

RESEARCH

Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis

 OPEN ACCESS



Measures of chronic kidney disease and risk of incident peripheral artery disease: a collaborative meta-analysis of individual participant data



*Kunihiro Matsushita, Shoshana H Ballew, Josef Coresh, Hisatomi Arima, Johan Ärnlöv, Massimo Cirillo, Natalie Ebert, Jade S Hiramoto, Heejin Kimm, Michael G Shlipak, Frank L J Visseren, Ron T Gansevoort, Csaba P Kovesdy, Varda Shalev, Mark Woodward, Florian Kronenberg, for the Chronic Kidney Disease Prognosis Consortium**

Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data



*Kunihiro Matsushita, Josef Coresh, Yingying Sang, John Chalmers, Caroline Fox, Eliseo Guallar, Tazeen Jafar, Simerjot K Jassal, Gijs W D Landman, Paul Muntner, Paul Roderick, Toshimi Sairenchi, Ben Schöttker, Anoop Shankar, Michael Shlipak, Marcello Tonelli, Jonathan Townsend, Arjan van Zuijlen, Kazumasa Yamagishi, Kentaro Yamashita, Ron Gansevoort, Mark Sarnak, David G Warnock, Mark Woodward, Johan Ärnlöv, for the Chronic Kidney Disease Prognosis Consortium**

<http://www.kidney-international.org>

clinical investigation

© 2014 International Society of Nephrology

Relative risks of chronic kidney disease for mortality and end-stage renal disease across races are similar

Chi Pang Wen^{1,2}, Kunihiro Matsushita³, Josef Coresh³, Kunitoshi Iseki⁴, Muhammad Islam⁵, Ronit Katz⁶, William McClellan⁷, Carmen A. Peralta⁸, HaiYan Wang⁹, Dick de Zeeuw¹⁰, Brad C. Astor^{11,12}, Ron T. Gansevoort¹³, Andrew S. Levey¹⁴, Adeera Levin¹⁵ and for the Chronic Kidney Disease Prognosis Consortium

Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts

Marije van der Velde¹, Kunihiro Matsushita², Josef Coresh², Brad C. Astor², Mark Woodward³, Andrew S. Levey⁴, Paul E. de Jong¹, Ron T. Gansevoort¹ and the Chronic Kidney Disease Prognosis Consortium

Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts

Ron T. Gansevoort¹, Kunihiro Matsushita², Marije van der Velde¹, Brad C. Astor², Mark Woodward³, Andrew S. Levey⁴, Paul E. de Jong¹, Josef Coresh² and the Chronic Kidney Disease Prognosis Consortium

Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts

Brad C. Astor¹, Kunihiro Matsushita¹, Ron T. Gansevoort², Marije van der Velde², Mark Woodward³, Andrew S. Levey⁴, Paul E. de Jong², Josef Coresh¹ and the Chronic Kidney Disease Prognosis Consortium



Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis



Chronic Kidney Disease Prognosis Consortium*

Lancet 2010; 375: 2073-81

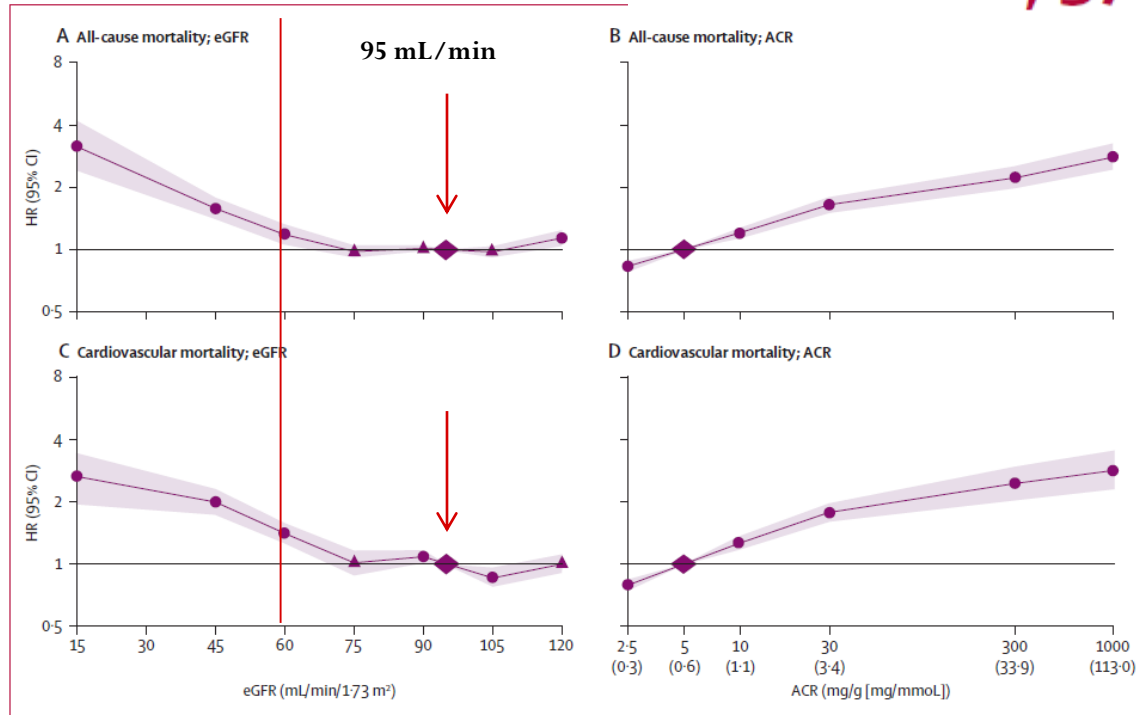


Figure 2: Hazard ratios and 95% CIs for all-cause and cardiovascular mortality according to spline estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR)

Hazard ratios and 95% CIs (shaded areas) according to eGFR (A, C) and ACR (B, D) adjusted for each other, age, sex, ethnic origin, history of cardiovascular disease, systolic blood pressure, diabetes, smoking, and total cholesterol. The reference (diamond) was eGFR 95 mL/min/1.73 m² and ACR 5 mg/g (0.6 mg/mmol), respectively. Circles represent statistically significant and triangles represent not significant. ACR plotted in mg/g. To convert ACR in mg/g to mg/mmol multiply by 0.113. Approximate conversions to mg/mmol are shown in parentheses.

- 105,872 sujets de 14 études avec ACR
- 1,128,310 sujets de 7 études avec BU



Il existe une discordance entre

les données descriptives qui démontrent un déclin du DFG
“normal” avec l’âge

=> argument pour une définition de la MRC adaptée à l’âge

les données prédictives qui confirment le choix d’un “cut-
off” unique pour la définition de la MRC

=> argument pour une définition basée sur un seuil fixe



- Notre hypothèse: la définition de la MRC devrait être adaptée à l'âge

Mais...

- Quid de l'argument prédictif?
- Avons-nous une alternative?
- Est-ce finalement important du point de vue épidémiologique?



- Notre hypothèse: la définition de la MRC devrait être adaptée à l'âge

Mais...

- Quid de l'argument prédictif?
- Avons-nous une alternative?
- Est-ce finalement important du point de vue épidémiologique?



Back to the « prognostic » argument

ORIGINAL CONTRIBUTION

ONLINE FIRST

Age and Association of Kidney Measures With Mortality and End-stage Renal Disease

Stein I. Hallan, MD, PhD

Kunihiro Matsushita, MD, PhD

Yingying Sang, MS

Bakhtawar K. Mahmoodi, MD, PhD

Corri Black, MBChB, MSc, FFPH

Areef Ishani, MD, MS

Nanne Kleefstra, MD, PhD

David Naimark, MD, MSc, FRCP(C)

Paul Roderick, MD, FRCP

Marcello Tonelli, MD, SM

Jack F. M. Wetzels, MD, PhD

Brad C. Astor, PhD, MPH

Ron T. Gansevoort, MD, PhD

Adeera Levin, MD

Chi-Pang Wen, MD, MPH, DrPH

Josef Coresh, MD, PhD

for the Chronic Kidney Disease
Prognosis Consortium

JAMA. 2012;308(22):2349-2360

N=2,051,044

33 cohortes de population “générale” ou “à risque”

