Which method to measure GFR and in which clinical conditions?

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BELGIUM

- WHY?
- How?

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)

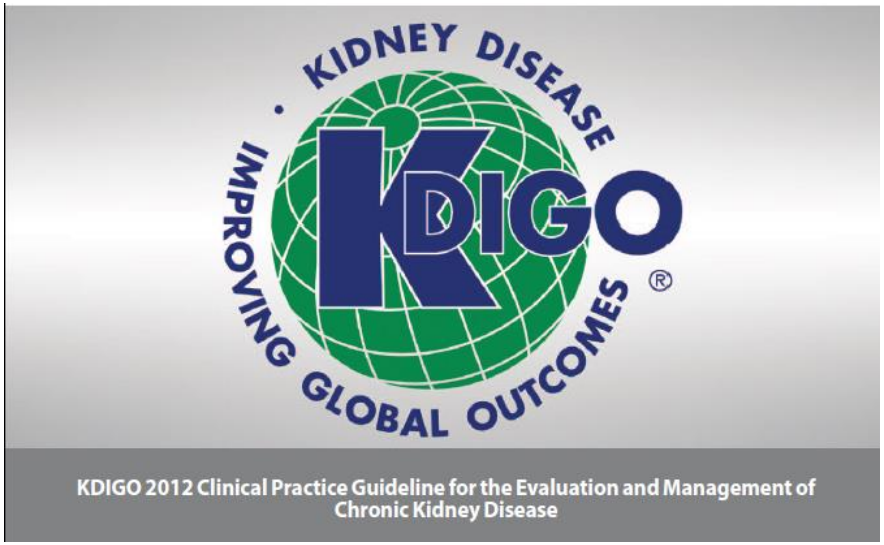
REVIEWS

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 but when measured GFR is required

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



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)
- Young women
- Hyperfiltration
- Living Kidney Donor selection
- Dosing potential nephrotoxic drug
- EMA

Agarwal R, Nephrol Dial Transplant, 2019, 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.

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A question of precision!

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- Young women
- Hyperfiltration
- Living Kidney Donor selection
- Dosing potential nephrotoxic drug
- EMA
- GFR follow-up

Agarwal R, Nephrol Dial Transplant, 2019, in press

Nephrol Dial Transplant (2018) 1–9
doi: 10.1093/ndt/gfy278

ndt
Nephrology Dialysis Transplantation

Performance of creatinine-based equations for estimating glomerular filtration rate changes over time

Marieke H.C. van Rijn[1,2], Marie Metzger[2], Martin Flamant[3,4], Pascal Houillier[5,6,7], Jean-Philippe Haymann[8,9], Jan A.J.G. van den Brand[1], Marc Froissart[10] and Benedicte Stengel[2] on behalf of the NephroTest Study Group

[1]Department of Nephrology, Radboud Institute of Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands, [2]CESP, INSERM, Université Paris-Sud, UVSQ, Université Paris-Saclay, Villejuif, France, [3]AP-HP, Hôpital Bichat, Paris, France, [4]Centre de Recherche sur l'Inflammation, INSERM, Université Paris-Diderot, Paris, France, [5]AP-HP, Hôpital Européen Georges Pompidou, Paris, France, [6]INSERM UMRS, Centre de Recherche des Cordeliers, Paris, France, [7]Faculté de Médecine, Université Paris Descartes, Paris, France, [8]AP-HP, Hôpital Tenon, Paris, France, [9]INSERM UMRS, Université Pierre et Marie-Curie, Paris, France and [10]Clinical Research Center, Education and Research Department, CHUV – Unil, Lausanne, Switzerland

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- Nephrotest Cohort
- ^{51}Cr-EDTA
- 5324 mGFR in 1955 patients

