Glomerular Filtration Rate

eGFR and mGFR

Pierre Delanaye, MD, PhD
University of Liège
CHU Sart Tilman
BELGIUM

Summary

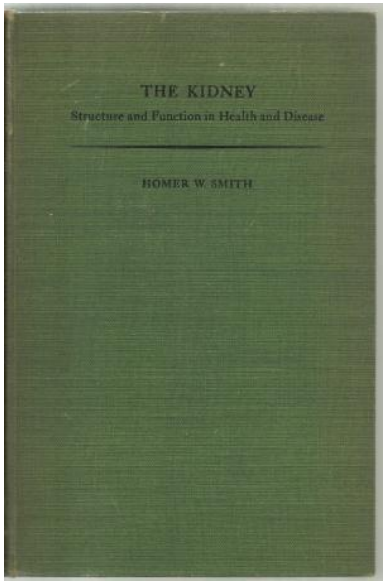
- Estimating GFR (creatinine, eGFR, cystatin C)
- Measuring GFR
- (CKD diagnosis)

Summary

- Estimating GFR (creatinine, eGFR, cystatin C)
- Measuring GFR
- (CKD diagnosis)

The Glomerular Filtration Rate is usually the best parameter to assess the global kidney function.

So, how to measure (or estimate GFR)?



Renal function: concept of clearance

- Clearance of a solute (ml/min):

  volume of plasma cleared (« purified ») of this substance per time

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

- Ideal marker for GFR:
  - Constant production
  - No effect on GFR, non toxic
  - Not bound to protein, freely filtrated through glomerulus
  - No secretion, no absorption in the tubules
  - No extra renal clearance
  - Easy to measure

Serum creatinine

- One of the most prescribed analyte in clinical chemistry
- …but the most important is to know its limitations
- Physiological limitations
- Analytical limitations

Measurements of serum creatinine

- Jaffe method: colorimetric
- Enzymatic methods
- Jaffe and enzymatic methods gives slightly different results

Analytical limitations

- Jaffe: Pseudochromogen: glucose, fructose, ascorbate, proteins, urate, acetoacetate, acetone, pyruvate => false « high »
- Bilirubins: false « low »
- Few (fewer) interferences with enzymatic methods

Analytical limitations

- Different Jaffe-Enzymatic methods, different calibration by different manufacturers

Physiological limitations

- Production (relatively) constant but muscular production => serum creatinine is dependent of muscualr mass, not only GFR
    - gender
    - age
    - ethnicity
    - Muscular mass(creatine)
- Extra-renal production (bacterial)

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

Physiological limitations

Tubular secretion of creatinine

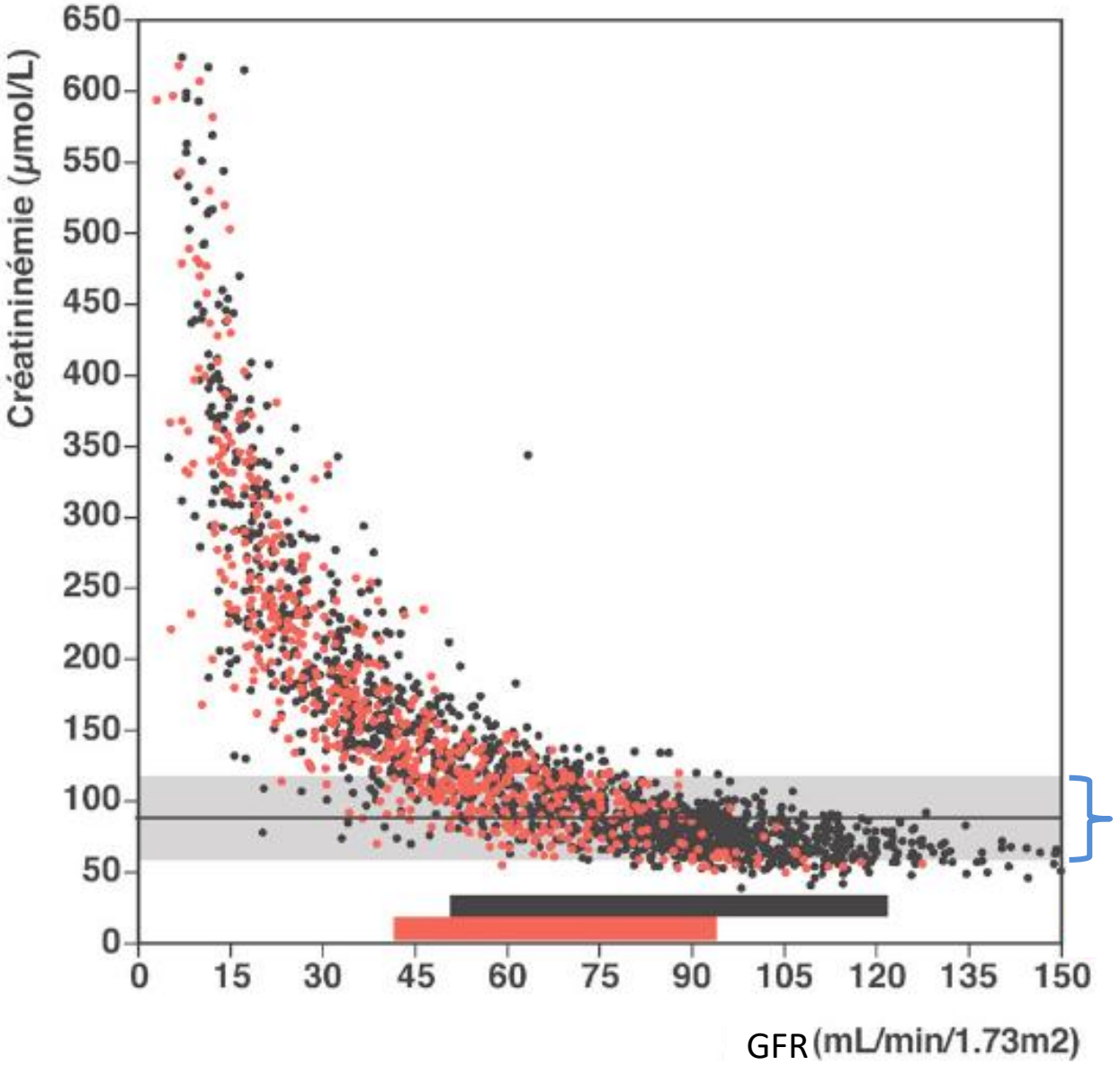
- 10 to 40%
- Increase with decreased GFR
- Unpredictable at the individual level !

Drugs interaction with creatinine

- tubular secretion inhibitor
  cimetidin, trimethoprim
- fibrates
- « high concentrations » interactions
  acetylcystein, dobutamin, lidocain, ascorbate

Creatinine: to the trash?

- Very cheap (0.04€ /Jaffe)
- Good specificty
- Good analytical CV
- Favor for enzymatic methods



NephroTest Cohort (France)
Which GFR for patients with serum creatinine measured at 80 µmol/L (0.9 mg/dL)?

IC 95% for subjects<65 years old
IC 95% for subjects>65 years old

S. Creatinine lab normality range

With the kind permission of Marc Froissart

Serum Creatinine

- Exponential relationship between serum creatinine and GFR!!!

  In a given patient,

  if serum creatinine increased from 0.6 to 1.2 mg/dl
  => decrease in GFR of 50%

  if serum creatinine increased from 2.0 to 3.0 mg/dl
  => decrease in GFR of 25%

Creatinine clearance

- Not recommended by guidelines
- Creatinine tubular secretion
- Lack of precision:

errors in urine collection

22 to 27% for « trained » patients

50 to 70 % for others

large intra-individual variability for creatinine excretion

Creatinine clearance

- The Cockcroft original study
- Final sample n=236
- But the starting sample was 534 with 2 available creatinine clearance in medical wards
- Exclusion of 56% (!) because :

1. Variability of serum creatinine > 20%: n=29
2. Creatinine excretion/24 h < 10 mg/d: n=31
3. Inadequate (?) data: n=65
4. Variability of creatinine excretion > 20%: n=173 (32%)

Creatinine-based equations

Goals of the equations:

- Conceptualize the exponential relationship
- Adapt creatinine for age, gender, ethnicity
- Decrease the IC

Creatinine-based equations

- MDRD, Cockcroft
- Strengths
- Limitations
- CKD-EPI
- Others (FAS)

Table 1. MDRD study equations and Cockcroft equation commonly used for GFR estimation

Cockcroft and Gault

$$\text{GFR (ml/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{7.2 \times \text{SCr (mg/dl)}} \times 0.85 \text{ if woman}$$

4-Variable MDRD study equation (IDMS traceable)

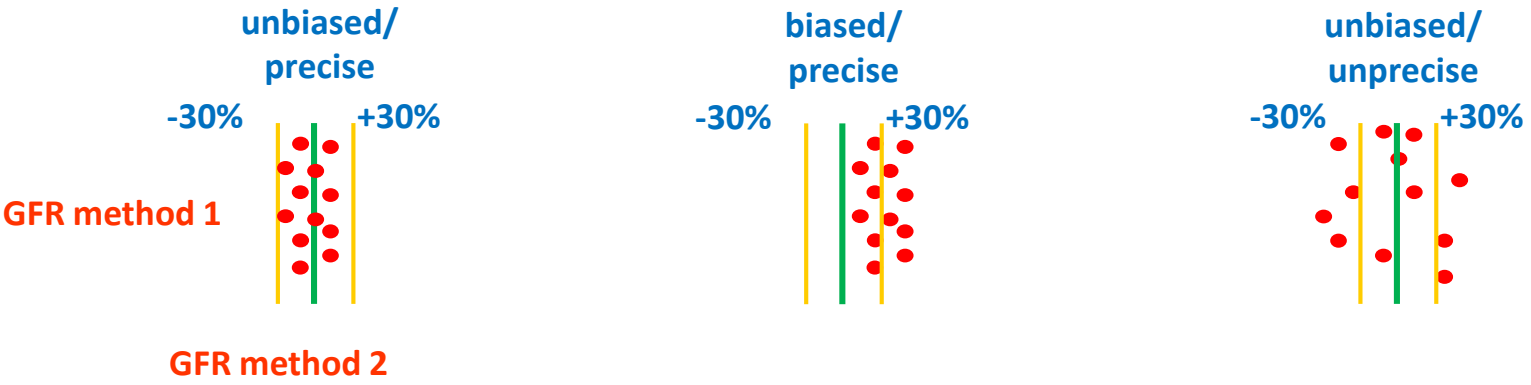
$$\text{GFR (ml/min/1.73 m}^2) = 175 \times \text{SCr (mg/dl)}^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if woman)} \times 1.21 \text{ for Black-American}$$

Cockcroft versus MDRD

	Cockcroft	MDRD
Population	Canada 1976	USA 1999
N	249	1628
Mean GFR	73	40
Measured GFR	Creatinine Clearance	Iothalamate
Assay	Jaffe	Jaffe
% women	4	40
% black	0 (?)	12
Mean age	18-92	51
Mean weight	72	79.6
Indexation for BSA	No	yes
Internal validation	no	yes

Statistics

- Good correlation: a *"sine qua non"* condition but insufficient
- Bias: mean difference between two values = the systematic error
- Precision: SD around the bias = the random error
- Accuracy 30% = % of eGFR between ± 30% of measured GFR



Predictive Performance of the Modification of Diet in Renal Disease and Cockcroft-Gault Equations for Estimating Renal Function

Marc Froissart,*†§ Jerome Rossert,†‖ Christian Jacquot,‡§ Michel Paillard,*†§ and Pascal Houillier*†§

*Department of Physiology and Biophysics, Georges Pompidou Hospital (AP-HP); †INSERM U652 and IFR 58; ‡Department of Nephrology, Georges Pompidou Hospital (AP-HP); §René Descartes Medical School, Paris V University; and ‖Paris VI University, Paris, France

Recent recommendations emphasize the need to assess kidney function using creatinine-based predictive equations to optimize the care of patients with chronic kidney disease. The most widely used equations are the Cockcroft-Gault (CG) and the simplified Modification of Diet in Renal Disease (MDRD) formulas. However, they still need to be validated in large samples of subjects, including large non-U.S. cohorts. Renal clearance of ^{51}Cr-EDTA was compared with GFR estimated using either the CG equation or the MDRD formula in a cohort of 2095 adult Europeans (863 female and 1232 male; median age, 53.2 yr; median measured GFR, 59.8 ml/min per 1.73 m^2). When the entire study population was considered, the CG and MDRD equations showed very limited bias. They overestimated measured GFR by 1.94 ml/min per 1.73 m^2 and underestimated it by 0.99 ml/min per 1.73 m^2, respectively. However, analysis of subgroups defined by age, gender, body mass index, and GFR level showed that the biases of the two formulas could be much larger in selected populations. Furthermore, analysis of the SD of the mean difference between estimated and measured GFR showed that both formulas lacked precision; the CG formula was less precise than the MDRD one in most cases. In the whole study population, the SD was 15.1 and 13.5 ml/min per 1.73 m^2 for the CG and MDRD formulas, respectively. Finally, 29.2 and 32.4% of subjects were misclassified when the CG and MDRD formulas were used to categorize subjects according to the Kidney Disease Outcomes Quality Initiative chronic kidney disease classification, respectively.

J Am Soc Nephrol 16: 763–773, 2005. doi: 10.1681/ASN.2004070549

Table 3. Bias, precision, and accuracy of the MDRD and CG formulas[a]

	N	Bland and Altman (ml/min per 1.73 m^2)		Accuracy within (% of Subjects)			CRMSE (ml/min per 1.73 m^2)
		Bias	Precision	15%	30%	50%	
MDRD formula							
high GFR[b]	1044	−3.3	17.2	61.3	92.4	98.8	17.5
low GFR[c]	1051	1.3	8.5	54.8	82.9	93.3	8.6
overall	2095	−1.0	13.7	58.0	87.2	96.0	13.8
CG formula							
high GFR[b]	1044	0.4	19.4	56.1	88.0	97.4	19.4
low GFR[c]	1051	3.5	9.7	41.2	69.0	85.2	10.3
overall	2095	1.9	15.4	48.7	78.5	91.3	15.5

[a]Results obtained with these formulas were compared with GFR values obtained by measuring the renal clearance of ^{51}Cr EDTA. Bias is defined as the mean difference between estimated and measured GFR. Precision is 1 SD of bias. Accuracy was assessed by determining the percentage of subjects who did not deviate >15, 30, and 50% from measured GFR and by calculating the combined root mean square error (CRMSE).

[b]Measured GFR ≥60 ml/min per 1.73 m^2.

[c]Measured GFR <60 ml/min per 1.73 m^2.

CLINICAL EPIDEMIOLOGY www.jasn.org

Evaluation of the Modification of Diet in Renal Disease Study Equation in a Large Diverse Population

Lesley A. Stevens,* Josef Coresh,† Harold I. Feldman,‡ Tom Greene,§ James P. Lash,‖ Robert G. Nelson,¶ Mahboob Rahman,** Amy E. Deysher,* Yaping (Lucy) Zhang,* Christopher H. Schmid,* and Andrew S. Levey*

*Tufts-New England Medical Center, Boston, Massachusetts; †Johns Hopkins University, Baltimore, Maryland; ‡University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; §University of Utah, Salt Lake City, Utah; ‖University of Illinois at Chicago, Chicago, Illinois; ¶National Institutes of Health, Phoenix, Arizona; and **Case Western Reserve University, Cleveland, Ohio

J Am Soc Nephrol 18: 2749–2757, 2007.

- CKD-EPI
- Urinary clearance of iothalamate in at least 250 subjects
- 5504 subjects (2874 with GFR<60)
- Creatinine calibrated (different ways)

Table 2. Comparison of performance of MDRD Study equation by level of eGFR[a]

eGFR	*N*	Difference		% Difference		P_{30} (CI)
		Median (CI)	IQR	Median (CI)	IQR	
Overall	5504	2.7 (2.4 to 3.1)	16.4	5.8 (5.1 to 6.4)	27.6	83 (83 to 84)
>120	325	−9.0 (−12.3 to −5.9)	31.2	−7.1 (−10.1 to −4.6)	26.6	82 (80 to 84)
90 to 119	941	11.1 (9.7 to 12.6)	25.6	9.9 (8.6 to 11)	20.8	89 (88 to 90)
60 to 89	1364	9.5 (8.3 to 10.7)	25.4	11.7 (10.2 to 12.7)	28.0	82 (81 to 83)
30 to 59	1782	1.7 (1.1 to 2.3)	13.0	3.5 (2.4 to 4.9)	27.4	84 (83 to 85)
16 to 29	793	0.0 (−0.4 to 0.5)	6.7	0.0 (−1.8 to 2.4)	31.4	81 (80 to 82)
<15	299	0.8 (0.3 to 1.4)	5.0	6.3 (2.5 to 11.1)	34.5	72 (69 to 75)

[a]Units of GFR are in ml/min per 1.73 m^2. Difference is calculated as mGFR − eGFR. Percentage difference is calculated as (mGFR − eGFR)/mGFR. Median values measure bias, and IQR measure precision. mGFR ranges in the rows correspond to GFR cutoffs for CKD stages: Stage 1, GFR >90; stage 2, GFR 60 to 89; stage 3, GFR 30 to 59; stage 4, GFR 15 to 29; stage 5, GFR <15. CI, confidence interval.

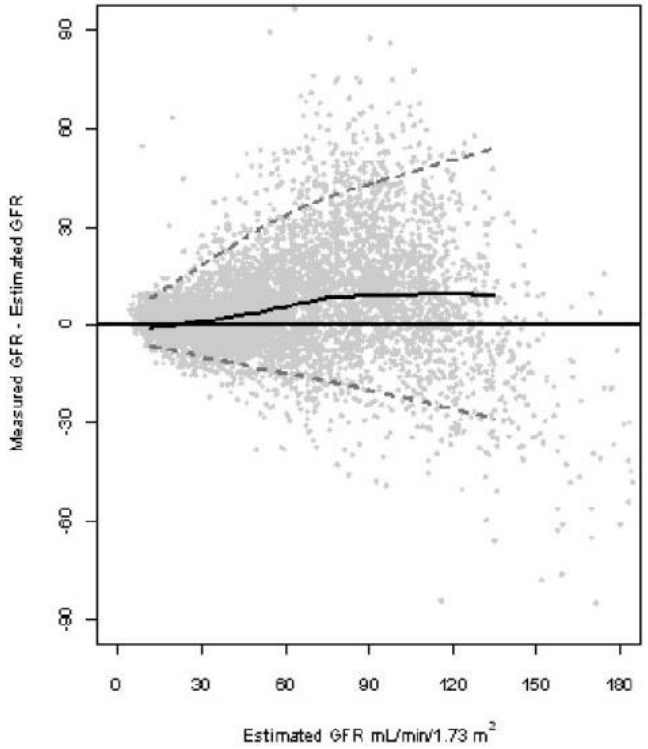


Figure 2. Difference of the MDRD Study equation by level of eGFR. Difference is calculated as (mGFR − eGFR). Solid horizontal

MDRD: the strengths

- Excellent accuracy, bias, precision in stage 3-4 CKD
- Best accuracy observed: 80-85%
- Better than Cockcroft especially in precision, in stage 3-4, in obese

MDRD: the limitations

- MDRD more bias (absolute) and less precision in high GFR
- Non negligible proportion of subjects with stage 2 classified as stage 3 CKD
- Trend to underestimate GFR especially in young women

MDRD: limitations = creatinine (exp -1.154)
1) analytical limitation

- MDRD study equation: Cleveland Laboratory

  Modified Kinetic Jaffe (Beckman Astra CX3)

- NHANES study :

  Modified Kinetic Jaffe (Hitachi 737)

difference of 0.23 mg/dl between two methods

(higher results with Hitachi)

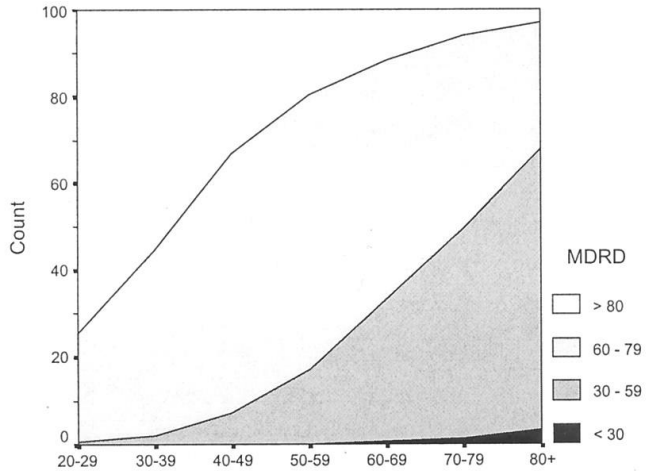
If creatinine is 1 mg/dL: difference in eGFR will be 21 ml/min/1.73m² with MDRD

If creatinine is 2 mg/dL: difference in eGFR will be 6 ml/min/1.73m² with MDRD

Coresh, J. et al. J Am Soc Nephrol 2002;13:2811-2816

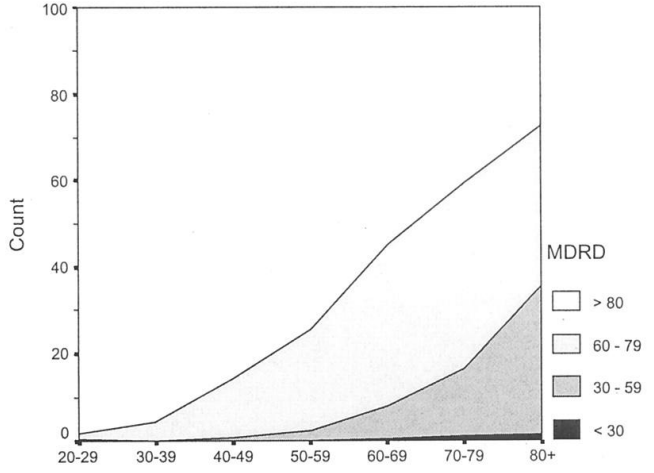
MDRD: limitations = creatinine
1) analytical limitation

UNCALIBRATED



N	3037	2827	2138	1422	1670	1241	916	Total 13251
≥ 80	74.6%	55.2%	33.0%	19.5%	11.7%	6.1%	2.8%	41.8%
60-79	24.8%	42.7%	59.7%	63.3%	54.9%	44.2%	29.4%	45.4%
30-59	0.6%	2.0%	7.2%	17.2%	32.7%	48.5%	64.6%	12.5%
< 30	<0.1%	<0.1%	<0.1%	<0.1%	0.7%	1.2%	3.2%	0.3%

CALIBRATED



3037	2827	2138	1422	1670	1241	916	Total 13251
98.3%	95.7%	85.7%	74.4%	55.1%	40.7%	27.5%	82.1%
1.5%	4.2%	13.5%	23.3%	36.9%	42.7%	37.0%	14.5%
0.2%	<0.1%	0.8%	2.4%	7.6%	15.7%	34.3%	3.2%
<0.1%	<0.1%	<0.1%	<0.1%	0.5%	0.9%	1.2%	0.2%

Coresh, J. et al. J Am Soc Nephrol 2002;13:2811-2816

IDMS traceability

A multicentric evaluation of IDMS-traceable creatinine enzymatic assays

Laurence Piéroni [a], Pierre Delanaye [b,*], Anne Boutten [c], Anne-Sophie Bargnoux [d], Eric Rozet [e], Vincent Delatour [f], Marie-Christine Carlier [g], Anne-Marie Hanser [h], Etienne Cavalier [i], Marc Froissart [j], and Jean-Paul Cristol [d]
On behalf of the Société Française de Biologie Clinique [1]

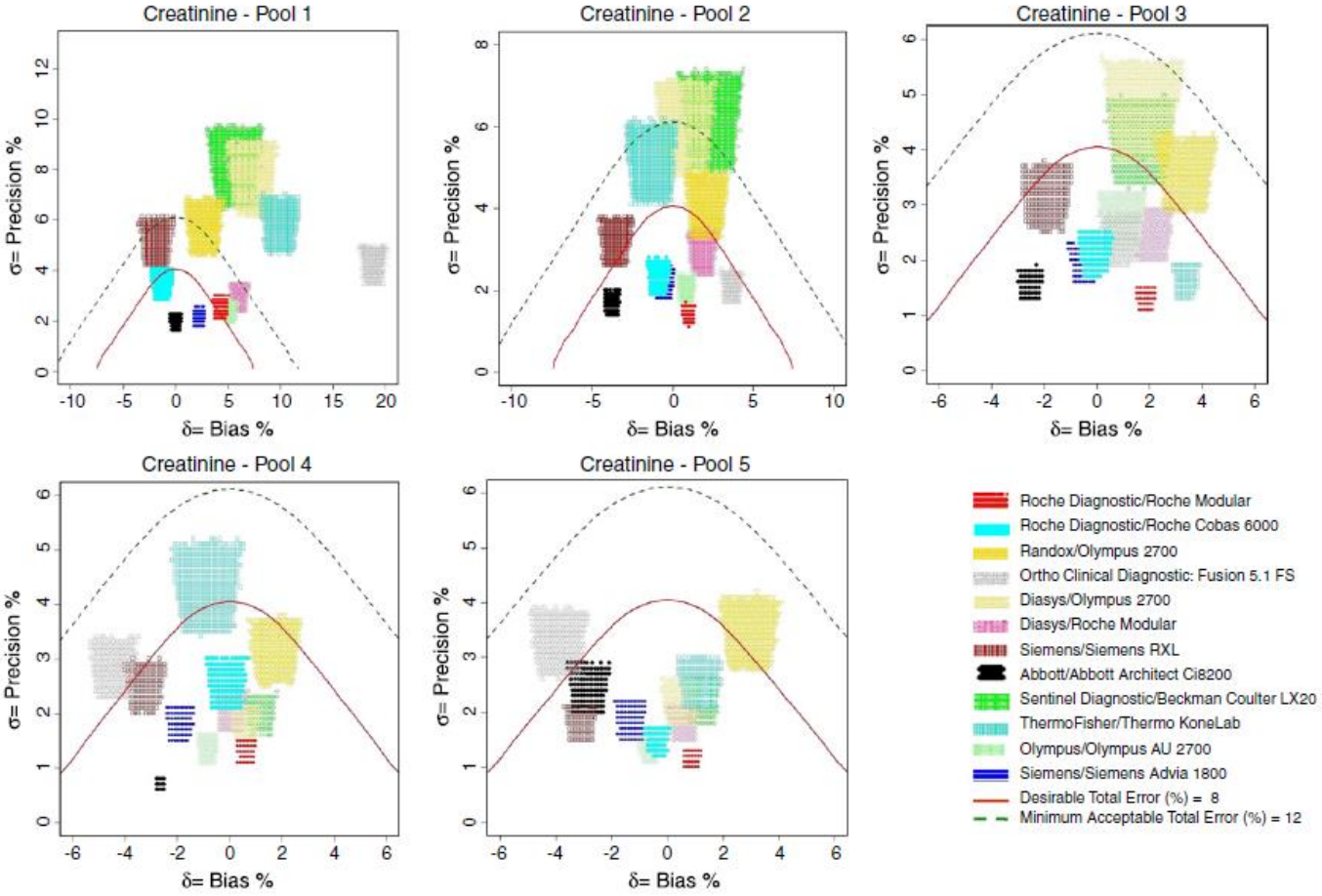
[a] Biochimie Métabolique, Groupe Hospitalier Pitié-Salpêtrière, APHP, Paris, France
[b] Nephrology–Dialysis–Transplantation, University of Liège, CHU Sart Tilman, Liège, Belgium
[c] Biochimie, CHU Bichat, APHP, Paris, France
[d] Biochimie, CHU Lapeyronie, Montpellier, France
[e] Analytical Chemistry Laboratory, CIRM, University of Liège, Liège, Belgium
[f] Laboratoire National de Métrologie et d'Essais, Paris, France
[g] Biochimie, Hôpitaux de Lyon Sud, Lyon, France
[h] Biochimie, Hospices civils, Colmar, France
[i] Clinical Chemistry, University of Liège, CHU Sart Tilman, Liège, Belgium
[j] Physiologie Rénale, Hôpital Européen Georges Pompidou, APHP, Paris, France

