GFR and Drug Dosage Adaptation: Are We still in the Mist?

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EUROMEDLAB ATHENS 2017

I have no conflict of interest to declare

Renal function (GFR) is important

- Especially for renal excreted drugs
- Especially for renal excreted drugs potentially nephrotoxic
- Especially for renal excreted drugs potentially nephrotoxic with a narrow therapeutic window
- But not Only…

CKD can influence:

Bioavailability (ex: propanolol: +300%)

Drug Distribution (increased for water soluble drugs if edema)

Plasma binding to protein (nephrotic syndrome, uremic toxins)

Decreased extra-renal clearance

TABLE 55.3 Effect of CKD on Non-Renal Clearance in Humans

Drug	% Change Non-Renal Clearance	Enzyme	Metabolism Decreased
Captopril	–50	TPMT*	sulfoxidation
Morphine	–40	UGT2B7	glucuronidation
		NAT-2	acetylation
		CYP3A4	
		CYP3A4	
		CYP2D6	
		CYP2C9	

ference[2], court

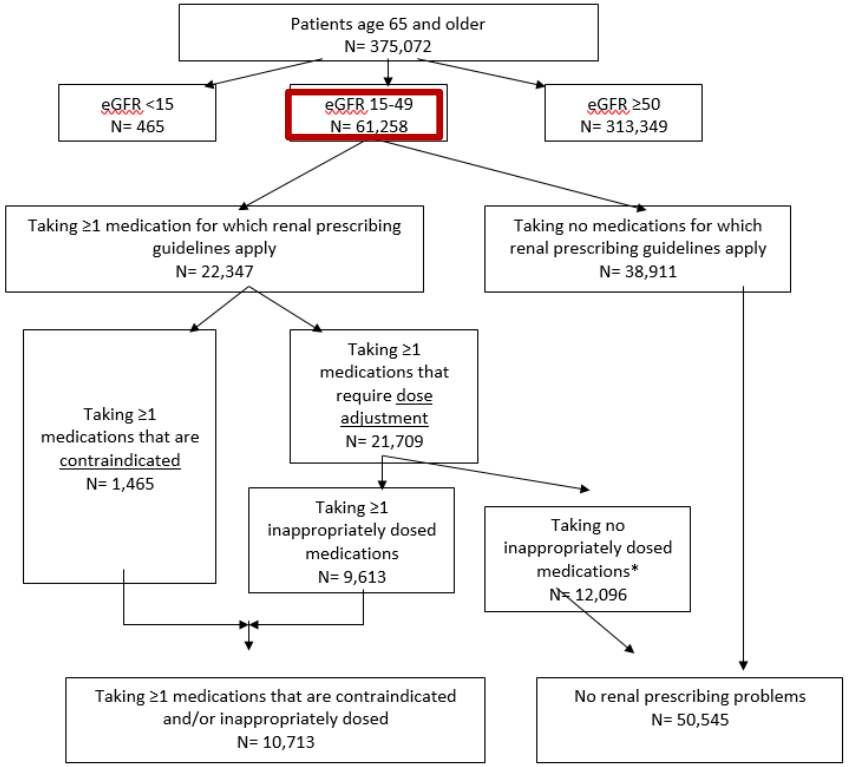
n and Chronic Kidney Disease,
nel and Rosenberg, 2015

A pharmacokinetic study is required for every drug according to different stages of CKD

Inappropriately drug prescription: Is it frequent? Is it relevant?

Is it frequent?

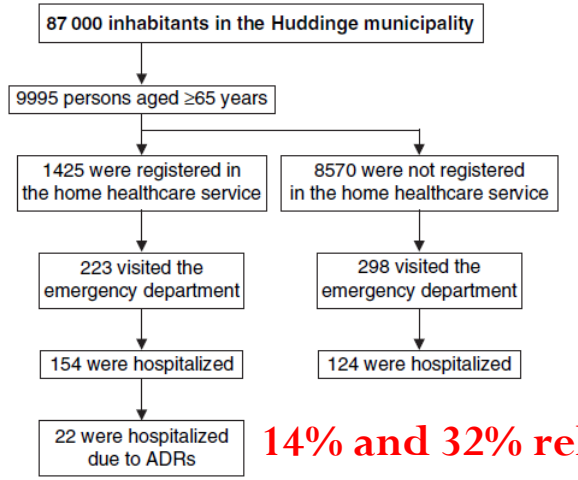
- VA
- MDRD



17,5% Chang F, J Am Soc Geriar, 2015, 2015, p2290

Is it relevant?

