26ste Belgisch Dialyse
26ème Symposium
Belge de Dialyse
Online

Accurate assessment of kidney function: for whom, when, how

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Nephrology Dialysis and Transplantation

University of Liège

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BELGIUM

FRESENIUS MEDICAL CARE

LIÈGE université

- WHY?
- How?

Ann Intern Med. 2021;174:183-191.

Annals of Internal Medicine ORIGINAL RESEARCH

Development and Validation of a Modified Full Age Spectrum Creatinine-Based Equation to Estimate Glomerular Filtration Rate

A Cross-sectional Analysis of Pooled Data

Hans Pottel, PhD*; Jonas Björk, PhD*; Marie Courbebaisse, MD, PhD; Lionel Couzi, MD, PhD; Natalie Ebert, MD, MPH; Björn O. Eriksen, MD, PhD; R. Neil Dalton, PhD; Laurence Dubourg, MD, PhD; François Gaillard, MD, PhD; Cyril Garrouste, MD; Anders Grubb, MD, PhD; Lola Jacquemont, MD, PhD; Magnus Hansson, MD, PhD; Nassim Kamar, MD, PhD; Edmund J. Lamb, PhD; Christophe Legendre, MD; Karin Littmann, MD; Christophe Mariat, MD, PhD; Toralf Melsom, MD, PhD; Lionel Rostaing, MD, PhD; Andrew D. Rule, MD; Elke Schaeffner, MD, PhD, MSc; Per-Ola Sundin, MD, PhD; Stephen Turner, MD, PhD; Arend Bökenkamp, MD; Ulla Berg, MD, PhD; Kajsa Åsling-Monemi, MD, PhD; Luciano Selistre, MD, PhD; Anna Åkesson, BSc; Anders Larsson, MD, PhD; Ulf Nyman, MD, PhD†; and Pierre Delanaye, MD, PhD†

- Subjects with measured GFR and standardized creatinine
- 11,251 development and internal validation
- 8,378 external validation
- 1,254 aged between 2 to 18 years
- 7 + 6 cohorts
- Only White people

Figure 1. The new EKFC equation.

Age	SCr/Q	Equation
2–40 y	<1	$107.3 \times (SCr/Q)^{-0.322}$
	≥1	$107.3 \times (SCr/Q)^{-1.132}$
>40 y	<1	$107.3 \times (SCr/Q)^{-0.322} \times 0.990^{(Age - 40)}$
	≥1	$107.3 \times (SCr/Q)^{-1.132} \times 0.990^{(Age - 40)}$

Q Values

For ages 2–25 y:

Males:

$$\ln(Q) = 3.200 + 0.259 \times Age - 0.543 \times \ln(Age) - 0.00763 \times Age^2 + 0.0000790 \times Age^3$$

Females:

$$\ln(Q) = 3.080 + 0.177 \times Age - 0.223 \times \ln(Age) - 0.00596 \times Age^2 + 0.0000686 \times Age^3$$

For ages >25 y:

Males:

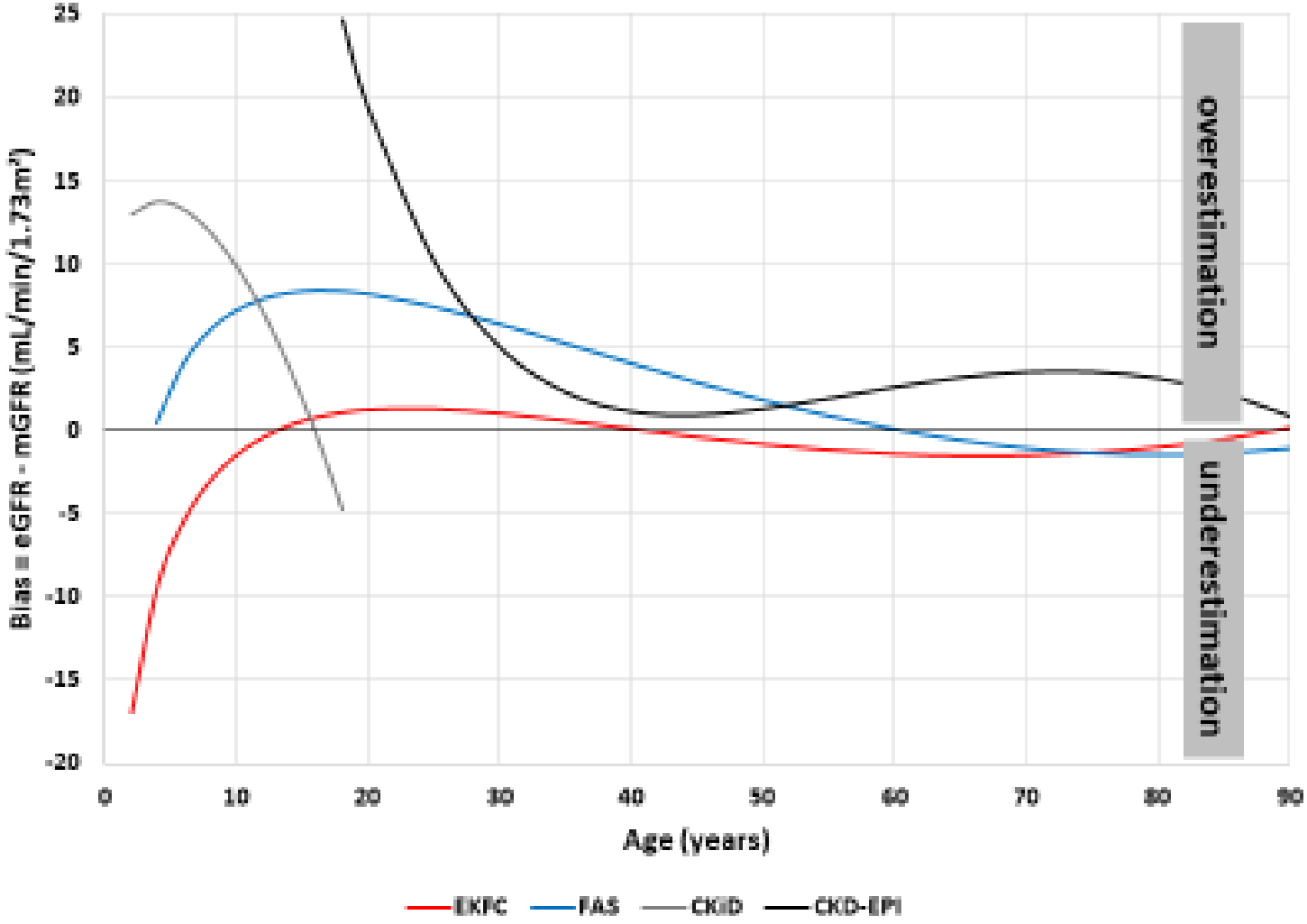
$Q = 80$ µmol/L (0.90 mg/dL)