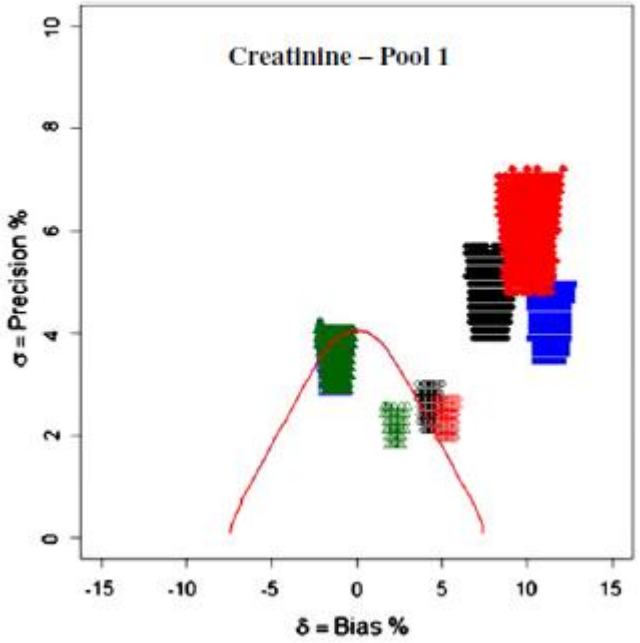
Clinica Chimica Acta 412 (2011) 2070–2075

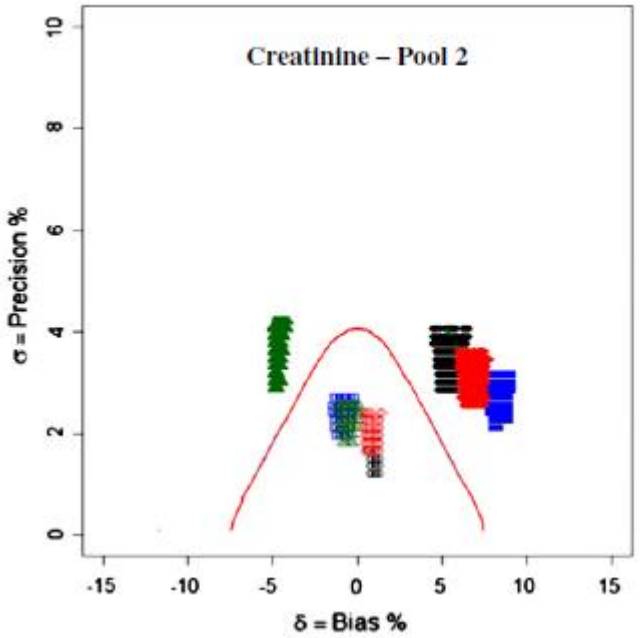
MDRD: 186 => 175

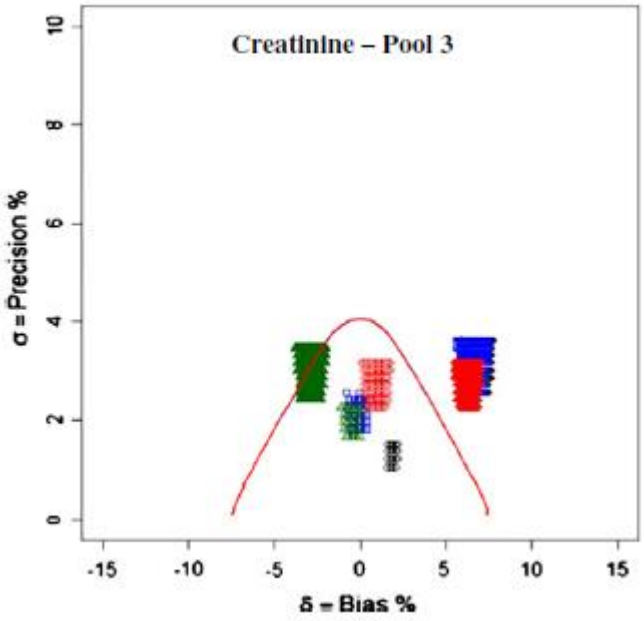
Results of GC-IDMS from LNE

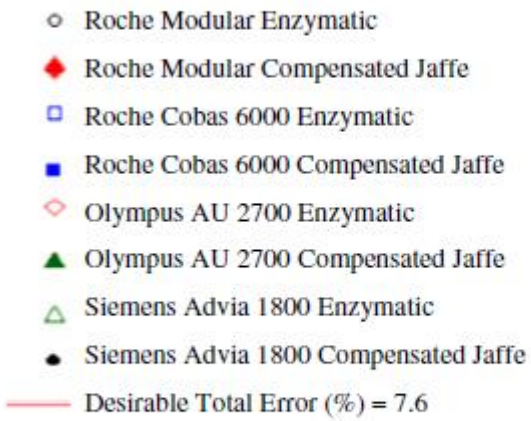
Pool 5: 174.5 +/-3.1 µmol/L
Pool 4: 149.7 +/-2.9 µmol/L
Pool 3: 97.9 +/-1.7 µmol/L
Pool 2: 74.4 +/-1.4 µmol/L
Pool 1 : 35.9 +/-0.9 µmol/L




Creatinine – Pool 1
σ = Precision %
δ = Bias %
0
2
4
6
8
10
-15
-10
-5
0
5
10
15


Creatinine – Pool 2
σ = Precision %
δ = Bias %
0
2
4
6
8
10
-15
-10
-5
0
5
10
15


Creatinine – Pool 3
σ = Precision %
δ = Bias %
0
2
4
6
8
10
-15
-10
-5
0
5
10
15


Roche Modular Enzymatic
Roche Modular Compensated Jaffe
Roche Cobas 6000 Enzymatic
Roche Cobas 6000 Compensated Jaffe
Olympus AU 2700 Enzymatic
Olympus AU 2700 Compensated Jaffe
Siemens Advia 1800 Enzymatic
Siemens Advia 1800 Compensated Jaffe
Desirable Total Error (%) = 7.6

MDRD: limitations = creatinine
1) analytical limitations

CRITICAL DIFFERENCE = f(CVa, CVi)

= 19% (Jaffe)

Male, Caucasian, 60 y:

If MDRD higher than 60 ml/min/1,73m² => just use >60 mL/min/1.73 m²

Creat = 1.00 mg/dL

≈ GFR_{MDRD}=76 ml/min/1.73m²

Creatinine= 0.81 mg/dL

GFR_{MDRD}= 97 ml/min/1,73m²

Creatinine= 1.19 mg/dL

GFR_{MDRD}= 62 ml/min/1,73m²

Kuster N, Clinica Chimica Acta, 2014, 428C, 89

Delanaye P, J Nephrol, 2014, 27, 467

MDRD: limitations = creatinine
2) clinical limitations

Specific population: MDRD is not magic!!
Keep our clinical feeling!!

Anorexia Nervosa (Delanaye P, Clin Nephrol, 2009, 71, 482)

Cirrhotic (Skluzacek PA, Am J Kidney Dis, 2003, 42, 1169)

Intensive Care (Delanaye P, BMC Nephrology, 2014, 15, 9)

Severely ill (Poggio ED, Am J Kidney Dis, 2005, 46, 242)

Heart transplanted (Delanaye P, Clin Transplant, 2006, 20, 596)

Kidney transplantation (Masson I, Transplantation, 2013, 95, 1211)

Obese (Bouquegneau A, NDT, 2013, 28, iv122)

Elderly (Schaeffner E, Ann Intern Med, 2012, 157, 471)

MDRD: limitations
3) the ethnicity factors

- Asian factor: Chinese: 1.233 Japan: 0.808

  How explain this discrepancy?

(Delanaye P, Rule AD, Kidney Int, 2011 80, 439*)*

- African-American factor: 1.21

  Factor too high in AA “healthy” population

(Delanaye P, Clin J Am Soc, 2011, 6, 906)

Epidemiological paradox

(Peralta CA, NDT, 2010, 25, 3934)

The new CKD-EPI equation

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, *μmol/L (mg/dL)*	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$

- CKD-EPI
- Development dataset: n=5504
- Internal validation: n=2750
- External validation: n=3896
- Creatinine calibrated
- Median GFR in the development = 68 mL/min/1.73 m^2

Figure. Performance of the CKD-EPI and MDRD Study equations in estimating measured GFR in the external validation data set.

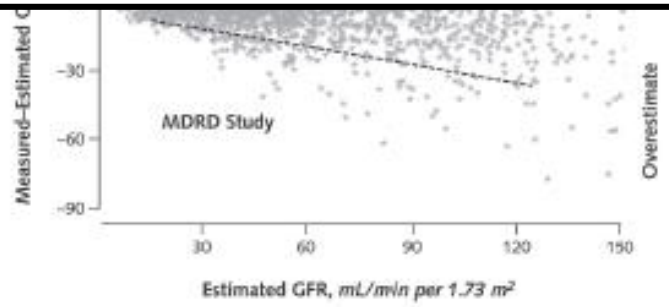


Table 3. Comparison of the CKD-EPI and MDRD Study Equations in Estimating Measured GFR in the Validation Data Set*

Variable and Equation	All Patients	Patients With Estimated GFR <60 mL/min per 1.73 m²	Patients With Estimated GFR ≥60 mL/min per 1.73 m²
Median difference (95% CI), *mL/min per 1.73 m²*†			
CKD-EPI	2.5 (2.1–2.9)	2.1 (1.7–2.4)	3.5 (2.6–4.5)
MDRD Study	5.5 (5.0–5.9)	3.4 (2.9–4.0)	10.6 (9.8–11.3)
Interquartile range for differences (95% CI), *mL/min per 1.73 m²*‡			
CKD-EPI	16.6 (15.9–17.3)	11.3 (10.7–12.1)	24.2 (22.8–25.3)
MDRD Study	18.3 (17.4–19.3)	12.9 (12.0–13.6)	25.7 (24.4–27.1)
P_{30} (95% CI), %§			
CKD-EPI	84.1 (83.0–85.3)	79.9 (78.1–81.7)	88.3 (86.9–89.7)
MDRD Study	80.6 (79.5–82.0)	77.2 (75.5–79.0)	84.7 (83.0–86.3)
Root mean square error (95% CI)			
CKD-EPI	0.250 (0.241–0.259)	0.284 (0.270–0.298)	0.213 (0.203–0.223)
MDRD Study	0.274 (0.265–0.283)	0.294 (0.280–0.308)	0.248 (0.238–0.258)

CKD-EPI: discussion

- PubMed database (last accessed June 18, 2012)
- Research for GFR, MDRD, and CKD-EPI in adults with a minimum of 50 mGFRs

Provided data for ±30% accuracy

recovered 26 publications

Delanaye P, Nephrol Dial Transplant, 2013, 28, 1396

Study	GFR method	SCr calibration	Population	N mGFRs	Mean mGFR±SD (range)	Accuracy				Bias				Precision	
						30%		15%		Mean		Median		SD of Mean Bias	
						MDRD	CKD-EPI	MDRD	CKD-EPI	MDRD	CKD-EPI	MDRD	CKD-EPI	MDRD	CKD-EPI
Murata et al.[21]	Iothalamate	Yes IDMS	Mixed	5238	56±30	77.6	78.4			*-4.1*	*-0.7*				
Levey et al.[7]	^{125}I-iothalamate, Iohexol, ^{99m}Tc-DTPA	Yes IDMS	Mixed	3896	68±36	80.6	84.1					5.5	2.5		
Eriksen et al.[39]	Iohexol plasma	Yes IDMS	General (no CKD)	1621	92±14	93	95					1.3	2.9		
Bjork et al.[32]	Iohexol plasma	Yes IDMS	Mixed	1397	44 (12-116)	79.5	79.1			*-2.0*	*2.0*	-0.8	0.8		
Buron et al.[58]	Inulin	Yes LCMS	KT recipients	1249	54±18 (15-90)	85	81			-0.5	3.9			12.2	12.6
Nyman et al.[47]	Iohexol plasma	Yes IDMS	Mixed	850	55 (9-121)	79.9	79.5			*1.0*	*4.0*	1.2	2.3		
Iliadis et al. [57]	^{51}Cr-EDTA plasma	Yes IDMS	DM Type 2	448	73±23	78.8	80.7			7.5	7.1			13.4	12.0
Lane et al.[60]	^{125}I-iothalamate	Yes ClClin	Pre and Post Nephrectomy	425	50 (median) (4-142)	75	80					-1.0	-1.7		
Cirillo et al.[56]	Inulin	Yes IDMS	Mixed	356	72±36	87.4	88.2			-5.2	-0.9			14.9	13.2
Michels et al. [@26]	^{125}I-iothalamate	Yes IDMS	Mixed	271	73±30	81.2	84.5			0.8	4.5			24.7	16.7
Tent et al.[50]	^{125}I-iothalamate	Yes ClClin	Pre nephrectomy	253	103±15	73	89			*-22.0*	*-14.0*	-22.0	-14.0		
			Post nephrectomy	253	66±11	71	89			*-15.0*	*-10.0*	-15.0	-11.0		
Teo et al.[54]	^{99m}Tc-DTPA plasma	Yes IDMS	CKD	232	52±28	79.7	82.8	50	50	*-1.0*	*1.1*	-3.0	-1.2		
White et al.[46]	^{99m}Tc-DTPA plasma	Yes IDMS	KT recipients	207	58±22	79	84			-8.0	-4.5	-7.4	-5.2	12.1	12.6
Redal-Baigorri et al. [@ 48]	^{51}Cr-EDTA plasma	Yes IDMS	Oncology	185	85±20	88.6	89.7			0.8	1.2			16.5	13.4
Poge et al.[55]	^{99m}Tc-DTPA plasma	Yes IDMS	KT recipients	170	40 12-83	71.8	64.1			4.5	8.1	4.1	7.4	10.0	10.9
Jones et al.[63]	^{99m}Tc-DTPA plasma	Yes IDMS	Evaluation of GFR	169	71 (5-150)	81	86								
Kukla et al.[51]	^{125}I-iothalamate	Yes IDMS	KT recipients	107	56±17	71.7	58.5			8.2	13.3			16.0	16.3
			KT recipients 1 year post KT	81	57±18	75.0	66.7			2.4	6.9			15.7	15.9
Silveiro et al.[59]	^{51}Cr-EDTA plasma	Yes IDMS	DM Type 2	105	103±23	64	67			-25.0	-20.0			22.0	21.0
Orskov et al. [@ 52]	^{51}Cr-EDTA plasma	Yes IDMS	Polycystic kidney disease	101	64 (7-118)	83	90	37	50	-10.8	-5.0			10.5	10.2
Praditprnsilpa et al.[62]	^{99m}Tc-DTPA plasma	Yes IDMS	CKD	100	51±28	62.7	68.0	27.3	30.7	*-9.2*	*-7.9*				
Soares et al.[53]	^{51}Cr-EDTA plasma	Yes IDMS	Healthy	96	112±24	69	85	40	55	-18.0	-10.0			26.0	24.0
Bargnoux et al.[64]	^{99m}Tc-DTPA	Yes IDMS	KT recipients	85	53±21	72.9	72.9			-4.3	-0.2			14.1	14.7
Tent et al.[61]	^{125}I-iothalamate	Yes ClClin	CKD	65	78±27	66	82			*-15.0*	*-8.0*	-15.0	-8.0		
			CKD	65	58±29	77	82			*-11.0*	*-7.0*	-8.0	-6.0		
Gerhardt et al.[44]	^{99m}Tc-DTPA plasma	Yes IDMS	Liver transplant	59	52 (48-57)	69.5	64.4			-4.3	-9.7				
Camargo et al.[49]	^{51}Cr-EDTA plasma	Yes IDMS	DM Type 2	56	106±27	64	66	27	41	-26.0	-24.0			26.0	24.0
			Healthy	55	98±20	80	90	47	60	-19.0	-9.0			20.0	18.0
Van Deventer et al.[45]	^{51}Cr-EDTA plasma	Yes IDMS	CKD	50	N/A	74	72	52	46			-1.5	4.9		

CKD-EPI: really better?

	Accuracy		Bias		Precision	
	30%		Mean		SD	
	MDRD	CKD-EPI	MDRD	CKD-EPI	MDRD	CKD-EPI
Calculated average weighted values from available data in **all studies**	**80.2**	**82.0**	**-3.5**	**0.0**	**14.9**	**13.8**
Calculated average weighted values from available data in all studies with analysis for strata of **mGFR>60 ml/min/1.73m^2**	**87.1**	**89.4**	**-2.0**	**2.2**	**13.4**	**13.0**

Delanaye P, Nephrol Dial Transplant, 2013, 28, 1396

Discussion:
MDRD or CKD-EPI ?

- Lower CKD prevalence in epidemiological studies
- Better prediction of CVD => better at the population level
- Better bias in GFR >60 (90?) ml/min/1.73m² but not better precision => not better at the individual level

- Ethnicity factor: probably not better
- Impact of the analytical error is less in high GFR

The price to pay…

Annals of Internal Medicine | REVIEW

Estimating Equations for Glomerular Filtration Rate in the Era of Creatinine Standardization

A Systematic Review

Amy Earley, BS; Dana Miskulin, MD, MS; Edmund J. Lamb, PhD; Andrew S. Levey, MD; and Katrin Uhlig, MD, MS

Background: Clinical laboratories are increasingly reporting estimated glomerular filtration rate (GFR) by using serum creatinine assays traceable to a standard reference material.

Purpose: To review the performance of GFR estimating equations to inform the selection of a single equation by laboratories and the interpretation of estimated GFR by clinicians.

Data Sources: A systematic search of MEDLINE, without language restriction, between 1999 and 21 October 2011.

Study Selection: Cross-sectional studies in adults that compared the performance of 2 or more creatinine-based GFR estimating equations with a reference GFR measurement. Eligible equations were derived or reexpressed and validated by using creatinine measurements traceable to the standard reference material.

Data Extraction: Reviewers extracted data on study population characteristics, measured GFR, creatinine assay, and equation performance.

Data Synthesis: Eligible studies compared the MDRD (Modification of Diet in Renal Disease) Study and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equations or modifications thereof. In 12 studies in North America, Europe, and Australia, the CKD-EPI equation performed better at higher GFRs (approximately >60 mL/min per 1.73 m^2) and the MDRD Study equation performed better at lower GFRs. In 5 of 8 studies in Asia and Africa, the equations were modified to improve their performance by adding a coefficient derived in the local population or removing a coefficient.

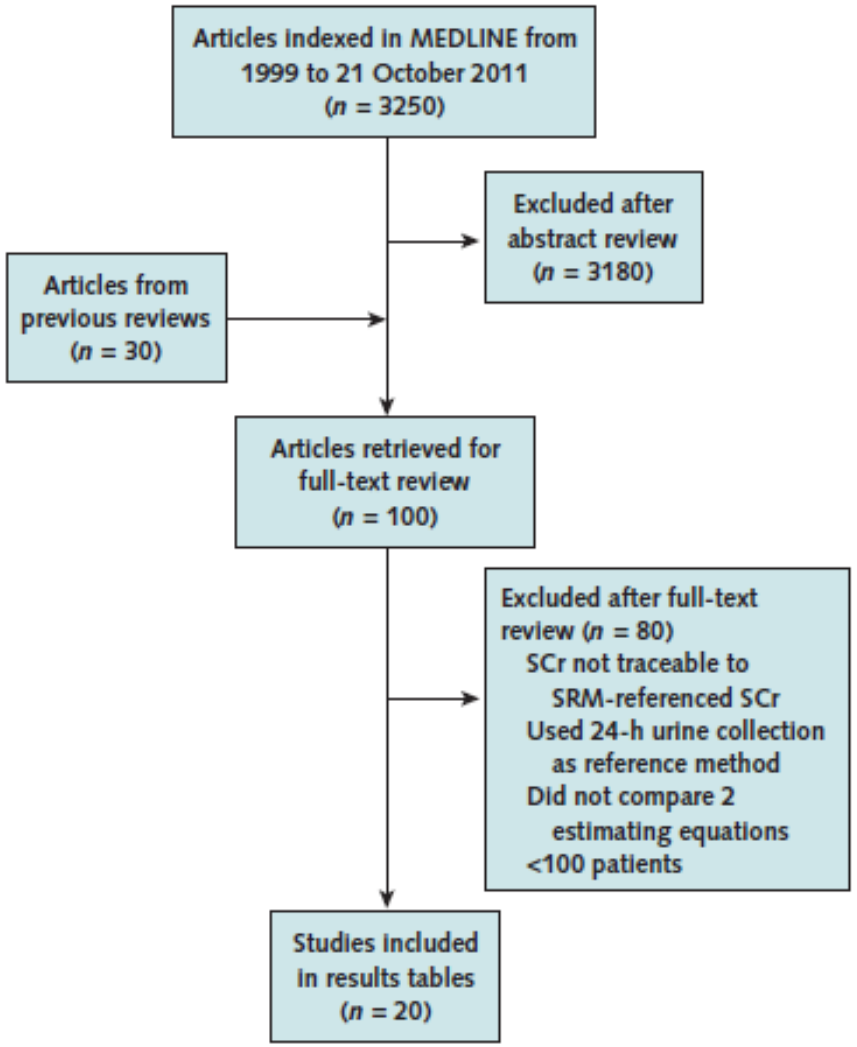
Limitation: Methods of GFR measurement and study populations were heterogeneous.

Conclusion: Neither the CKD-EPI nor the MDRD Study equation is optimal for all populations and GFR ranges. Using a single equation for reporting requires a tradeoff to optimize performance at either higher or lower GFR ranges. A general practice and public health perspective favors the CKD-EPI equation.

Primary Funding Source: Kidney Disease: Improving Global Outcomes.

Ann Intern Med. 2012;156:785-795. www.annals.org
For author affiliations, see end of text.
This article was published at www.annals.org on 7 February 2012.

Figure 1. **Summary of evidence search and selection.**



SCr = serum creatinine; SRM = standard reference material.

The CKD-EPI equation seems to be more accurate and less biased in studies with higher mean measured GFRs (approximately >60 mL/min per 1.73 m^2), whereas the MDRD Study equation has greater accuracy and less bias at lower GFRs.

Because the differences between the equations are greater at higher GFRs, the implications of introducing the CKD-EPI equation would be larger for public health and general clinical practice than for nephrology practices.

In summary, neither the CKD-EPI nor the MDRD Study equation is optimal across all populations and GFR ranges.

The price to pay…

Relative Performance of the MDRD and CKD-EPI Equations for Estimating Glomerular Filtration Rate among Patients with Varied Clinical Presentations

Kazunori Murata, Nikola A. Baumann,* Amy K. Saenger,* Timothy S. Larson,*† Andrew D. Rule,†‡ and John C. Lieske*†*

*Department of Laboratory Medicine and Pathology, †Department of Internal Medicine, Division of Nephrology and Hypertension, and ‡Department of Health Sciences Research, Division of Epidemiology, Mayo Clinic, Rochester, Minnesota

Correspondence: Dr. John C. Lieske, Mayo Clinic Division of Nephrology and Hypertension, 200 First Street SW, Rochester, MN 55905. Phone: 507-266-7960; Fax: 507-266-7891; E-mail: Lieske.John@mayo.edu

Summary

Background The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was developed using both CKD and non-CKD patients to potentially replace the Modification of Diet in Renal Disease (MDRD) equation that was derived with only CKD patients. The objective of our study was to compare the accuracy of the MDRD and CKD-EPI equations for estimating GFR in a large group of patients having GFR measurements for diverse clinical indications.

Design, setting, participants, and measurements A cross-sectional study was conducted of patients who underwent renal function assessment for clinical purposes by simultaneous measurements of serum creatinine and estimation of GFR using the MDRD and CKD-EPI equations and renal clearance of iothalamate (n = 5238).

Results Bias compared with measured GFR (mGFR) varied for each equation depending on clinical presentation. The CKD-EPI equation demonstrated less bias than the MDRD equation in potential kidney donors (−8% *versus* −18%) and postnephrectomy donors (−7% *versus* −15%). However, the CKD-EPI equation was slightly more biased than the MDRD equation in native CKD patients (6% *versus* 3%), kidney recipients (8% *versus* 1%), and other organ recipients (9% *versus* 3%). Among potential kidney donors, the CKD-EPI equation had higher specificity than the MDRD equation for detecting an mGFR <60 ml/min per 1.73 m^2 (98% *versus* 94%) but lower sensitivity (50% *versus* 70%).

Conclusions Clinical presentation influences the estimation of GFR from serum creatinine, and neither the CKD-EPI nor MDRD equation account for this. Use of the CKD-EPI equation misclassifies fewer low-risk patients as having reduced mGFR, although it is also less sensitive for detecting mGFR below specific threshold values used to define CKD stages.

Clin J Am Soc Nephrol 6: 1963–1972, 2011. doi: 10.2215/CJN.02300311

The price to pay…

- What would be your choice?

Better estimate the GFR of a *subject* with measured GFR between 90 and 120 mL/min/1.73 m^2?

Better estimate the GFR of a *patient* with measured GFR between 30 and 60 mL/min/1.73 m^2?

The applicability of eGFR equations to different populations

Pierre Delanaye and Christophe Mariat

Nat. Rev. Nephrol. **9**, 513–522 (2013)

Performance of equations in specific populations

Performance of Creatinine-Based Estimates of GFR in Kidney Transplant Recipients: A Systematic Review

Christine A. White, MD,[1] David Huang, BSc,[1] Ayub Akbari, MD,[2,3] Jocelyn Garland, MD,[1] and Greg A. Knoll, MD[2,3,4]

Am J Kidney Dis 56:1140-1157.

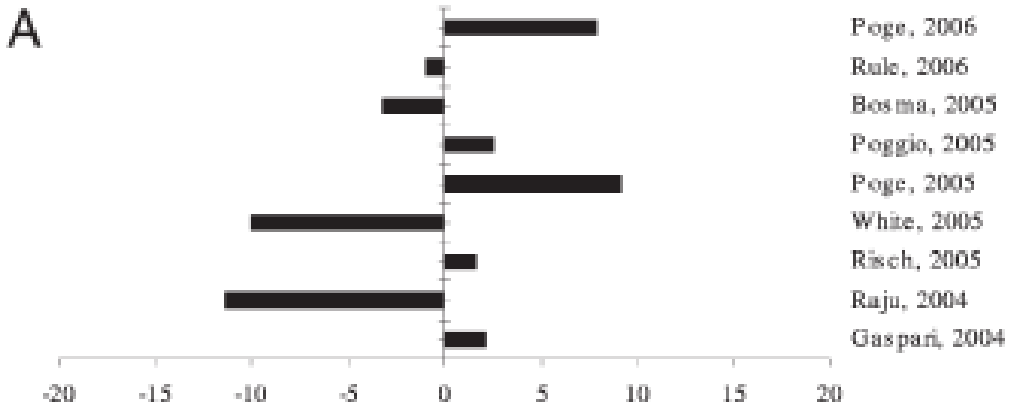


Table 3. Accuracy of Prediction Equations

Equations and Studies	Percent of Estimates Within 10%	20%	30%
4-Variable MDRD Study equation			
Poge et al,[32] 2006	25		67
Gera et al,[16] 2006			69
Bosma et al,[12] 2005	38		88
Poggio et al,[23] 2005		53	
Poge et al,[22] 2005	25		60
White et al,[30] 2005	24		74
Risch & Huber,[26] 2005			66
Raju et al,[25] 2005			66
Gaspari et al,[14] 2004	44	76	
Pooled estimate (95% CI)			
All studies	35 (32-38)	59 (54-65)	76 (74-78)
High quality*	34 (32-37)	53 (46-60)	77 (75-79)

CKD-EPI Equation

Is an Equation that was derived from a population with a mean GFR of 68 ml/min applicable to a transplant population
(with a mean GFR of 50-55 ml/min) ?