13 cohortes de MRC

Suivi moyen: 5.3 années



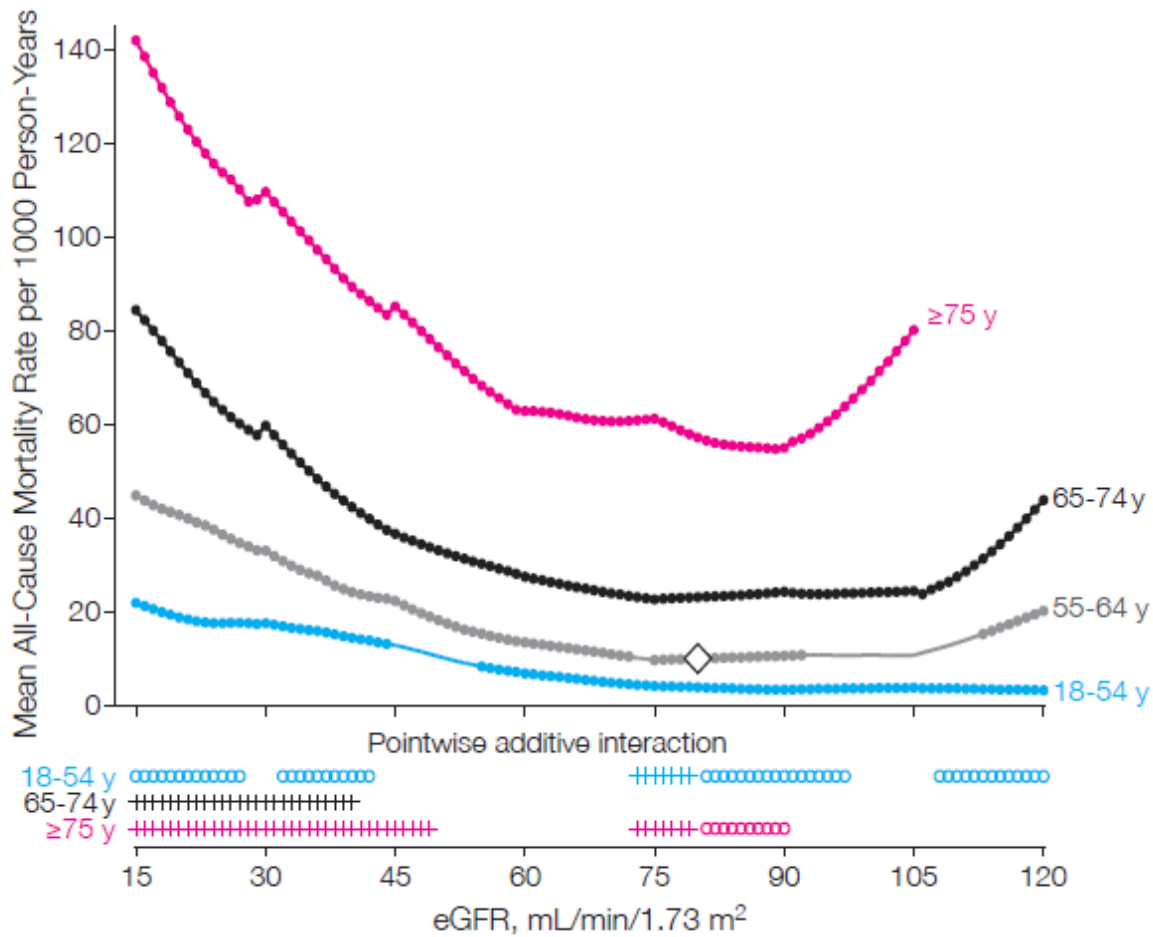
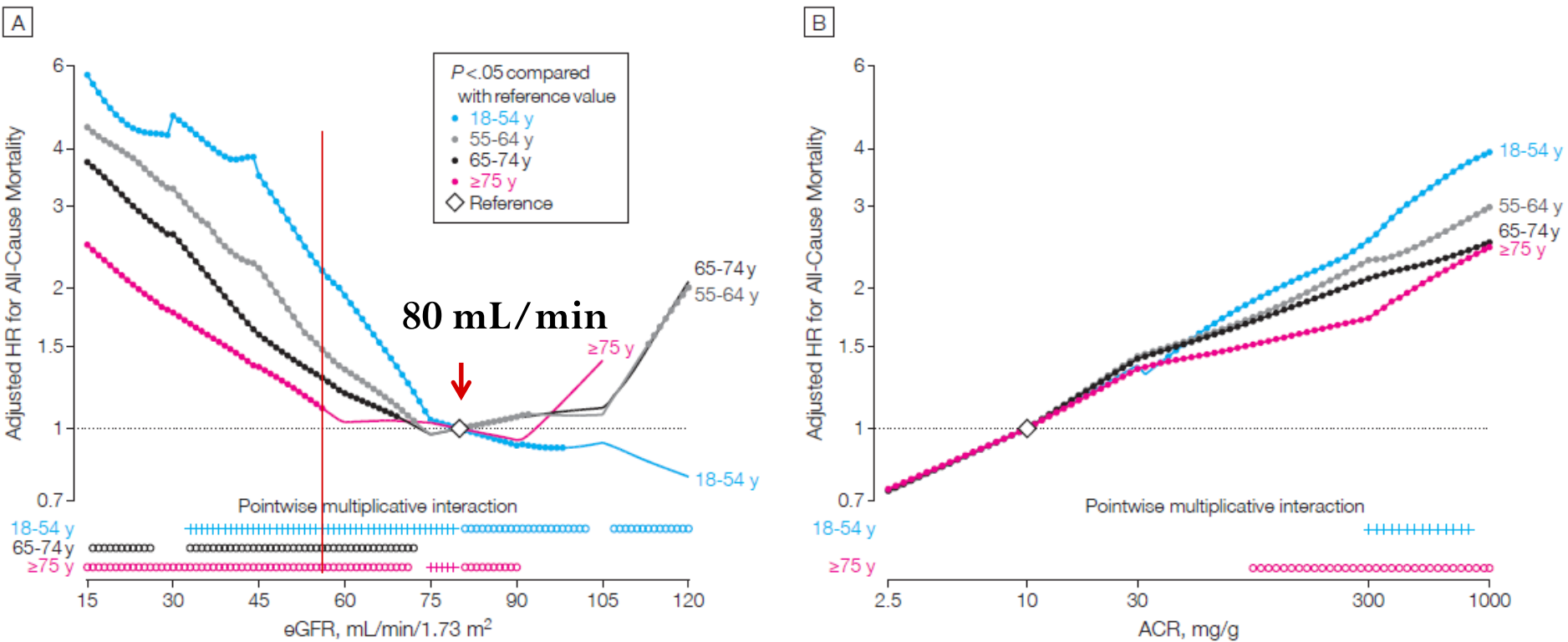


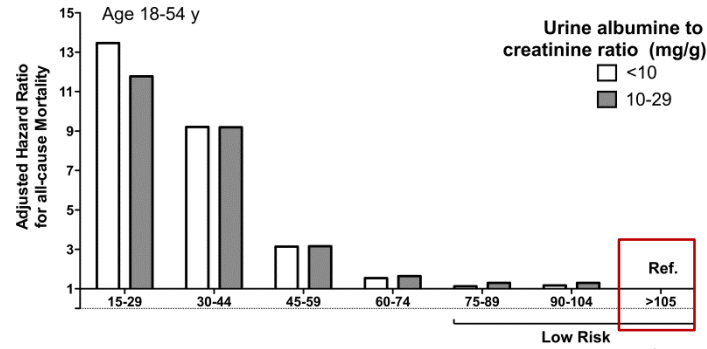
Figure 1. Adjusted Hazard Ratios (HRs) for All-Cause Mortality and Mean Mortality Rates According to eGFR and ACR Within Each Age Category



- Le DFG de “référence” est le même pour toutes les tranches d’âge
- On peut imaginer que cette référence change selon les âges
- Dans chaque tranche d’âge, nous proposons de choisir la référence comme étant la tranche de DFG avec la mortalité la plus basse



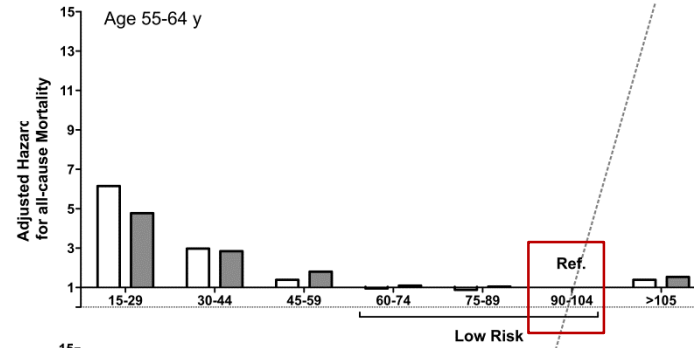
Age 18-54 ans =>



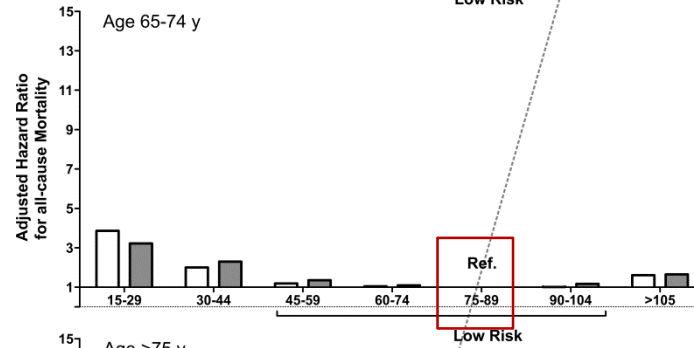
Data from:

JAMA. 2012;308(22):2349-2360

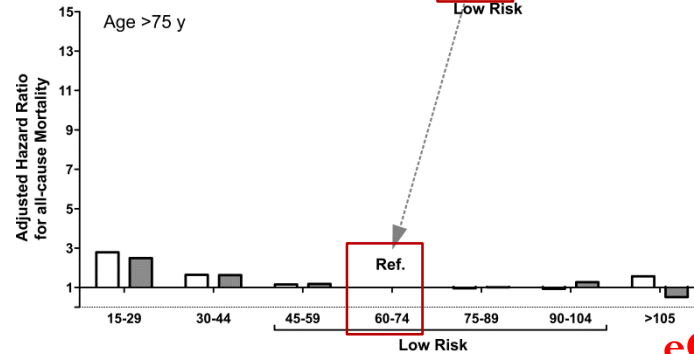
Age 55-64 ans =>



Age 65-74 ans =>



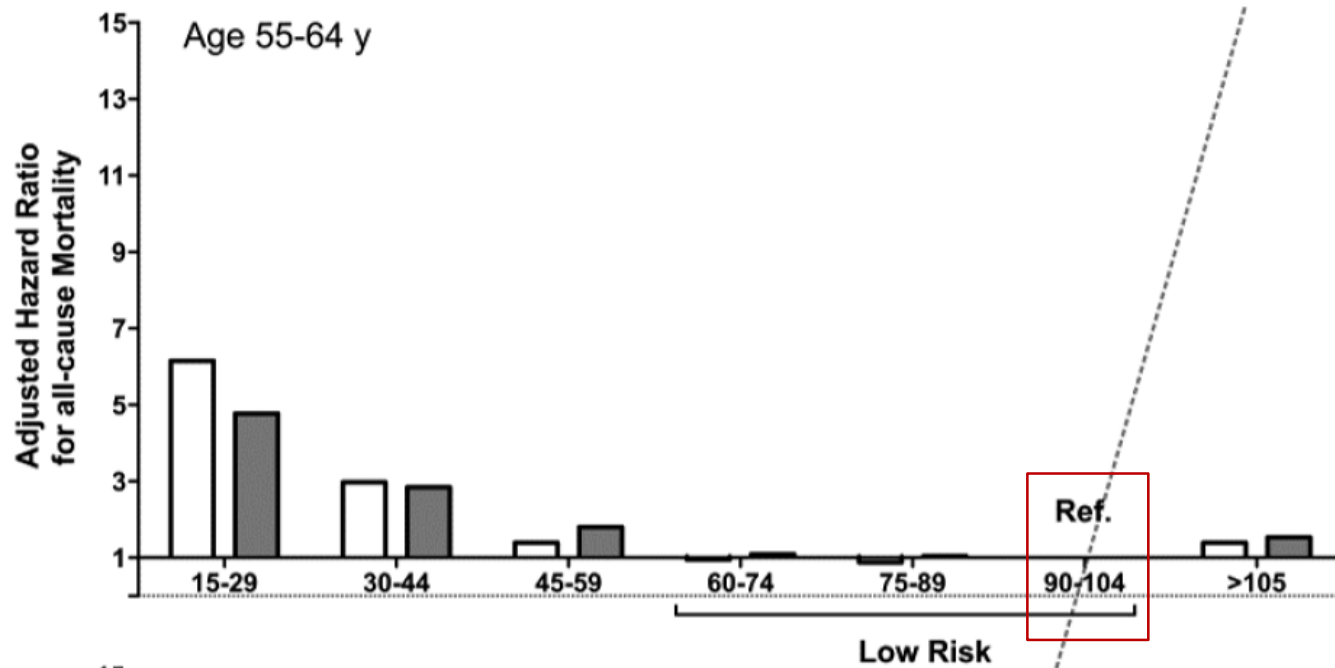
Age >75 ans =>



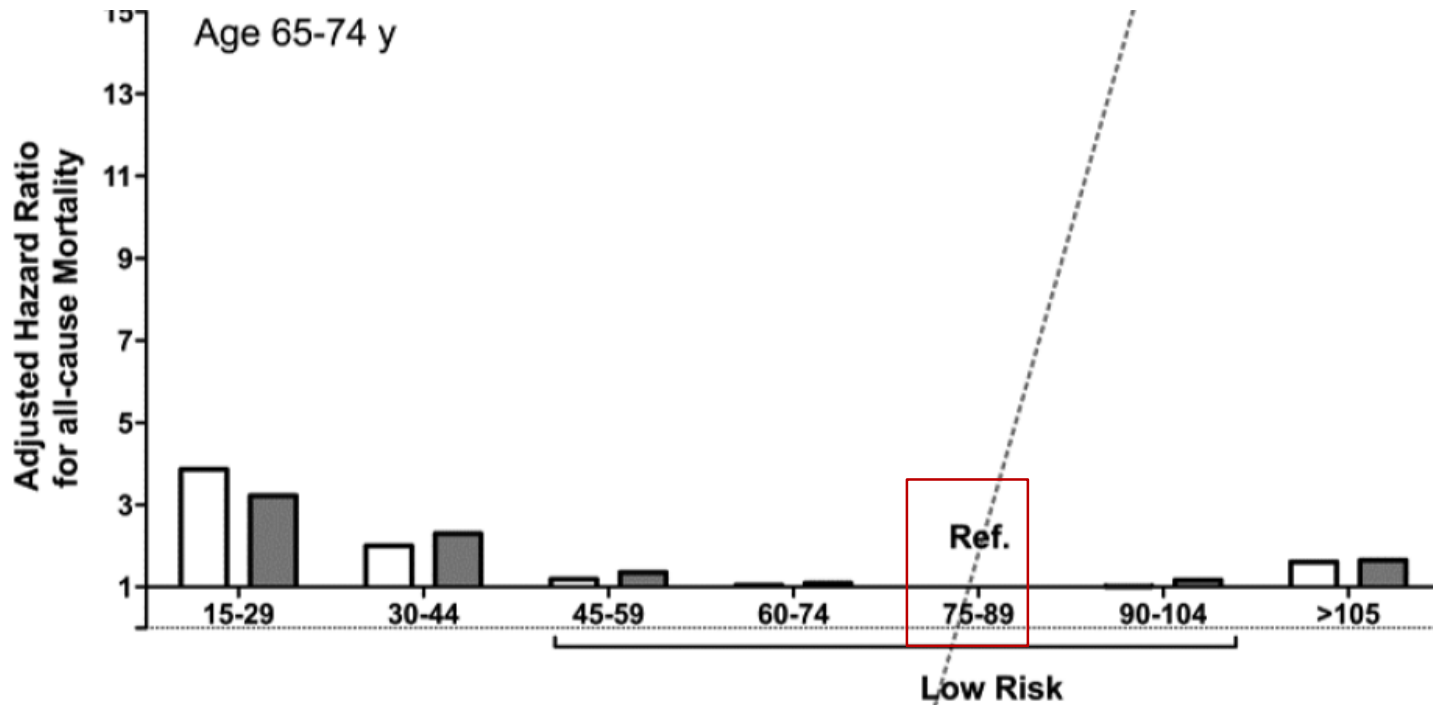
Delanaye P, Clin Biochem Rev, 2016, p17
Glasscock RJ, J Bras Nefrol, 2017, p59



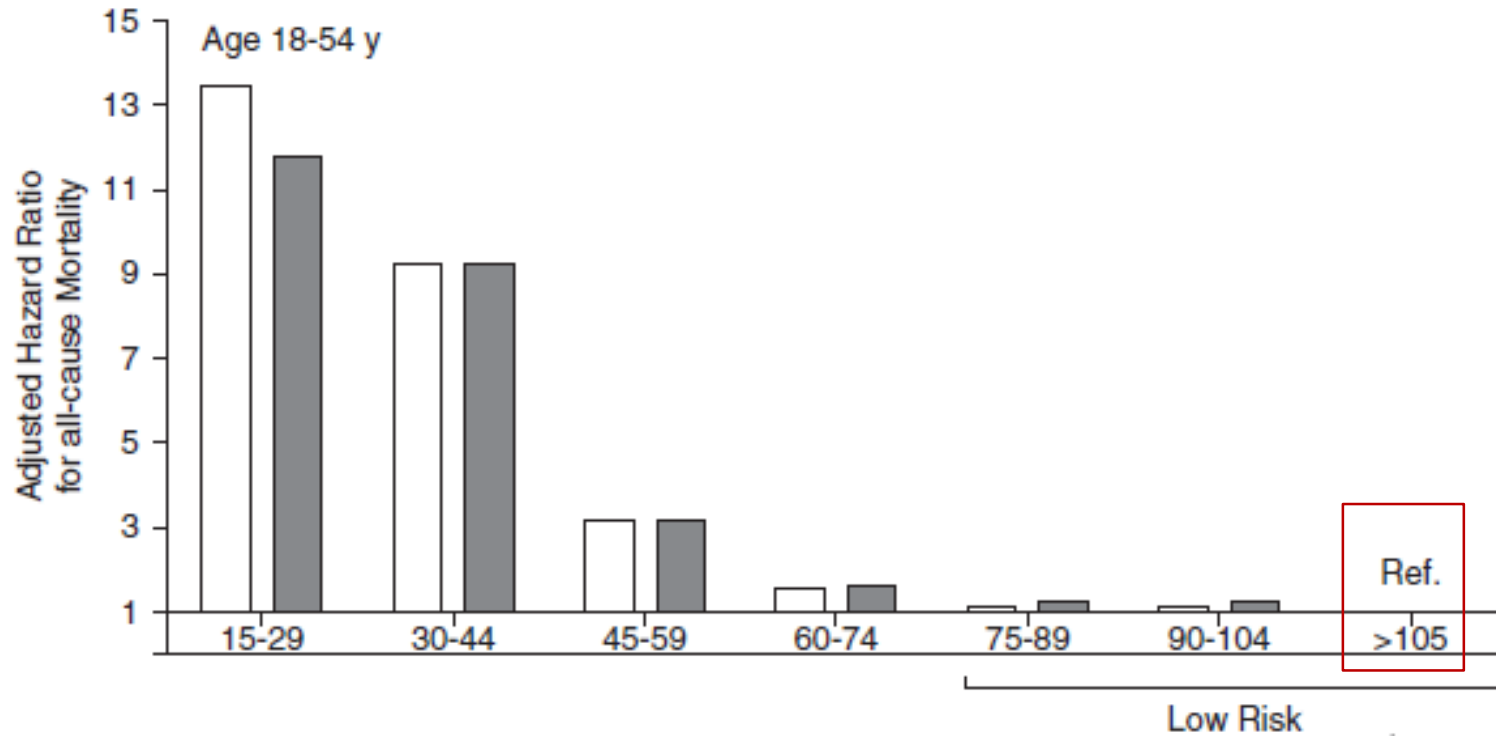
Age 55-64 ans

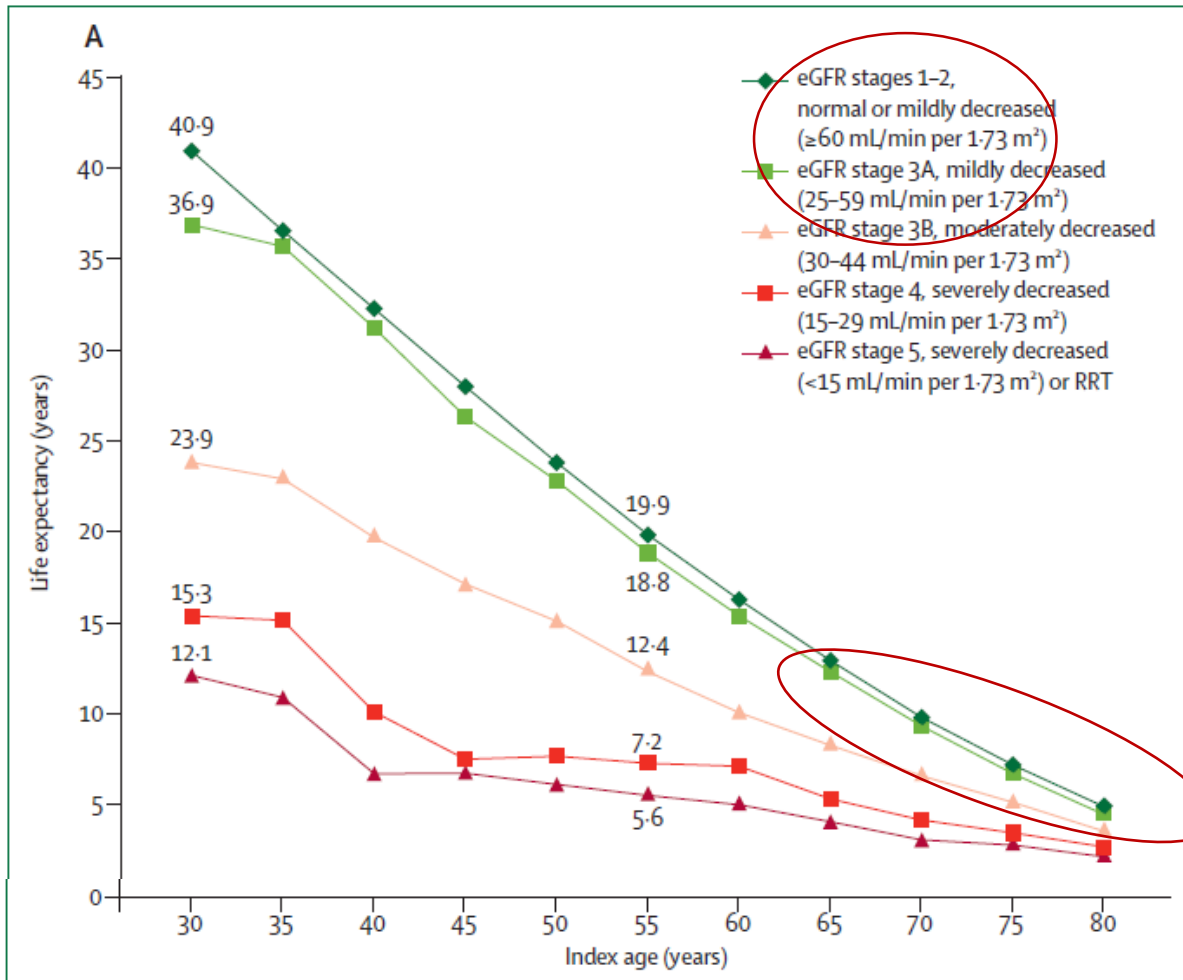


Age 64-75 ans



Age 18-55 ans





Life expectancy for stage 3A
N=949,119

Figure 2: Life expectancy, according to chronic kidney disease stages (Canadian data)

(A) eGFR stages and (B) albuminuria stages. Data are adjusted per eGFR and albuminuria stage for sex to the WHO world average in 2000-05. eGFR=estimated glomerular filtration rate. RRT=renal replacement therapy. Based on data in references 24 and 25 (appendix pp 1-2).