Females:

$Q = 62$ µmol/L (0.70 mg/dL)

SCr and Q in µmol/L (to convert to mg/dL, divide by 88.4)

Q values (in µmol/L or mg/dL) correspond to the median SCr values for the age- and sex-specific populations. EKFC = European Kidney Function Consortium; SCr = serum creatinine.


Bias = eGFR - mGFR (mL/min/1.73m²)
25
20
15
10
5
0
-5
-10
-15
-20
0
10
20
30
40
50
60
70
80
90
Age (years)
overestimation
underestimation
EKFC
FAS
CKiD
CKD-EPI

	EKFC	FAS	CKD-EPI
Adults aged 18 to <40 y			
Median bias (95% CI), *mL/min/1.73 m²*			
All (*n* = 972)	0.8 (0.0 to 2.2)	7.3 (5.9 to 8.6)	7.8 (6.3 to 9.2)
eGFR <75 mL/min/1.73 m² (*n* = 137)	2.3 (0.3 to 4.2)	7.5 (4.7 to 8.8)	3.4 (1.7 to 5.8)
eGFR ≥75 mL/min/1.73 m² (*n* = 835)	0.6 (-0.5 to 1.9)	7.2 (5.8 to 8.8)	8.7 (7.2 to 10.6)
Imprecision, SD (P25–P75)			
All (*n* = 972)	17.2 (-8.3 to 10.3)	41.7 (-3.7 to 18.2)	20.5 (-2.0 to 18.2)
eGFR <75 mL/min/1.73 m² (*n* = 137)	14.2 (-3.2 to 9.2)	14.3 (1.4 to 13.4)	14.4 (-2.1 to 12.8)
eGFR ≥75 mL/min/1.73 m² (*n* = 835)	17.6 (-8.9 to 10.8)	44.6 (-4.3 to 19.3)	21.2 (-2.0 to 19.4)
Accuracy P30 (95% CI), %			
All (*n* = 972)	89.6 (87.7 to 91.5)	82.1 (79.7 to 84.5)	84.0 (81.6 to 86.3)
eGFR <75 mL/min/1.73 m² (*n* = 137)	80.3 (73.5 to 87.0)	71.5 (63.9 to 79.2)	78.8 (71.9 to 85.8)
eGFR ≥75 mL/min/1.73 m² (*n* = 835)	91.1 (89.2 to 93.1)	83.8 (81.3 to 86.3)	84.8 (82.3 to 87.2)
Adults aged 40 to <65 y			
Median bias (95% CI), *mL/min/1.73 m²*			
All (*n* = 3585)	-1.1 (-1.6 to -0.6)	1.1 (0.5 to 1.6)	1.8 (1.3 to 2.4)
eGFR <60 mL/min/1.73 m² (*n* = 492)	1.9 (1.3 to 2.8)	4.7 (4.1 to 5.3)	1.5 (0.7 to 2.5)
eGFR ≥60 mL/min/1.73 m² (*n* = 3093)	-2.0 (-2.5 to -1.5)	-0.2 (-0.8 to 0.6)	1.9 (1.3 to 2.5)
Imprecision, SD (P25–P75)			
All (*n* = 3585)	15.1 (-9.4 to 7.4)	17.8 (-8.3 to 10.5)	15.4 (-6.1 to 10.9)
eGFR <60 mL/min/1.73 m² (*n* = 492)	9.2 (-2.5 to 7.3)	9.4 (-0.5 to 10.0)	9.2 (-2.8 to 6.9)
eGFR ≥60 mL/min/1.73 m² (*n* = 3093)	15.8 (-10.5 to 7.5)	18.7 (-9.4 to 10.6)	16.1 (-6.8 to 11.6)
Accuracy P30 (95% CI), %			
All (*n* = 3585)	89.5 (88.5 to 90.5)	85.9 (84.8 to 87.1)	88.2 (87.1 to 89.3)
eGFR <60 mL/min/1.73 m² (*n* = 492)	78.4 (72.7 to 84.2)	67.7 (60.5 to 74.8)	77.4 (73.7 to 81.1)
eGFR ≥60 mL/min/1.73 m² (*n* = 3093)	91.6 (90.6 to 92.5)	88.8 (87.7 to 89.9)	89.9 (88.9 to 91.0)
Adults aged ≥65 y			
Median bias (95% CI), *mL/min/1.73 m²*			
All (*n* = 2567)	-1.2 (-1.0 to -1.6)	-1.1 (-1.5 to -0.6)	3.0 (2.5 to 3.6)
eGFR <45 mL/min/1.73 m² (*n* = 852)	-0.5 (-0.9 to -0.1)	0.7 (0.2 to 1.2)	0.5 (0.1 to 0.9)
eGFR ≥45 mL/min/1.73 m² (*n* = 1715)	-2.0 (-2.6 to -1.3)	-2.9 (-3.7 to -2.4)	5.1 (4.3 to 6.0)
Imprecision, SD (P25–P75)			
All (*n* = 2567)	12.1 (-7.6 to 5.0)	14.3 (-8.5 to 5.3)	12.5 (-2.9 to 10.2)
eGFR <45 mL/min/1.73 m² (*n* = 852)	7.1 (-4.3 to 3.8)	7.2 (-3.5 to 5.1)	7.2 (-2.9 to 5.1)
eGFR ≥45 mL/min/1.73 m² (*n* = 1715)	13.9 (-9.6 to 6.1)	16.7 (-10.8 to 5.8)	14.3 (-2.9 to 13.1)
Accuracy P30 (95% CI), %			
All (*n* = 2567)	85.3 (83.9 to 86.7)	83.6 (82.1 to 85.0)	80.7 (79.2 to 82.2)
eGFR <45 mL/min/1.73 m² (*n* = 852)	78.8 (73.9 to 83.8)	73.9 (71.0 to 76.9)	81.8 (80.3 to 83.3)
eGFR ≥45 mL/min/1.73 m² (*n* = 1715)	89.6 (88.1 to 91.0)	88.4 (86.9 to 89.9)	83.7 (81.9 to 85.4)