Relative Performance of the MDRD and CKD-EPI Equations for Estimating Glomerular Filtration Rate among Patients with Varied Clinical Presentations

Kazunori Murata, Nikola A. Baumann,* Amy K. Saenger,* Timothy S. Larson,*† Andrew D. Rule,†‡ and John C. Lieske*†*

MDRD= 80%

CKD-EPI= 78%

CLINICAL AND TRANSLATIONAL RESEARCH

Estimating Glomerular Filtration Rate in Kidney Transplant Recipients: Performance Over Time of Four Creatinine-Based Formulas

Fanny Buron,[1] Aoumer Hadj-Aissa,[2] Laurence Dubourg,[2] Emmanuel Morelon,[1] Jean-Paul Steghens,[3] Michel Ducher,[4] and Jean-Pierre Fauvel[4,5]

MDRD= 85%

CKD-EPI= 81%

CLINICAL AND TRANSLATIONAL RESEARCH

MDRD Versus CKD-EPI Equation to Estimate Glomerular Filtration Rate in Kidney Transplant Recipients

Ingrid Masson,[1] Martin Flamant,[2] Nicolas Maillard,[1] Andrew D. Rule,[3] François Vrtovsnik,[4] Marie-Noëlle Peraldi,[5] Lise Thibaudin,[1] Etienne Cavalier,[6] Emmanuelle Vidal-Petiot,[2] Christine Bonneau,[7] Olivier Moranne,[8] Eric Alamartine,[1] Christophe Mariat,[1] and Pierre Delanaye[9,10]

MDRD= 80%

CKD-EPI= 74%

Clinical Nephrology, Vol. 71 – No. 5/2009 (482-491)

Estimation of GFR by different creatinine- and cystatin-C-based equations in anorexia nervosa

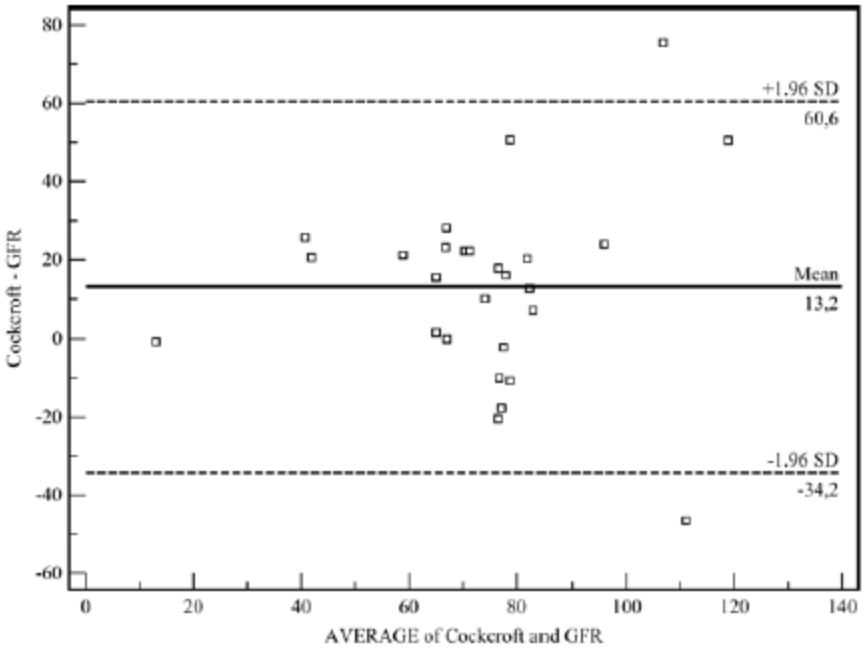
P. Delanaye[1], E. Cavalier[2], R.P. Radermecker[3], N. Paquot[3], G. Depas[4], J.-P. Chapelle[2], A.J. Scheen[3] and J.-M. Krzesinski[1]

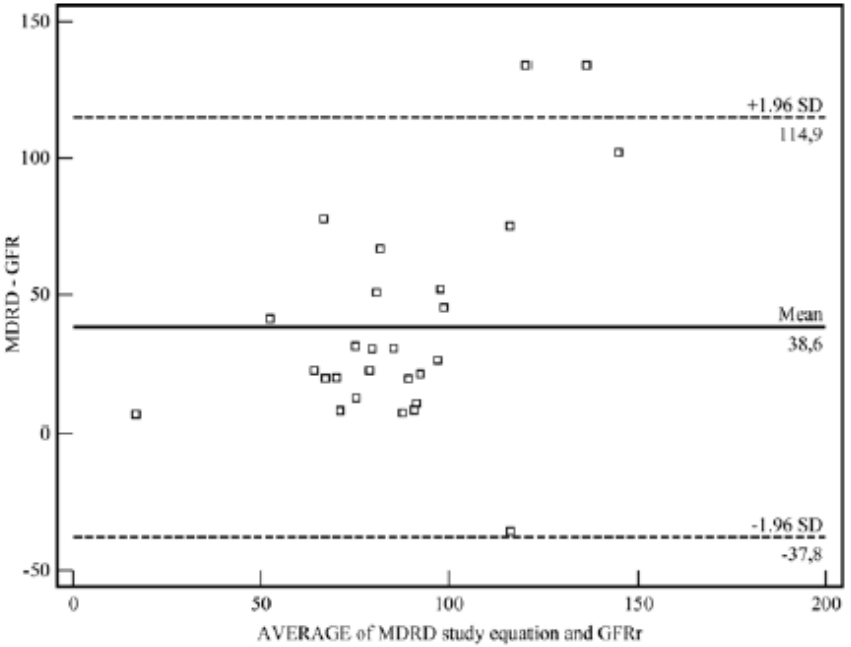
[1]Department of Nephrology-Dialysis, [2]Department of Clinical Chemistry, [3]Department of Diabetes, Nutrition and Metabolic Disorders, and [4]Department of Nuclear Medicine, University of Liège, CHU Sart Tilman, Liège, Belgium

- n=27, ^{51}Cr-EDTA, calibrated creatinine
- Mean GFR = 67 mL/min

	Mean difference with measured GFR (ml/min) for the whole population (n = 27)	SD of difference for the whole population
MDRD study	39	39
Cockcroft and Gault	13	24

If a relative difference was used, the estimated GFR was found within 30% measured GFR in 30% and 63% cases for the MDRD study and the Cockcroft and Gault equations,





What about **obese** subjects

Cockcroft : not good in obese subjects…

- Verhave JC, AJKD 2005
- Cirillo, NDT, 2005
- Rigalleau, Metab Clin Exper, 2005
- Froissart, JASN, 2006
- Cockcroft, Nephron, 1976
- Logical because weight in the equation…

Nephrol Dial Transplant (2013) 28 (Suppl. 4): iv122–iv130
doi: 10.1093/ndt/gft329
Advance Access publication 11 September 2013

ndt
Nephrology Dialysis Transplantation

Original Articles

Modification of Diet in Renal Disease versus Chronic Kidney Disease Epidemiology Collaboration equation to estimate glomerular filtration rate in obese patients

Antoine Bouquegneau[1],
Emmanuelle Vidal-Petiot[2],
François Vrtovsnik[3],
Etienne Cavalier[4],
Marcelle Rorive[5],
Jean-Marie Krzesinski[1],
Pierre Delanaye[1]
and Martin Flamant[2]

[1]Department of Nephrology-Dialysis-Transplantation, University of Liège, CHU Sart Tilman, Liège, Belgium,
[2]Department of Renal Physiology, Hôpital Bichat, AP-HP and Denis Diderot University, Paris, France,
[3]Department of Nephrology, Hôpital Bichat, AP-HP and Denis Diderot University, Paris, France,
[4]Department of Clinical Chemistry, University of Liège, CHU Sart Tilman, Liège, Belgium and
[5]Department of Diabetology, University of Liège, CHU Sart Tilman, Liège, Belgium

- Paris-Liège
- n=366, ^{51}Cr-EDTA, calibrated creatinine

Main characteristics of the population, $n = 366$	
Age (year)	55 ± 14 [18–86]
Female	185 (51%)
Weight (kg)	100 ± 22 [67–258]
Height (cm)	166 ± 10 [144–193]
African origin	50 (14%)
BMI (kg/m^2)	36 ± 7 [30–77]
30–35 kg/m^2	217 (59%)
35–40 kg/m^2	76 (21%)
>40 kg/m^2	73 (20%)

Table 2. Predictive performances of the MDRD study and CKD-EPI equations in the total obese population and according to different GFR levels

Population	Mean mGFR	Mean mGFR	Mean eGFR	Mean bias	Median bias (IQR)	Relative bias	Accuracy within 30%
	mL/min						%
Total							
MDRD	71 ± 35					± 28.7	80*
CKD-EPI	71 ± 35					± 30.0	76
mGFR < 30 mL/min/1.73 m^2 (n =							
MDRD	26 ± 7					± 44.9	70*
CKD-EPI	26 ± 7					± 45.5	62
30 < mGFR < 59 mL/min/1.73 m^2							
MDRD	55 ± 13					± 22.6	85*
CKD-EPI	55 ± 13					± 25.9	79
mGFR < 60 mL/min/1.73 m^2 (n =							
MDRD	45 ± 18					± 32.0	80*
CKD-EPI	45 ± 18					± 33.9	73
60 < mGFR < 89 mL/min/1.73 m^2							
MDRD	94 ± 17					± 24.1	79
CKD-EPI	94 ± 17					± 23.8	75
mGFR > 90 mL/min/1.73 m^2 (n =							
MDRD	126 ± 15					± 19.0	87
CKD-EPI	126 ± 15					± 16.4	89
mGFR > 60 mL/min/1.73 m^2(n = 139)							
MDRD	103 ± 22	81 ± 15	86 ± 21	4.6 ± 18.4*	2.1 (25.3)*	6.7 ± 23.2	81
CKD-EPI	103 ± 22	81 ± 15	91 ± 20	9.3 ± 17.2	8.5 (23.4)	12.7 ± 22.6	79

*P < 0.05 versus CKD-EPI. **P < 0.05 for SD versus CKD-EPI.

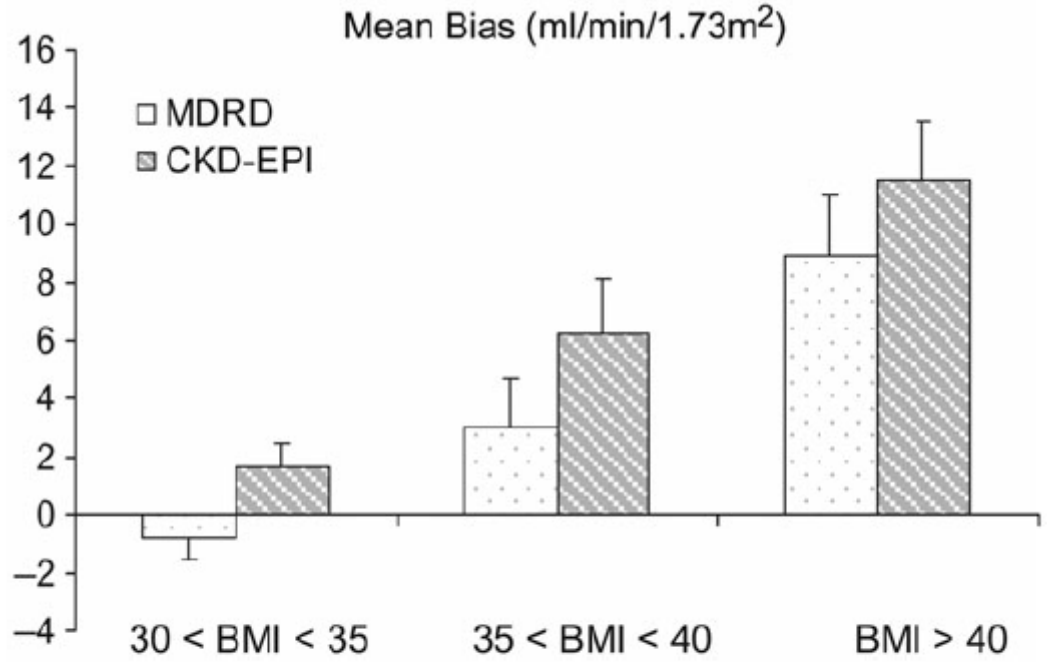


FIGURE 3: Mean bias of the MDRD and CKD-EPI equations in BMI subgroups. Mean bias is significantly lower for the MDRD equation and increases with BMI stage (two-way ANOVA test).

Conclusions from studies

- CKD-EPI = MDRD
- Cockcroft: very bad
- Performance of CKD-EPI (and MDRD) slightly less in obese than in non-obese populations
- Bias increases (or become « positive») with increased BMI and precision decreased
- CKD-EPI (and MDRD) overestimates mGFR (even high)

OK but this is not logical…

Impact of BSA indexation

- Great Impact in obese GFRs
- Over-correction by BSA (GFR too low)

Non-indexed mGFR (mL/min)	71 ± 35 [11–169]
CKD stage	
GFR ≥ 90 mL/min	110 (30%)
GFR 60–89 mL/min	100 (27%)
GFR 30–59 mL/min	107 (29%)
GFR 15–29 mL/min	44 (12%)
Hyperfiltrating status (GFR > 120 mL/min)	37 (10%)
Indexed mGFR (mL/min/1.73 m^2)	56 ± 26 [8–125]
CKD stage	
GFR ≥ 90 mL/min/1.73 m^2	44 (12%)
GFR 60–89 mL/min/1.73 m^2	114 (31%)
GFR 30–59 mL/min/1.73 m^2	137 (37%)
GFR 15–29 mL/min/1.73 m^2	62 (17%)
Hyperfiltrating status (GFR > 120 mL/min/1.73 m^2)	1 (<1%)

Delanaye P, NDT, 2005
Eriksen BO, JASN, 2011

The GFR and GFR decline cannot be accurately estimated in type 2 diabetics

Flavio Gaspari[1,7], Piero Ruggenenti[1,2,7], Esteban Porrini[1,3,7], Nicola Motterlini[1], Antonio Cannata[1], Fabiola Carrara[1], Alejandro Jiménez Sosa[3], Claudia Cella[1], Silvia Ferrari[1], Nadia Stucchi[1], Aneliya Parvanova[1], Ilian Iliev[1], Roberto Trevisan[4], Antonio Bossi[5], Jelka Zaletel[6] and Giuseppe Remuzzi[1,2]; for the GFR Study Investigators

[1]Clinical Research Center for Rare Diseases 'Aldo & Cele Daccò', Mario Negri Institute for Pharmacological Research, Bergamo, Italy; [2]Unit of Nephrology, Azienda Ospedaliera 'Ospedali Riuniti di Bergamo', Bergamo, Italy; [3]Research Unit, Hospital Universitario de Canarias, Tenerife, Spain; [4]Unit of Diabetology, Azienda Ospedaliera 'Ospedali Riuniti di Bergamo', Bergamo, Italy; [5]Unit of Diabetology, Treviglio Hospital, Treviglio, Italy and [6]Department of Endocrinology, Diabetes and Metabolic Diseases, University Medical Center, Ljubljana, Slovenia

- **Diabetic**
- **GFR measured by iohexol**
- **n=600**
- **Hyperfiltrating (GFR>120 mL/min/1.73 m²) n=90**
- **CKD (<80 mL/min/1.73 m²) n=76**

	Accuracy		Bias		Precision	
	30% 10%		Mean		SD	
	MDRD	CKD-EPI	MDRD	CKD-EPI	MDRD	CKD-EPI
All	85 25%	91 33%	-16	-13	17	16
Normofiltrating (80-120 mL/min/1.73 m²)	88	96	-15	-11	14	12
Hypofiltrating (lower than 80 mL/min/1.73 m²)	88	82	+0.6	+4	16	16
Hyperfiltrating (over 120 mL/min/1.73 m²)	68 10%	77 2%	-33	-33	18	13

All hyperfiltrating status are missed…

MDRD – CKD-EPI: nothing else?

- The Bis Equation
- The Lund-Malmö equation
- The FAS equation
- Other biomarkers: cystatin C

Schaeffner, Ann intern Med, 2012, 157, 471
Bjork, Scand J Urol Nephrol, 2012, 46, 212
Pottel H, Nephrol Dial Transplant, 2016
Seronie-Vivien, CCLM, 2008

The elderly


SI ON AVAIT SON ANNIVERSAIRE DEUX FOIS PAR AN
ON VIVRAIT DEUX FOIS PLUS VIEUX
© casterman - geluck

Annals of Internal Medicine | ORIGINAL RESEARCH

Two Novel Equations to Estimate Kidney Function in Persons Aged 70 Years or Older

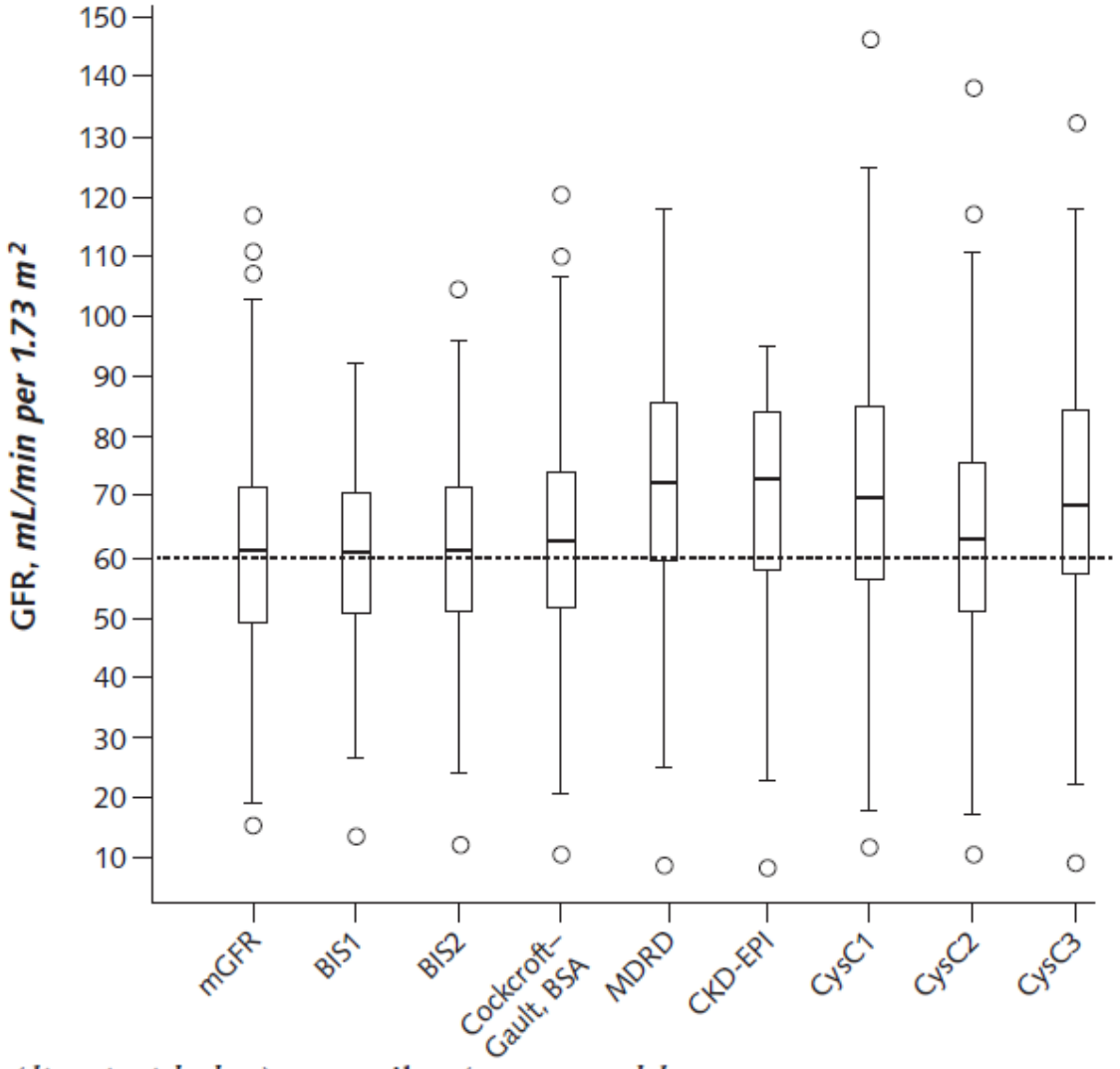
Elke S. Schaeffner, MD, MS*; Natalie Ebert, MD, MPH*; Pierre Delanaye, MD, PhD; Ulrich Frei, MD; Jens Gaedeke, MD; Olga Jakob; Martin K. Kuhlmann, MD; Mirjam Schuchardt, PhD; Markus Tölle, MD; Reinhard Ziebig, PhD; Markus van der Giet, MD; and Peter Martus, PhD

BIS1:

$$3736 \times \text{creatinine}^{-0.87} \times \text{age}^{-0.95} \times 0.82 \text{ (if female)}$$

Ann Intern Med. 2012;157:471-481

Figure 1. **Comparison of mGFR with eGFR equations in the validation sample.**



Boxes indicate medians (*line inside box*), quartiles (*upper and lower margins of box*). Antennae are defined by the rule upper–lower box margin ± 1.5 × interquartile range. Circles indicate outliers.

CKD-EPI Equation *vs* BIS Equation

n=5504

- Mean Age: 47
- Mean GFR: 68 ml/min/1.73m^2
- Reference: Iothalamate
- Creatinine Assay: Multiple – recalibration

n=570

- Mean Age: 78.5
- Mean GFR: 60 ml/min/1.73m^2
- Reference: Iohexol
- Creatinine Assay:
- IDMS - Enzymatic

COMPARATIVE ACCURACY-30%
- CKD-EPI vs BIS -

- *Koppe L et al. J Nephrol, 2013*
  - **n=224, Mean Age=75** 72% vs 76%
- *Lopes M et al. BMC Nephrology, 2013*
  - **n=95, Mean Age=85** 75% vs 80%
- *Alshoer I et al. AJKD, 2014*
  - **n=394, Median Age=80** 83% vs 88%
- *Vidal-Petiot E et al. AJKD, 2014*
  - **N=609, Mean Age=76** 82% vs 84%

Comparing GFR Estimating Equations Using Cystatin C and Creatinine in Elderly Individuals

Li Fan,*† Andrew S. Levey,* Vilmundur Gudnason,‡§ Gudny Eiriksdottir,‡ Margret B. Andresdottir,‖ Hrefna Gudmundsdottir,§‖ Olafur S. Indridason,‖ Runolfur Palsson,§‖ Gary Mitchell,¶ and Lesley A. Inker*

J Am Soc Nephrol 26: 1982–1989, 2015.

Equation	Bias Median Difference	Precision IQR	Accuracy P_{30}
eGFRcr			
CKD-EPI	−2.7 (−3.3 to −2.1)	12.1 (11.2 to 13.4)	91.7 (89.9 to 93.4)
Japanese	10.5 (9.8 to 11.2)[c]	10.9 (9.7 to 12.1)[a]	86.3 (83.9 to 88.6)[c]
BIS	5.7 (5.1 to 6.4)[c]	11.9 (10.6 to 12.7)[a]	95.8 (94.4 to 97.1)[b]

- The BIS Equation is more accurate than the CKD-EPI Equation to predict the true GFR of the elderly.

- This better ACCURACY is likely to be explained by a better PRECISION.

Do We Want a System Using 2 Separate Equations Depending on Patient Age?

- The Elderly : A growing population
- The Elderly: A vulnerable population
- Haven't we already endorsed such a system ?

…the SCHWARTZ equation

Ulf Nyman*, Anders Grubb, Anders Larsson, Lars-Olof Hansson, Mats Flodin, Gunnar Nordin, Veronica Lindström and Jonas Björk

The revised Lund-Malmö GFR estimating equation outperforms MDRD and CKD-EPI across GFR, age and BMI intervals in a large Swedish population

Clin Chem Lab Med 2014, 52(6), 815-824

Revised Lund-Malmö Study equation (LM Revised) [34]

$$e^{X-0.0158\times Age+0.438\times \ln(Age)}$$

Female	pCr<150 µmol/L:	$X=2.50+0.0121\times(150-pCr)$
Female	pCr≥150 µmol/L:	$X=2.50-0.926\times\ln(pCr/150)$
Male	pCr<180 µmol/L:	$X=2.56+0.00968\times(180-pCr)$
Male	pCr≥180 µmol/L:	$X=2.56-0.926\times\ln(pCr/180)$

- Lund-Malmo study
- n=3495 (chez 2847 sujets), iohexol, standardized creatinine
- Mean GFR = 52 mL/min/1,73 m²

Nephrol Dial Transplant (2016) 31: 798–806
doi: 10.1093/ndt/gfv454
Advance Access publication 29 February 2016

An estimated glomerular filtration rate equation for the full age spectrum

Hans Pottel[1], Liesbeth Hoste[1], Laurence Dubourg[2], Natalie Ebert[3], Elke Schaeffner[3], Bjørn Odvar Eriksen[4], Toralf Melsom[4], Edmund J. Lamb[5], Andrew D. Rule[6], Stephen T. Turner[6], Richard J. Glassock[7], Vandréa De Souza[8], Luciano Selistre[9], Christophe Mariat[10], Frank Martens[11] and Pierre Delanaye[12]

$$\text{FAS} - \text{eGFR} = \frac{107.3}{(\text{SCr}/Q)} \quad \text{for } 2 \leq \text{age} \leq 40 \text{ years}$$

$$\text{FAS} - \text{eGFR} = \frac{107.3}{(\text{SCr}/Q)} \times 0.988^{(\text{Age}-40)} \quad \text{for age} > 40 \text{ years}$$

A concept more than a regression…

Table 1. *Q*-values [=median serum creatinine in µmol/L (mg/dL)] for the FAS equation, according to age or height (from refs [4, 5, 10])

Age, years	Height[a], cm	*Q*[b], µmol/L (mg/dL)
Boys and girls		
1	75.0	23 (0.26)
2	87.0	26 (0.29)
3	95.5	27 (0.31)
4	102.5	30 (0.34)
5	110.0	34 (0.38)
6	116.7	36 (0.41)
7	123.5	39 (0.44)
8	129.5	41 (0.46)
9	135.0	43 (0.49)
10	140.0	45 (0.51)
11	146.0	47 (0.53)
12	152.5	50 (0.57)
13	159.0	52 (0.59)
14	165.0	54 (0.61)
Male adolescents		
15	172.0	64 (0.72)
16	176.0	69 (0.78)
17	178.0	72 (0.82)
18	179.0	75 (0.85)
19	180.0	78 (0.88)
Male adults		
≥20	≥181.5	80 (0.90)
Female adolescents		
15	164.5	57 (0.64)
16	166.0	59 (0.67)
17	166.5	61 (0.69)
18	167.0	61 (0.69)
19	167.5	62 (0.70)
Female adults		
≥20	≥168.0	62 (0.70)

[a]Height is the median height of a child or adolescent at the specified age (Belgian growth curves).