	Mean ± SD, median (IQR) or % (*n*)	Missing (*n*)	Range
Age (years)	58.7 ± 15.2		17–88
Women	33.1 (647)		
African origin	13.9 (259)	94	
Primary kidney disease			
DKD	10.0 (195)		
GN	14.1 (275)		
HT	26.0 (508)		
PKD	5.7 (111)		
TIN	9.0 (176)		
Other or undetermined	35.3 (692)		
Diabetes	27.5 (535)	7	
Hypertension	90.9 (1769)		
BP ≥ 140/90 (mm Hg)	36.4 (689)	62	
BSA (m^2)	1.83 ± 0.22		0.94–2.60
BMI (kg/m^2)			
<20	6.8 (132)		13–51
20–24	34.5 (676)		
25–29	37.3 (730)		
≥30	21.4 (419)		
ACR (mg/mmol)		55	0.1–879
3–29	33.8 (642)		
≥30	30.6 (582)		
mGFR ($mL/min/1.73\ m^2$)	44.0 ± 19.0		15–135
CKD-EPI eGFR ($mL/min/1.73\ m^2$)	46.4 ± 22.2		6.9–155
MDRD eGFR ($mL/min/1.73\ m^2$)	44.5 ± 20.9		6.8–212
Follow-up (years)	3.4 (2.0–5.6)		0–13
Number of visits			1–13
1	40.7 (797)		
2	21.7 (424)		
3	12.7 (248)		
≥4	24.9 (488)		

Table 2. Mean GFR slopes and overall performance of estimating equations

Absolute slope (mL/min/1.73 m^2/year)	Mean ± SD	Bias ± SD
mGFR	−1.6 ± 1.2	
CKD-EPI eGFR	−1.5 ± 1.4	−0.1 ± 1.1
MDRD eGFR	−1.3 ± 1.3	−0.3 ± 1.0
FAS eGFR	−1.5 ± 1.0	−0.1 ± 1.0
Relative slope (%/per year)		
mGFR	−5.9 ± 5.3	
CKD-EPI eGFR	−5.3 ± 5.3	−0.5 ± 2.7
MDRD eGFR	−4.8 ± 5.2	−1.0 ± 2.7
FAS eGFR	−4.9 ± 4.3	−0.9 ± 2.7

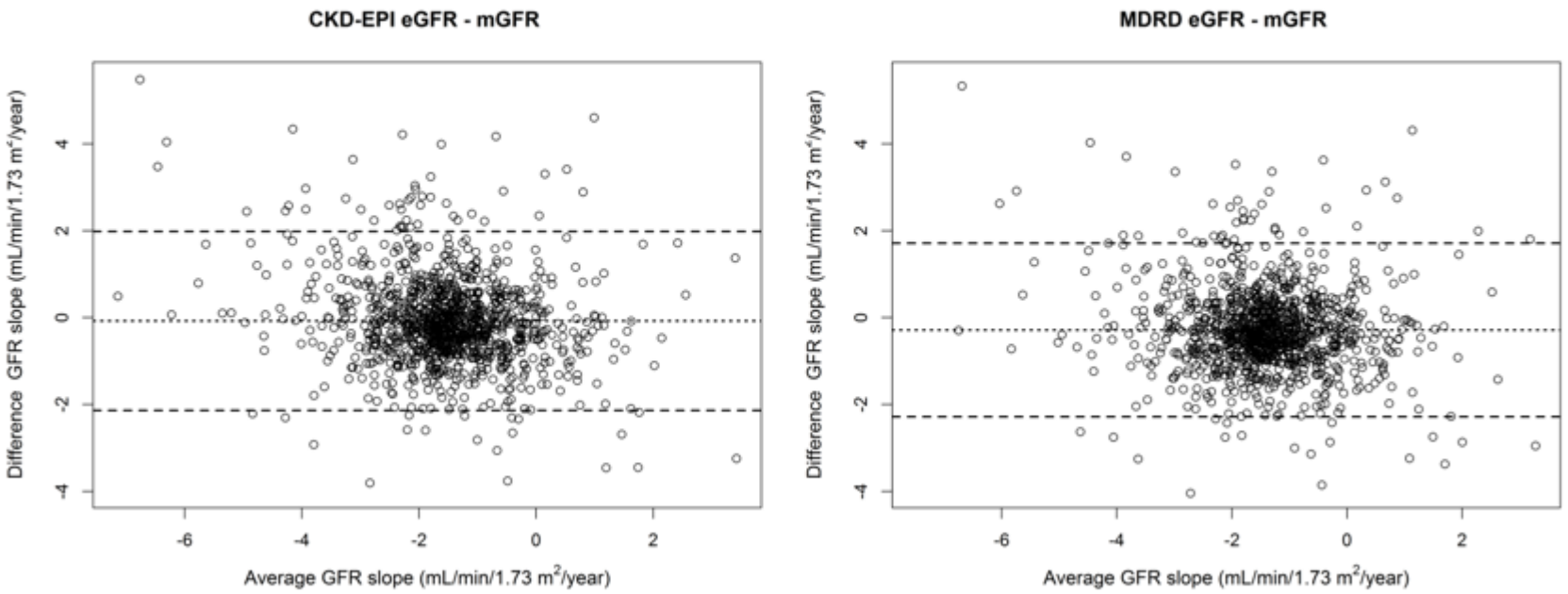
P10, percentage of patients with eGFR slopes within 10% of the mGFR slope; P30, percentage of patients with eGFR slopes within 30% of the mGFR slope.