Limitations of eGFR = creatinine

Specific population: eGFR 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)

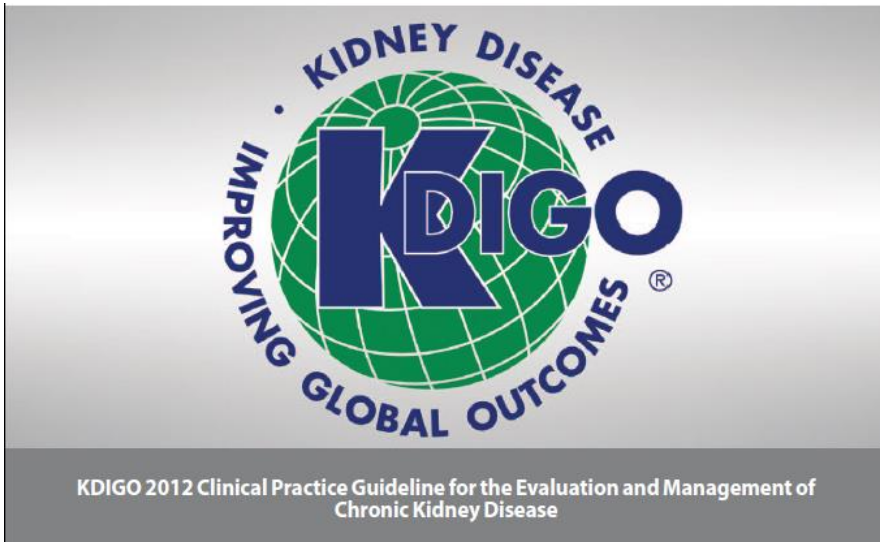
Heart transplanted (Delanaye P, Clin Transplant, 2006, 20, 596)

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

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

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

Hyperfiltration (Gaspari F, Kidney Int, 2013, 84, 164)



1.4.3.3: We recommend that clinicians (*1B*):

- use a GFR estimating equation to derive GFR from serum creatinine ($eGFR_{creat}$) rather than relying on the serum creatinine concentration alone.
- understand clinical settings in which $eGFR_{creat}$ is less accurate.

Measuring GFR: Why?
A question of precision!

- Starting dialysis
- Sarcopenia
- Extreme body size
- Cirrhosis, USI
- Fibrates, cimetidine, trimethoprim (and other therapies)
- Hyperfiltration

Agarwal R, Nephrol Dial Transplant, 2019, 34, p2001
Ebert N, Clin Kidney J, 2021, in press

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

- **Type 2 diabetics**
- **Iohexol**
- **n=600**
- **Hyperfiltration (DFG>120 mL/min/1.73 m²) n=90**
- **CKD (<80 mL/min/1.73 m²) n=76**

	Accuracy		Bias		Precision	
	30%		Mean		SD	
	MDRD	CKD-EPI	MDRD	CKD-EPI	MDRD	CKD-EPI
All	85	91	-16	-13	17	16
Normofiltrating (80-120 mL/min/1.73 m²) N=434	88	96	-15	-11	14	12
Hypofiltrating (lower than 80 mL/min/1.73 m²) N=76	88	82	+0.6	+4	16	16
Hyperfiltrating (over 120 mL/min/1.73 m²) N=90	68	77	-33	-33	18	13

All hyperfiltrating patients are missed !

Measuring GFR: Why?
A question of precision!