Table 3. Prediction performance results of different eGFR equations on the pooled databases according to age group and measured GFR categories (mGFR below or above 60 mL/min/1.73 m^2)

Pooled data	eGFR equivalent	RMSE (95% CI)	Constant bias (95% CI)	Proportional bias (95% CI)	P10, % (95% CI)	P30, % (95% CI)
Children and adolescents <18 years						
All (n = 735)	FAS	20.1 (18.5, 21.6)	−1.7 (−3.1, −0.2)*,†	1.01 (0.99, 1.03)*,†	40.1 (36.6, 43.7)	87.5 (85.1, 89.9)*
mGFR = 94.5	FAS-height	19.8 (18.1, 21.4)	−2.7 (−4.1, −1.3)*,‡	1.00 (0.98, 1.01)*,‡	41.9 (38.3, 45.5)	88.8 (86.6, 91.1)†
	Schwartz	21.7 (19.5, 23.7)	6.0 (4.5, 7.5)†,‡	1.09 (1.07, 1.11)†,‡	40.1 (36.6, 43.7)	83.8 (81.1, 86.5)*,†
mGFR < 60 (n = 99)	FAS	14.6 (8.5, 18.9)	6.2 (3.6, 8.9)*,†	1.15 (1.09, 1.21)*,†	34.3 (24.8, 43.9)	75.8 (67.2, 84.3)
mGFR = 45.1	FAS-height	13.5 (4.2, 18.6)	4.7 (2.2, 7.2)*,‡	1.12 (1.06, 1.17)*,‡	39.4 (25.6, 49.2)	77.8 (69.4, 86.1)*
	Schwartz	16.7 (8.2, 22.1)	9.4 (6.7, 12.2)†,‡	1.22 (1.16, 1.28)†,‡	31.3 (22.0, 40.6)	70.7 (61.6, 79.8)*
mGFR ≥ 60 (n = 636)	FAS	20.8 (19.1, 22.4)	−2.9 (−4.5, −1.3)*,†	0.99 (0.97, 1.00)*,†	41.0 (37.2, 44.9)	89.3 (86.9, 91.7)*
mGFR = 102.2	FAS-height	20.6 (18.9, 22.3)	−3.8 (−5.4, −2.3)*,‡	0.98 (0.96, 0.99)*,‡	42.3 (38.4, 46.1)	90.6 (88.3, 92.8)†
	Schwartz	22.4 (20.0, 24.5)	5.4 (3.7, 7.1)†,‡	1.07 (1.05, 1.09)†,‡	41.5 (37.7, 45.3)	85.8 (83.1, 88.6)*,†
Adults 18–70 years						
All (n = 4371)	FAS	17.2 (16.6, 17.8)	5.0 (4.5, 5.5)*	1.12 (1.11, 1.12)*	40.4 (38.9, 41.9)*	81.6 (80.4, 82.7)
mGFR = 78.6	CKD-EPI	16.4 (15.8, 16.9)	6.3 (5.9, 6.8)*	1.13 (1.12, 1.14)*	42.5 (41.1, 44.0)*	81.9 (80.7, 83.0)
mGFR < 60 (n = 1089)	FAS	19.0 (17.7, 20.2)	13.4 (12.6, 14.2)*	1.35 (1.33, 1.37)*	19.1 (16.8, 21.4)*	52.2 (49.3, 55.2)*
mGFR = 42.3	CKD-EPI	19.2 (18.1, 20.3)	12.7 (11.8, 13.5)*	1.31 (1.29, 1.34)*	21.9 (19.4, 24.3)*	55.2 (52.2, 58.1)*
mGFR ≥ 60 (n = 3282)	FAS	16.6 (15.9, 17.2)*	2.2 (1.6, 2.7)*	1.04 (1.03, 1.04)*	47.5 (45.8, 49.2)*	91.3 (90.3, 92.3)
mGFR = 90.6	CKD-EPI	15.3 (14.7, 15.8)*	4.2 (3.7, 4.7)*	1.07 (1.06, 1.07)*	49.4 (47.7, 51.1)*	90.7 (89.7, 91.7)
Older adults ≥70 years						
All (n = 1764)	FAS	11.2 (10.7, 11.7)*	−1.1 (−1.6, −0.6)*	1.02 (1.01, 1.03)*	39.7 (37.5, 42.0)*	86.1 (84.4, 87.7)*
mGFR = 55.6	CKD-EPI	12.9 (12.4, 13.4)*	5.6 (5.1, 6.2)*	1.13 (1.12, 1.15)*	35.0 (32.8, 37.3)*	77.6 (75.7, 79.6)*
	BIS1[a]	12.0 (11.4, 12.6)	−1.2 (−1.9, −0.6)	1.05 (1.03, 1.07)	34.7 (32.0, 37.4)	81.8 (79.7, 84.0)
mGFR < 60 (n = 986)	FAS	9.5 (8.8, 10.1)*	2.2 (1.6, 2.7)*	1.09 (1.07, 1.11)*	36.6 (33.6, 39.6)*	81.0 (78.6, 83.5)*
mGFR = 40.7	CKD-EPI	13.1 (12.3, 13.8)*	6.9 (6.2, 7.6)*	1.19 (1.17, 1.21)*	29.5 (26.7, 32.4)*	67.7 (64.8, 70.7)*
	BIS1[a]	9.7 (9.0, 10.3)	3.7 (3.0, 4.4)	1.16 (1.13, 1.18)	35.3 (31.8, 38.8)	75.4 (72.2, 78.5)
mGFR ≥ 60 (n = 778)	FAS	13.1 (12.3, 13.8)	−5.2 (−6.1, −4.4)*	0.94 (0.93, 0.95)*	43.7 (40.2, 47.2)	92.4 (90.6, 94.3)
mGFR = 74.4	CKD-EPI	12.7 (12.1, 13.3)	4.1 (3.2, 4.9)*	1.07 (1.06, 1.08)*	42.0 (38.6, 45.5)	90.1 (88.0, 92.2)
	BIS1[a]	14.8 (13.7, 15.7)	−8.6 (−9.7, −7.5)	0.90 (0.88, 0.91)	33.9 (29.6, 38.1)	91.5 (89.0, 94.0)

The same symbols (*,†,‡) within each subgroup and column indicate significant differences (paired t-test for constant and proportional bias, McNemar's test for P10 and P30 = % of subjects with an eGFR value within 10% and 30% of measured GFR).

[a]For the BIS1 performance results, the data (n= 570) from the BIS1 study were not included (therefore, no comparisons with FAS and CKD-EPI were made).

MDRD – CKD-EPI: nothing else?

- The Bis Equation
- The Lund-Malmö equation
- The FAS equation
- Other biomarkers: cystatin C

Schaeffner, Ann intern Med, 2012, 157, 471
Bjork, Scand J Urol Nephrol, 2012, 46, 212
Pottel H, Nephrol Dial Transplant, 2016
Seronie-Vivien, CCLM, 2008

Cystatin C

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C

Lesley A. Inker, M.D., Christopher H. Schmid, Ph.D., Hocine Tighiouart, M.S., John H. Eckfeldt, M.D., Ph.D., Harold I. Feldman, M.D., Tom Greene, Ph.D., John W. Kusek, Ph.D., Jane Manzi, Ph.D., Frederick Van Lente, Ph.D., Yaping Lucy Zhang, M.S., Josef Coresh, M.D., Ph.D., and Andrew S. Levey, M.D., for the CKD-EPI Investigators*

Table 1. Characteristics of Study Participants, According to Data Set.*

Characteristic	Development and Internal Validation (N = 5352)	External Validation (N = 1119)	P Value
Age — yr	47±15	50±17	<0.001
Age group — no. (%)			
<40 yr	2008 (38)	357 (32)	<0.001
40–65 yr	2625 (49)	530 (47)	
>65 yr	719 (13)	232 (21)	
Male sex — no. (%)	3107 (58)	663 (59)	0.46
Black race — no. (%)†	2123 (40)	30 (3)	<0.001
Diabetes — no. (%)	1726 (32)	594 (53)	<0.001
Body-mass index‡			
Mean	28±6	25±4	<0.001
<20 — no. (%)	214 (4)	81 (7)	<0.001
20–24 — no. (%)	1585 (30)	503 (45)	
25–30 — no. (%)	1881 (35)	386 (35)	
>30 — no. (%)	1671 (31)	149 (13)	
Mean weight — kg	83±20	74±15	<0.001
Mean height — cm	171±10	170±9	0.017
Mean body-surface area — m^2	1.94±0.24	1.85±0.21	<0.001
Mean serum cystatin C — ml/liter	1.4±0.7	1.5±0.8	0.01
Mean serum creatinine — mg/dl§	1.6±0.9	1.6±1.1	0.15
Mean measured GFR — ml/min/1.73 m^2 of body-surface area	68±39	70±41	0.13
Measured GFR — no. (%)			
<15 ml/min/1.73 m^2	160 (3)	51 (5)	<0.001
15–29 ml/min/1.73 m^2	785 (15)	166 (15)	
30–59 ml/min/1.73 m^2	1765 (33)	316 (28)	
60–89 ml/min/1.73 m^2	1105 (21)	215 (19)	
90–119 ml/min/1.73 m^2	862 (16)	199 (18)	
>120 ml/min/1.73 m^2	675 (13)	172 (15)	

Table 2. Creatinine Equation (CKD-EPI 2009), Cystatin C Equation (CKD-EPI 2012), and Creatinine–Cystatin C Equation (CKD-EPI 2012) for Estimating GFR, Expressed for Specified Sex, Serum Creatinine Level, and Serum Cystatin C Level.*

Basis of Equation and Sex	Serum Creatinine†	Serum Cystatin C	Equation for Estimating GFR
	mg/dl	*mg/liter*	
CKD-EPI creatinine equation‡			
Female	≤0.7		$144 \times (\text{Scr}/0.7)^{-0.329} \times 0.993^{\text{Age}}$ [× 1.159 if black]
Female	>0.7		$144 \times (\text{Scr}/0.7)^{-1.209} \times 0.993^{\text{Age}}$ [× 1.159 if black]
Male	≤0.9		$141 \times (\text{Scr}/0.9)^{-0.411} \times 0.993^{\text{Age}}$ [× 1.159 if black]
Male	>0.9		$141 \times (\text{Scr}/0.9)^{-1.209} \times 0.993^{\text{Age}}$ [× 1.159 if black]
CKD-EPI cystatin C equation§			
Female or male		≤0.8	$133 \times (\text{Scys}/0.8)^{-0.499} \times 0.996^{\text{Age}}$ [× 0.932 if female]
Female or male		>0.8	$133 \times (\text{Scys}/0.8)^{-1.328} \times 0.996^{\text{Age}}$ [× 0.932 if female]
CKD-EPI creatinine–cystatin C equation¶			
Female	≤0.7	≤0.8	$130 \times (\text{Scr}/0.7)^{-0.248} \times (\text{Scys}/0.8)^{-0.375} \times 0.995^{\text{Age}}$ [× 1.08 if black]
		>0.8	$130 \times (\text{Scr}/0.7)^{-0.248} \times (\text{Scys}/0.8)^{-0.711} \times 0.995^{\text{Age}}$ [× 1.08 if black]
Female	>0.7	≤0.8	$130 \times (\text{Scr}/0.7)^{-0.601} \times (\text{Scys}/0.8)^{-0.375} \times 0.995^{\text{Age}}$ [× 1.08 if black]
		>0.8	$130 \times (\text{Scr}/0.7)^{-0.601} \times (\text{Scys}/0.8)^{-0.711} \times 0.995^{\text{Age}}$ [× 1.08 if black]
Male	≤0.9	≤0.8	$135 \times (\text{Scr}/0.9)^{-0.207} \times (\text{Scys}/0.8)^{-0.375} \times 0.995^{\text{Age}}$ [× 1.08 if black]
		>0.8	$135 \times (\text{Scr}/0.9)^{-0.207} \times (\text{Scys}/0.8)^{-0.711} \times 0.995^{\text{Age}}$ [× 1.08 if black]
Male	>0.9	≤0.8	$135 \times (\text{Scr}/0.9)^{-0.601} \times (\text{Scys}/0.8)^{-0.375} \times 0.995^{\text{Age}}$ [× 1.08 if black]
		>0.8	$135 \times (\text{Scr}/0.9)^{-0.601} \times (\text{Scys}/0.8)^{-0.711} \times 0.995^{\text{Age}}$ [× 1.08 if black]

Table 3. Use of the CKD-EPI Creatinine Equation (2009), CKD-EPI Cystatin C Equation (2012), and CKD-EPI Creatinine–Cystatin C Equations (2012) in the External-Validation Data Set Comprising 1119 Participants.*

Variable	Estimated GFR			
	Overall	<60	60–89	≥90
		ml/min/1.73 m² of body-surface area		
Bias — median difference (95% CI)				
Creatinine equation	3.7 (2.8 to 4.6)	1.8 (1.1 to 2.5)	6.6 (3.5 to 9.2)	11.1 (8.0 to 12.5)
Cystatin C equation	3.4 (2.3 to 4.4)	0.4 (–0.5 to 1.4)	6.0 (4.6 to 8.5)	8.5 (6.5 to 11.2)
Creatinine–cystatin C equation	3.9 (3.2 to 4.5)	1.3 (0.5 to 1.8)	6.9 (5.0 to 8.9)	10.6 (9.5 to 12.7)
Average of creatinine and cystatin C†	3.5 (2.8 to 4.1)	0.4 (–0.3 to 0.8)	6.5 (4.6 to 8.4)	11.9 (9.9 to 13.9)
Precision — IQR of the difference (95% CI)				
Creatinine equation	15.4 (14.3 to 16.5)	10.0 (8.9 to 11.0)	19.6 (17.3 to 23.2)	25.0 (21.6 to 28.1)
Cystatin C equation	16.4 (14.8 to 17.8)	11.0 (10.0 to 12.4)	19.6 (16.1 to 23.1)	22.6 (18.8 to 26.3)
Creatinine–cystatin C equation	13.4 (12.3 to 14.5)	8.1 (7.3 to 9.1)	15.9 (13.9 to 18.1)	18.8 (16.8 to 22.5)
Average of creatinine and cystatin C equations†	13.9 (12.9 to 14.7)	7.9 (7.1 to 9.0)	15.8 (13.9 to 17.7)	18.6 (16.1 to 22.2)
Accuracy — % (95% CI)‡				
$1-P_{30}$				
Creatinine equation	12.8 (10.9 to 14.7)	16.6 (13.6 to 19.7)	10.2 (6.4 to 14.2)	7.8 (5.1 to 11.0)
Cystatin C equation	14.1 (12.2 to 16.2)	21.4 (18.2 to 24.9)	12.7 (8.5 to 17.4)	2.2 (0.6 to 3.9)
Creatinine–cystatin C equation	8.5 (7.0 to 10.2)	13.3 (10.7 to 16.1)	5.3 (2.7 to 8.2)	2.3 (0.9 to 4.2)
Average of creatinine and cystatin C equations†	8.2 (6.7 to 9.9)	12.1 (9.5 to 14.8)	6.4 (3.6 to 9.7)	2.9 (1.3 to 4.9)
$1-P_{20}$				
Creatinine equation	32.9 (30.1 to 35.7)	37.2 (33.1 to 41.2)	31.1 (25.1 to 37.4)	26.5 (21.7 to 31.4)
Cystatin C equation	33.0 (30.3 to 35.7)	42.1 (38.2 to 46.1)	29.3 (23.6 to 35.4)	19.4 (15.4 to 23.7)
Creatinine–cystatin C equation	22.8 (20.4 to 25.2)	28.6 (25.1 to 32.4)	17.8 (13.3 to 22.9)	16.2 (12.4 to 20.5)
Average of creatinine and cystatin C equations†	23.7 (21.3 to 26.1)	29.1 (25.7 to 32.8)	17.6 (13.2 to 22.4)	18.8 (14.6 to 23.2)

Nephrol Dial Transplant (2016) 1–11
doi: 10.1093/ndt/gfw425

ndt
Nephrology Dialysis Transplantation

Original Article

Estimating glomerular filtration rate for the full age spectrum from serum creatinine and cystatin C

Hans Pottel[1], Pierre Delanaye[2], Elke Schaeffner[3], Laurence Dubourg[4], Bjørn Odvar Eriksen[5], Toralf Melsom[5], Edmund J. Lamb[6], Andrew D. Rule[7], Stephen T. Turner[7], Richard J. Glassock[8], Vandréa De Souza[9], Luciano Selistre[9,10], Karolien Goffin[11], Steven Pauwels[12,13], Christophe Mariat[14], Martin Flamant[15] and Natalie Ebert[3]

$$FAS_{cysC} = \frac{107.3}{\frac{ScysC}{Q_{cysC}}} \times \left[0.988^{(Age-40)} \text{ when age} > 40 \text{ years}\right].$$

$$FAS_{combi} = \frac{107.3}{\alpha \times \frac{Scr}{Q_{crea}} + (1-\alpha) \times \frac{ScysC}{Q_{cysC}}} \times \left[0.988^{(Age-40)} \text{ when age} > 40 \text{ years}\right].$$

Table 5. Patient characteristics in the different age groups (mean ± SD)

Group	*n*	No. of males	No. of females	mGFR	Scr	ScysC
Children ≤18 years	368	193	175	89.2 ± 30.4	0.65 ± 0.31	1.15 ± 0.42
Adults 18–70 years	4295	2301	1994	80.2 ± 25.6	1.00 ± 0.50	0.99 ± 0.51
Older adults ≥70 years	1469	771	698	58.5 ± 20.0	1.13 ± 0.52	1.24 ± 0.51
Total	6132	3265	2867			

n, number of patients; mGFR, measured glomerular filtration rate (mL/min/1.73 m^2); Scr, serum creatinine (mg/dL); ScysC, serum cystatin C (mg/L).

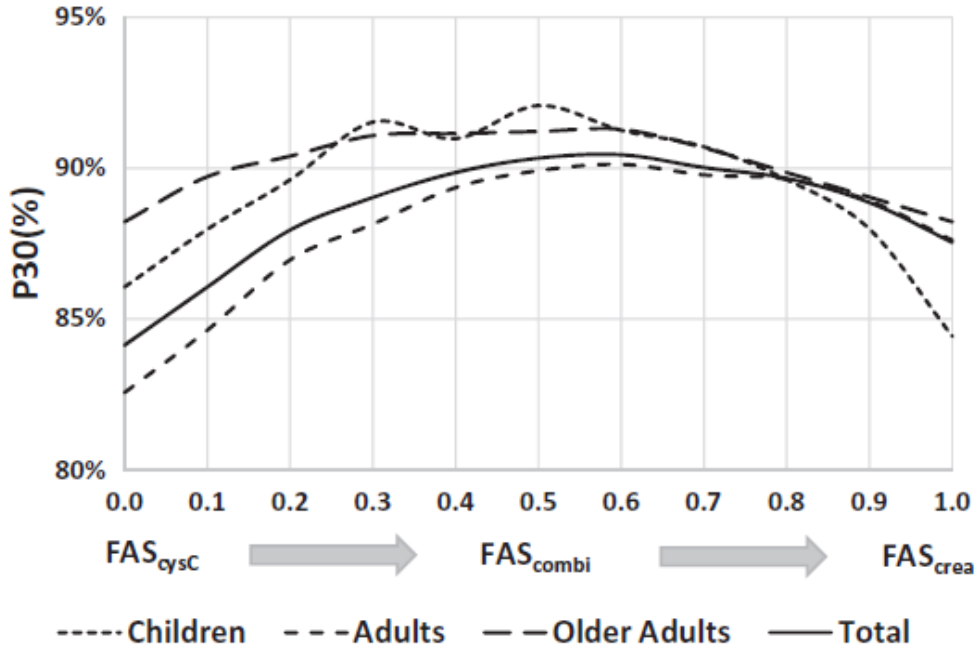


FIGURE 3: P30 as a function of the weighting factor α for the different age groups.

Cystatin C

- Combined
- Cost-effectiveness?
- At the individual level, the imprecision remains…

Conclusions: eGFR a double message ?

- For General Physicians:

  MDRD (or CKD-EPI or FAS) is probably the best and simplest way to estimate GFR

- For Nephrologists:

  MDRD (or CKD-EPI) is not “magic”, keep our critical feeling, there are several limitations we have to know

→ **Go back to measured GFR if necessary**

The applicability of eGFR equations to different populations

Pierre Delanaye and Christophe Mariat

Today the true question is maybe not about which equation is the best

- When is it necessary to measure GFR?
- « Measuring GFR is costly and cumbersome »

Delanaye P, Nature Rev Nephrol, 2013, 9, 513

Summary

- Estimating GFR (creatinine, eGFR, cystatin C)
- Measuring GFR
- (CKD diagnosis)

Measuring GFR

- WHY?

- How?

Indication = the patient

- Serum creatinine is potentially incorrect
- High Precision required (drug toxicity, kidney donation)

But also in clinical research…

Effect of longacting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicentre trial

Anna Caroli, Norberto Perico*, Annalisa Perna*, Luca Antiga, Paolo Brambilla, Antonio Pisani, Bianca Visciano, Massimo Imbriaco, Piergiorgio Messa, Roberta Cerutti, Mauro Dugo, Luca Cancian, Erasmo Buongiorno, Antonio De Pascalis, Flavio Gaspari, Fabiola Carrara, Nadia Rubis, Silvia Prandini, Andrea Remuzzi, Giuseppe Remuzzi*, Piero Ruggenenti*, for the ALADIN study group†*

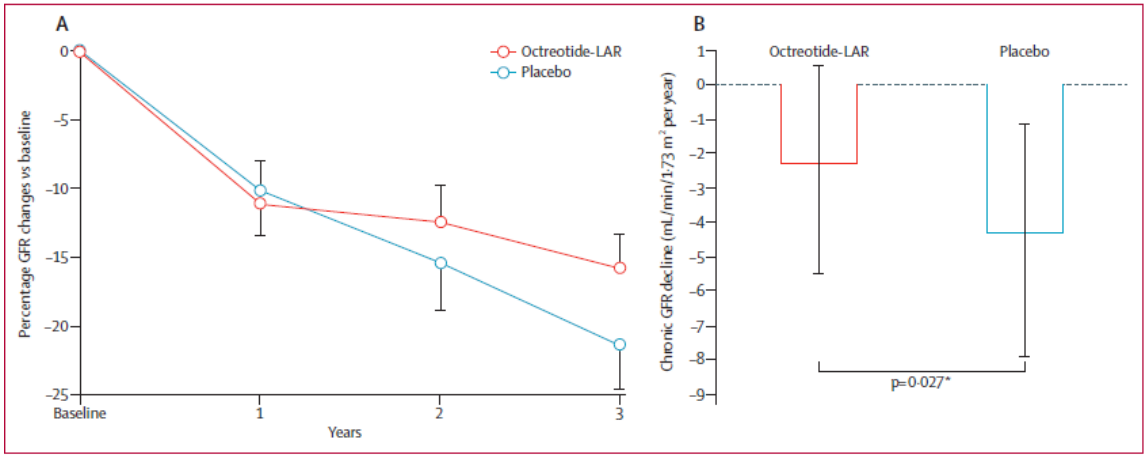


Figure 5: **Effect of placebo or Octreotide-LAR treatment on kidney function**
Percentage change in GFR, measured by iohexol plasma clearance, compared with baseline in placebo and Octreotide-LAR groups during the 3 year treatment (A). Chronic GFR decline from year 1 to year 3 after randomisation in the two treatment groups (B). Values are mean (SEM) and median (IQR). p values calculated after log-tranformation of GFR values. p values from Wilcoxon rank-sum test. GFR=glomerular filtration rate.

	Octreotide-LAR (n=40)	Placebo (n=39)
Age (years)	36 (8)	38 (8)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease

Vicente E. Torres, M.D., Ph.D., Arlene B. Chapman, M.D., Olivier Devuyst, M.D., Ph.D., Ron T. Gansevoort, M.D., Ph.D., Jared J. Grantham, M.D., Eiji Higashihara, M.D., Ph.D., Ronald D. Perrone, M.D., Holly B. Krasa, M.S., John Ouyang, Ph.D., and Frank S. Czerwiec, M.D., Ph.D., for the TEMPO 3:4 Trial Investigators*

ABSTRACT

N Engl J Med 2012;367:2407-18.
DOI: 10.1056/NEJMoa1205511

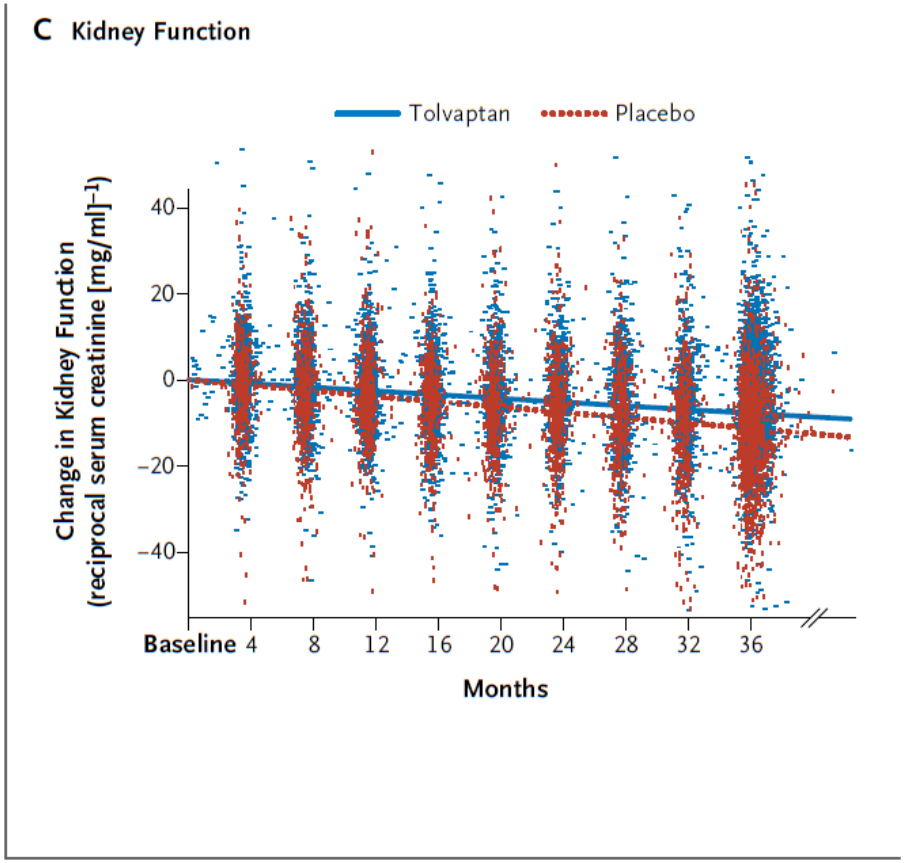


Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Tolvaptan (N = 961)	Placebo (N = 484)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Belatacept and Long-Term Outcomes in Kidney Transplantation

Flavio Vincenti, M.D., Lionel Rostaing, M.D., Ph.D., Joseph Grinyo, M.D., Ph.D., Kim Rice, M.D., Steven Steinberg, M.D., Luis Gaite, M.D., Marie-Christine Moal, M.D., Guillermo A. Mondragon-Ramirez, M.D., Jatin Kothari, M.D., Martin S. Polinsky, M.D., Herwig-Ulf Meier-Kriesche, M.D., Stephane Munier, M.Sc., and Christian P. Larsen, M.D., Ph.D.

N Engl J Med 2016;374:333-43.
DOI: 10.1056/NEJMoa1506027

Belatacept, a fusion protein composed of the Fc fragment of human IgG1 linked to the extracellular domain of cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), selectively inhibits T-cell activation through costimulation blockade.[13-15]

CONCLUSIONS

Seven years after transplantation, patient and graft survival and the mean eGFR were significantly higher with belatacept (both the more-intensive regimen and the less-intensive regimen) than with cyclosporine. (Funded by Bristol-Myers Squibb; ClinicalTrials.gov number, NCT00256750.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Costimulation Blockade with Belatacept in Renal Transplantation

Flavio Vincenti, M.D., Christian Larsen, M.D., Ph.D., Antoine Durrbach, M.D., Ph.D., Thomas Wekerle, M.D., Björn Nashan, M.D., Ph.D., Gilles Blancho, M.D., Ph.D., Philippe Lang, M.D., Josep Grinyo, M.D., Philip F. Halloran, M.D., Ph.D., Kim Solez, M.D., David Hagerty, M.D., Elliott Levy, M.D., Wenjiong Zhou, Ph.D., Kannan Natarajan, Ph.D., and Bernard Charpentier, M.D., for the Belatacept Study Group*

N Engl J Med 2005;353:770-81.

6 months

Table 3. Renal Function and Histologic Findings.*

End Point	Intensive Belatacept	Less-Intensive Belatacept	Cyclosporine
Measured GFR			
No. of patients	32	37	27
Mean GFR — ml/min/1.73 m²†	66.3±20.7	62.1±15.9	53.5±16.4
Difference from cyclosporine group — ml/min/1.73 m² (95% CI)	12.8 (2.9 to 22.7)	8.6 (0.4 to 16.8)	—
Calculated GFR			
No. of patients	60	59	50
Mean GFR — ml/min/1.73 m²	72.4±22.5	73.2±22.5	68.0±28.1
Difference from cyclosporine group — ml/min/1.73 m² (95% CI)	4.4 (−5.2 to 14.0)	5.2 (−4.4 to 14.8)	—

† $P<0.05$ for the comparison of both belatacept regimens with cyclosporine.