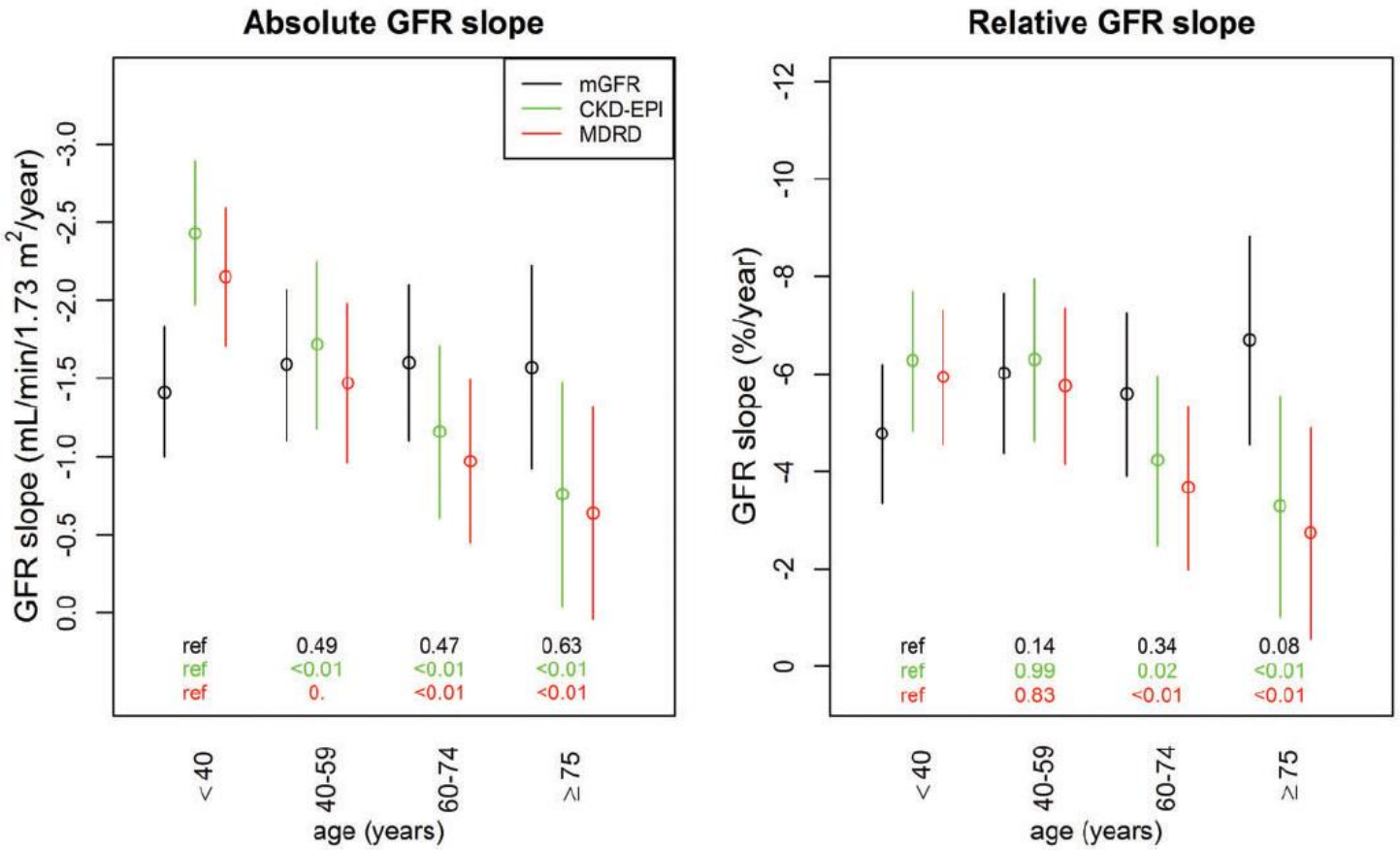
Table 2. Mean GFR slopes and overall performance of estimating equations