- 2-10% of drug-related hospitalization (9-31% in the elderly)
  Salvi F, Drug Saf, 2012, p29 Oscanoa TJ, Eur J Clin Pharmcol, 2017, p759
- 10% of these hospitalizations are related to CKD Leendertse AJ, Ann Pharmacother, 2012, p625
- Elderly: Hellden A, Drugs Aging, 2009, p595



14% and 32% related to CKD

Fig. 1. Flow chart of patients aged ≥65 years from the Huddinge, Sweden municipality hospitalized after admission to the emergency department. **ADR** = adverse drug reaction.

1.1.1: CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health (Table 2). (*Not Graded*)

Table 5 | GFR categories in CKD

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.

Drug Dosage Adaptation is personalized medicine

GFR is usually indexed by BSA (1.73m²)

- BSA indexation is questionable *per se* (Eriksen BO, JASN, 2001, p1517)
- Why? To make comparison between people/patients of different body size (ex: gender)
- But for a given patient in term drug of dosage, we must know his « true » GFR….not the GFR he would have if BSA was 1.73m²
- It is recommended (FDA/EMA/KDIGO) to use GFR not indexed for BSA (measured GFR and Cockcroft) OR « desindexed » for BSA (MDRD/CKD-EPI)

BSA desindexation

- Is it relevant?

Table 3. Mean differences between absolute (ml/min) and indexed (ml/min/1.73 m^2) GFR

	n	Mean absolute GFR	Mean indexed GFR (Du Bois)	Mean indexed GFR (Livingston)	Mean difference between indexed GFR (Du Bois) and absolute GFR	Mean difference between indexed GFR (Livingston) and absolute GFR
BMI 18.5–25	40	44.47	43.38	43.53	−1.09	−0.95
BMI >30	81	98.55	81.73	70.94	−18.2*	−27.62*
BMI >40	33	110.17	87.76	72.29	−24.85*	−37.88*

*$P < 0.0001$. BMI is given in kg/m^2.

Delanaye P, Nephrol Dial Transplant, 2005, p2024

- Is it problematic?

Few studies (purely theoretical)

The desindexation is mathematically questionable

Skip one major advantage of recent equations: the automatic report by the lab

One more step for the clinicians

Serum creatinine: Analytical limitations

- Jaffe: Pseudochromogen: glucose, fructose, ascorbate, proteins, urate, acetoacetate, acetone, pyruvate => false « high »
- Bilirubins: false « low »
- Few (fewer) interferences with enzymatic methods
- Different Jaffe-Enzymatic methods, different calibration by different manufacturers
- IDMS-traceability (enzymatic methods)

Serum creatinine: Physiological limitations

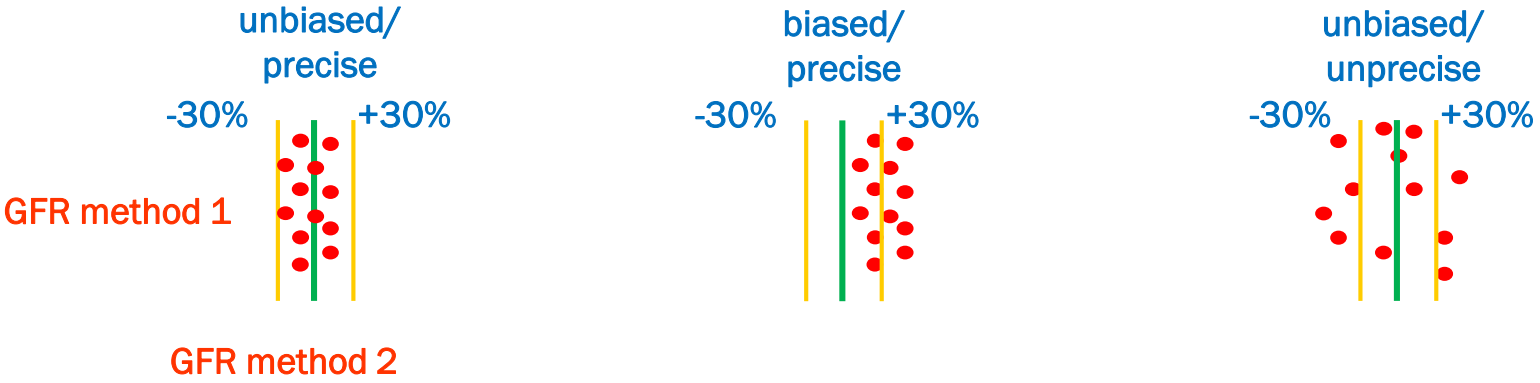
- Production (relatively) constant but muscular production => serum creatinine is dependent of muscualr mass, not only GFR
  - gender
  - age
  - ethnicity
  - Muscular mass(creatine)
- Tubular secretion of creatinine
  - 10 to 40%
  - Increase with decreased GFR
  - Unpredictable at the individual level