Clin Pharmacokinet (2017) 56:193–205
DOI 10.1007/s40262-016-0434-z

ORIGINAL RESEARCH ARTICLE

Discrepancies between the Cockcroft–Gault and Chronic Kidney Disease Epidemiology (CKD-EPI) Equations: Implications for Refining Drug Dosage Adjustment Strategies

Pierre Delanaye[1] · Fabrice Guerber[2] · André Scheen[3] · Timothy Ellam[4] · Antoine Bouquegneau[1] · Dorra Guergour[5] · Christophe Mariat[6] · Hans Pottel[7]

Males

Age 50		Length 177																									
BSA	W/Scr	0,5	0,6	0,7	0,8	0,9	1	1,1	1,2	1,3	1,4	1,5	1,6	1,7	1,8	1,9	2	2,1	2,2	2,3	2,4	2,5	2,6	2,7	2,8	2,9	3
1,20	25	-25,4	-29,4	-31,9	-33,4	-34,3	-29,5	-25,7	-22,7	-20,2	-18,1	-16,4	-14,9	-13,6	-12,5	-11,5	-10,7	-9,9	-9,2	-8,6	-8,1	-7,6	-7,1	-6,7	-6,3	-6,0	-5,7
1,30	30	-19,9	-25,6	-29,1	-31,4	-32,9	-28,2	-24,4	-21,4	-19,0	-16,9	-15,2	-13,8	-12,5	-11,4	-10,5	-9,6	-8,9	-8,3	-7,7	-7,2	-6,7	-6,3	-5,9	-5,5	-5,2	-4,9
1,39	35	-13,9	-21,1	-25,8	-28,9	-31,0	-26,3	-22,7	-19,8	-17,4	-15,4	-13,8	-12,4	-11,2	-10,1	-9,2	-8,4	-7,8	-7,1	-6,6	-6,1	-5,7	-5,3	-4,9	-4,6	-4,3	-4,0
1,47	40	-7,3	-16,2	-22,0	-25,9	-28,7	-24,2	-20,7	-17,8	-15,6	-13,7	-12,1	-10,8	-9,6	-8,7	-7,8	-7,1	-6,4	-5,9	-5,4	-4,9	-4,5	-4,1	-3,8	-3,5	-3,2	-3,0
1,54	45	-0,3	-10,9	-17,9	-22,7	-26,1	-21,7	-18,4	-15,7	-13,5	-11,8	-10,3	-9,0	-8,0	-7,1	-6,3	-5,6	-5,0	-4,5	-4,0	-3,6	-3,3	-2,9	-2,6	-2,4	-2,1	-1,9
1,62	50	7,0	-5,3	-13,4	-19,1	-23,2	-19,1	-15,9	-13,3	-11,3	-9,7	-8,3	-7,1	-6,2	-5,4	-4,6	-4,0	-3,5	-3,0	-2,6	-2,3	-1,9	-1,7	-1,4	-1,2	-1,0	-0,8
1,68	55	14,7	0,6	-8,8	-15,3	-20,1	-16,2	-13,2	-10,8	-9,0	-7,4	-6,2	-5,2	-4,3	-3,5	-2,9	-2,4	-1,9	-1,5	-1,1	-0,8	-0,6	-0,3	-0,1	0,1	0,3	0,4
1,75	60	22,5	6,7	-3,9	-11,3	-16,8	-13,1	-10,4	-8,2	-6,5	-5,1	-4,0	-3,1	-2,3	-1,6	-1,1	-0,6	-0,2	0,1	0,4	0,7	0,9	1,1	1,3	1,4	1,5	1,6
1,81	65	30,6	13,1	1,2	-7,2	-13,3	-9,9	-7,4	-5,4	-3,9	-2,7	-1,7	-0,9	-0,2	0,3	0,8	1,2	1,5	1,8	2,0	2,2	2,4	2,5	2,6	2,8	2,8	2,9
1,86	70	38,9	19,6	6,5	-2,8	-9,7	-6,6	-4,3	-2,6	-1,2	-0,2	0,7	1,4	1,9	2,4	2,7	3,0	3,3	3,5	3,7	3,8	3,9	4,0	4,1	4,1	4,2	4,2
1,92	75	47,3	26,2	11,9	1,7	-5,9	-3,2	-1,1	0,4	1,5	2,4	3,1	3,7	4,1	4,5	4,7	5,0	5,1	5,3	5,4	5,4	5,5	5,5	5,6	5,6	5,6	5,6
1,97	80	56,0	33,0	17,4	6,3	-2,0	0,4	2,1	3,4	4,4	5,1	5,7	6,1	6,4	6,6	6,8	6,9	7,0	7,1	7,1	7,1	7,1	7,1	7,1	7,0	7,0	6,9
2,02	85	64,7	39,9	23,1	11,0	2,0	4,0	5,5	6,6	7,3	7,8	8,2	8,5	8,7	8,8	8,9	8,9	8,9	8,9	8,9	8,8	8,7	8,7	8,6	8,5	8,4	8,3
2,07	90	73,6	47,0	28,8	15,8	6,1	7,8	9,0	9,7	10,3	10,6	10,9	11,0	11,0	11,0	11,0	11,0	10,9	10,8	10,7	10,5	10,4	10,3	10,2	10,0	9,9	9,8
2,12	95	82,5	54,1	34,7	20,7	10,2	11,6	12,5	13,0	13,3	13,5	13,5	13,5	13,4	13,3	13,2	13,0	12,9	12,7	12,5	12,3	12,1	11,9	11,7	11,6	11,4	11,2
2,17	100	91,6	61,4	40,6	25,7	14,5	15,5	16,0	16,3	16,4	16,4	16,3	16,1	15,9	15,6	15,4	15,1	14,9	14,6	14,3	14,1	13,8	13,6	13,3	13,1	12,9	12,7
2,21	105	100,8	68,7	46,7	30,8	18,8	19,4	19,7	19,7	19,5	19,3	19,0	18,7	18,3	18,0	17,6	17,3	16,9	16,6	16,2	15,9	15,6	15,3	15,0	14,7	14,4	14,1
2,26	110	110,1	76,1	52,8	35,9	23,2	23,5	23,4	23,1	22,7	22,3	21,8	21,3	20,8	20,4	19,9	19,4	19,0	18,5	18,1	17,7	17,3	17,0	16,6	16,3	15,9	15,6
2,30	115	119,4	83,6	59,0	41,1	27,7	27,5	27,1	26,6	26,0	25,3	24,7	24,0	23,4	22,8	22,2	21,6	21,1	20,5	20,0	19,6	19,1	18,7	18,3	17,9	17,5	17,1
2,34	120	128,9	91,2	65,2	46,4	32,3	31,7	30,9	30,1	29,2	28,4	27,5	26,7	25,9	25,2	24,5	23,8	23,2	22,6	22,0	21,4	20,9	20,4	19,9	19,5	19,1	18,6
2,38	125	138,4	98,9	71,6	51,8	36,8	35,8	34,7	33,6	32,5	31,4	30,4	29,4	28,5	27,6	26,8	26,0	25,3	24,6	23,9	23,3	22,7	22,2	21,6	21,1	20,6	20,2

Males

Age 60		Length 177																									
BSA	W/Scr	0,5	0,6	0,7	0,8	0,9	1	1,1	1,2	1,3	1,4	1,5	1,6	1,7	1,8	1,9	2	2,1	2,2	2,3	2,4	2,5	2,6	2,7	2,8	2,9	3
1,20	25	-26,4	-29,7	-31,6	-32,8	-33,5	-28,9	-25,2	-22,3	-19,9	-17,9	-16,2	-14,7	-13,5	-12,4	-11,4	-10,6	-9,9	-9,2	-8,6	-8,1	-7,6	-7,2	-6,8	-6,4	-6,1	-5,7
1,30	30	-21,8	-26,6	-29,5	-31,3	-32,5	-27,9	-24,2	-21,3	-18,9	-16,9	-15,3	-13,8	-12,6	-11,5	-10,6	-9,8	-9,1	-8,4	-7,9	-7,3	-6,9	-6,5	-6,1	-5,7	-5,4	-5,1
1,39	35	-16,7	-22,9	-26,7	-29,3	-31,0	-26,5	-22,9	-20,0	-17,7	-15,7	-14,1	-12,7	-11,5	-10,5	-9,6	-8,8	-8,1	-7,5	-7,0	-6,5	-6,0	-5,6	-5,3	-4,9	-4,6	-4,3
1,47	40	-11,1	-18,7	-23,6	-26,9	-29,2	-24,7	-21,2	-18,4	-16,2	-14,3	-12,7	-11,4	-10,3	-9,3	-8,4	-7,7	-7,0	-6,5	-5,9	-5,5	-5,1	-4,7	-4,4	-4,0	-3,8	-3,5
1,54	45	-5,1	-14,2	-20,1	-24,2	-27,0	-22,7	-19,3	-16,7	-14,5	-12,7	-11,2	-9,9	-8,9	-7,9	-7,1	-6,5	-5,8	-5,3	-4,8	-4,4	-4,0	-3,7	-3,4	-3,1	-2,8	-2,6
1,62	50	1,1	-9,4	-16,4	-21,2	-24,6	-20,5	-17,3	-14,7	-12,6	-10,9	-9,5	-8,4	-7,4	-6,5	-5,8	-5,1	-4,6	-4,1	-3,6	-3,2	-2,9	-2,6	-2,3	-2,1	-1,8	-1,6
1,68	55	7,7	-4,4	-12,4	-18,0	-22,0	-18,1	-15,0	-12,6	-10,6	-9,1	-7,8	-6,7	-5,7	-5,0	-4,3	-3,7	-3,2	-2,7	-2,4	-2,0	-1,7	-1,4	-1,2	-1,0	-0,8	-0,6
1,75	60	14,5	0,9	-8,2	-14,6	-19,2	-15,5	-12,6	-10,4	-8,5	-7,1	-5,9	-4,9	-4,0	-3,3	-2,7	-2,2	-1,8	-1,4	-1,0	-0,7	-0,5	-0,2	0,0	0,1	0,3	0,5
1,81	65	21,5	6,3	-3,9	-11,1	-16,3	-12,8	-10,1	-8,0	-6,3	-5,0	-3,9	-3,0	-2,3	-1,6	-1,1	-0,7	-0,3	0,1	0,3	0,6	0,8	1,0	1,2	1,3	1,4	1,6
1,86	70	28,7	11,9	0,6	-7,4	-13,2	-9,9	-7,5	-5,6	-4,1	-2,8	-1,9	-1,1	-0,4	0,1	0,6	0,9	1,3	1,5	1,8	2,0	2,1	2,3	2,4	2,5	2,6	2,7
1,92	75	36,0	17,7	5,3	-3,5	-10,0	-7,0	-4,7	-3,0	-1,7	-0,6	0,2	0,9	1,5	1,9	2,3	2,6	2,8	3,1	3,2	3,4	3,5	3,6	3,7	3,7	3,8	3,8
1,97	80	43,5	23,6	10,0	0,4	-6,7	-4,0	-1,9	-0,4	0,8	1,7	2,4	3,0	3,4	3,8	4,1	4,3	4,5	4,6	4,7	4,8	4,9	4,9	5,0	5,0	5,0	5,0
2,02	85	51,1	29,6	14,9	4,5	-3,3	-0,8	1,0	2,3	3,3	4,0	4,6	5,1	5,4	5,7	5,9	6,0	6,1	6,2	6,3	6,3	6,3	6,3	6,3	6,3	6,3	6,2
2,07	90	58,8	35,7	19,9	8,6	0,2	2,4	3,9	5,0	5,8	6,4	6,9	7,2	7,4	7,6	7,7	7,8	7,8	7,8	7,8	7,8	7,8	7,7	7,7	7,6	7,5	7,5
2,12	95	66,7	41,9	25,0	12,9	3,8	5,7	6,9	7,8	8,5	8,9	9,2	9,4	9,5	9,6	9,6	9,6	9,5	9,5	9,4	9,3	9,2	9,1	9,0	8,9	8,8	8,7
2,17	100	74,6	48,2	30,2	17,2	7,5	9,0	10,0	10,7	11,1	11,4	11,5	11,6	11,6	11,6	11,5	11,4	11,3	11,2	11,0	10,9	10,7	10,6	10,4	10,3	10,1	10,0
2,21	105	82,6	54,6	35,4	21,6	11,2	12,4	13,2	13,6	13,9	13,9	13,9	13,9	13,8	13,6	13,4	13,3	13,1	12,9	12,7	12,4	12,2	12,0	11,8	11,7	11,5	11,3
2,26	110	90,7	61,1	40,7	26,0	15,1	15,9	16,4	16,6	16,6	16,5	16,4	16,2	15,9	15,7	15,4	15,1	14,9	14,6	14,3	14,0	13,8	13,5	13,3	13,0	12,8	12,6
2,30	115	98,9	67,6	46,1	30,6	18,9	19,4	19,6	19,6	19,4	19,1	18,8	18,5	18,1	17,8	17,4	17,0	16,7	16,3	16,0	15,7	15,3	15,0	14,7	14,4	14,2	13,9
2,34	120	107,1	74,2	51,5	35,2	22,9	23,0	22,9	22,6	22,2	21,8	21,3	20,8	20,4	19,9	19,4	19,0	18,5	18,1	17,7	17,3	16,9	16,5	16,2	15,9	15,5	15,2
2,38	125	115,5	80,9	57,1	39,8	26,8	26,7	26,2	25,7	25,1	24,5	23,8	23,2	22,6	22,0	21,4	20,9	20,4	19,9	19,4	18,9	18,5	18,1	17,7	17,3	16,9	16,6

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 December 2015
EMA/CHMP/83874/2014
Committee for Medicinal Products for Human use (CHMP)

Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function

5.2. Measures of renal function

In order to have a reference measure of renal function that is independent of clinical practice at the time of conduct of the pharmacokinetic study, it is recommended that a method accurately measuring GFR using an exogenous marker is used to determine renal function in the subjects in the pharmacokinetic study, if possible.

Measuring GFR

- Why?
- HOW ?

Available on the market…

Markers	Strenghts	Limitations
Inulin		
Iothalamate		
Iohexol		
EDTA		
DTPA		

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

We have biomarkers
Now, how to proceed?

- Urinary clearance

- Plasma clearance

Urinary clearance

- Constant infusion, marker at equilibrium
- Plasma measurement of the marker
- Collect Urine (every half or every hour) and measurement of urine flow, urine measurement of the marker
- Repeated 3 or 4-fold
- Cl = [U] x [V]/ [P] (mean of three collections)

Plasmatic Clearance = Dose / AUC

Theoritically, α and β must be calculated

↓

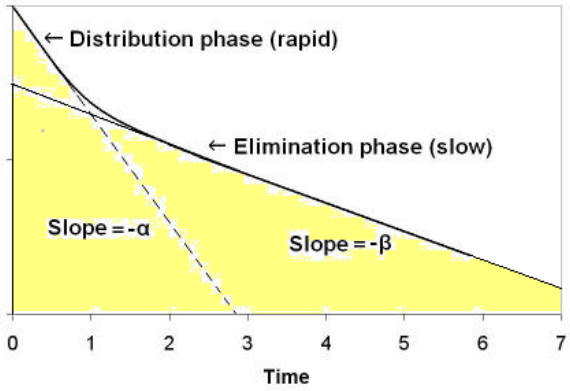
Not easy in practice (many samples)

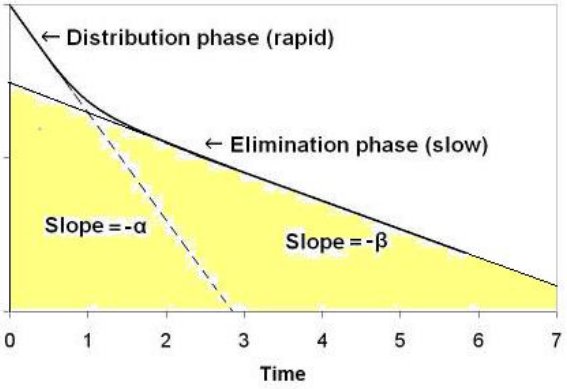
↓

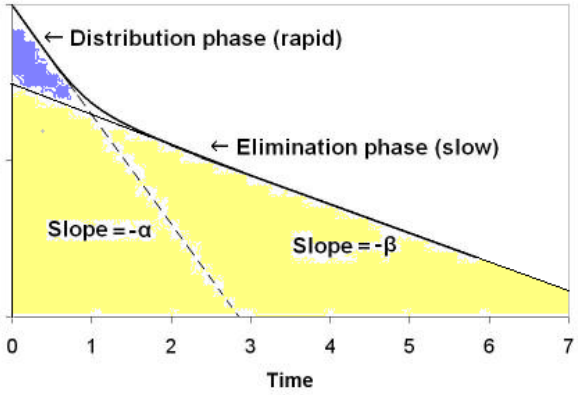
Only slope ß after equilibrium is calculated

↓

Brochner-Mortensen mathematical correction for estimation of distribution phase
= 0,990778 x C2 – 0,001218 $C2^2$







M

Are they equivalent?

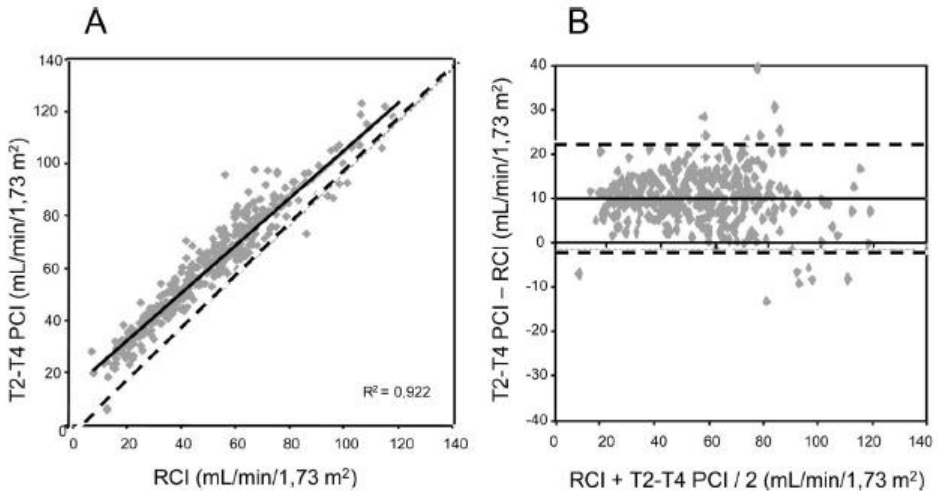
Plasma v urinary:
Are they equivalent?

- A lot of studies showing a good correlation…
- Few studies with Bland and Altman analysis

Plasma versus Urinary clearances

Evaluation of Sample Bias for Measuring Plasma Iohexol Clearance in Kidney Transplantation

Arnaud Stolz,[1] Guillaume Hoizey,[2] Olivier Toupance,[1] Sylvie Lavaud,[1] Fabien Vitry,[3] Jacques Chanard,[1] and Philippe Rieu[1,4,5]



	n	Bias ml/min/1.73m² (%)	Precision (SD) (ml/min/1.73m²)
T2-T4	342	+10 (+27%)	±6
T2-T6	342	+8 (+21%)	±6
T2-T24	215	+3 (+8.8%)	±5

Stolz A, Transplantation, 2010, 89, 440

Urinary and plasma methods: pro-con

- More physiological
- More costly
- More cumbersome
- Less precision, less repeatability (urine recolt!)
- Differences are sytematic

Several plasma clearance procedures are available on the market…

Available on the market…

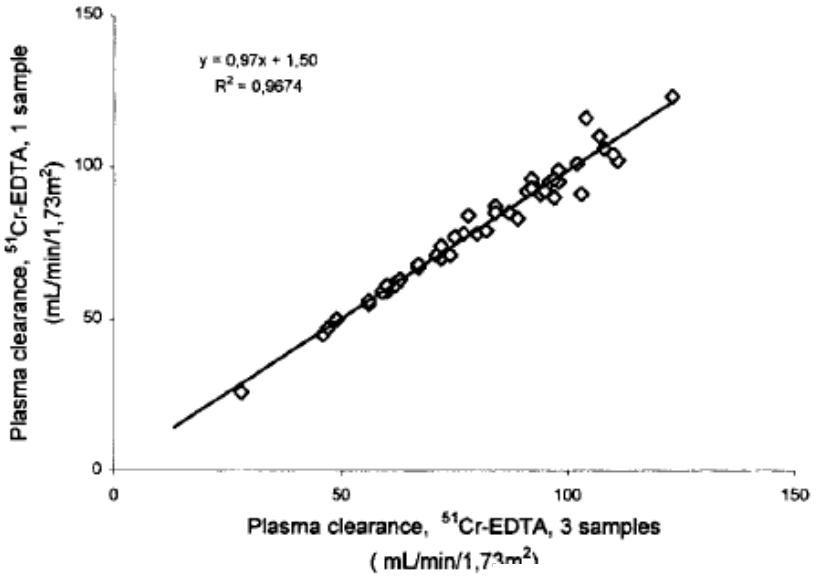
Markers	Strenghts	Limitations
Inulin	Gold standard (or historic) Safe	Costly Dosage neither easy nor standardized Doubt with plasma clearance
Iothalamate	The most popular in USA Isotopic or "cold" method	Tubular secretion Cannot be used if allergy to iodine
Iohexol		
EDTA	Easy to measure	Only isotopic Not available in USA
DTPA	Easy to measure	Only isotopic Binding to proteins Short half-time

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

Are they equivalent?

EDTA versus iohexol

N=49



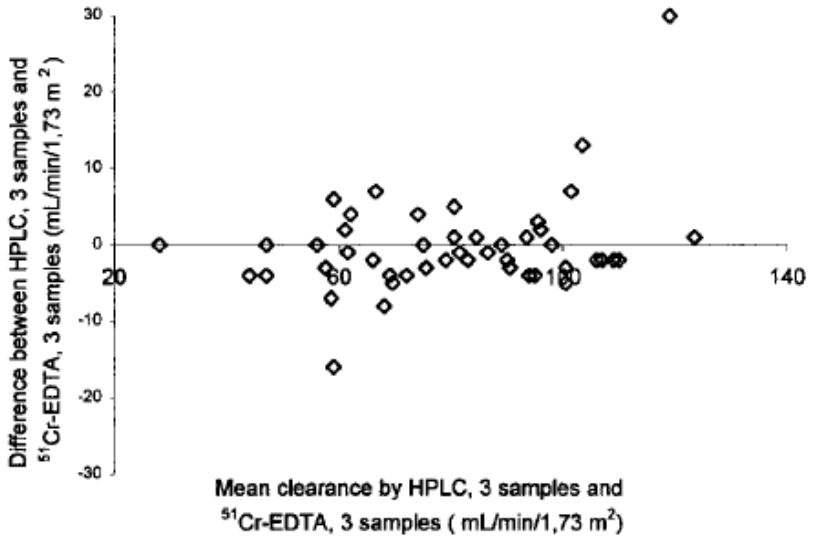


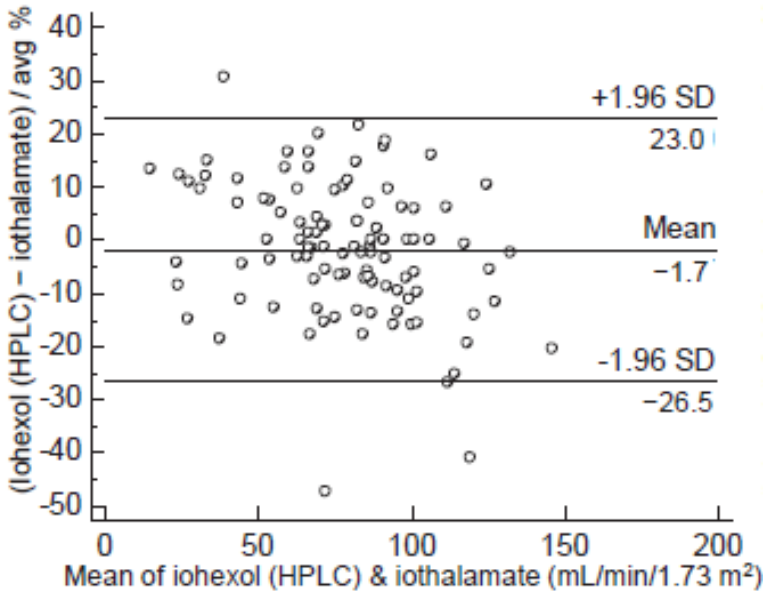
Table 3. Clearance range, mean of differences and standard deviation for multiple-point clearance and single-point clearance measurements

	Clearance range (ml/min)	Difference (ml/min)	
		Mean	SD
Multiple-point clearance: 3 samples ^{51}Cr-EDTA *vs* 3 samples iohexol			
^{51}Cr-EDTA *vs* HPLC	28–134	−0.16	6.17
^{51}Cr-EDTA *vs* X-ray fluorescence	29–134	0.58	4.95
Single-point clearance: 3 samples ^{51}Cr-EDTA *vs* 1 sample			
^{51}Cr-EDTA *vs* ^{51}Cr-EDTA	26–123	−0.7	3.59
^{51}Cr-EDTA *vs* HPLC	27–125	−1.7	5.94
^{51}Cr-EDTA *vs* X-ray fluorescence	32–116	−1.32	5.78

Brandstrom E, NDT, 1998, 13, 1176

Iothalamate versus iohexol

N=102



Accuracy (concordance):
Within 30%: 98%
Within 15%: 80%

Delanaye, AJKD, 2016, 68, 329

AJKD
Original Investigation

Measuring GFR: A Systematic Review

*Inga Soveri, MD, PhD,[1] Ulla B. Berg, MD, PhD,[2] Jonas Björk, PhD,[3] Carl-Gustaf Elinder, MD, PhD,[4] Anders Grubb, MD, PhD,[5] Ingegerd Mejare, PhD,[6] Gunnar Sterner, MD, PhD,[7] and Sten-Erik Bäck, MSc, PhD,[5] on behalf of the SBU GFR Review Group**

Table 1. Bias and Accuracy of Index Methods Compared to Reference Method When Measuring Glomerular Filtration Rate

	No. of Pts/ Studies	Median Bias[a] (95% CI)	Mean Bias (95 % CI)	P_{30} (95% CI)	P_{10} (95% CI)	Sufficient Accuracy	Scientific Evidence	Comments[b]
Criteria for sufficient precision		≤±5%	≤±10%	≥80%	≥50%			
Index method								
DTPA								
Renal clearance	126/5	−2 (−4 to 2)	−1 (−6 to 5)	87 (81 to 93)	53 (45 to 62)	Yes	⊕⊕◯◯	Inconsistency, −1; imprecision, −1
Plasma clearance	89/2	20 (18 to 35)	13 (5 to 22)	56 (47 to 68)	19 (13 to 29)	No	⊕⊕◯◯	Study limitations −1; imprecision −1
^{51}Cr-EDTA								
Renal clearance	198/9	−5 (−7 to −3)	−2 (−8 to 4)	95 (92 to 98)	56 (50 to 64)	Yes	⊕⊕⊕◯	Imprecision, −1
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Iohexol								
Renal clearance	47/2	−7 (−10 to 0)	−7 (−16 to 2)	100[c]	53 (41 to 70)	Yes	⊕⊕◯◯	Imprecision, −2
Plasma clearance	172/5	3 (0 to 6)	2 (−4 to 9)	86 (81 to 91)	50 (43 to 58)	Yes	⊕⊕⊕◯	Imprecision, −1
Iothalamate								
Renal clearance	548/13	−1 (−2 to 0)	6 (1 to 11)	97 (95 to 98)	66 (62 to 70)	Yes	⊕⊕⊕⊕	
Plasma clearance	61/1	9 (0 to 15)	11 (−6 to 29)	82 (73 to 92)	33 (23 to 47)	—	⊕◯◯◯	Study limitations, −1; imprecision, −2
Inulin								
Plasma clearance	39/2	2 (−3 to 6)	1 (−9 to 11)	100[c]	72 (59 to 87)	Yes	⊕⊕◯◯	Imprecision, −1; indirectness, −1

Note: Modified with permission of the Swedish Council on Health Technology Assessment.[3] Accuracy and bias expressed as percentage. Renal inulin clearance served as reference method. Mean bias, P_{10}, and P_{30} were estimated using generalized linear mixed models based on normal distribution (mean bias) or Poisson distribution (P_{10}, P_{30}; log-transformed outcome and robust variance estimation), with a random intercept for each study and a fixed effect for each index method ("unadjusted model results"; see Statistical Methods section). All analyses were weighed with respect to number of participants in each study. Estimates were obtained as marginal means.