- Starting dialysis
- Sarcopenia
- Extreme body size
- Cirrhosis, USI
- Fibrates, cimetidine, trimethoprim (and other therapies)
- Hyperfiltration
- Living Kidney Donor selection

Agarwal R, Nephrol Dial Transplant, 2019, 34, p2001
Ebert N, Clin Kidney J, 2021, in press

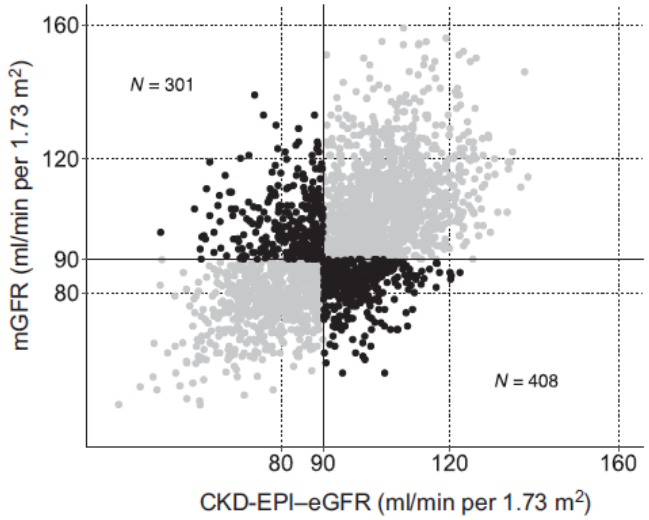
Impact of estimation versus direct measurement of predonation glomerular filtration rate on the eligibility of potential living kidney donors

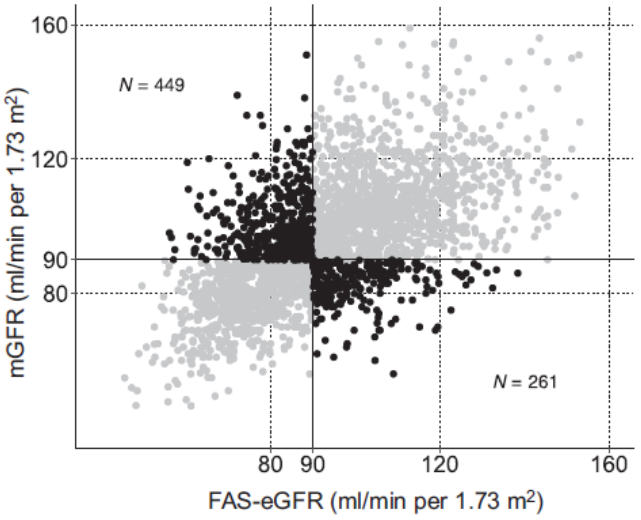
see commentary on page 738

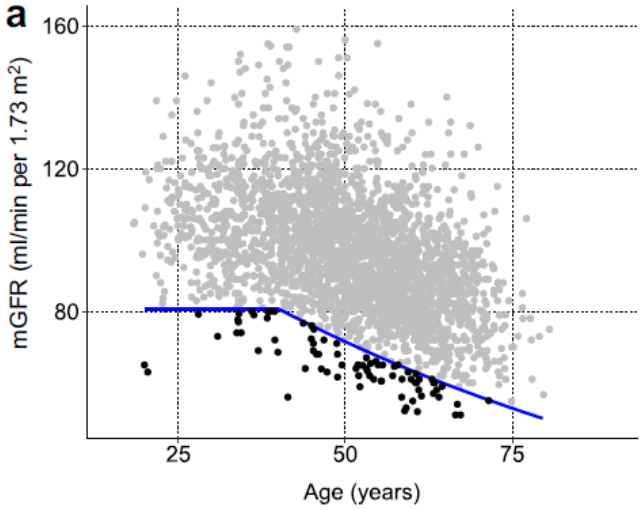
François Gaillard[1,2], Marie Courbebaisse[2,3], Nassim Kamar[4,5,18], Lionel Rostaing[6,18], Lola Jacquemont[7,8], Maryvonne Hourmant[7,8], Arnaud Del Bello[4], Lionel Couzi[9,10], Pierre Merville[9,10], Paolo Malvezzi[6], Benedicte Janbon[6], Bruno Moulin[11], Nicolas Maillard[12], Laurence Dubourg[13,14], Sandrine Lemoine[13], Cyril Garrouste[15], Hans Pottel[16], Christophe Legendre[1,2], Pierre Delanaye[17,19] and Christophe Mariat[12,19]

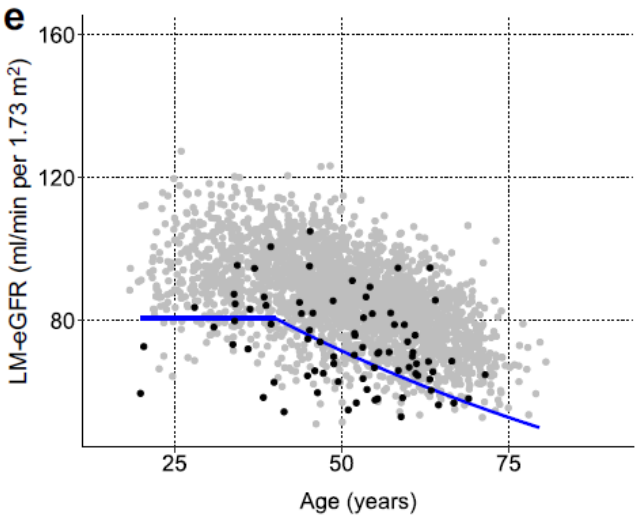
Kidney International (2019) **95,** 896–904;

- N=2,733 candidates for living kidney donation
- Measured GFR and standardized creatinine


160
120
90
80
N = 301
N = 408
mGFR (ml/min per 1.73 m²)
80 90 120 160
CKD-EPI–eGFR (ml/min per 1.73 m²)


160
120
90
80
N = 449
N = 261
mGFR (ml/min per 1.73 m²)
80 90 120 160
FAS-eGFR (ml/min per 1.73 m²)


a
160
120
80
mGFR (ml/min per 1.73 m²)
25 50 75
Age (years)


e
160
120
80
LM-eGFR (ml/min per 1.73 m²)
25 50 75
Age (years)

Measuring GFR: Why?
A question of precision!