Risks for All-Cause Mortality: Stratified by Age, Estimated Glomerular Filtration Rate and Albuminuria

David G. Warnock^a Pierre Delanaye^c Richard J. Glassock^b

^aDepartment of Medicine, University of Alabama at Birmingham, Birmingham, AL, and ^bDepartment of Medicine, Geffen School of Medicine at UCLA, Los Angeles, CA, USA; ^cNephrology-Dialysis-Transplantation, University of Liège, Liège, Belgium

REGARDS,
n=26,887
3890 deaths (15%)

b. Relative risk ($\pm 95\%$ CI) for all-cause mortality: age, eGFR, and ACR strata^b

eGFR, mL/min/1.73 m ²	Age: <60		Age: 60–70		Age: >70	
	ACR <30 mg/g	ACR \geq 30 mg/g	ACR <30 mg/g	ACR \geq 30 mg/g	ACR <30 mg/g	ACR \geq 30 mg/g
>100	1.20 (0.95–1.52)	2.49 (1.77–3.49)	1.12 (0.97–1.38)	1.78 (1.29–2.45)	0.87 (0.67–1.12)	1.57 (1.07–2.31)
80–100	1.00 (reference) ^a	2.02 (1.36–3.01)	1.00 (reference) ^a	2.28 (1.79–2.91)	1.00 (reference) ^a	1.69 (1.42–2.00)
60–80	1.58 (1.17–2.12)	2.28 (1.40–3.73)	1.12 (0.94–1.34)	1.92 (1.46–2.53)	1.13 (1.01–1.26)	1.88 (1.60–2.12)
45–60	2.11 (1.23–3.61)	4.00 (2.13–7.51)	1.47 (1.08–1.99)	3.21 (2.32–4.43)	1.48 (1.28–1.70)	2.38 (2.00–2.84)
<45	2.96 (0.94–9.30)	6.80 (4.08–11.3)	2.59 (1.64–4.08)	7.13 (5.36–9.50)	2.22 (1.84–2.67)	3.71 (3.12–4.42)

^a Incidence rate ratio; relative to reference group for each age strata.

Color coding for relative risk of all-cause mortality: green, <1.5; yellow, >1.5 and <2.5; orange, >2.5 and <4.0; red, >4.0. Color version available online.



RESEARCH ARTICLE

Chronic Kidney Disease in Primary Care: Outcomes after Five Years in a **Prospective** Cohort Study

Adam Shardlow^{1,2*}, Natasha J. McIntyre¹, Richard J. Fluck¹, Christopher W. McIntyre³,
Maarten W. Taal^{1,2}

1 Renal Unit, Royal Derby Hospital, Derby, United Kingdom, **2** Centre for Kidney Research and Innovation, Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, The University of Nottingham, Royal Derby Hospital, Derby, United Kingdom, **3** Division of Nephrology, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada

* adam.shardlow@nhs.net

2016 PLOS Medicine | DOI:10.1371



- Renal Risk in Derby study: une étude de cohorte prospective et longitudinale
- Suivi (5 ans) de patients avec MRC stade 3 confirmée (soins primaires)
- N=1741
- Régression de la MRC: DFG_e>60 mL/min/1.73m² et pas d'albuminurie
- Progression de la MRC: 25% de déclin du DFG couple à un passage de stade de la MRC ou une augmentation du stade d'albuminurie

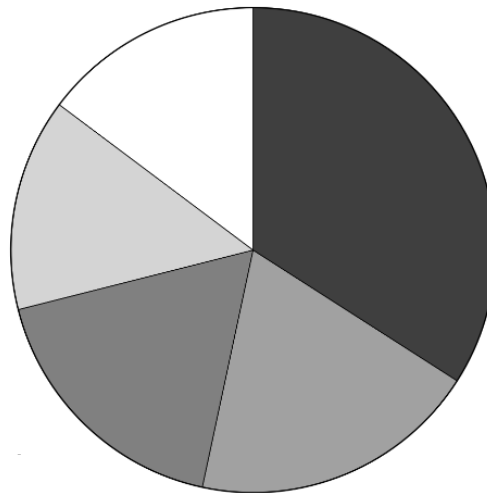


Variable (n)	Total (1,741)
Female Sex (%)	1,052 (60.4)
Age (years)	72.9 ± 9.0
eGFR-CKD-EPI (ml/min/1.73 m ²)	53.5 ± 11.8
eGFR-MDRD (ml/min/1.73 m ²)	52.5 ± 10.4
uACR (mg/mmol)	0.3 (0.0–1.5)

Diabetes (%)	294 (16.9)
CVD (%)	387 (22.2)
Current or Previous Smoker (%)	947 (54.4)
ACE/ARB use (%)	1,123 (64.5)
Weight (kg)	78.2 ± 15.5
BMI (kg/m ²)	29.0 ± 5.1
Waist:Hip Ratio	0.91 ± 0.09
SBP (mmHg)	134.0 ± 18.3
DBP (mmHg)	72.8 ± 11.0

Lost to Follow-up
n = 257 (14.7%)

Total Cohort
n = 1,741

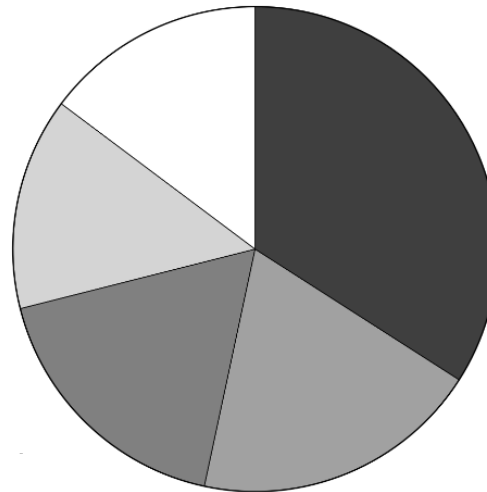


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■ Stable CKD
n = 593 (34.1%)

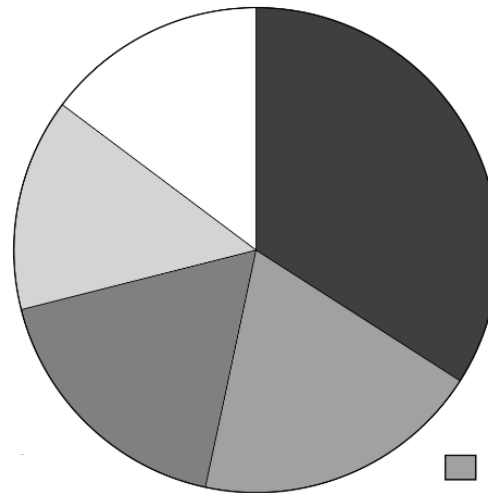


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□ Lost to Follow-up
n = 257 (14.7%)

Total Cohort
n = 1,741



■ Stable CKD
n = 593 (34.1%)

■ CKD Remission
n = 336 (19.3%)

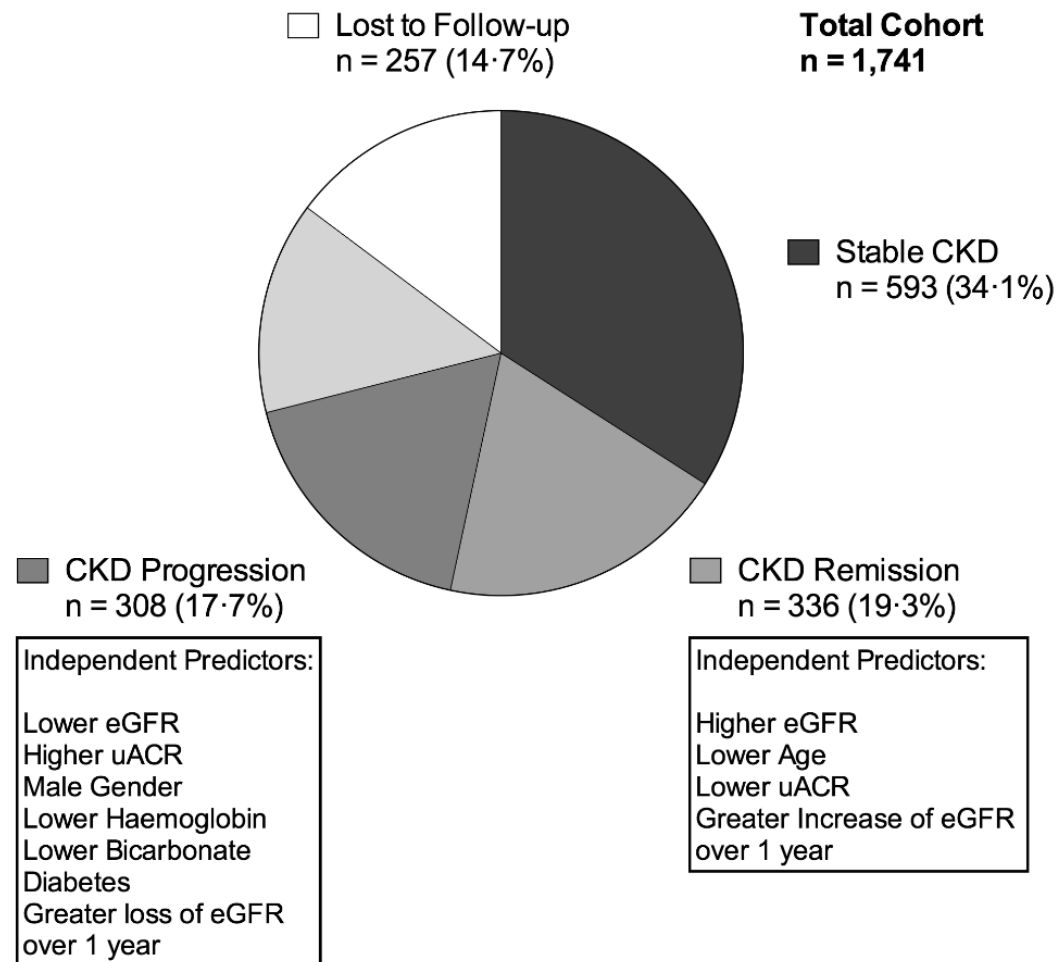
Independent Predictors:

Higher eGFR
Lower Age
Lower uACR
Greater Increase of eGFR
over 1 year



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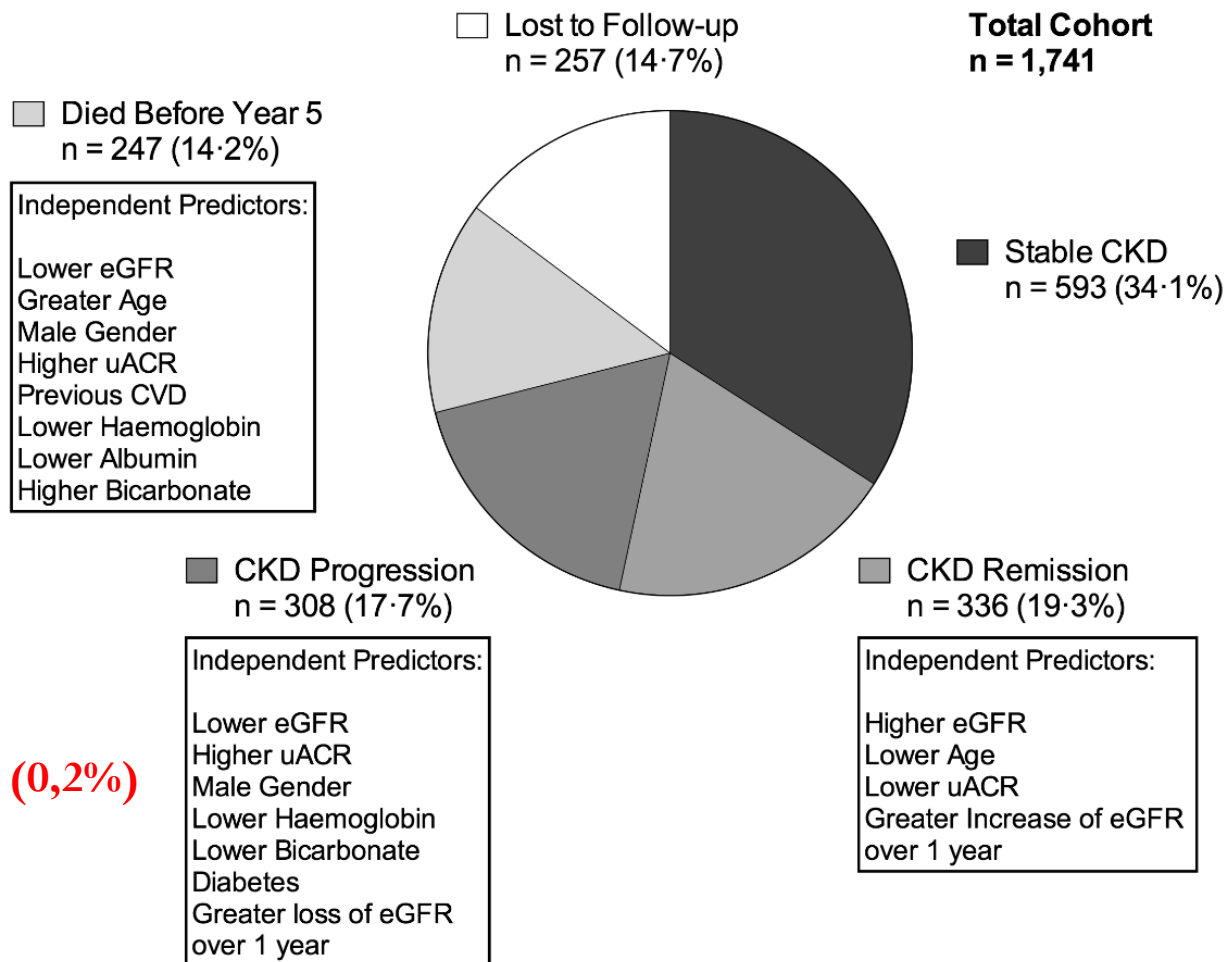


IRCT: n=4 (0,2%)



Variable (n)	Total (1,741)
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ESRD: n=4 (0,2%)



«overall age- and sex-standardized mortality rates were similar to general population rates, mortality was higher among participants with stage 3b or stage 4 CKD at baseline.»



Donc...

- Notre hypothèse: la définition de la MRC devrait être adaptée à l'âge

Mais...

- Quid de l'argument prédictif?

Il peut être discuté

Stade 3a chez le patient âgé SANS albuminurie n'est pas une MRC

- Avons-nous une alternative?
- Est-ce finalement important du point de vue épidémiologique?



Donc...

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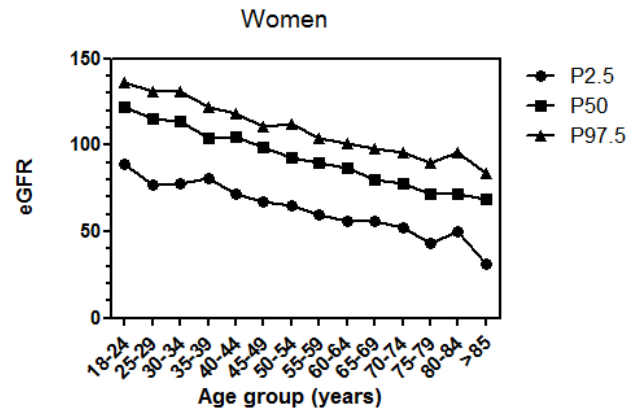
Stade 3a chez le patient âgé SANS albuminurie n'est pas une MRC

- Avons-nous une alternative?
- Est-ce finalement important du point de vue épidémiologique?



Alternative 1

- Percentiles (comme les pédiatres)



- Trop complexe...
- ...peut-être pas tant que cela à l'ère de l'informatique et avec l'aide des labos...



https://www.kuleuven-kulak.be/egfr_calculator/ by Pr Hans Pottel

Patient characteristics

Patient id

Age (years) 75

Sex Male
 Female

Race Afr. Am.
 Caucasian
 Other

Scr (mg/dL) 1.1

Cystatin C
(mg/L)

Height (cm) 175

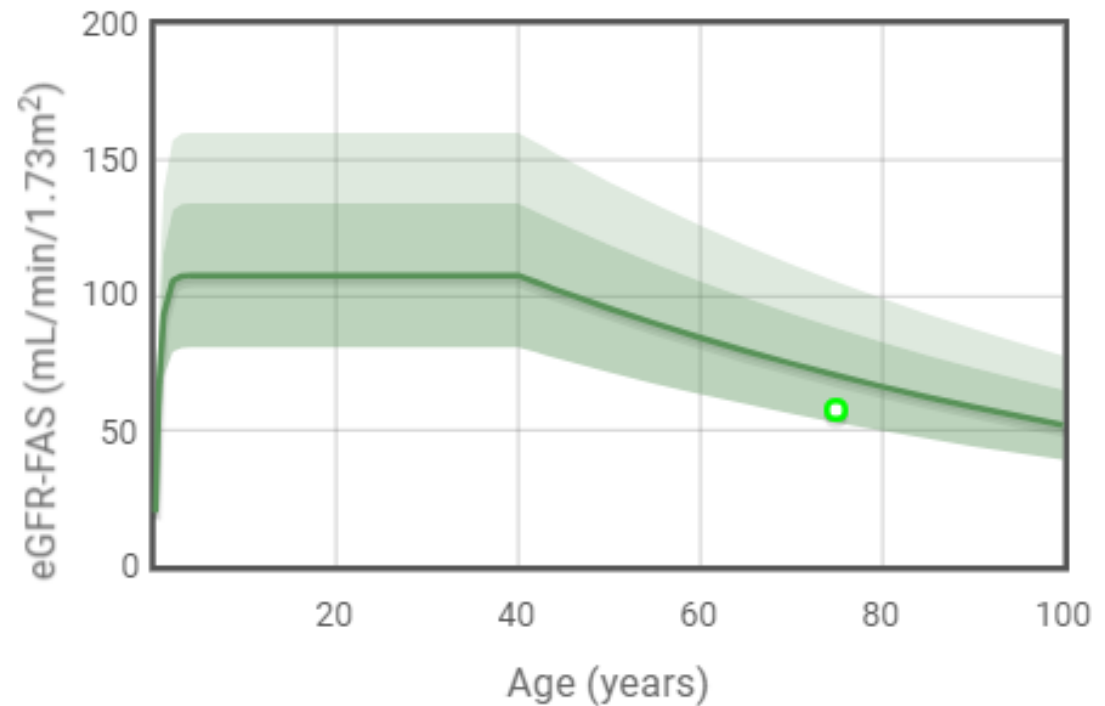
Weight (kg) 75

BSA (m²) 1.90

CALCULATE

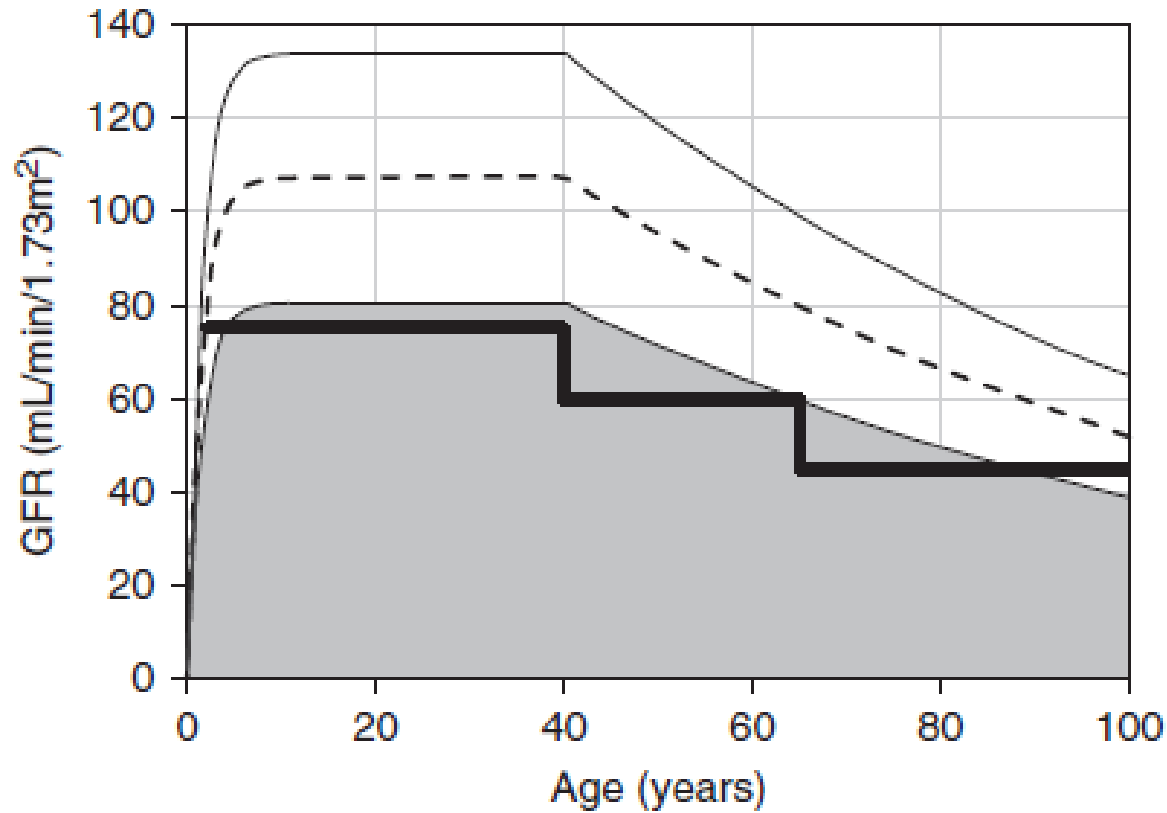
RESET

FAS prediction



Alternative 2

Seuils adaptés à l'âge



40 – 65 ans: 60 mL/min/1.73m²

<40 ans: 75 mL/min/1.73m²

>65 ans: 45 mL/min/1.73m²



Donc...