Abbreviations and definitions: ⊕⊕⊕⊕, strong evidence; ⊕⊕⊕◯, moderately strong evidence; ⊕⊕◯◯, limited evidence; ⊕◯◯◯, insufficient evidence; ^{51}Cr-EDTA, chromium 51–labeled ethylenediaminetetraacetic acid; DTPA, diethylenetriaminepentaacetic acid; CI, confidence interval; Imprecision, N < 100 in meta-analysis (−1), P_{30} lower 95% CI ≤ 80%, P_{10} lower 95% CI ≤ 50%, or median bias 95% CI ≥ ±5% (−1); Inconsistency, inconsistency in study outcomes that cannot be explained by differences in study design (−1); Indirectness, limited generalizability (−1); P_{10}, percentage of measurements by index method that differed no more than 10% from reference method; P_{30}, percentage of measurements by index method that differed no more than 30% from reference method; pts, patients; Study limitations, risk of bias due to shortcomings in individual studies (−1).

[a]Median bias was calculated directly (using the weights) for each index method together with nonparametric CIs.

[b]Strength of scientific evidence.

[c]The generalized linear mixed model does not yield valid estimates of confidence limits when estimated proportion (eg, P_{30}) is 100%.

What about Isotopic nephrogram (Gates method)

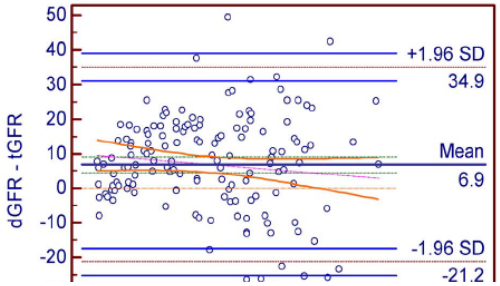
OPEN ACCESS Freely available online

PLOS ONE

^{99m}Tc-DTPA Renal Dynamic Imaging Method May Be Unsuitable To Be Used as the Reference Method in Investigating the Validity of CDK-EPI Equation for Determining Glomerular Filtration Rate

Peng Xie[1]*, Jian-Min Huang[1], Xiao-Mei Liu[1], Wei-Jie Wu[1], Li-Ping Pan[1], Hai-Ying Lin[2]

1 Department of Nuclear Medicine, The Third Hospital, Hebei Medical University, Shijiazhuang, P.R. China, 2 Department of Nephrology, The Third Hospital, Hebei Medical University, Shijiazhuang, P.R. China



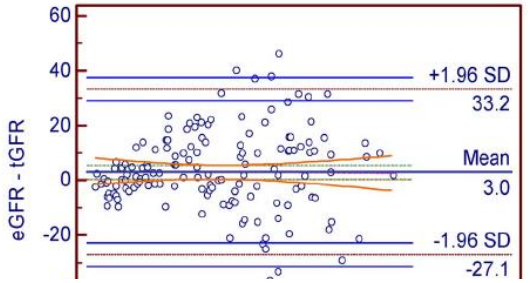


Table 1. The comparison of the dynamic renal imaging method and the CDK-EPI equation on the performance in estimating GFR.

Method	Bias (Mean)	Precision (SD)	Accuracy with 50%, %	Accuracy with 30%, %	Accuracy wwith 15%, %
Whole cohort (n = 149)					
dGFR	6.85	14.34	83.22	66.44	41.61
eGFR	3.01**	15.39*	91.28**	71.14*	48.99*

Need for Standardization

Standardization for the marker

- Only cold methods can easily be implemented worldwide
- Iothalamate is difficult to obtain in Europe
- Inulin is expensive and only available as urinary clearance
- Iohexol is available worldwide
- Very stable (central and/or “reference” laboratories)

Standardization for procedure

- Urinary versus plasma
- Number of samples and timing of samples
- Whatever the marker…

Table 4. Available procedures to perform iohexol clearance

Methodology	Indication in clinical practice	Indication in clinical research	Bibliographic examples where the procedure is described into details
Urinary clearance	Increased extracellular volume (oedema, ascites, intensive care units, etc.)	Basic (physiologic) studies Specific populations (cirrhotic, intensive care, nephrotic syndrome, oedema, etc.)	[36, 77, 125, 170]
Plasma clearance			
Multiple samples (first or fast, second or slow exponential curves and calculation of area under the curve)	High GFR values ('hyperfiltrating') subjects	Development of equations to estimate GFR Studies in hyperfiltrating patients	[52, 93, 171]
Multiple samples only for second and slow component (2 h after injection, 4 samples over 5 or 6 h, 1 sample/h) + BM correction	High precision determination (see text)	Development of equations to estimate GFR Clinical research with GFR as main endpoint	[126, 172]
Idem + late sample (8 h or 24 h)	Pre-dialysis subjects	Research in pre-dialysis subjects	[52, 77]
Simplified two or three sample method (2 samples: first at 2 or 3 h and second at 4 or 5 h) + BM correction	CKD or healthy population	Development of equations to estimate GFR Clinical research with GFR as a secondary endpoint	[69, 116]
Simplified single-sample method + Jacobsson correction [110]	CKD or healthy population	Development of equations to estimate GFR Clinical research with GFR as a secondary endpoint Epidemiological research	[14, 173]

Suggestions (expert opinion-based) according to the clinical or experimental context.
GFR, glomerular filtration rate; CKD, chronic kidney disease; BM, Brochner-Mortensen correction [116].

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

Iohexol in CHU of Liège

- Iohexol (plasma clearance)
- 5 hours
- Samples at 2, 3, 4 et 5 hours
- 150 euros

Standardization for the measurement

- Iothalamate
- Iohexol

Never forget biological variation…

Table 1. Examples of GFR variability with different iohexol procedures

Author Reference	Sample	Protocol	Population	GFR variability (CV)
Krutzen [30]	9	PC: samples at 120 and 240 min + BM correction	Healthy	11.4%
Delanaye [73]	12	PC: samples at 120 and 240 min + BM correction	Healthy	4.5%
Eriksen [99]	88	PC: single-sample + Jacobsson correction	General population	4.2%
Gaspari [6]	24	PC: samples at 120, 150, 180, 210 and 240 if eGFR >40 mL/minand at 120, 180, 240, 300, 450 and 600 min if eGFR <40 mL/min + BM correction	Healthy and CKD	5.6%

eGFR, estimated glomerular filtration rate; CV, coefficient of variation; CKD, chronic kidney disease; PC, plasma clearance; BM, Brochner-Mortensen [116].

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

Conclusions

- Measuring GFR is useful in clinical practice
- Measuring GFR is useful in clinical research
- Measuring GFR is useful in epidemiology

Table 1 | **Prevalence of CKD* in the elderly by eGFR equation**

Equation	Frequency of CKD (%) according to age				
	70–74 years	75–79 years	80–84 years	85–89 years of age	>90 years
CKD–EPIcr	20	29	43	46	66
CKD–EPIcys	19	32	50	61	79
CKD–EPIcr-cys	16	28	47	58	76
BIS-1cr	33	52	76	84	93
BIS-2cr-cys	24	42	66	76	90
Range	16–33	28–52	43–76	46–84	66–93

*CKD stages 3–5. BIS, Berlin Initiative Study; CKD, chronic kidney disease; CKD–EPI, Chronic Kidney Disease Epidemiology Collaboration; cr, creatinine; cys, cystatin C; eGFR, estimated glomerular filtration rate. Data adapted from Ebert, N. et al. (2016) [7].

Nat Rev Nephrol. 2017 Feb;13(2):104-114.

Conclusions

- Measuring GFR is not so cumbersome
- Standardization (marker, procedure and measurement) might still be improved
- Iohexol is the best balance between physiology and feasibility
- Iohexol is safe
- Iohexol is the only chance for a worldwide standardized mGFR

Clinical Kidney Journal

ckj OXFORD

Clinical Kidney Journal, 2016, vol. 9, no. 5, 682–699

doi: 10.1093/ckj/sfw070
Advance Access Publication Date: 23 August 2016
CKJ Review

CKJ REVIEW

Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 1: How to measure glomerular filtration rate with iohexol?

Pierre Delanaye[1], Natalie Ebert[2], Toralf Melsom[3,4], Flavio Gaspari[5], Christophe Mariat[6], Etienne Cavalier[7], Jonas Björk[8], Anders Christensson[9], Ulf Nyman[10], Esteban Porrini[11], Giuseppe Remuzzi[12,13], Piero Ruggenenti[12,13], Elke Schaeffner[2], Inga Soveri[14], Gunnar Sterner[15], Bjørn Odvar Eriksen[3,4] and Sten-Erik Bäck[16]

[1]Department of Nephrology, Dialysis and Transplantation, University of Liège Hospital (ULg CHU), Liège, Belgium, [2]Charité University Medicine, Institute of Public Health, Berlin, Germany, [3]Metabolic and Renal Research Group, UiT The Arctic University of Norway, Tromsø, Norway, [4]Section of Nephrology, University Hospital of North Norway, Tromsø, Norway, [5]IRCCS - Istituto di Ricerche Farmacologiche 'Mario Negri', Centro di Ricerche Cliniche per le Malattie Rare 'Aldo e Cele Daccò', Ranica, Bergamo, Italy, [6]Department of Nephrology, Dialysis, Transplantation and Hypertension, CHU Hôpital Nord, University Jean Monnet, PRES Université de LYON, Saint-Etienne, France, [7]Department of Clinical Chemistry, University of Liège Hospital (ULg CHU), Liège, Belgium, [8]Department of Occupational and Environmental Medicine, Lund University, Lund, Sweden, [9]Department of Nephrology, Skåne University Hospital, Lund, Sweden, [10]Department of Translational Medicine, Division of Medical Radiology, Skåne University Hospital, Malmö, Sweden, [11]University of La Laguna, CIBICAN-ITB, Faculty of Medicine, Hospital Universtario de Canarias, La Laguna, Tenerife, Spain, [12]Centro di Ricerche Cliniche per le Malattie Rare 'Aldo e Cele Daccò, Istituto di Ricerche Farmacologiche Mario Negri, Centro Anna Maria Astori, Science and Technology Park Kilometro Rosso, Bergamo, Italy, [13]Unit of Nephrology, Azienda Socio Sanitaria Territoriale (ASST) Ospedale Papa Giovanni XXIII, Bergamo, Italy, [14]Department of Medical Sciences, Uppsala University, Uppsala, Sweden, [15]Department of Nephrology, Skåne University Hospital, Malmö, Sweden and [16]Department of Clinical Chemistry, Skåne University Hospital, Lund, Sweden

Clinical Kidney Journal

ckj OXFORD

Clinical Kidney Journal, 2016, vol. 9, no. 5, 700–704

doi: 10.1093/ckj/sfw071
Advance Access Publication Date: 9 September 2016
CKJ Review

CKJ REVIEW

Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 2: Why to measure glomerular filtration rate with iohexol?

Pierre Delanaye[1], Toralf Melsom[2], Natalie Ebert[3], Sten-Erik Bäck[4], Christophe Mariat[5], Etienne Cavalier[6], Jonas Björk[7], Anders Christensson[8], Ulf Nyman[9], Esteban Porrini[10], Giuseppe Remuzzi[11,12], Piero Ruggenenti[11,12], Elke Schaeffner[3], Inga Soveri[13], Gunnar Sterner[14], Bjørn Odvar Eriksen[2] and Flavio Gaspari[15]

[1]Department of Nephrology, Dialysis and Transplantation, University of Liège Hospital (ULg CHU), 4000 Liège, Belgium, [2]Metabolic and Renal Research Group, UiT The Arctic University of Norway and Section of Nephrology, University Hospital of North Norway, Tromsø, Norway, [3]Charité University Medicine, Institute of Public Health, Berlin, Germany, [4]Department of Clinical Chemistry, Skåne University Hospital, Lund, Sweden, [5]Department of Nephrology, Dialysis, Transplantation and Hypertension, CHU Hôpital Nord, University Jean Monnet, PRES Université de LYON, Saint-Etienne, France, [6]Department of Clinical Chemistry, University of Liège Hospital (ULg CHU), Liège, Belgium, [7]Department of Occupational and Environmental Medicine, Lund University, Lund, Sweden, [8]Department of Nephrology, Skåne University Hospital, Lund, Sweden, [9]Department of Translational Medicine, Division of Medical Radiology, Skåne University Hospital, Malmö, Sweden, [10]University of La Laguna, CIBICAN-ITB, Faculty of Medicine, Hospital Universitario de Canarias, Tenerife, Spain, [11]Centro di Ricerche Cliniche per le Malattie Rare 'Aldo e Cele Daccò', Istituto di Ricerche Farmacologiche Mario Negri, Centro Anna Maria Astori, Science and Technology Park Kilometro Rosso, Bergamo, Italy, [12]Unit of Nephrology, Azienda Socio Sanitaria Territoriale (ASST) Ospedale Papa Giovanni XXIII, Bergamo, Italy, [13]Department of Medical Sciences, Uppsala University, Uppsala, Sweden, [14]Department of Nephrology, Skåne University Hospital, Malmö, Sweden and [15]IRCCS - Istituto di Ricerche Farmacologiche 'Mario Negri', Centro di Ricerche Cliniche per le Malattie Rare 'Aldo e Cele Daccò', Ranica, Bergamo, Italy

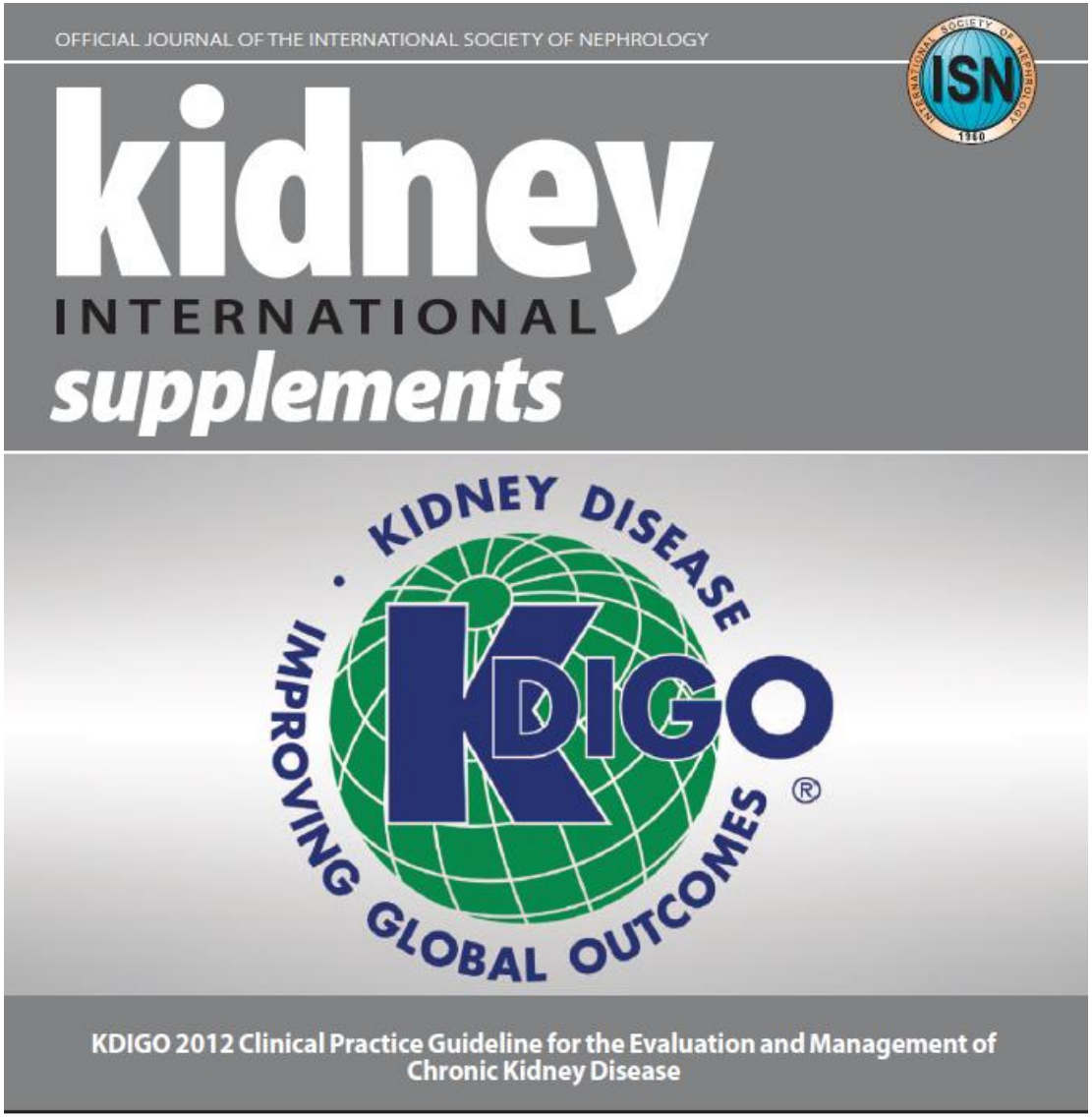
Summary

- Estimating GFR (creatinine, eGFR, cystatin C)
- Measuring GFR
- (CKD diagnosis)

Defining normality in medicine…

- Difficult (at least not so simple)
- Relevant
- Sometimes « dangerous » (risk of «oversimplification»)

International guidelines in Nephrology



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 m^2 (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

Justification of this cut-off

- Half of normal measured GFR but arbitrary
- Simplicity
- Because GFR < 60 mL/min/1.73 m^2 is associated with a higher mortality risk

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, Hiddo 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)

RESEARCH

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

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

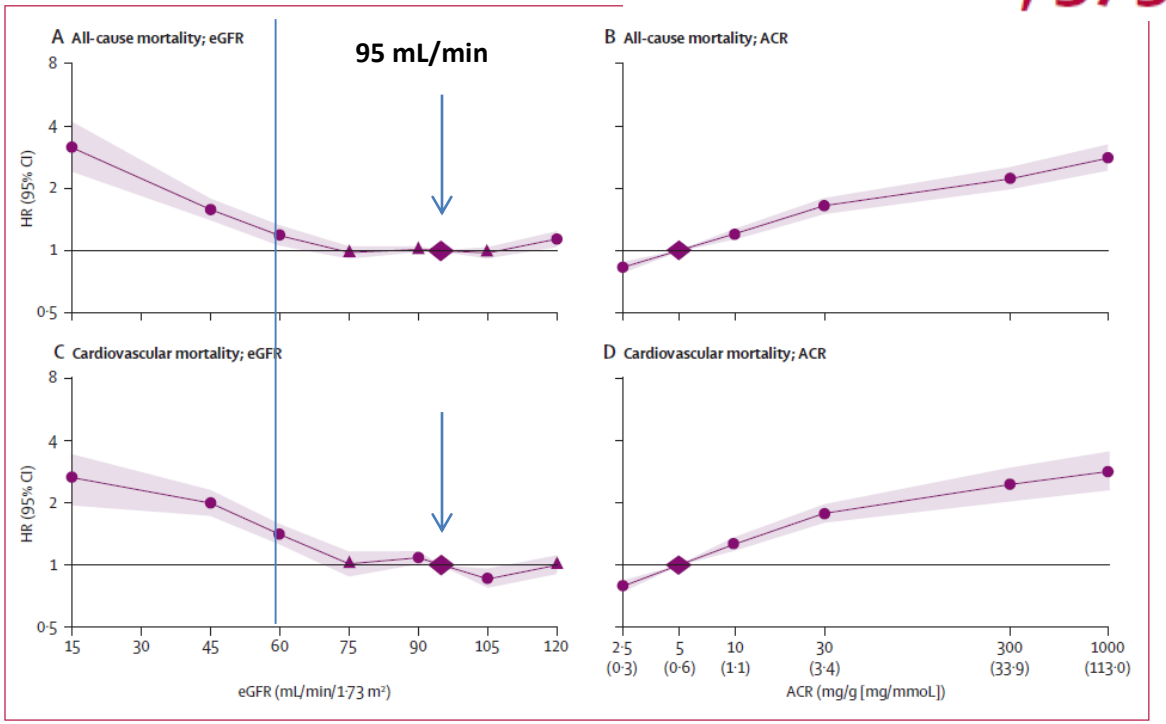


Figure 2: **Hazard ratios and 95% CIs for all-cause and cardiovascular mortality according to spline estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR)**

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 subjects from 14 studies with ACR
- 1,128,310 subjects from 7 studies with dipstick

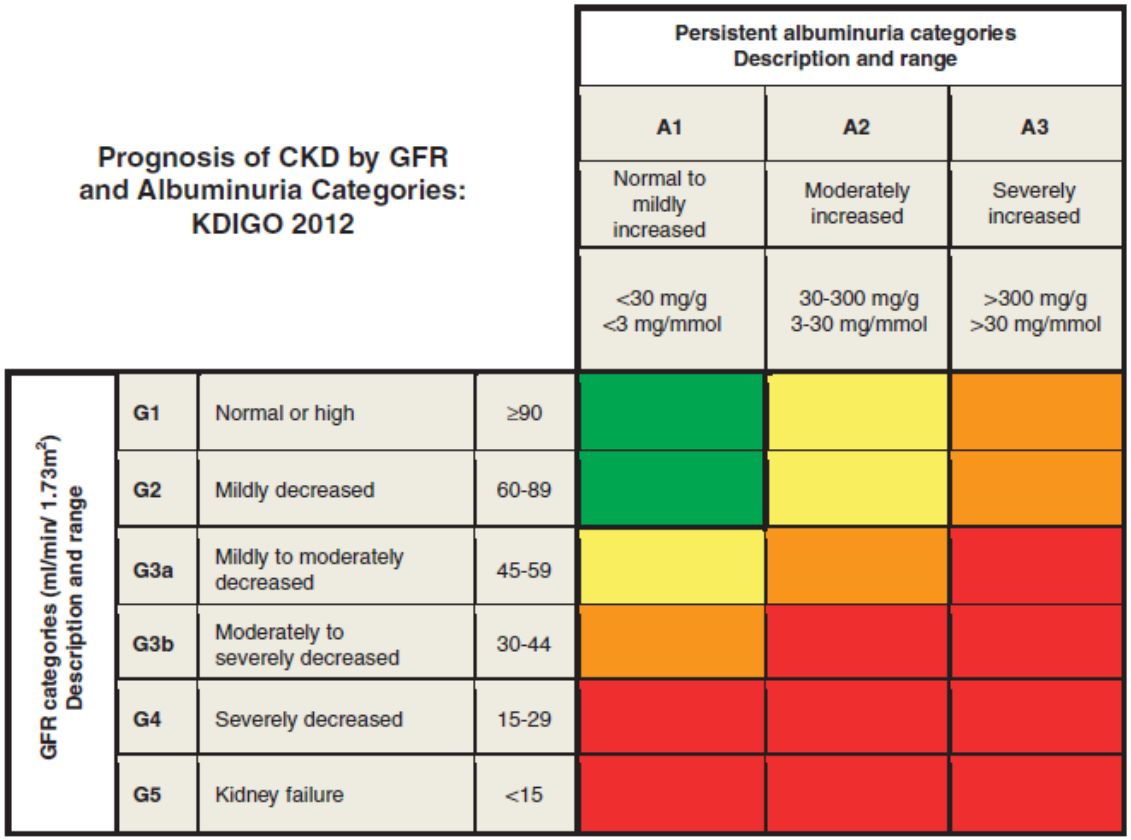


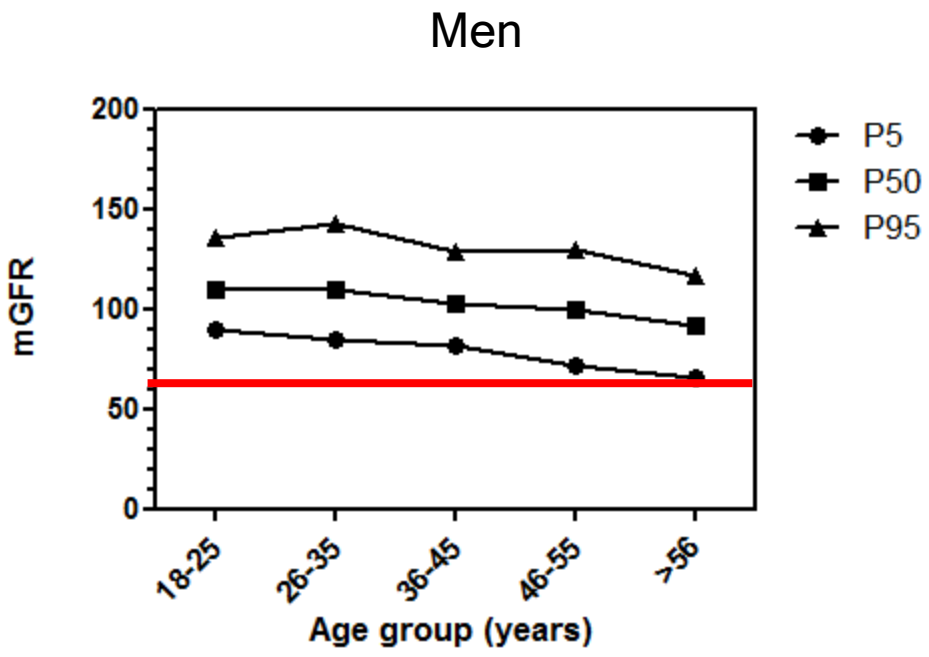
Figure 9 | Prognosis of CKD by GFR and albuminuria category. Green, low risk (if no other markers of kidney disease, no CKD); Yellow, moderately increased risk; Orange, high risk; Red, very high risk. CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes. Modified with permission from Macmillan Publishers Ltd: *Kidney International*. Levey AS, de Jong PE, Coresh J, et al.[30] The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int 2011; 80: 17-28; accessed http://www.nature.com/ki/journal/v80/n1/full/ki2010483a.html

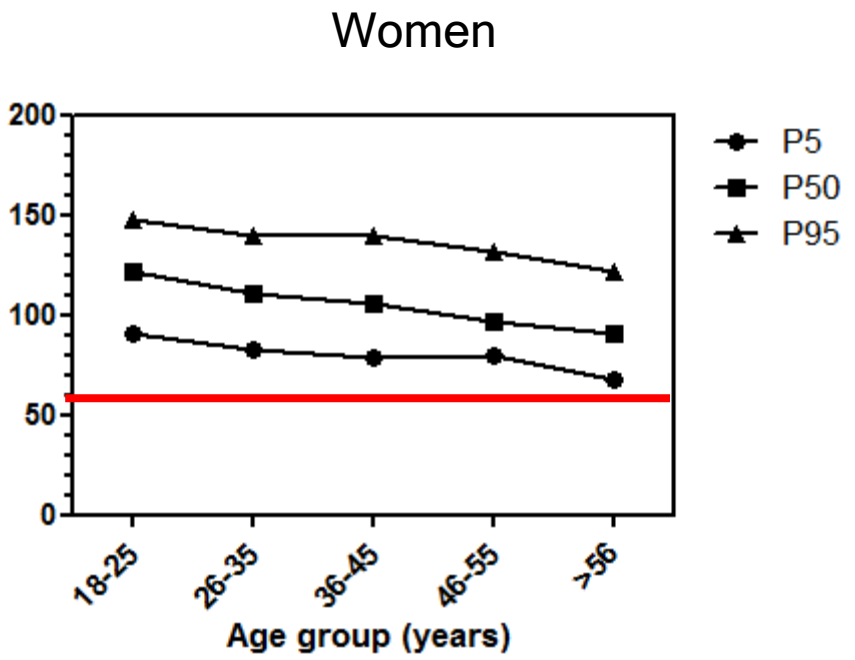
- Impressive sample but…
- Observational
- Estimated GFR
- Jaffe and non (or few) calibrated creatinine
- Not confirmed at 3 months
- Statistics

Why to focus on the elderly?