Perrone RD, Clin Chem, 1992, p1933

eGFR equations

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



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

Less performant (less precision) than all modern estimating equations

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

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.

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.

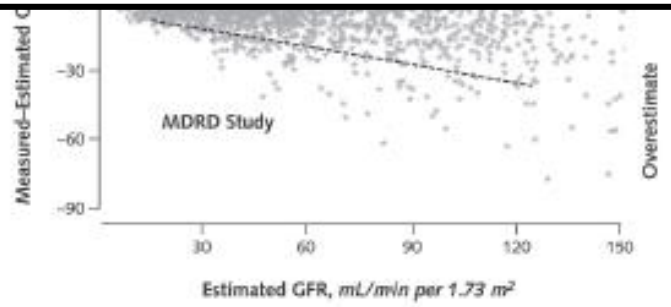


Table 3. Comparison of the CKD-EPI and MDRD Study Equations in Estimating Measured GFR in the Validation Data Set*

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)

Cockcroft/MDRD/CKDEPI: limitations = 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)

MDRD/CKDEPI are better to estimate GFR than Cockcroft

- Methodologically more solid
- Estimate « true » GFR (not clearance creatinine)
- Precision, bias, accuracy are better…especially in the relevant range of GFR for drug adaptation (<45 mL/min)
- Can be used with IDMS-traceable creatinine
- Weight

CKDEPI against Cockcroft:

The debate is closed…

in the Nephrological community

But Cockcroft is still used in the context of drug dosage adaptation…

- The historical perspective
- The weight
- Safety in geriatric

Evaluation of Renal Drug Dosing: Prescribing Information and Clinical Pharmacist Approaches

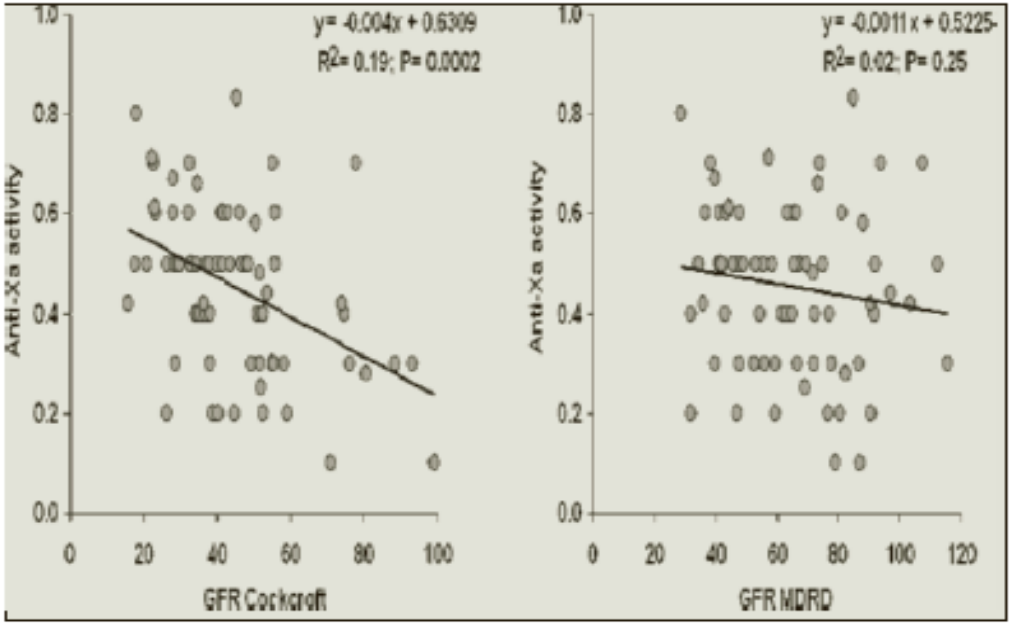
Thomas C. Dowling, Pharm.D., Ph.D., FCP, Gary R. Matzke, Pharm.D., FCCP,
John E. Murphy, Pharm.D., FCCP, FASHP, and Gilbert J. Burckart, Pharm.D., FCCP, FCP
(Pharmacotherapy 2010;30(8):776–786)