Absolute slope (mL/min/1.73 m^2/year)	Mean ± SD	Bias ± SD	95% LoA	P10 (%)	P30 (%)
mGFR	−1.6 ± 1.2				
CKD-EPI eGFR	−1.5 ± 1.4	−0.1 ± 1.1	−2.1–2.0	20	55
MDRD eGFR	−1.3 ± 1.3	−0.3 ± 1.0	−2.3–1.7	17	52
FAS eGFR	−1.5 ± 1.0	−0.1 ± 1.0	−1.9 to −1.8	23	62
Relative slope (%/per year)					
mGFR	−5.9 ± 5.3				
CKD-EPI eGFR	−5.3 ± 5.3	−0.5 ± 2.7	−5.8–4.7	22	57
MDRD eGFR	−4.8 ± 5.2	−1.0 ± 2.7	−6.3–4.2	18	53
FAS eGFR	−4.9 ± 4.3	−0.9 ± 2.7	−6.1–4.3	23	59

P10, percentage of patients with eGFR slopes within 10% of the mGFR slope; P30, percentage of patients with eGFR slopes within 30% of the mGFR slope.

1 Supplementary Figure 2: Bland-Altman difference plots




Absolute GFR slope
mGFR
CKD-EPI
MDRD
GFR slope (mL/min/1.73 m²/year)
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
ref 0.49 0.47 0.63
ref <0.01 <0.01 <0.01
ref 0. <0.01 <0.01
< 40
40-59
60-74
≥ 75
age (years)
Relative GFR slope
GFR slope (%/year)
0
-2
-4
-6
-8
-10
-12
ref 0.14 0.34 0.08
ref 0.99 0.02 <0.01
ref 0.83 <0.01 <0.01
< 40
40-59
60-74
≥ 75
age (years)

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A question of precision!

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- Young women
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- EMA
- GFR follow-up
- Clinical Research

Agarwal R, Nephrol Dial Transplant, 2019, in press

7-years

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] Belatacept was approved by the U.S.

No. at Risk

Belatacept MI	219
Belatacept LI	226
Cyclosporine	221

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
mGFR by iohexol plasma clearance

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)	—

Measuring GFR: Why?
A question of precision!

- Starting dialysis
- Sarcopenia
- Extreme body size
- Cirrhosis, USI
- Fibrates, other therapies
- Young women
- Hyperfiltration
- Living Kidney Donor selection
- Dosing potential nephrotoxic drug
- EMA
- Clinical Research
- GFR follow-up
- NO DEFINITIVE PROOF

Agarwal R, Nephrol Dial Transplant, 2019, in press

- 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, 2305
Cavalier E, Clin Chim Acta, 2008, 396, 80
Delanaye P, Clin Kidney J, 2016, 9, 700

Different markers
But how to use it??

- Urinary clearance

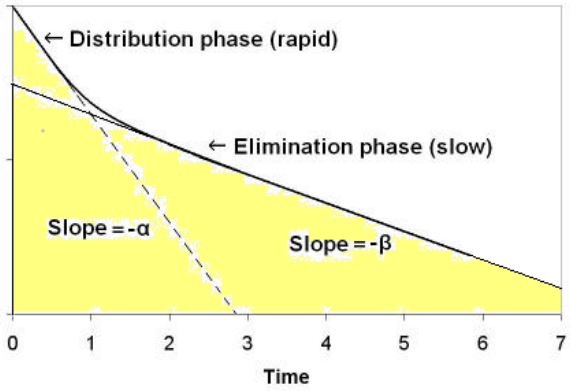
- Plasma clearance

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)