- Starting dialysis
- Sarcopenia
- Extreme body size
- Cirrhosis, USI
- Fibrates, cimetidine, trimethoprim (and other therapies)
- Hyperfiltration
- Living Kidney Donor selection
- Dosing potential nephrotoxic drug (especially if abnormal BMI)

Agarwal R, Nephrol Dial Transplant, 2019, 34, p2001
Ebert N, Clin Kidney J, 2021, in press

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?
A question of precision!

- Starting dialysis
- Sarcopenia
- Extreme body size
- Cirrhosis, USI
- Fibrates, other therapies
- Hyperfiltration
- Living Kidney Donor selection
- Dosing potential nephrotoxic drug
- NO DEFINITIVE PROOF

Agarwal R, Nephrol Dial Transplant, 2019, 2019, 34, p2001

- Why?
- HOW ?

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:

  - 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

Available on the market…

Markers	Strenghts	Limitations
Inulin		
Iothalamate		
Iohexol		
EDTA		
DTPA		

Stevens LA, J Am Soc Nephrol, 2009, 20, p2305
Cavalier E, Clin Chim Acta, 2008, 396, p80
Delanaye P, Clin Kidney J, 2016, 9, p700

Different markers
But how to use it??

- Urinary clearance

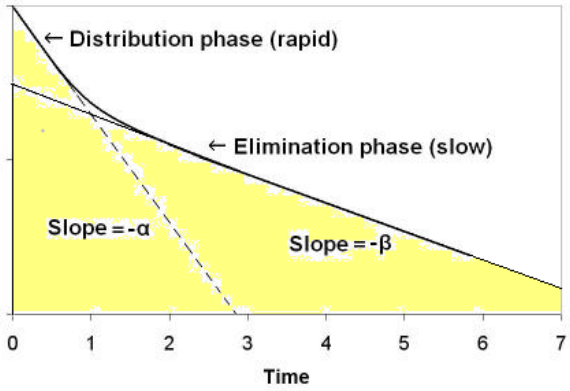
- Plasma clearance

Urinary clearance

- Constant infusion until equilibrium
- Measurement of plasma and urinary concentrations
- Urine collection (every 30 or 60 minutes) and measuring urinary flow
- To be repeated 3 or 4 times
- Cl = [U] x [V]/ [P] (mean of 3 or 4 collections)

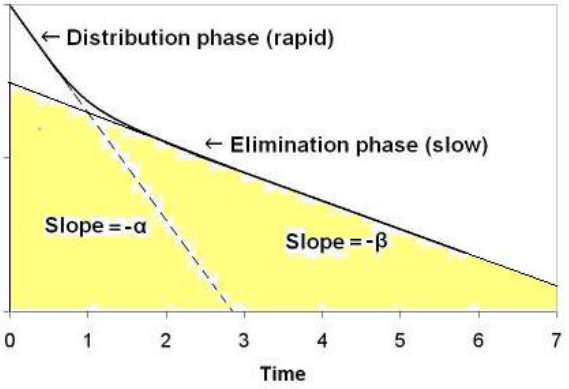
Plasmatic Clearance = Dose / AUC

Theoritically, α and β must be calculated



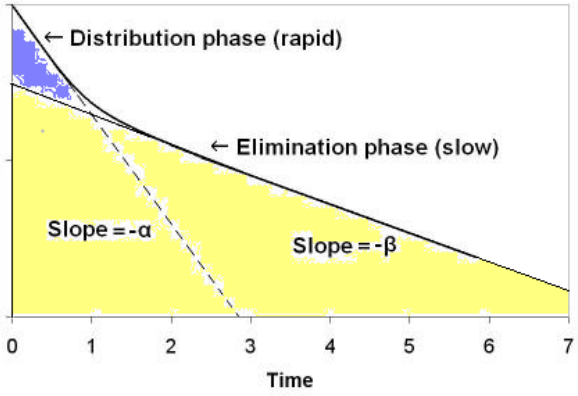
Not easy in practice (many samples)

Only slope ß after equilibrium is calculated



Brochner-Mortensen mathematical correction for estimation of distribution phase

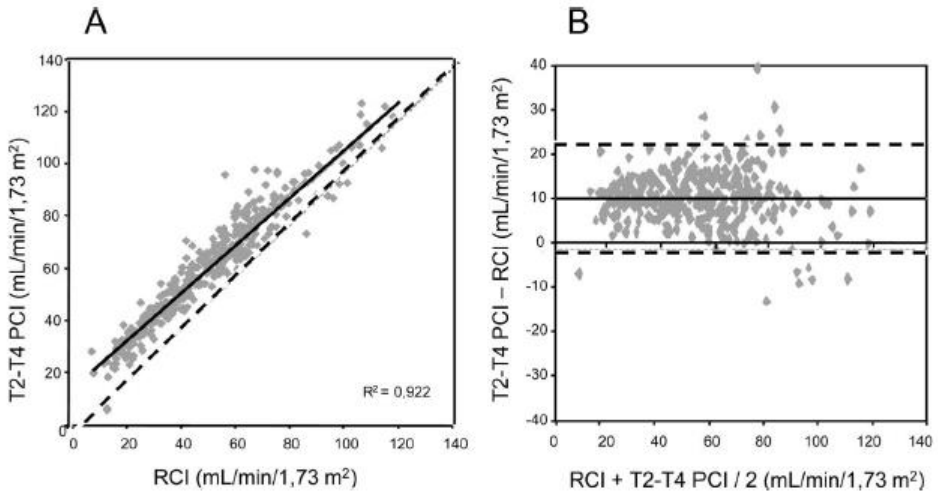
$= 0{,}990778 \times C2 - 0{,}001218\ C2^2$