- Notre hypothèse: la définition de la MRC devrait être adaptée à l'âge

Mais...

- Quid de l'argument prédictif?

Il peut être discuté

Stade 3a chez le patient âgé SANS albuminurie n'est pas une MRC

- Avons-nous une alternative?
- Est-ce finalement important du point de vue épidémiologique?



Is it relevant or purely semantic?

CKD prevalence: 11.5%

CKD prevalence based on eGFR only: 4.8%

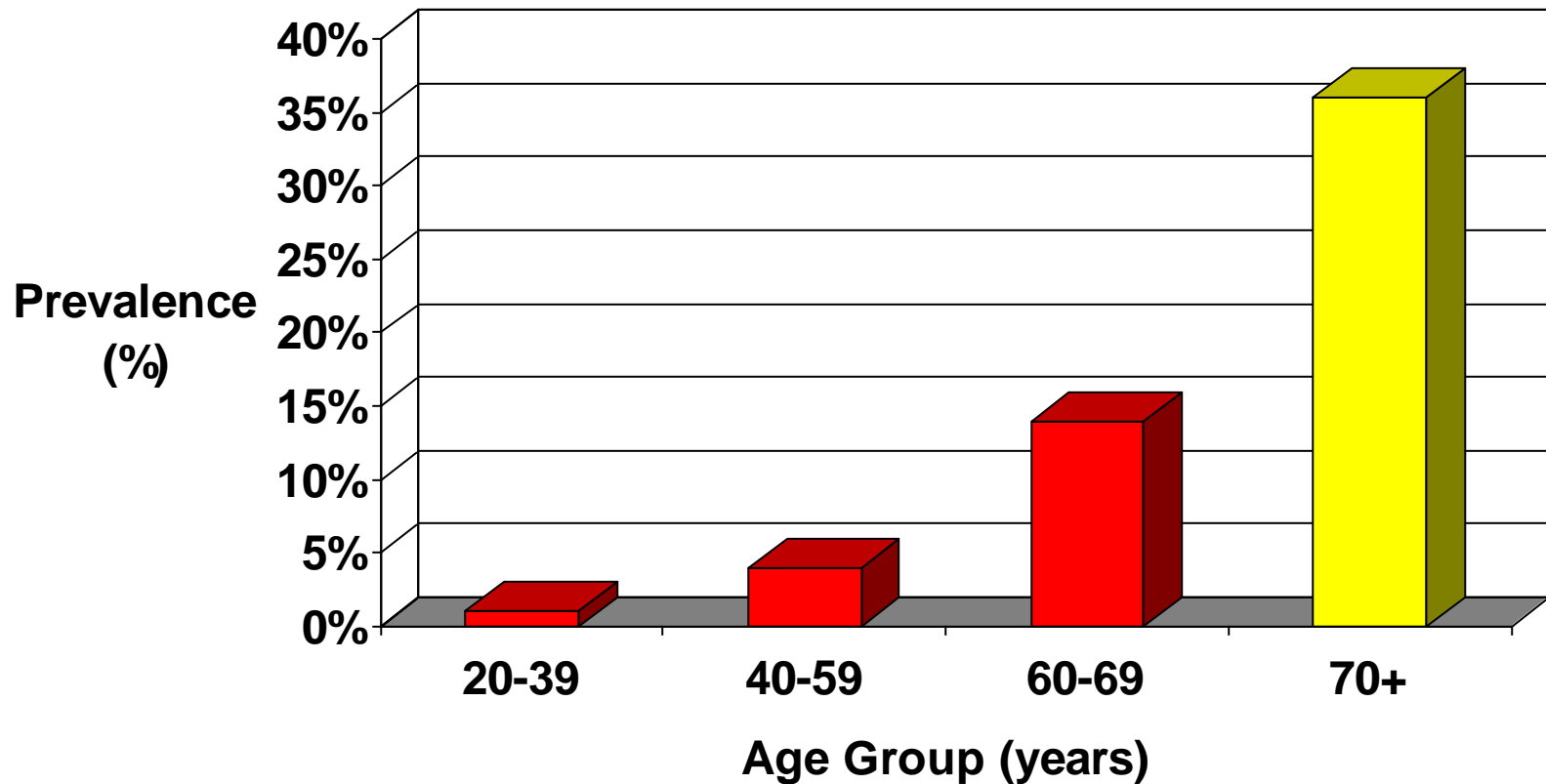
**Percentage of US Population by eGFR and Albuminuria
Category: KDIGO 2012 and NHANES 1999-2006**

				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 >30mg/mmol	
GFR categories (ml/min/1.73m ²) Description and range	G1	Normal or high	≥90	55.6	1.9	0.4	57.9
	G2	Mildly decreased	60-89	23.0	0.2	0.3	35.4
	G3a	Mildly to moderately decreased	45-59	3.6	0.8	0.2	4.6
	G3b	Moderately to severely decreased	30-44	1.0	0.4	0.2	1.6
	G4	Severely decreased	15-29	0.2	0.1	0.1	0.4
	G5	Kidney failure	<15	0.0	0.0	0.1	0.1
				93.2	5.4	1.3	100.0

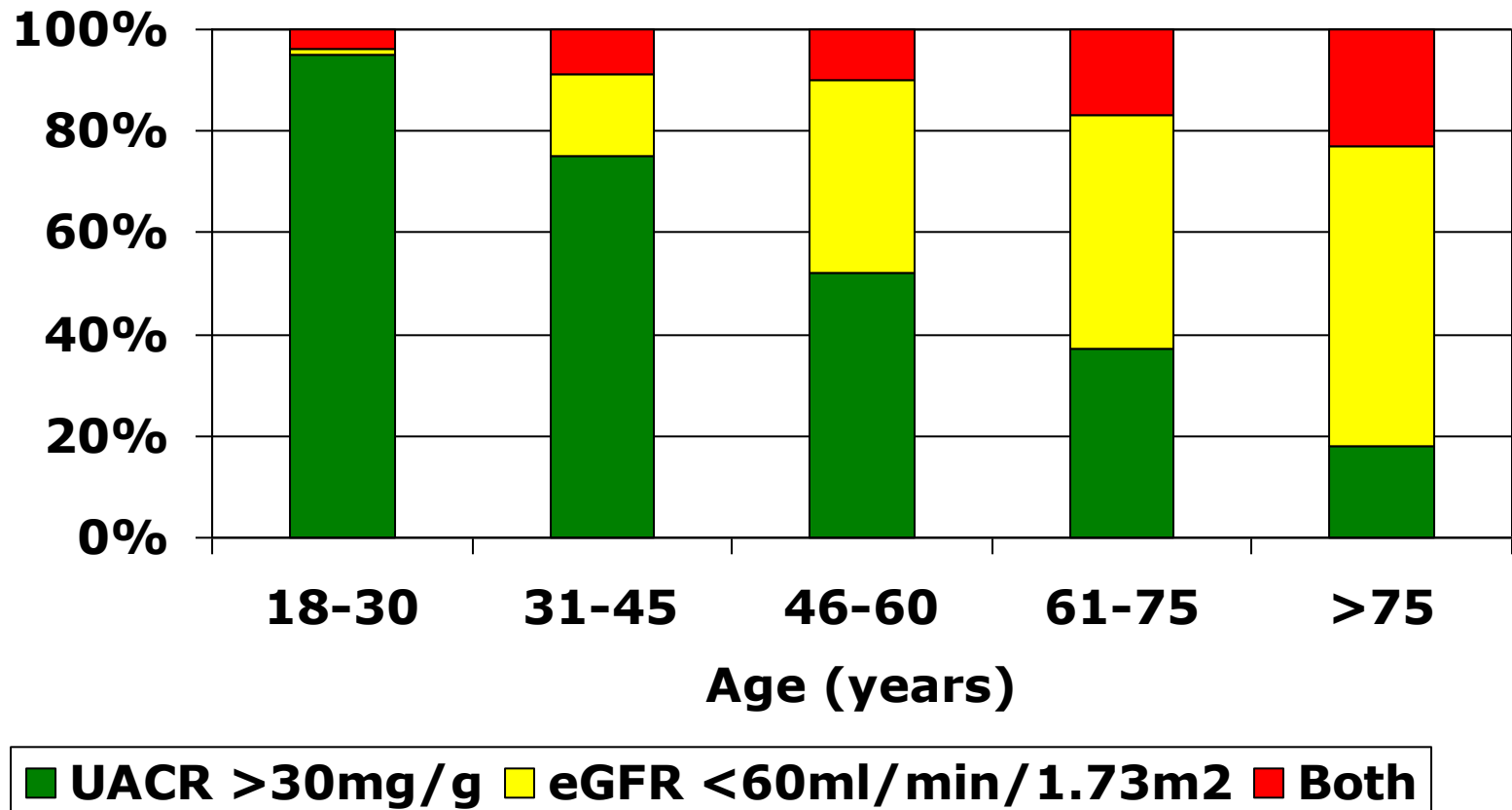


Prevalence of stage 3 according to age in NHANES study

(and all other studies)



Characteristics of CKD populations



Courtesy by RJ Glasscock, Adapted from James MT, et al Lancet 375:1296, 2010



Chronic kidney disease, hypertension, diabetes, and obesity in the adult population of Morocco: how to avoid “over”- and “under”-diagnosis of CKD

Mohammed Benghanem Gharbi^{1,6}, Monique Elseviers^{2,6}, Mohamed Zamd¹, Abdelali Belghiti Alaoui³, Naïma Benahadi³, El Hassane Trabelssi³, Rabia Bayahia⁴, Benyounès Ramdani¹ and Marc E. De Broe^{5,6}