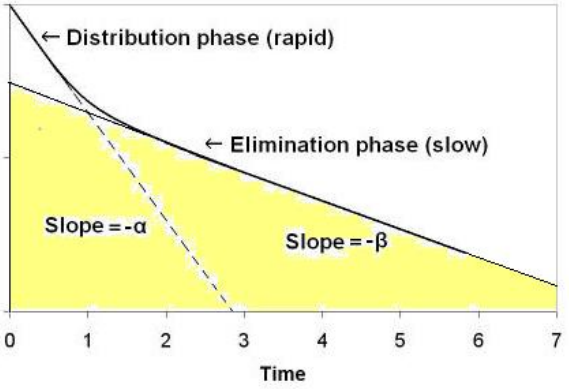
Plasmatic Clearance = Dose / AUC

Theoritically, α and β must be calculated



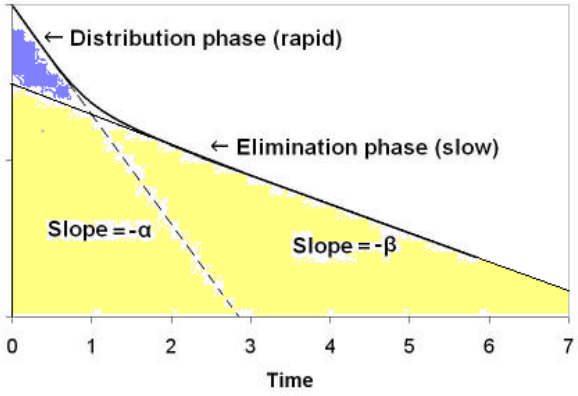
Not easy in practice (many samples)

Only slope ß after equilibrium is calculated



Brochner-Mortensen mathematical correction for estimation of distribution phase

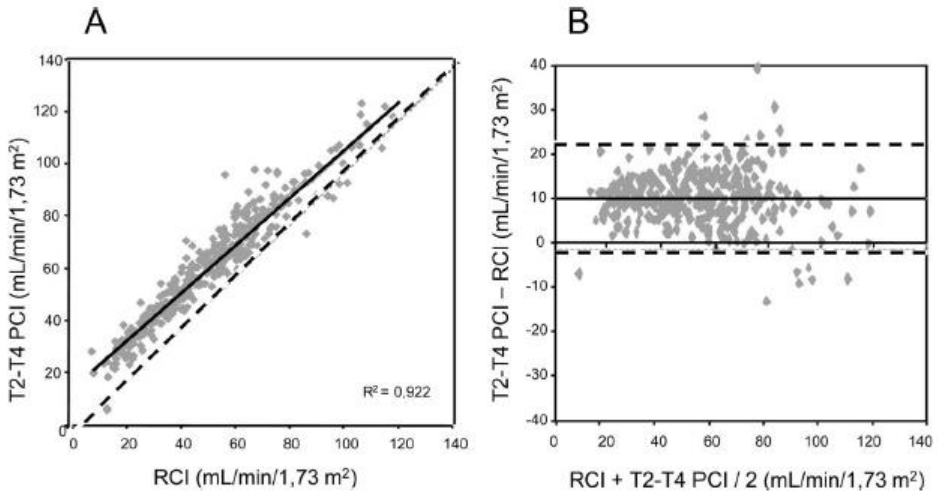
$= 0{,}990778 \times C2 - 0{,}001218\ C2^2$



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, 440

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, 700

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, 2305
Cavalier E, Clin Chim Acta, 2008, 396, 80
Delanaye P, Clin Kidney J, 2016, 9, 700

Available on the market…

Markers	Strength	Limitations
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Iothalamate	The most used in US Isotopic or "cold"	Tubular secretion Allergy Iodine

Stevens LA, J Am Soc Nephrol, 2009, 20, 2305
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Stevens LA, J Am Soc Nephrol, 2009, 20, 2305
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Delanaye P, Clin Kidney J, 2016, 9, 700

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Iothalamate	The most used in US Isotopic or "cold"	Tubular secretion Allergy Iodine
Iohexol	The most used in Europe Cold	Allergy Iodine
EDTA	Easy to measure	Only isotopic, costly Not available in US…and in Europe!!

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

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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, 2305
Cavalier E, Clin Chim Acta, 2008, 396, 80
Delanaye P, Clin Kidney J, 2016, 9, 700

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]