M

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, p440

Urinary and plasma methods: pro-con

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

Nephrol Dial Transplant (2018) 33: 1778–1785
doi: 10.1093/ndt/gfx345
Advance Access publication 8 January 2018

Single- versus multiple-sample method to measure glomerular filtration rate

Pierre Delanaye[1,*], Martin Flamant[2,*], Laurence Dubourg[3,4], Emmanuelle Vidal-Petiot[2], Sandrine Lemoine[3], Etienne Cavalier[5], Elke Schaeffner[6], Natalie Ebert[6,**] and Hans Pottel[7,**]

[1]Department of Nephrology, Dialysis, Transplantation, University of Liège (CHU ULg), Liège, Belgium, [2]Department of Renal Physiology, DHU-FIRE, Hôpital Bichat, AP-HP, Inserm U1149, and Paris Diderot University, Sorbonne Paris-Cité, Paris, France, [3]Néphrologie, Dialyse, Hypertension artérielle et Exploration fonctionnelle rénale, Groupement Hospitalier Edouard Herriot, Hospices Civils de Lyon, Lyon, France, [4]Laboratory of Tissue Biology and Therapeutic Engineering, UMR 5305 CNRS, University Claude Bernard Lyon 1, Lyon, France, [5]Department of Clinical Chemistry, University of Liège (CHU ULg), Liège, Belgium, [6]Charité University Hospital, Institute of Public Health, Berlin, Germany and [7]Department of Public Health and Primary Care, KU Leuven Campus Kulak Kortrijk, Kortrijk, Belgium

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*These authors equally contributed as first author.
**These authors equally contributed as last senior author.

Table 2. Comparison of concordance within 10% between the multiple-sample and the single-sample method (at different time points) according to GFR levels ($n = 5106$)

GFR range (mL/min)	120 min (%)	180 min (%)	240 min (%)
$\leq$30 ($n = 313$)	20.8	29.4	44.1
]30–45] ($n = 889$)	34.5	59.1	83.6
]45–60] ($n = 1205$)	56.5	85.5	96.9
]60–90] ($n = 1828$)	81.9	96.4	98.2
]90–130] ($n = 813$)	96.3	98.4	94.3
>130 ($n = 58$)	100	98.3	94.8

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, p700

Available on the market…

Markers	Strength	Limitations
Inulin	"Gold standard" (or historical)	Costly No standardized dosage, not available in US Impossible for plasma clearance Anaphylactic shock

Stevens LA, J Am Soc Nephrol, 2009, 20, p2305
Cavalier E, Clin Chim Acta, 2008, 396, p80
Delanaye P, Clin Kidney J, 2016, 9, p700

Available on the market…

Markers	Strength	Limitations
Inulin	"Gold standard" (or historical)	Costly No standardized dosage, not available in US Impossible for plasma clearance Anaphylactic shock
Iothalamate	The most used in US Isotopic or "cold"	Tubular secretion Allergy Iodine

Stevens LA, J Am Soc Nephrol, 2009, 20, p2305
Cavalier E, Clin Chim Acta, 2008, 396, p80
Delanaye P, Clin Kidney J, 2016, 9, p700

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Iohexol	The most used in Europe Cold	Allergy Iodine

Stevens LA, J Am Soc Nephrol, 2009, 20, p2305
Cavalier E, Clin Chim Acta, 2008, 396, p80
Delanaye P, Clin Kidney J, 2016, 9, p700

Available on the market…

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EDTA	Easy to measure	Only isotopic, costly Not available in US…and in Europe!!

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Iohexol	The most used in Europe Cold	Allergy Iodine
EDTA	Easy to measure	Only isotopic, costly not available in US…and in Europe!!
DTPA	Easy to measure	Only isotopic Binding to proteins Costly

Stevens LA, J Am Soc Nephrol, 2009, 20, p2305
Cavalier E, Clin Chim Acta, 2008, 396, p80
Delanaye P, Clin Kidney J, 2016, 9, p700

RAPID COMMUNICATION www.jasn.org

A Novel Method for Rapid Bedside Measurement of GFR

Dana V. Rizk,[1] Daniel Meier,[2] Ruben M. Sandoval,[2,3] Teresa Chacana,[1] Erinn S. Reilly,[2] Jesse C. Seegmiller,[4] Emmanuel DeNoia,[5] James S. Strickland,[2] Joseph Muldoon,[2] and Bruce A. Molitoris[2,3]