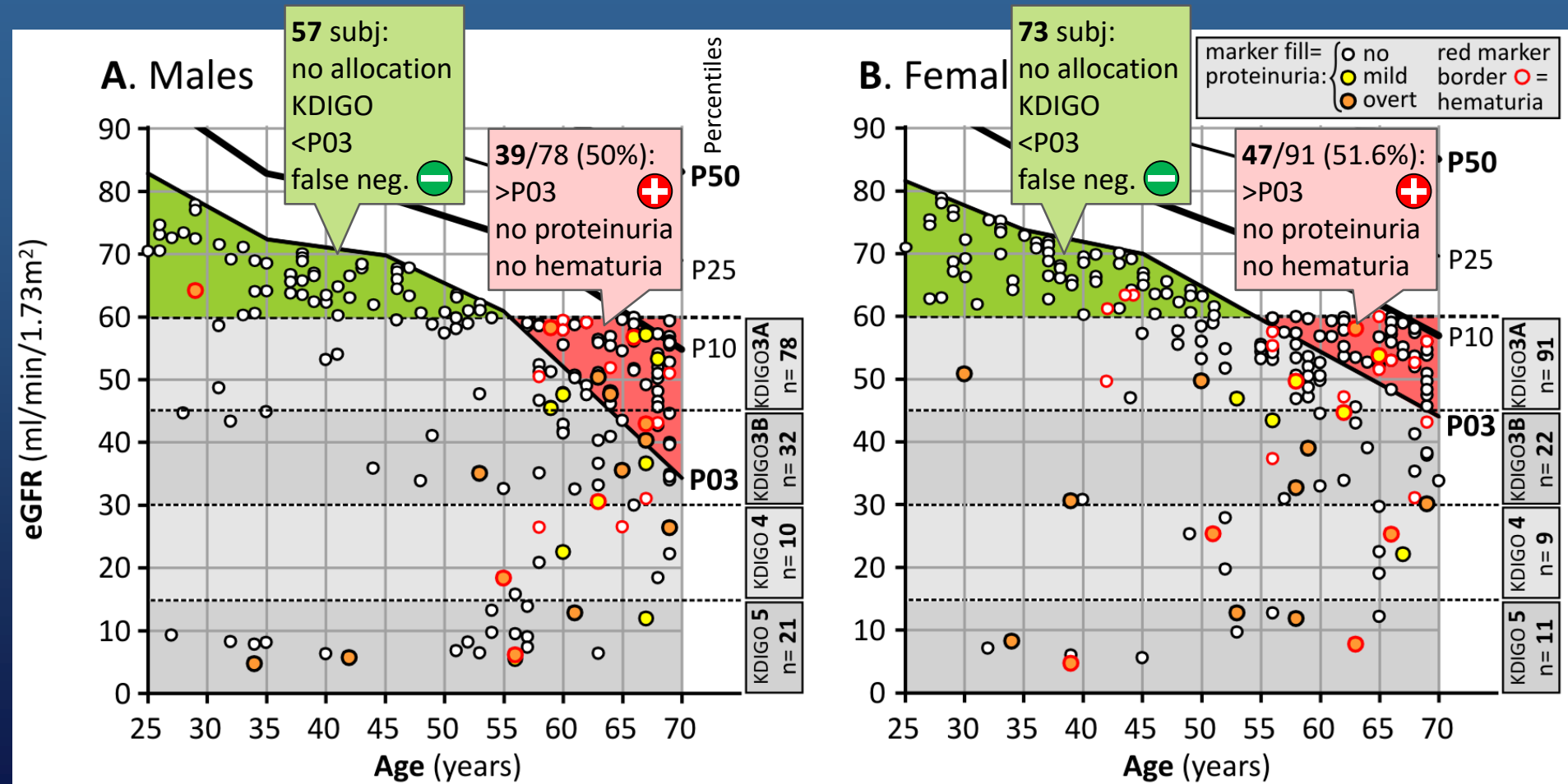
¹Faculty of Medicine and Pharmacy, University Hassan II, Casablanca, Morocco; ²Department of Biostatistics, Center for Research and Innovation in Care, University of Antwerp, Antwerp, Belgium; ³Ministry of Health, Rabat, Morocco; ⁴Faculty of Medicine and Pharmacy, University Mohammed V, Rabat, Morocco; and ⁵University of Antwerp, Antwerp, Belgium

Kidney Int, 2016, 89, 1363-1371

- Deux villes au Maroc
- 26-70 ans et n=10,524
- Créatinine et BU
- Chronicité confirmée à 3 mois



False negatives and false positives by using the arbitrary threshold of eGFR for classifying CKD3-5



Alternative 2

Exemples belge et italien

Delanaye et al. *BMC Nephrology* 2013, 14:57
<http://www.biomedcentral.com/1471-2369/14/57>



RESEARCH ARTICLE

Open Access

Creatinine-or cystatin C-based equations to estimate glomerular filtration in the general population: impact on the epidemiology of chronic kidney disease

Pierre Delanaye^{1*}, Etienne Cavalier², Olivier Moranne³, Laurence Lutteri², Jean-Marie Krzesinski¹ and Olivier Bruyère⁴

Dépistage (bus) sur base volontaire >50 ans
n=4189
Age moyen: 63±7 ans

Prevalence of CKD in Northeastern Italy: Results of the INCIPE Study and Comparison with NHANES

Giovanni Gambaro,^{*,†} Tewoldemedhn Yabarek,^{*} Maria Stella Graziani,[‡] Alessandro Gemelli,[§] Cataldo Abaterusso,^{*} Anna Chiara Frigo,^{||} Nicola Marchionna,^{*} Lorenzo Citron,[§] Luciana Bonfante,[§] Francesco Grigoletto,^{||} Salvatore Tata,[§] Pietro Manuel Ferraro,[†] Angelo Legnaro,[§] Gina Meneghel,[¶] Piero Conz,^{**} Paolo Rizzotti,^{‡,‡} Angela D'Angelo,[§] and Antonio Lupo,^{*} for the INCIPE Study Group

Clin J Am Soc Nephrol 5: 1946–1953, 2010.

Sélection aléatoire
>40 ans
n=3870
Age moyen: 60y



Unpublished data

- Si la MRC est définie par DFG<60 mL/min/1.73 m², la prevalence de MRC est de 9.8%/4,6%
- Si la MRC est définie par DFG<60 mL/min/1.73 m² pour les moins de 65 ans ET DFG<45 mL/min/1.73 m² pour les plus de 65 ans, la prevalence de MRC est de 4.4%/1,5%



Donc...

- Notre hypothèse: la définition de la MRC devrait être adaptée à l'âge

Mais...

- Quid de l'argument prédictif?

Il peut être discuté

Stade 3a chez le patient âgé SANS albuminurie n'est pas une MRC

- Avons-nous une alternative?
- Est-ce finalement important du point de vue épidémiologique?

Gros impact sur l'épidémiologie de la MRC



Nihilisme?



Research

Original Investigation

Interpreting Treatment Effects From Clinical Trials in the Context of Real-World Risk Information End-Stage Renal Disease Prevention in Older Adults

Ann M. O'Hare, MA, MD; John R. Hotchkiss, MD; Manjula Kurella Tamura, MD, MPH; Eric B. Larson, MD, MPH;
Brenda R. Hemmelgarn, MD, PhD; Adam Batten, BA; Thy P. Do, PhD; Kenneth E. Covinsky, MD, MPH

JAMA Intern Med. 2014;174(3):391-397.

VA

97% d'hommes

Age > 70 ans

Age moyen: 77.8 ± 4.6 y

DFGe: 48 ± 11.7 ml/min/1.73 m²

n=371.470



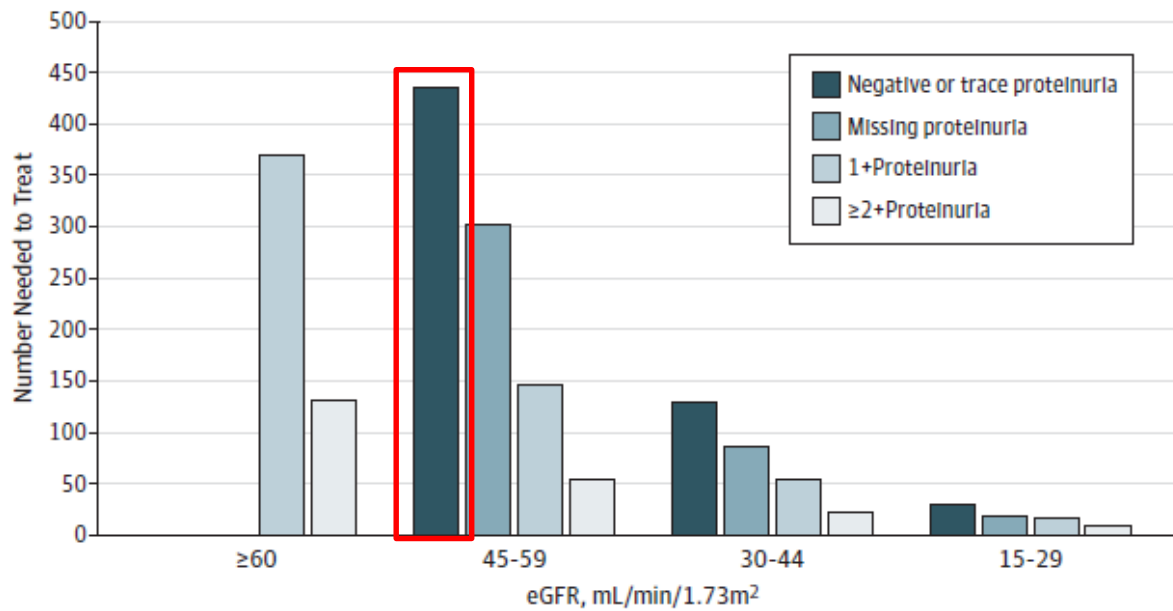
Protective effect of ACE inhibitors to prevent ESRD

Table 1. Entry Criteria and Outcomes of Major Trials Reporting a Protective Effect of ACE Inhibitors or ARBs on Progression to ESRD

Source	No. of Patients	Intervention	Mean FU, y	Entry Criteria				Mortality, %		ESRD, %		ESRD Outcomes ^a		
				Age, y	DM	Renal Function	Dipstick Proteinuria Measurement	Control Group	INT Group	Control Group	INT Group	RRR, %	ARR, %	NNT
Brenner et al, ¹⁸ 2001	1513	Losartan potassium vs placebo	3.4	31-70	Yes	Scr level, 1.3-3.0 mg/dL	ACR >300 mg/g	20.3	21.0	25.5	19.6	23.0	5.9	17
Lewis et al, ¹⁹ 1993	409	Captopril vs placebo	3.0	18-49	Yes	Scr level, ≤2.5 mg/dL	Urine protein level, ≥500 mg/g	6.9	3.9	15.4	9.7	37.0	5.7	18
Ruggenti et al, ²⁰ 1999	352	Ramipril vs placebo	2.6	18-70	Type 1 DM excluded	CrCl, 20-70 mL/min	Stratum 1: urine protein level ≥1 and <3 g/d	0	1.0	20.7	9.1	56.0	11.6	9
Agodoa et al, ²¹ 2001	1094	Ramipril vs amlodipine besylate	3.0	18-70	No	GFR, 20-65 mL/min/1.73 m ²	Urinary ratio of protein to creatinine levels, ≤2.5 mg/mg	6.0	4.1	14.8	10.8	27.0	4.0	25



Figure. Number Needed to Treat (NNT) to Prevent 1 Case of End-Stage Renal Disease (ESRD) Over 10 Years



The NNT is calculated assuming a 30% reduction in relative risk over 10 years.