Why does it matter in the elderly?

- Aging is not a disease
- Aging is the highest risk factor for mortality
- Aging is « normally » associated with decline in functions
- …and this is also the case for GFR…





GFR measured by iothalamate in 1057 living kidney donors

Poggio ED, et al, Kidney Int, 2009, p1079

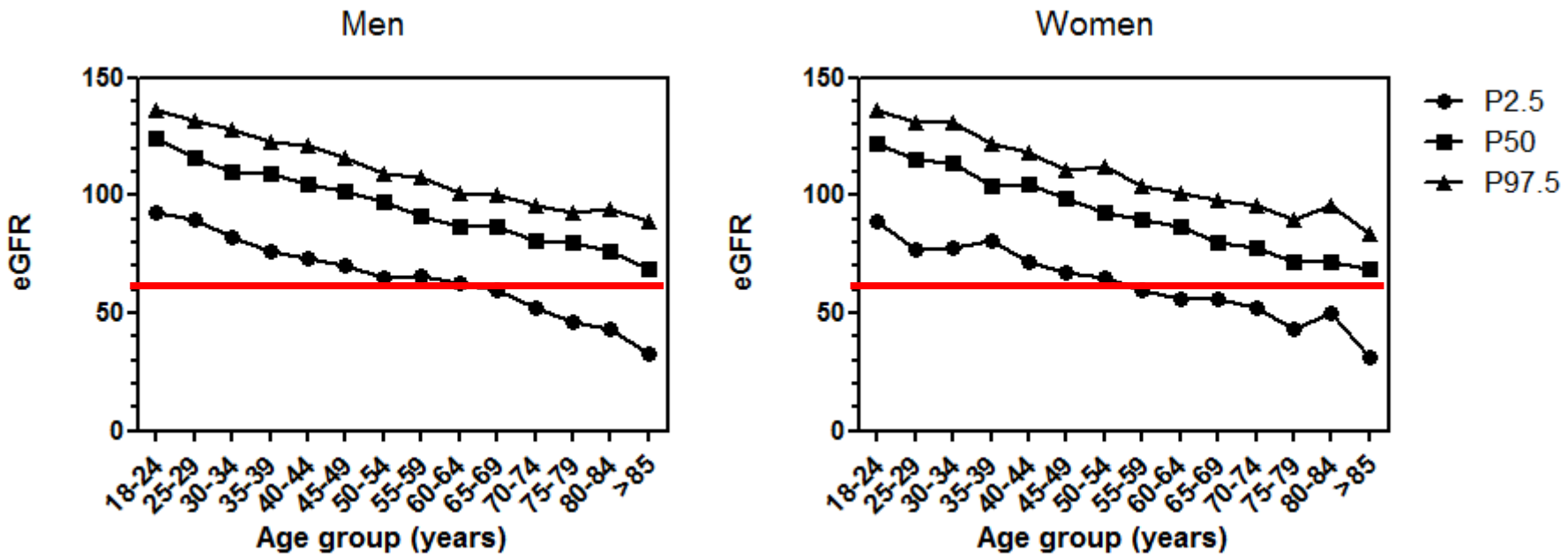
- Healthy population in the Netherlands
- CKD-EPI equation to estimate GFR
- No diabetes, no hypertension, no specific therapy, no albuminuria
- 1663 men 2073 women

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 Brand[1], Gerben A.J. van Boekel[1], Hans L. Willems[2], Lambertus A.L.M. Kiemeney[3], Martin den Heijer[3,4] and Jack F.M. Wetzels[1]

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


Men
Women
eGFR
150
100
50
0
18-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
>85
Age group (years)
P2.5
P50
P97.5

So…

- A unique cut-off overestimates CK**D** in the elderly

But…

- What about the prognostic argument?
- Is it relevant from an epidemiological point of view?
- Is it nihilism?
- Do we have an alternative?

Justifying the choice of an equation and/or a threshold because a better prognostic performance is questionable

Comparison of Risk Prediction Using the CKD-EPI Equation and the MDRD Study Equation for Estimated Glomerular Filtration Rate

Kunihiro Matsushita, MD, PhD
Bakhtawar K. Mahmoodi, MD, PhD
Mark Woodward, PhD
Jonathan R. Emberson, PhD
Tazeen H. Jafar, MD, MPH
Sun Ha Jee, PhD, MHS
Kevan R. Polkinghorne, FRACP, PhD
Anoop Shankar, MD, MPH, PhD
David H. Smith, RPh, PhD
Marcello Tonelli, MD, SM
David G. Warnock, MD
Chi-Pang Wen, MD, DrPH
Josef Coresh, MD, PhD
Ron T. Gansevoort, MD, PhD
Brenda R. Hemmelgarn, MD, PhD
Andrew S. Levey, MD
for the Chronic Kidney Disease Prognosis Consortium

Context The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation more accurately estimates glomerular filtration rate (GFR) than the Modification of Diet in Renal Disease (MDRD) Study equation using the same variables, especially at higher GFR, but definitive evidence of its risk implications in diverse settings is lacking.

Objective To evaluate risk implications of estimated GFR using the CKD-EPI equation compared with the MDRD Study equation in populations with a broad range of demographic and clinical characteristics.

Design, Setting, and Participants A meta-analysis of data from 1.1 million adults (aged ≥18 years) from 25 general population cohorts, 7 high-risk cohorts (of vascular disease), and 13 CKD cohorts. Data transfer and analyses were conducted between March 2011 and March 2012.

Main Outcome Measures All-cause mortality (84 482 deaths from 40 cohorts), cardiovascular mortality (22 176 events from 28 cohorts), and end-stage renal disease (ESRD) (7644 events from 21 cohorts) during 9.4 million person-years of follow-up; the median of mean follow-up time across cohorts was 7.4 years (interquartile range, 4.2-10.5 years).

Results Estimated GFR was classified into 6 categories (≥90, 60-89, 45-59, 30-44, 15-29, and <15 mL/min/1.73 m^2) by both equations. Compared with the MDRD Study equation, 24.4% and 0.6% of participants from general population cohorts were reclassified to a higher and lower estimated GFR category, respectively, by the CKD-EPI equation, and the prevalence of CKD stages 3 to 5 (estimated GFR <60 mL/min/1.73 m^2) was reduced from 8.7% to 6.3%. In estimated GFR of 45 to 59 mL/min/1.73 m^2 by the MDRD Study equation, 34.7% of participants were reclassified to estimated GFR of 60 to 89 mL/min/1.73 m^2 by the CKD-EPI equation and had lower incidence rates (per 1000 person-years) for the outcomes of interest (9.9 vs 34.5 for all-cause mortality, 2.7 vs 13.0 for cardiovascular mortality, and 0.5 vs 0.8 for ESRD) compared with those not reclassified. The corresponding adjusted hazard ratios were 0.80 (95% CI, 0.74-0.86) for all-cause mortality, 0.73 (95% CI, 0.65-0.82) for cardiovascular mortality, and 0.49 (95% CI, 0.27-0.88) for ESRD. Similar findings were observed in other estimated GFR categories by the MDRD Study equation. Net reclassification improvement based on estimated GFR categories was significantly positive for all outcomes (range, 0.06-0.13; all $P < .001$). Net reclassification improvement was similarly positive in most subgroups defined by age (<65 years and ≥65 years), sex, race/ethnicity (white, Asian, and black), and presence or absence of diabetes and hypertension. The results in the high-risk and CKD cohorts were largely consistent with the general population cohorts.

Conclusion The CKD-EPI equation classified fewer individuals as having CKD and more accurately categorized the risk for mortality and ESRD than did the MDRD Study equation across a broad range of populations.

JAMA. 2012;307(18):1941-1951 www.jama.com

GLOMERULAR FILTRATION RATE (GFR) is used in the diagnosis of chronic kidney disease (CKD)[1,2] and is an independent predictor of all-cause and cardiovascular mortality and kidney failure in a wide range of populations.[3-6] Clinical guidelines recommend reporting estimated GFR when serum creatinine level is measured[1,2]; 84% of US laboratories report estimated GFR.[7] Although the Modification of Diet in Renal Disease (MDRD) Study equation is recommended for estimating GFR,[1,2,8,9] the Chronic Kidney

BMJ Open

Glomerular filtration rate (GFR) during and after STEMI: a single-centre, methodological study comparing estimated and measured GFR

Dimitrios Venetsanos, Joakim Alfredsson, Mårten Segelmark, Eva Swahn, Sofia Sederholm Lawesson

N=40

Table 4 Correlation, bias, precision and accuracy (P30) of prediction equations to estimate relative mGFR (mL/min/1.73 m^2)

At discharge	Correlation (R)	Bias, median error (%)	Precision (IQR), mL/min/1.73 m^2	P30 (95% CI)
CG	0.73	−1.2 (−1.3)	22.5	75.0% (62% to 88%)
MDRD-IDMS	0.78	−0.8 (−1.3)	17.9	82.5% (70.5% to 94.5%)
CKD-EPI	0.81	0.9 (1.5)	17.1	82.5% (70.5% to 94.5%)
rG-CystC	0.89	−12.2 (−17.8)	14.8	80.0% (68% to 92%)

Bias was defined as the median percentage error between eGFR and mGFR; positive values indicate an overestimation of mGFR. Precision was assessed as the IQR expressed in mL/min/1.73 m^2 of the difference eGFR—mGFR. Accuracy within 30% (P30) was the percentage of estimates within 30% of mGFR. Correlation between eGFR and mGFR was reported as correlation coefficients (R).
CG, Cockcroft-Gault; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; mGFR, measured GFR; MDRD-IDMS, Modification of Diet in Renal Disease—Isotope Dilution Mass Spectrometry; rG-CystC, relative Grubb cystatin C.

Cockcroft is the worst to estimate mGFR

Open Access Research

BMJ Open

Prevalence and prognostic impact of chronic kidney disease in STEMI from a gender perspective: data from the SWEDEHEART register, a large Swedish prospective cohort

Sofia Sederholm Lawesson,[1] Joakim Alfredsson,[1] Karolina Szummer,[2] Mats Fredrikson,[3] Eva Swahn[1]

Sederholm Lawesson S, *et al. BMJ Open* 2015;**5**:e008188.

N=37,991

Even though the two renal function equations both incorporate age in the equation, they handle the variables differently mathematically. In the present study, we could show that prognosis following an MI, both short-term and long term, is better described by the CG formula in men and women, and this is consistent with previous studies.[9]

nephron
Clinical
Practice

Clinical Practice: Mini-Review

Nephron
DOI: 10.1159/000444062

Received: December 16, 2015
Accepted after revision: January 14, 2016
Published online: February 5, 2016

Estimated Glomerular Filtration Rate: Fit for What Purpose?

David G. Warnock

Department of Medicine, University of Alabama at Birmingham, Birmingham, Ala., USA

- REGARDS
- N=25,952
- 3822 deaths
- 10 years followup

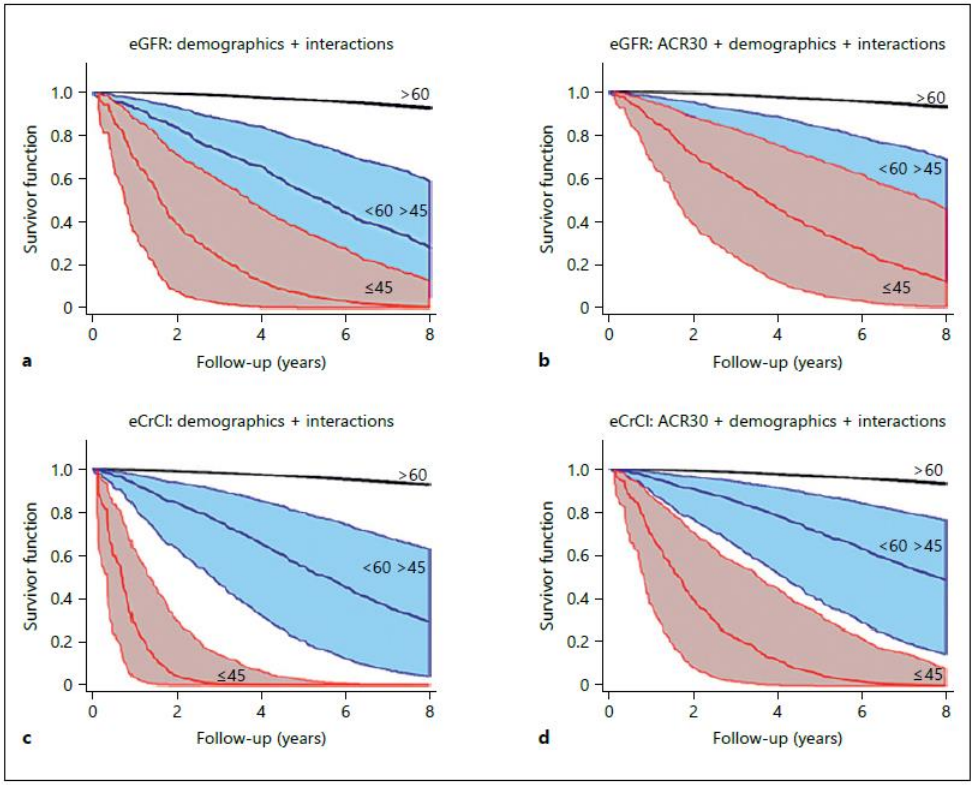


Fig. 1. Survivor functions: eGFR and eCrCl categories. Cox proportional hazard models included eGFR or eCrCl categories (>60; <60 and >45; <45), age, race and gender (**a**, **b**). Urinary ACRs (stratified at 30 mg/g) were added to the final model (**c**, **d**). Interactions between age and race and the effect variables were included in all models.

For the CKD-EPI consortium, cystatin C better estimates GFR (especially the combined equation)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C

Lesley A. Inker, M.D., Christopher H. Schmid, Ph.D., Hocine Tighiouart, M.S., John H. Eckfeldt, M.D., Ph.D., Harold I. Feldman, M.D., Tom Greene, Ph.D., John W. Kusek, Ph.D., Jane Manzi, Ph.D., Frederick Van Lente, Ph.D., Yaping Lucy Zhang, M.S., Josef Coresh, M.D., Ph.D., and Andrew S. Levey, M.D., for the CKD-EPI Investigators*

In conclusion, the combination of serum creatinine and serum cystatin C is more accurate than either marker alone for estimating GFR. The

Moreover, cystatin C (and equations) better predicts outcomes

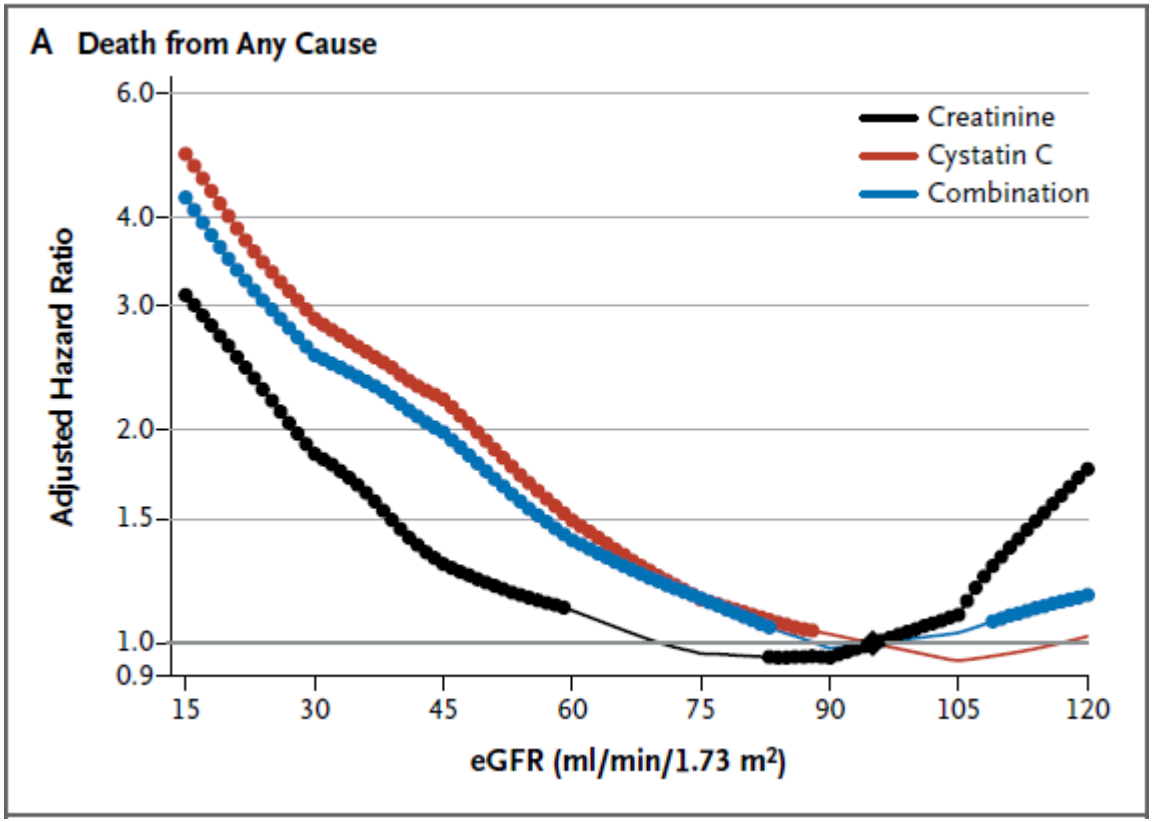
ORIGINAL ARTICLE

Cystatin C versus Creatinine in Determining Risk Based on Kidney Function

Michael G. Shlipak, M.D., M.P.H., Kunihiro Matsushita, M.D., Ph.D., Johan Ärnlöv, M.D., Ph.D., Lesley A. Inker, M.D., Ronit Katz, D.Phil., Kevan R. Polkinghorne, F.R.A.C.P., M.Clin.Epi., Ph.D., Dietrich Rothenbacher, M.D., M.P.H., Mark J. Sarnak, M.D., Brad C. Astor, Ph.D., M.P.H., Josef Coresh, M.D., Ph.D., Andrew S. Levey, M.D., and Ron T. Gansevoort, M.D., Ph.D., for the CKD Prognosis Consortium*

In conclusion, the use of cystatin C to calculate the eGFR strengthened the associations between eGFR categories and the risks of death and end-stage renal disease across diverse populations.

But the cut-off “cystatin C-based” equations are different…



This is clearly stated in the NEJM!

With a cystatin C–based eGFR, the risk of death from any cause was increased at eGFR values that were below the reference point of 95 ml per minute per 1.73 m^2, with a threshold of 88 ml per minute per 1.73 m^2 (i.e., the point at which the risk was significantly higher than the risk at the reference point) (Fig. 2A). The corresponding thresholds were 59 ml and 83 ml per minute per 1.73 m^2 for the creatinine-based eGFR and the combination-based eGFR, respectively.

So…

- If we keep the same reasoning used by the KDIGO to establish the “60 mL/min” cut-off
- There is no reason to use the “cystatin C” cut-off at 83 ml/min!!
- Indeed, cystatin C better estimates GFR and better predicts mortality!!

So…

- 80 (or even 85) mL/min should be the new cut-off

So

- All patients older than 75y are CKD
- No hope of recovery (because age is not curable)

- Estimation GFR
- Prediction of outcomes

- DIFFERENT TOPICS

Back to the « prognostic » argument

ORIGINAL CONTRIBUTION

ONLINE FIRST

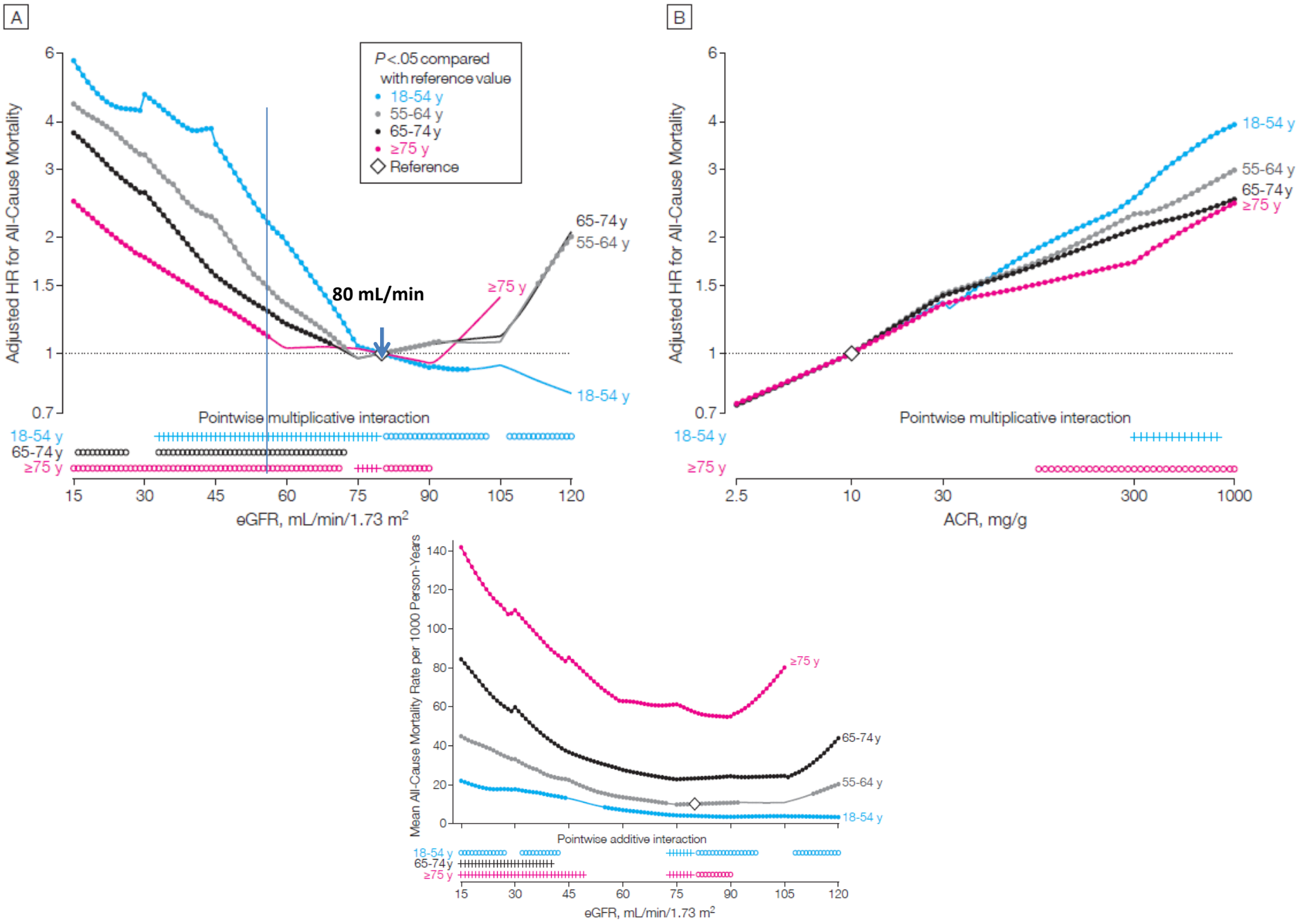
Age and Association of Kidney Measures With Mortality and End-stage Renal Disease

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 general or high risk cohorts
13 CKD cohorts
Mean follow-up: 5.3 years

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



Once again…

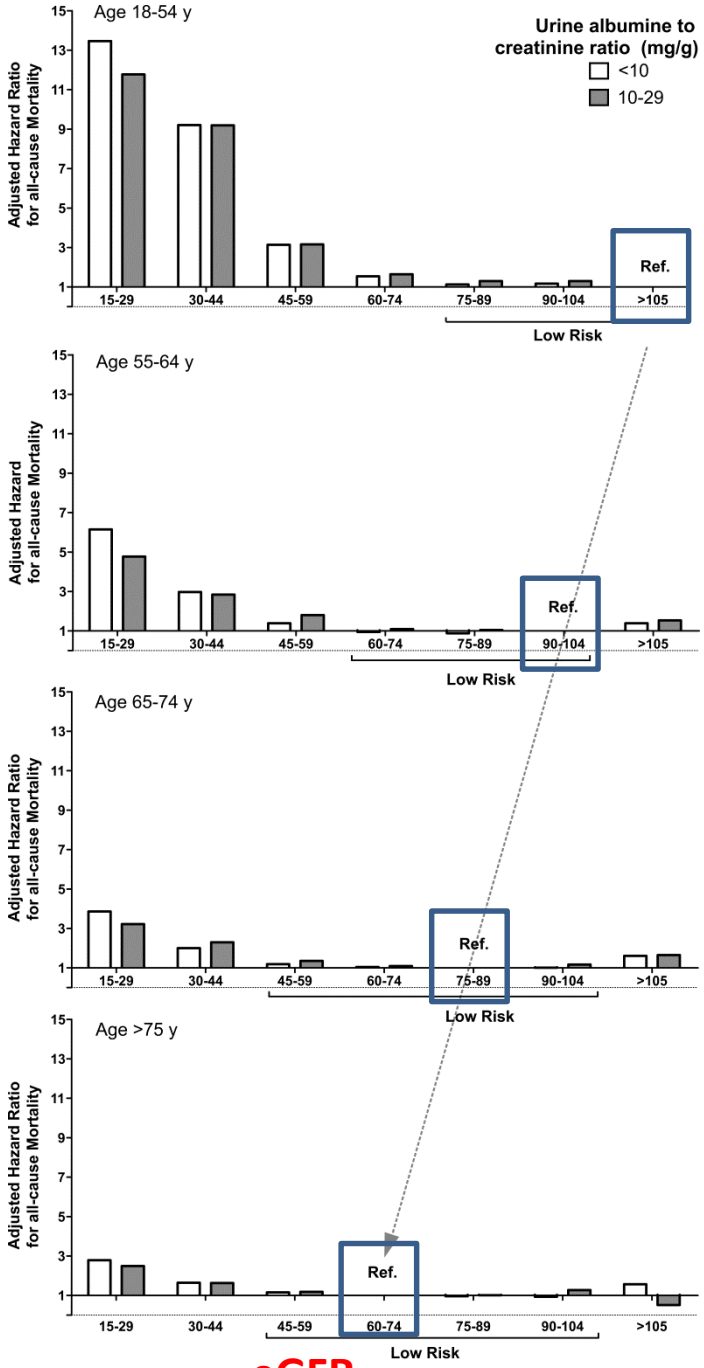
- *Impressive sample but…*
- *Estimated GFR*
- *Jaffe and non (or few) calibrated creatinine*
- *Not confirmed at 3 months*
- Age is a variable of the equation

Age 18-54 y =>

Age 55-64 y =>

Age 65-74 y =>

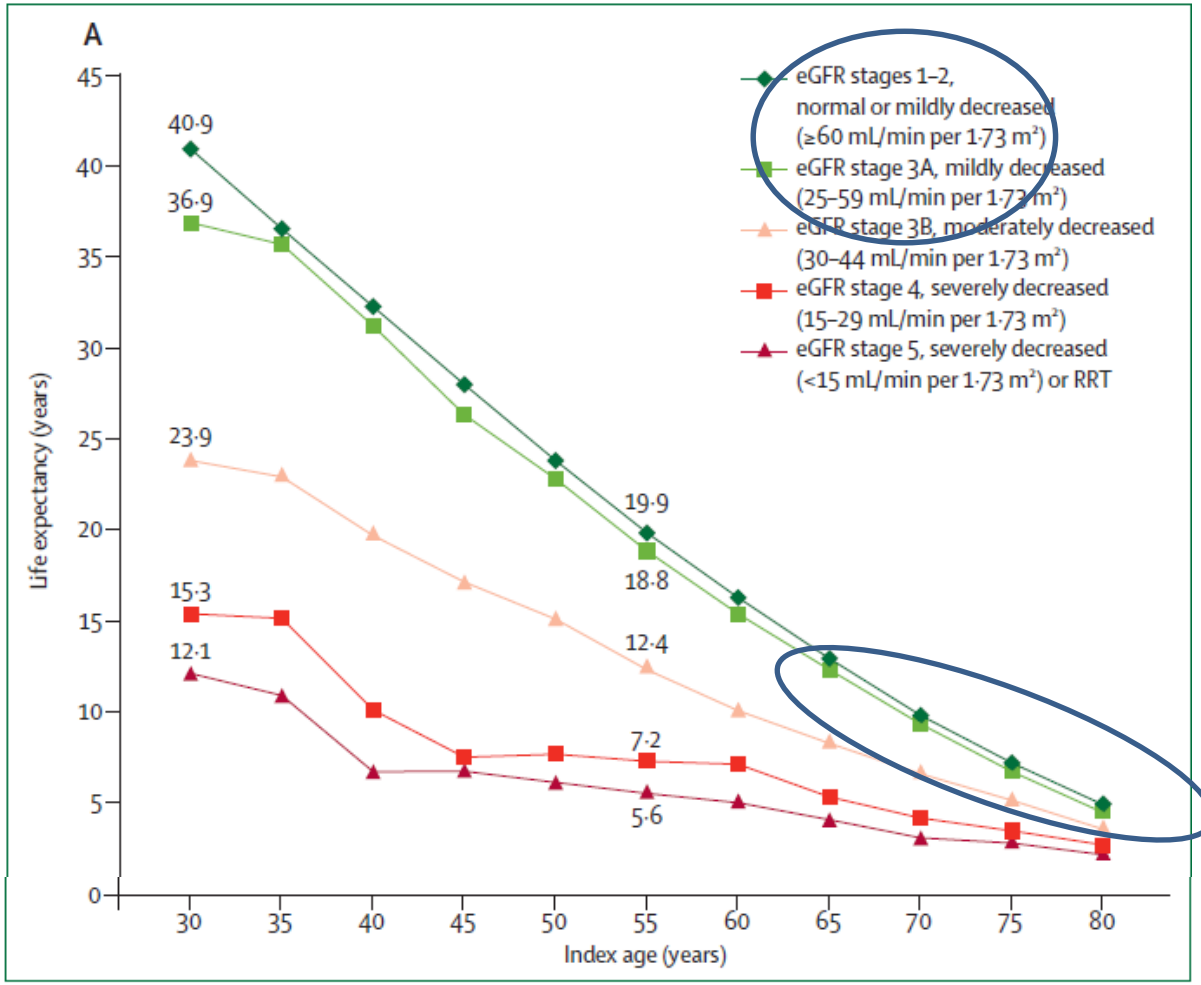
Age >75 y =>



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

Courtesy from Andrew Rule, Mayo Clinic
Adv Chronic Kidney Dis. 2016, 23, p19

Delanaye P, Clin Biochem Rev, 2016, 37, p17



Life expectancy for stage 3A

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).