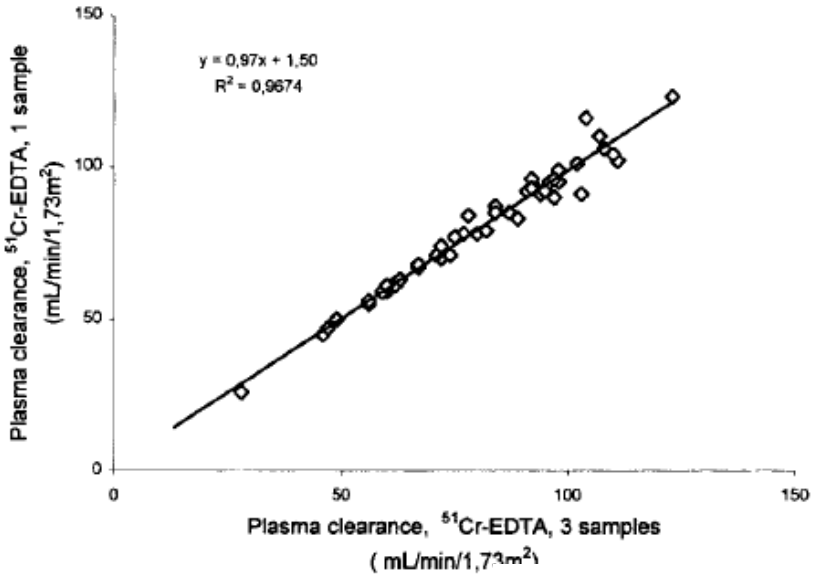
[1]Nephrology Division, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama; [2]FAST BioMedical, Carmel, Indiana; [3]Nephrology Division, Department of Medicine, Indiana University, Indianapolis, Indiana; [4]Advanced Research and Diagnostics Laboratory, University of Minnesota, 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



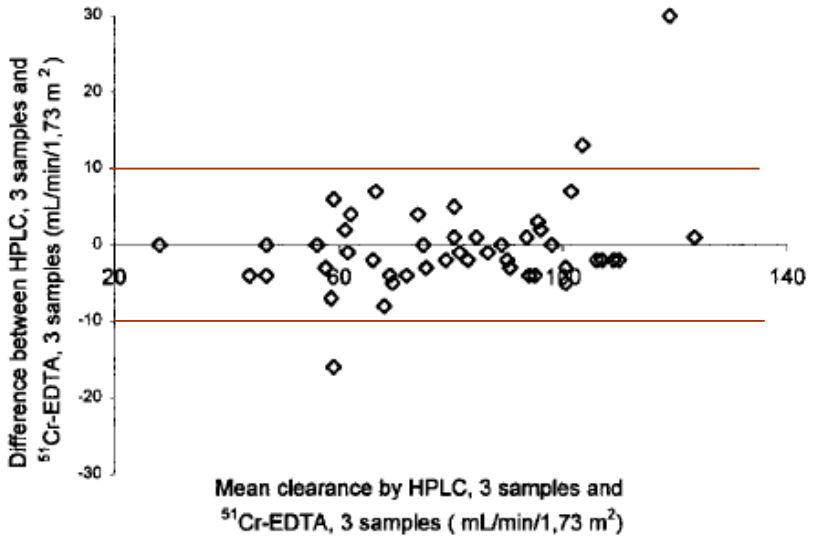


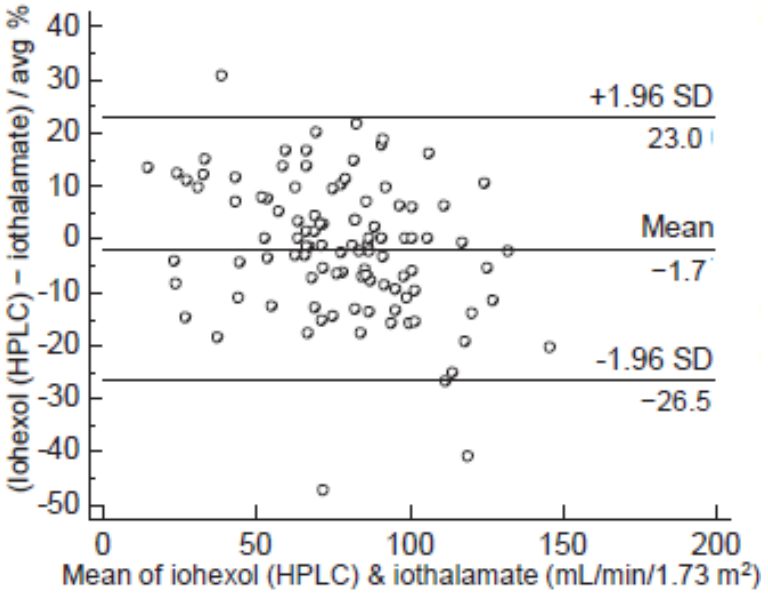
Table 3. Clearance range, mean of differences and standard deviation for multiple-point clearance and single-point clearance measurements