Conclusions

Une définition de la MRC adaptée à l'âge



- Prend en considération le déclin physiologique du DFG
- Correspond à la distribution du DFGm chez le sujet sain en fonction de l'âge
- Est en accord avec les associations retrouvées entre diminution du DFG et pronostic
- Réconcilie les deux façons de définir la maladie: distribution des valeurs normales et approche pronostique
- Evite le sur-diagnostic de la MRC chez le sujet âgé
- Facilite l'identification, l'évaluation et éventuellement le traitement précoce de patients jeunes avec un DFG trop bas pour leur âge



REVIEW

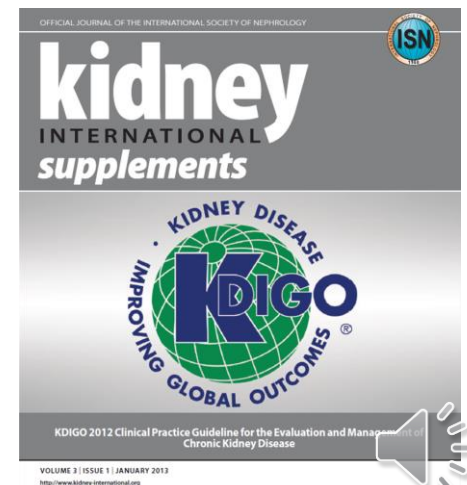
www.jasn.org

CKD: A Call for an Age-Adapted Definition

Pierre Delanaye ¹, Kitty J. Jager,² Arend Bökenkamp,³ Anders Christensson ⁴,
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Regarding the prognosis argument, we acknowledge that our proposal of an age-adapted definition for CKD is mainly based on mortality risk. We did not consider other outcomes, even though other publications have reported the risk of lower GFR with classic metabolic complications of CKD (anemia, hyperparathyroidism, acidosis, hyperphosphoremia)^{58,59} and other clinical complications (such as frailty, impaired quality of life, and fracture).^{60,61} These studies, unfortunately, are of little utility in informing our proposal of an age-adapted threshold. Although higher risk of these complications is frequently observed when eGFR is <45 ml/min per 1.73 m^2 ,⁵⁸ results are much more variable at higher eGFRs (unlike mortality, the definitions of specific complications or of clinical status are not uniform).



Modification of eGFR-Based CKD Definitions: Perfect, or Enemy of the Good?

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Finally, we disagree with the authors' contention that studies of other clinical complications (including frailty, fracture, physical function, cognitive function, and health-related quality of life) are "of little utility in informing. . .the age-adapted threshold." Although it is true that these and other conditions have not been uniformly studied (*e.g.*, performance-based versus self-reported assessments), they matter to patients and their loved ones.



Deux sujets

- Age et définition de la MRC
- Chronicité



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Original Article

Methodology used in studies reporting chronic kidney disease prevalence: a systematic literature review

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Table 1. Description of the method of general population sample selection per study

Author (Ref.)	Study name	Country	Time period	Number of subjects, N	Age range	Sampling frame	Sample design	Response, %
Aumann <i>et al.</i> [10]	SHIP	Germany	2001–6	2830	25–88	Not specified ^a	Multistage sampling	69
Bongard <i>et al.</i> [11]	MONA LISA	France	2006–7	4727	35–75	Electoral rolls	Age and sex stratified	Not given
Browne <i>et al.</i> [12]	SLAN	Ireland	2007	1098	45+	Other (Geo directory)	Multistage random sampling: by area and region	66
Capuano <i>et al.</i> [13]	VIP	Italy	1998–99 and 2008–9	2400	25–74	Electoral rolls	Age and sex stratified	Not given
Christensson <i>et al.</i> [14]	GAS	Sweden	2001–4	2815	60–93	Census	Stratified, age, sex and urban/rural location	60
Chudek <i>et al.</i> [15]	PolSenior	Poland	2007–11	3793	65+	Not specified ^a	Not specified ^a	32
Cirillo <i>et al.</i> [16]	Gubbio Population Study	Italy	Not specified	4574	18–95	Not specified ^a	Not specified ^a	Not given ^a
Codreanu <i>et al.</i> [17]	Early Detection and Intervention Program for Chronic Renal and Cardiovascular Disease in the Rep Moldova	Moldova	2006–7	973	18–77	Not specified	Not specified	Not given
De Nicola <i>et al.</i> [18]	CARHES	Italy	2008	4077	35–79	Electoral rolls	Age and sex stratified	45
Delanaye <i>et al.</i> [19]		Belgium	2008–9	1992	45–75	Not specified	Voluntary nature	Not given
Donfrancesco <i>et al.</i> [20]	MATISS	Italy	1993–96	2924	20–79	Electoral rolls	Age- and sex-stratified random sample	60
Formiga <i>et al.</i> [21]	Octabaix	Spain	2009	328	85	Not specified ^a	Not specified ^a	Not given
Fraser <i>et al.</i> [22]	HSE	England	2009–10	5799	16+	Other (address list)	Random two-stage sample	Not given ^a
Gambaro <i>et al.</i> [23]	INCIPE	Italy	2006	3629	40+	General practitioner list	Random sample	62
Giordano <i>et al.</i> [24]	LeChianti	Italy	1998–2000	676	65+	Not specified	Multistage stratified random sample	Not given
Otero <i>et al.</i> [35]	EPIRCE	Spain	2004–8	2746	20+	Census	Age-, sex- and region-stratified random sample	43
Pani <i>et al.</i> [36]	SARDINIA study	Italy	2001–	4471	14–102	Not specified ^a	Not specified ^a	56
Pattaro <i>et al.</i> [37]	MICROS	Italy	2002–3	1199	18+	Not specified ^a	Not specified ^a	Not given
Ponte <i>et al.</i> [38]	CoLaus	Switzerland	2003–6	5921	35–75	Population registry	Random sample	41
Redon <i>et al.</i> [39]	PREV-ICTUS	Spain	2005	6419	60+	General practitioner lists	Random sample	72
Robles <i>et al.</i> [40]	HERMEX	Spain	Not specified	2813	25–79	Other (health-care system database)	Age- and sex-stratified random sample	83
Roderick <i>et al.</i> [41]	MRC Older Age Study	UK	1994–99	13 179	75+	General practitioner list	Practices stratified by mortality score and deprivation score	73
Rothenbacher <i>et al.</i> [42]	ActiFE Ulm	Germany	2009–10	1471	65+	Census	Random sample	20
Rutkowski <i>et al.</i> [43]	PolNef	Poland	2004–5	2476	n/a	Other (address list)	Random sample	26
Sahin <i>et al.</i> [44]		Turkey	2005	1079	18–95	Not specified	Age, sex and region stratified	Not given
Schaeffner <i>et al.</i> [45]	BIS	Germany	2011	570	70+	Not specified ^a	Not specified ^a	Not given
Stengel <i>et al.</i> [48]	3C	France	1991–2001	8705	65+	Electoral rolls	Random sample	37
Suleymanlar <i>et al.</i> [49]	CREDIT	Turkey	Not specified	10 056	18+	Not specified	Age, sex and region stratified	Not given
Tavira <i>et al.</i> [50]	RENASTUR	Spain	2010–12	592	55–85	Not specified	Random sample	Not given
Van Pottelbergh <i>et al.</i> [51]	Crystal	Russia	2009	611	65–91	General practitioner list	All registered on list	66
Viktorsdottir <i>et al.</i> [52]	RHS	Iceland	1967–96	19 256	33–85	Not specified	All in birth cohort	Not given
Vinhas <i>et al.</i> [53]	PREVADIAB	Portugal	2008–9	5167	20–79	Other (universal health card)	Age, sex and region stratified	84
Wasen <i>et al.</i> [54]		Finland	1998–99	1246	64–100	Not specified	All residents born ≤1933	83
Wetmore <i>et al.</i> [55]		Iceland	2001–3	1630	18+	Not specified	Random sample	71
Zambon <i>et al.</i> [56]	ProV.A.	Italy	1995–97	3063	65+	Other (health district registries)	Age- and sex-stratified random sample	77 in men 64 in women
Zhang <i>et al.</i> [57]	ESTHER	Germany	2000–2	9806	50–74	General practitioners	All participants who underwent a general health check-up	Not given

^a N: Number of subjects with positive measurement (if not applicable)

Le critère de chronicité n'est jamais pris en compte



Chronic kidney disease, hypertension, diabetes, and obesity in the adult population of Morocco: how to avoid “over”- and “under”-diagnosis of CKD

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Kidney Int, 2016, 89, 1363-1371

- Chronicité confirmée à 3 mois chez 78.9% des MRC (n=285)
- Stage 3A: 32% sont retrouvés avec un DFG_e>60 ml/min/1.73m²
- Stage 3B: 7,4% sont retrouvés avec un DFG_e>60 ml/min/1,73m²



RESEARCH ARTICLE

Chronic Kidney Disease in Primary Care: Outcomes after Five Years in a Prospective Cohort Study

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Shardlow A et al, Plos Med, 2016



- “Confirmed” was at least 2 previous eGFR results of 30 to 59 ml/min per 1.73 m² in the course of clinical care
 - Then serum creatinine is re-measured at baseline for the study
- => 29% had eGFR > 60 mL/min/1.73m²





Clin Kidney J, 2017, 10, 370-374

EDITORIAL COMMENT

Epidemiology of chronic kidney disease: think (at least) twice!

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20 à 40% des MRC stade 3a ne sont pas confirmées !!



Conclusions

- La définition d'une maladie (et par conséquent la définition de la « normalité ») impacte nécessairement la prévalence de cette maladie
- La sénescence est-elle nécessairement un processus pathologique?
- Le risque doit-il faire partie de la définition d'une maladie?



Merci de votre attention

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