Gansevoort R et al, Lancet, 2013, p339

So…

- A unique cut-off overestimates CK**D** in the elderly

But…

- **What about the prognostic argument?**

It can be challenged…

Stage 3A (without other kidney damage) is not CKD in the elderly

- Is it relevant from an epidemiological point of view?
- Is it nihilism?
- Do we have an alternative?

Is it relevant or purely semantic?

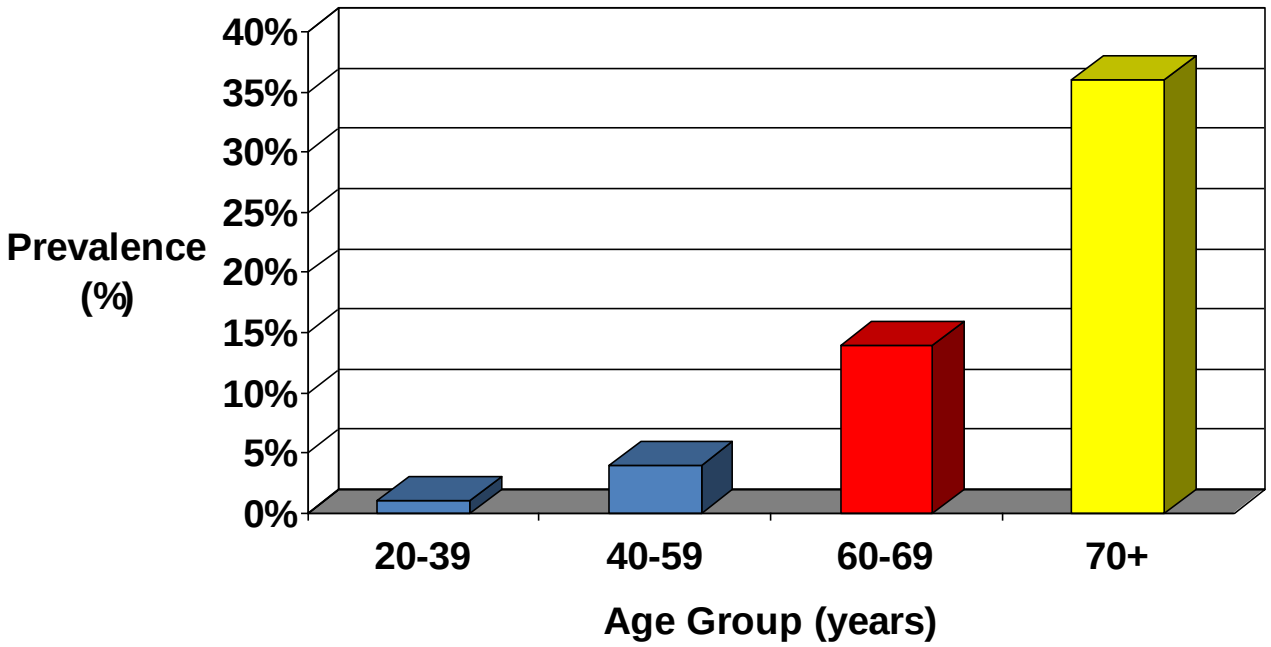
CKD prevalence: 11.5%

CKD prevalence based on eGFR only: 4.8%

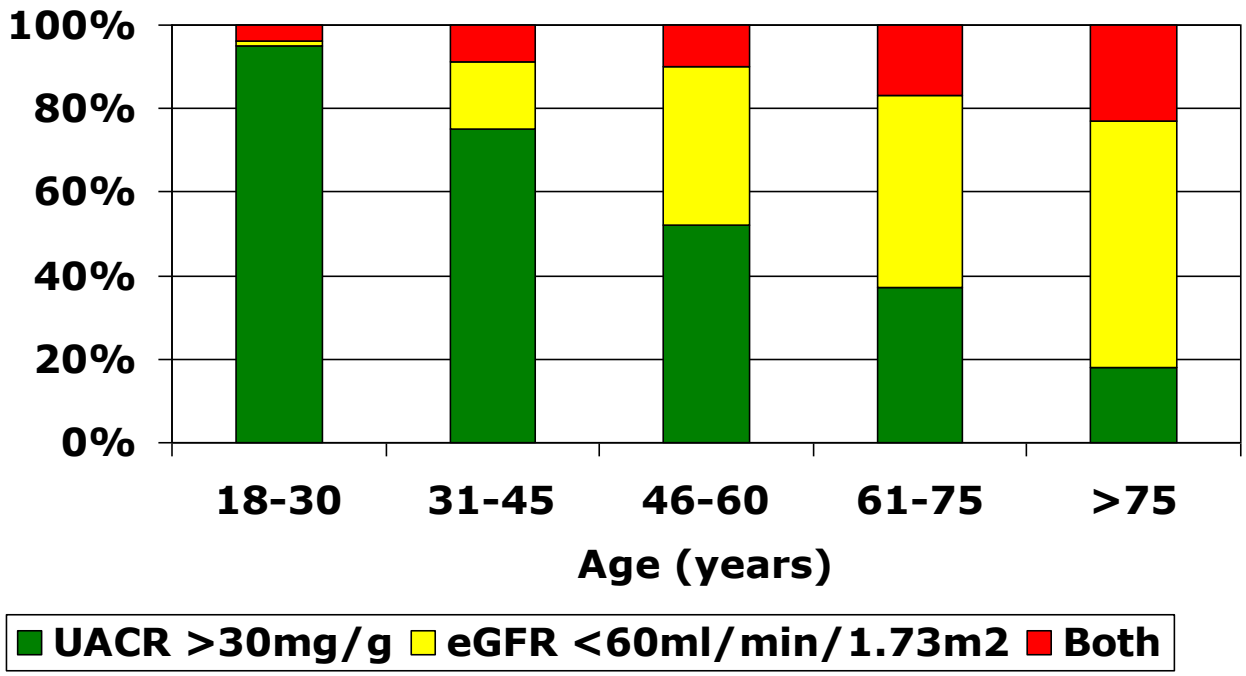
Percentage of US Population by eGFR and Albuminuria Category: KDIGO 2012 and NHANES 1999-2006

GFR categories (ml/min/ 1.73m^2) Description and range				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	
	G1	Normal or high	≥90	55.6	1.9	0.4	57.9
	G2	Mildly decreased	[illegible]	[illegible]	[illegible].2	0.3	35.4
	G3a	Mildly to moderately decreased	45-59	3.6	[illegible].8	0.2	4.6
	G3b	Moderately to severely decreased	[illegible]	[illegible].0	[illegible].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



Characteristics of CKD populations



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

Data from Belgium (Liège)

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

BMC Nephrology

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 Cavalier[2], Olivier Moranne[3], Laurence Lutteri[2], Jean-Marie Krzesinski[1] and Olivier Bruyère[4]

CKD screening (bus) on a voluntary basis, >50 y
n=4189,
Mean age:63±7 y

- If CKD is defined as eGFR<60 mL/min/1.73 m², CKD prevalence is 9.81%

- If CKD is defined as eGFR<60 mL/min/1.73 m² for younger than 65 y AND eGFR<45 mL/min/1.73 m² for older than 65 y, CKD prevalence is 4.37%

So…

- A unique cut-off overestimates CK**D** in the elderly

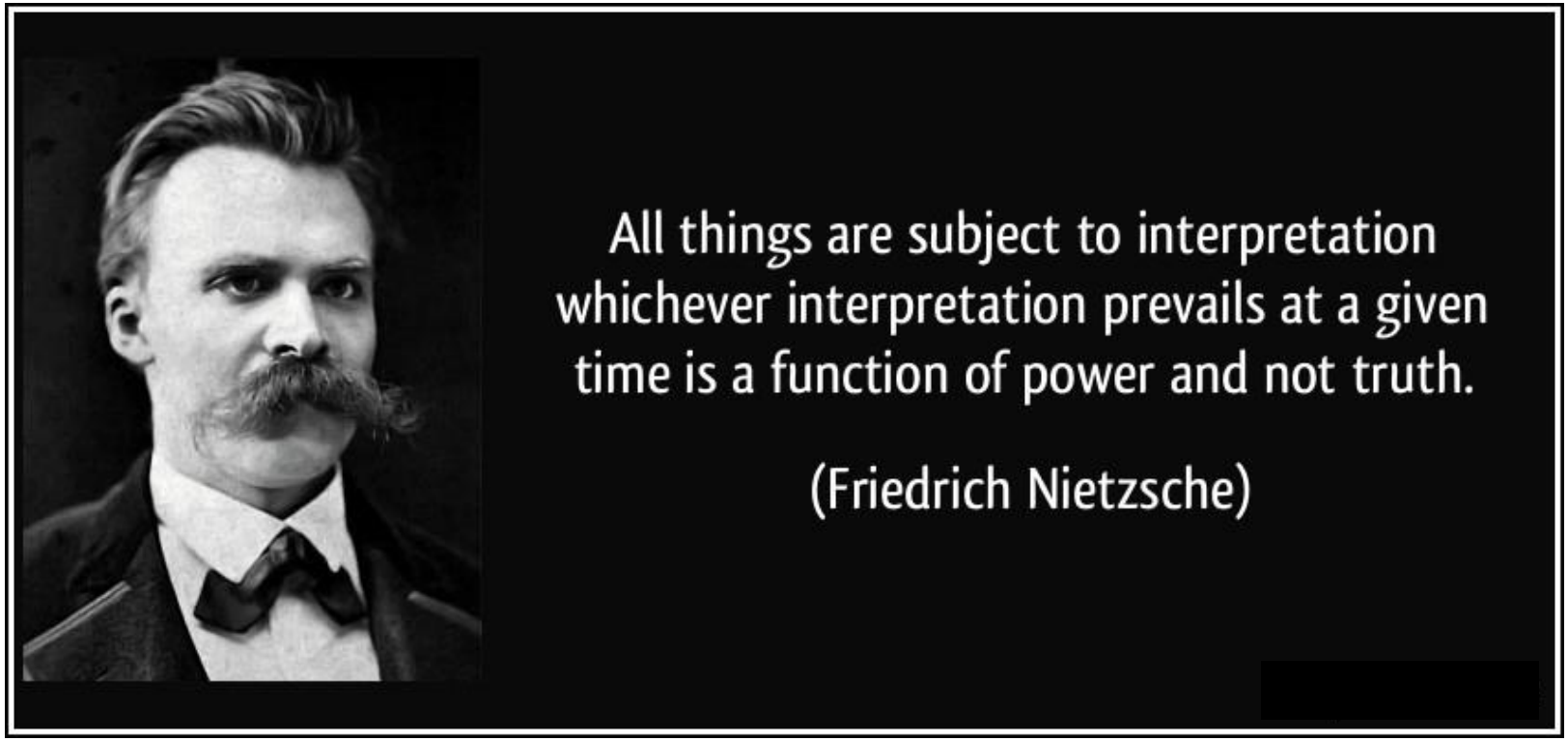
But…

- What about the prognostic argument?
- **Is it relevant from an epidemiological point of view?**

The impact on the epidemiology (epidemic?) of CKD is high!

- Is it nihilism?
- Do we have an alternative?

Is it nihilism?



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.

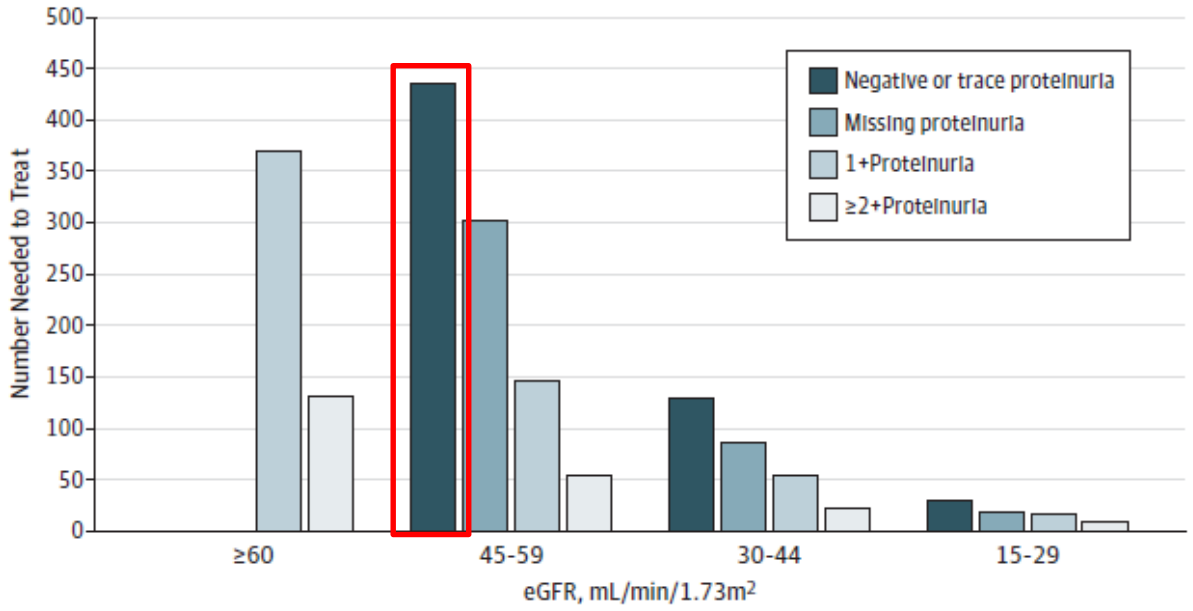
VA
Age>70 y
Mean age: 77.8 ± 4.6 y
eGFR: 48 ± 11.7 ml/min/1.73 m²
n=371.470

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

				Entry Criteria				Mortality, %		ESRD, %		ESRD Outcomes[a]		
Source	No. of Patients	Intervention	Mean FU, y	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
Ruggenenti 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.

So…

- A unique cut-off overestimates CK**D** in the elderly

But…

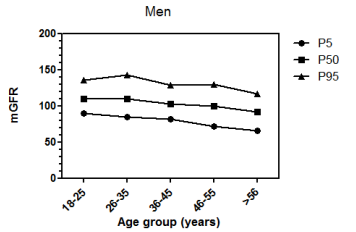
- What about the prognostic argument?
- Is it relevant from an epidemiological point of view?
- **Is it nihilism?**

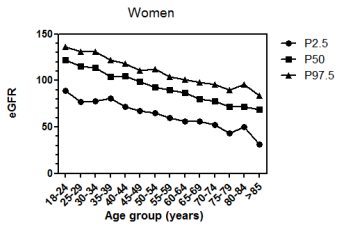
No, but to include the « true » CKD patients in future RCT and prevent disillusions if healthy subjects are actually included

- Do we have an alternative?

Alternatives

- Percentiles (like pediatrics)





- Too complex…
- …maybe not with help from labs…

Alternatives

- Stage 3A (without any kidney damage) is not CKD anymore if age > 65 years
- Stage 3B and 45 mL/min become the pathological level if age > 65 years

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m²) Description and range				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
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59	>65 y / ≤65 y		
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

With the unique threshold…

- We miss also young CKD patients…
- A 25 years old patient with an eGFR at 70 mL/min or 65 mL/min: is it really normal?

- We also propose that eGFR threshold for CKD is 75 mL/min for subjects younger than 40 y

Pediatr Nephrol (2015) 30:821–828
DOI 10.1007/s00467-014-3002-5

ORIGINAL ARTICLE

Abnormal glomerular filtration rate in children, adolescents and young adults starts below 75 mL/min/1.73 m^2

Hans Pottel · Liesbeth Hoste · Pierre Delanaye

www.kidney-international.org clinical investigation

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 Zamd[1], Abdelali Belghiti Alaoui[3], Naïma Benahadi[3], El Hassane Trabelssi[3], Rabia Bayahia[4], Benyounès Ramdani[1] and Marc E. De Broe[5,6]

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

- Two Moroccan towns
- 26-70y, n=10,524
- Creatinine and disptick
- Chronicity confirmed at 3 months

Chronicity of decreased eGFR was investigated in 78.9% of the subjects ($n = 285$) with CKD3A, 3B, 4, and 5. The remaining were deceased or lost to follow-up. The majority (75%) of false positives were found in the subjects with CKD3A. Thirty-two percent of the CKD3A subjects and 7.4% of the CKD3B subjects had an eGFR >60 ml/min/1.73 m^2 when reinvestigated after 3 months or longer. Subjects with CKD4 and 5 ($n = 51$) remained in these low eGFR categories, and 11 were on dialysis, died, or lost to follow-up after 3 months or longer.

32% false + in CKD3a

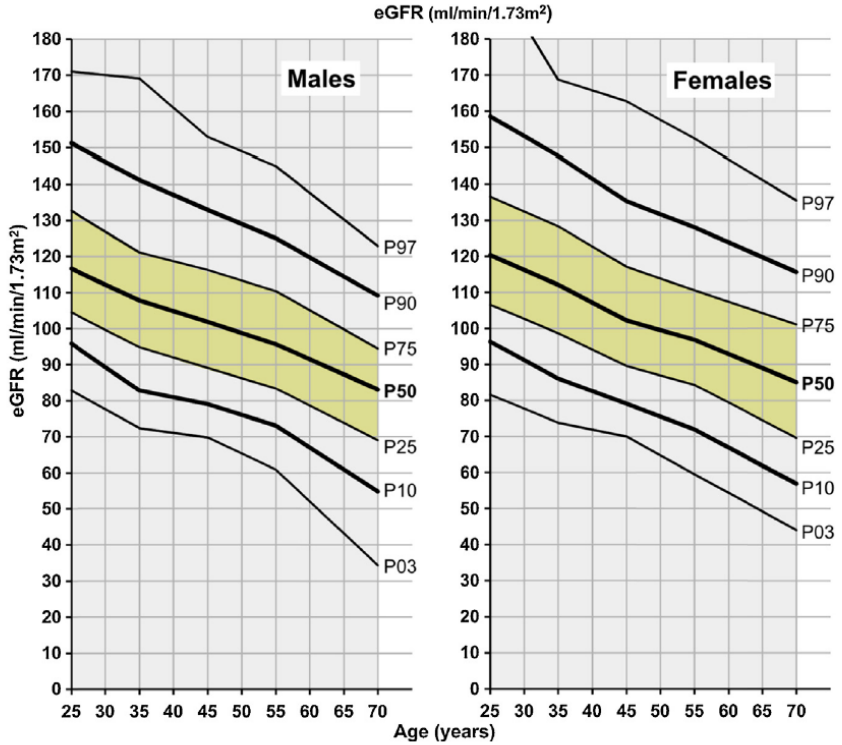


Fig. 2. Estimated glomerular filtration rate (eGFR) distribution showing the 3rd, 10th, 25th, 50th, 75th, 90th and 97th percentile within the gender and age categories ($n = 10{,}524$). The "normal" decline in eGFR of the study population is 0.75 mL/min/1.73 m^2 per year.
From [22] with permission.

Clinical Kidney Journal, 2017, 1–5

doi: 10.1093/ckj/sfw154
Editorial Comment

EDITORIAL COMMENT

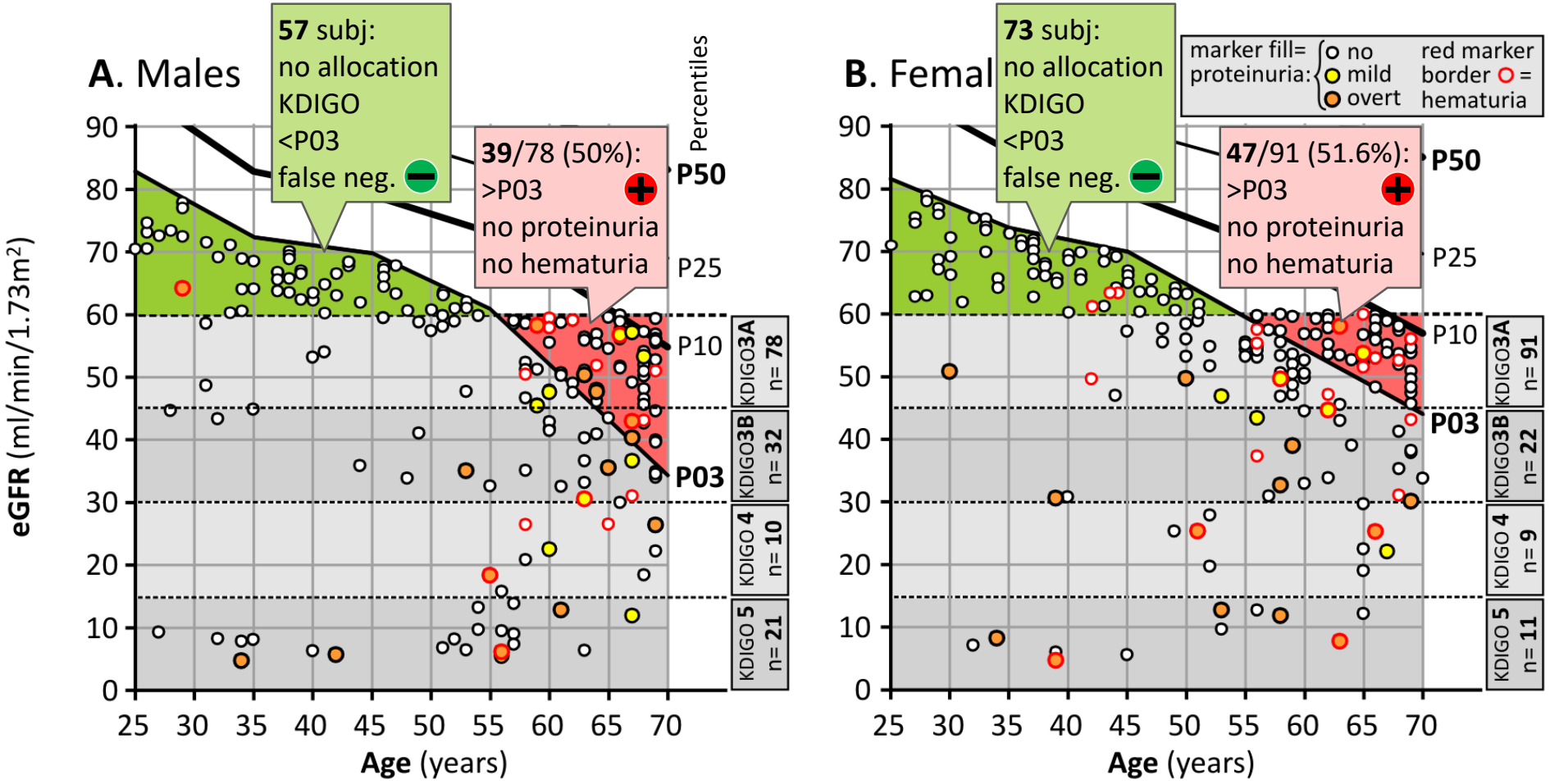
Epidemiology of chronic kidney disease: think (at least) twice!

Pierre Delanaye[1], Richard J. Glassock[2] and Marc E. De Broe[3]

[1]Department of Nephrology Dialysis Transplantation, CHU Sart Tilman, University of Liège, Liège, Belgium, [2]Department of Medicine, David Geffen School of Medicine at UCLA, Laguna Niguel, CA, USA and [3]Laboratory of Pathophysiology, University of Antwerp, Antwerp, Belgium

Correspondence and offprint requests to: Pierre Delanaye; E-mail: pierre_delanaye@yahoo.fr

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



Conclusions

- Defining normality is not easy
- There is still debate to know if elderly with decreased GFR (and no albuminuria) suffer from ***Disease***
- Decreasing GFR with aging is physiological
- Age-calibration for CKD definition could help for

  - a better apprehension of the CKD epidemiology
  - is considered in hypertension (see JNC-8 guidelines)
  - a better focus on diseased patients for future interventional RCT
  - reassure the elderly subject with "normal" decreased GFR without albuminuria, diabetes nor HTA
  - in the elderly, "*primum non nocere*" is important

- KDIGO should evolve !

VIEWPOINT

An Age-Calibrated Classification of Chronic Kidney Disease

Richard Glassock, MD
Geffen School of Medicine, University of California-Los Angeles, Laguna Niguel, California.

Pierre Delanaye, MD, PhD
Department of Nephrology, Dialysis, and Transplantation, University of Liege, Liege, Belgium.

Meguid El Nahas, MD, PhD, FRCP
Sheffield Kidney Institute, Global Kidney Academy, Sheffield, England.

Should current guidelines be changed to require age calibration for diagnosis and classification of chronic kidney disease? —Yes.

JAMA August 11, 2015 Volume 314, Number 6

VIEWPOINT

Chronic Kidney Disease in Older People

Andrew S. Levey, MD
Division of Nephrology, Tufts Medical Center, Boston, Massachusetts.

Lesley A. Inker, MD, MS
Division of Nephrology, Tufts Medical Center, Boston, Massachusetts.

Josef Coresh, MD, PhD
Departments of Epidemiology, Biostatistics, and Medicine, Johns Hopkins University, Baltimore, Maryland.

Should current guidelines be changed to rec calibration for diagnosis and classification o kidney disease? —No.

“There are no norms. All people are exceptions to a rule that doesn’t exist.”
— Fernando Pessoa

I thank you for your attention!

Jupiler

Questions?