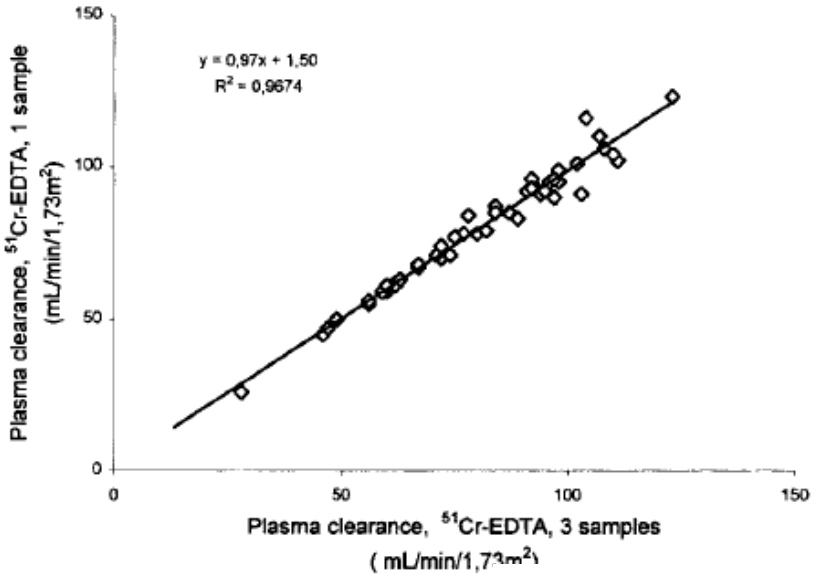
[1]Nephrology Division, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama; [2]FAST BioMedical, Carmel, Indiana; [3]Nephrology Division, Department of Medicine, Indiana University, Indianapolis, Indiana; [4]Advanced Research and Diagnostics Laboratory, University of Minnesota, Minneapolis, Minnesota; and [5]ICON Early Phase Services LLC, San Antonio, Texas

J Am Soc Nephrol 29: 1609–1613, 2018.

Are these markers equivalent?

EDTA versus iohexol

N=49



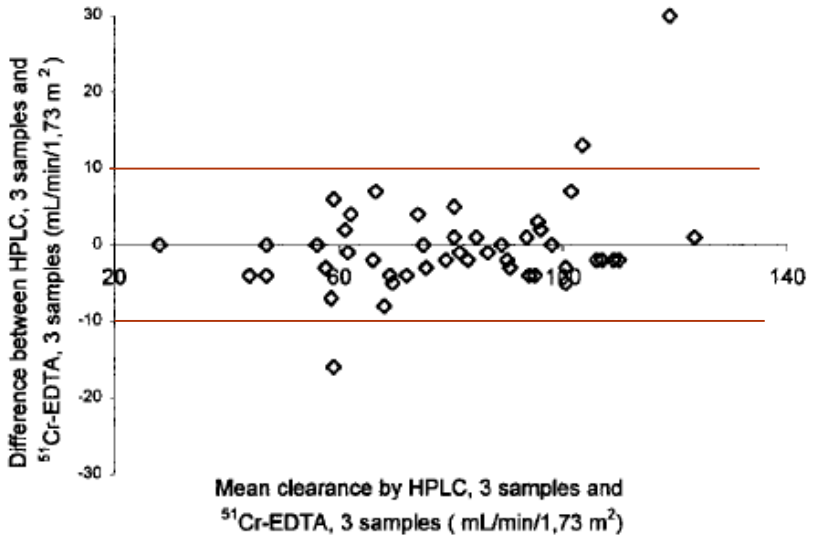


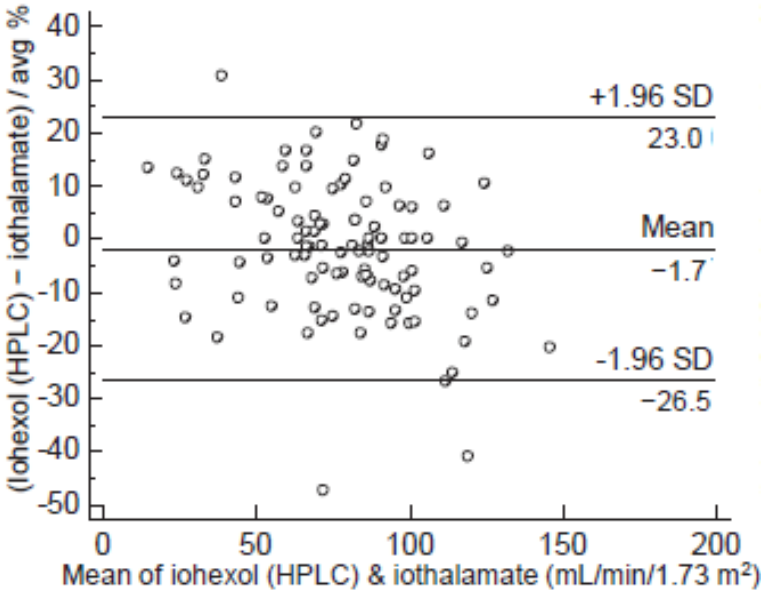
Table 3. Clearance range, mean of differences and standard deviation for multiple-point clearance and single-point clearance measurements

	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, p1176

Iothalamate versus iohexol

N=102



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

Delanaye P, AJKD, 2016, 68, p329

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%.

Soveri I, Am J Kidney Dis, 2014, 64, p411

We still need for a better standardization

EKFC

Nephrol Dial Transplant (2018) 33: 1778–1785
doi: 10.1093/ndt/gfx345
Advance Access publication 8 January 2018

Single- versus multiple-sample method to measure glomerular filtration rate

Pierre Delanaye[1,*], Martin Flamant[2,*], Laurence Dubourg[3,4], Emmanuelle Vidal-Petiot[2], Sandrine Lemoine[3], Etienne Cavalier[5], Elke Schaeffner[6], Natalie Ebert[6,**] and Hans Pottel[7,**]

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*These authors equally contributed as first author.
**These authors equally contributed as last senior author.