	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, 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

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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, 411

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

Gunnar Nordin, Sara Ekvall, Carolina Kristoffersson, Ann-Sofie Jonsson, Sten-Erik Bäck, Niclas Rollborn and Anders Larsson*

Accuracy of determination of the glomerular filtration marker iohexol by European laboratories as monitored by external quality assessment

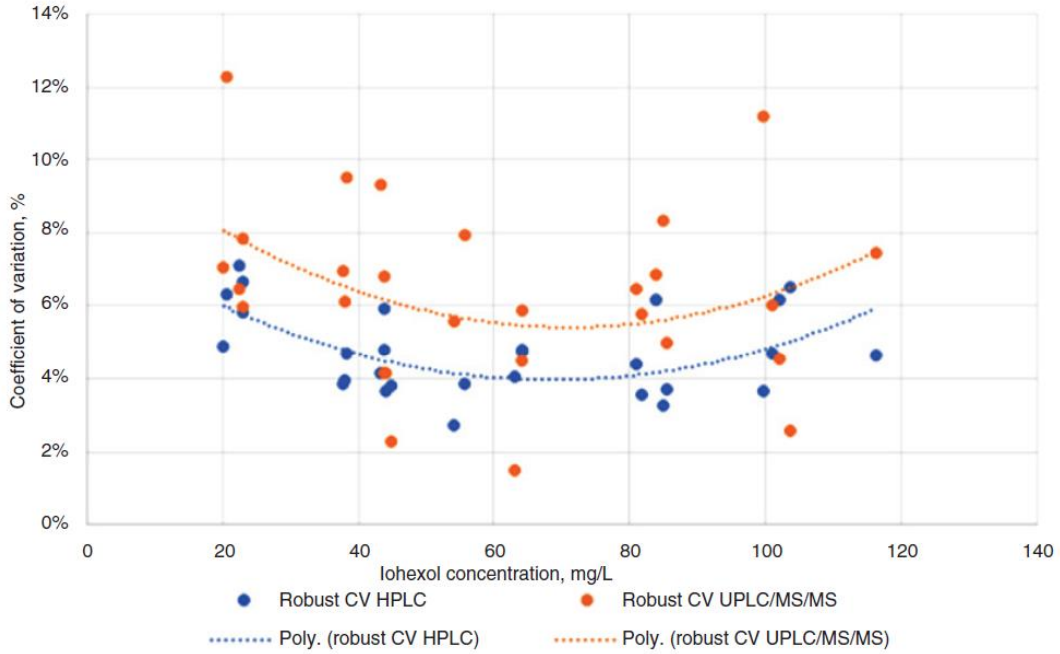

Figure 1: Mean interlaboratory CV (y-axis) vs. measured concentration of iohexol (x-axis) for laboratories using either HPLC or UPLC/MS/MS.

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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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…

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?

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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]
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Table 2. Immediate adverse reactions associated with radiocontrast agents in the cohort of 2,891 subjects

Events recorded at time of or near iohexol injection	Relation to iohexol injection	Severity	Comments
Flushing, urticaria, itching	Definite	Moderate	Resolution after corticosteroid treatment. Patient did not perform any further iohexol investigation
Itchy skin rash	None	Mild	The event occurred the day after the first iohexol procedure when the patient underwent per-protocol CT with iopamidol. After that, patient tolerated 3 other iohexol GFR measurements without pre-medication
Iodide mumps	None	Mild	The event occurred the day after the first iohexol procedure when the patient underwent per-protocol CT with iopamidol. Spontaneous resolution in few days. The patient well tolerated subsequent iohexol GFR procedures
Atopic dermatitis	None	–	Event already present before iohexol administration
Angiodermatitis	None	–	Event already present before iohexol administration
Head and neck pruritus	None	–	Event already present before iohexol administration
Left forearm phlebitis	None	–	Secondary to thrombosis of arterio-venous fistula 2 days before iohexol administration
Dermatitis (arms and groin)	None	–	Event already present before iohexol administration related to sirolimus treatment
Eczematous dermatitis	None	–	Event already present before iohexol administration related to sirolimus treatment

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**

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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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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!