ARTICLE IN PRESS

KI REPORTS
KIReports.org

CLINICAL RESEARCH

Comparison of Plasma Clearance With Early-Compartment Correction Equations and Urinary Clearance in High GFR Ranges

Pierre Delanaye[1,2*], Emmanuelle Vidal-Petiot[3,*], Thomas Stehlé[4,*], Laurence Dubourg[5], François Gaillard[6], Gunnar Sterner[7], Christine A. White[8], Sandrine Lemoine[5], Vincent Audard[4], Dominique Prié[9], Etienne Cavalier[10], Marie Courbebaisse[11], Hans Pottel[12] and Martin Flamant[3]

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AJKD

Correspondence

RESEARCH LETTER

Concordance Between Iothalamate and Iohexol Plasma Clearance

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Caroline Le Goff, EuSpLM, Etienne Cavalier, EuSpLM, PhD
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Original Investigation

AJKD

Comparability of Plasma Iohexol Clearance Across Population-Based Cohorts

Bjørn O. Eriksen, Elke Schaeffner, Toralf Melsom, Natalie Ebert, Markus van der Giet, Vilmundur Gudnason, Olafur S. Indridasson, Amy B. Karger, Andrew S. Levey, Mirjam Schuchardt, Liv K. Sørensen, and Runolfur Palsson

Rationale & Objective: Glomerular filtration rate (GFR) estimation based on creatinine or cystatin C level is currently the standard method for assessing GFR in epidemiologic research and clinical trials despite several important and well-known limitations. Plasma iohexol clearance has been proposed as an inexpensive method for measuring GFR that could replace estimated GFR in many research projects. However, lack of standardization for iohexol assays and the use of different protocols such as single- and multiple-sample methods could potentially hamper comparisons across studies. We compared iohexol assays and GFR measurement protocols in 3 population-based European cohorts.

Study Design: Cross-sectional investigation.

Setting & Participants: Participants in the Age, Gene/Environment Susceptibility-Kidney Study (AGES-Kidney; n = 805), the Berlin Initiative Study

Results: Frozen samples from the 3 studies were obtained and iohexol concentrations were remeasured in the laboratory at the University Hospital of North Norway. Lin's concordance correlation coefficient ρ was >0.96 and C_b (accuracy) was >0.99 for remeasured versus original serum iohexol concentrations in all 3 cohorts, and Passing-Bablok regression did not find differences between measurements, except for a slope of 1.025 (95% CI, 1.006-1.046) for the log-transformed AGES-Kidney measurements. The multiple-sample iohexol clearance measurements in AGES-Kidney and BIS were compared with single-sample GFRs derived from the same iohexol measurements. Mean bias for multiple-sample relative to single-sample GFRs in AGES-Kidney and BIS were −0.25 and −0.15 mL/min, and 99% and 97% of absolute differences were within 10% of the multiple-sample result, respectively.

Complete author and article information provided before references.

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Am J Kidney Dis. XX(XX):1-9. Published online Month X, XXXX.

doi: 10.1053/j.ajkd.2019.10.008

Comparison of Early-Compartment Correction Equations for GFR Measurements

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[10]PD, LD, MF, EC, ES, NE, and HP are members of the European Kidney Function Consortium.

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Kidney Int Rep (2020) **5**, 1079–1081; https://doi.org/10.1016/j.ekir.2020.04.015

Choice of the marker (personal opinion)

- Only « cold » methods are easy to implement worldwide
- Iohexol is available worldwide
- Perfect stability (central laboratory)
- EQUAS (Equalis, Sweden) is available
- Cr-EDTA, inulin, iothalamate not (or not easily) available in Europe…

Performance of creatinine- or cystatin C–based equations to estimate glomerular filtration rate in sub-Saharan African populations

see commentary on page 1017

Justine B. Bukabau[1,7], Eric Yayo[2,7], Appolinaire Gnionsahé[3], Dagui Monnet[2], Hans Pottel[4], Etienne Cavalier[5], Aliocha Nkodila[1], Jean Robert R. Makulo[1], Vieux M. Mokoli[1], François B. Lepira[1], Nazaire M. Nseka[1], Jean-Marie Krzesinski[6], Ernest K. Sumaili[1,7] and Pierre Delanaye[6,7]

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Kidney International (2019) **95,** 1181–1189;

Iohexol, example of protocol

- Iohexol (plasma clearance), 5 mL bolus (Omnipaque, 240 mg I/mL)
- 5 hours
- Samples at 2, 3, 4 and 5 hours (+later if very low GFR)
- Bröchner-Mortensen correction
- ± 100 euros
- Is it so complex?

nephron
Clinical Practice

Clinical Practice: Original Paper

Nephron
DOI: 10.1159/000489898

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Safety of Iohexol Administration to Measure Glomerular Filtration Rate in Different Patient Populations: A 25-Year Experience

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Matias Trillini[a] Maria Carolina Aparicio[a] Olimpia Diadei[a] Silvia Ferrari[a]
Antonio Cannata[a] Nadia Stucchi[a] Piero Ruggenenti[a, c] Giuseppe Remuzzi[a, c, d]
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Conclusions

- **Measuring GFR is not so cumbersome** (for a reference method)
- **Measuring GFR is not so costly** (for a reference method)
- **Standardization** (marker, procedure and measurement) **can still be improved**
- **Iohexol plasma clearance is the best balance between physiology and feasibility**
- **Iohexol is safe**
- **Iohexol is the only chance to have a standardized GFR measurement worldwide**

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]

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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]

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European Kidney Function Consortium (EKFC)

Thank you!