- Between 1998-2007, 44 new medications with recommendations according to CKD status
- 42 are based on creatinine clearance
- 11 used Cockcroft
- MDRD recommended (with Cockcroft) since 2008 by the FDA

The weight

- The weight is an estimation of volume of distribution

Figure 2
Correlation between anti-Xa activity (IU/mL) and GFR (estimated with the Cockcroft and MDRD formulae) (mL/min)



Pearson's correlations between anti-Xa activity and GFR estimation

Dufour B, J Nutrit Health Aging, 2012

Safety in geriatry

Nephrol Dial Transplant (2007) 22: 2894–2899
doi:10.1093/ndt/gfm289
Advance Access publication 16 June 2007

Original Article

Use of GFR equations to adjust drug doses in an elderly multi-ethnic group—a cautionary tale

Jagbir Gill, Rhonda Malyuk, Ognjenka Djurdjev and Adeera Levin

Division of Nephrology, UBC, Centre for Health Evaluation and Outcome Sciences, and Department of Pharmacy, St Paul's Hospital, Vancouver BC

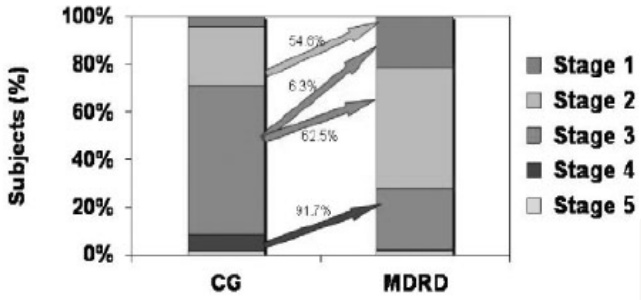


Fig. 2. Impact of MDRD on CG-based stages of CKD. In general, MDRD classified the majority of subjects into a different stage of CKD than CG. A 54.6% of subjects classified as stage 2 CKD by CG, were reclassified as stage 1 by MDRD. A 6.3% of patients classified as stage 3 CKD by CG were reclassified as stage 1 by MDRD and 62.5% were reclassified to stage 2 by MDRD. A 91.7% of patients classified as stage 4 by CG, were reclassified to stage 3 by MDRD.

DIGOXIN decreased dosage:

MDRD: 46/179

Cockcroft: 104/179

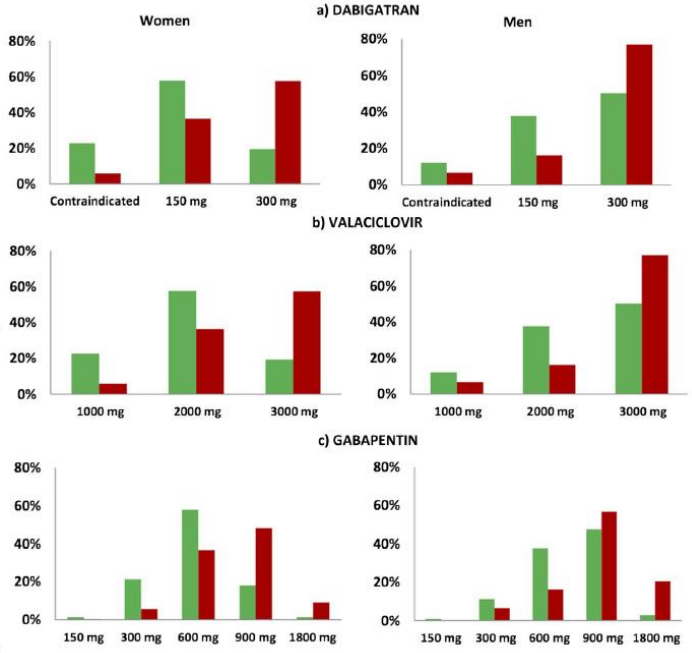
Open Access Research

BMJ open accessible medical research

Renal function estimations and dose recommendations for dabigatran, gabapentin and valaciclovir: a data simulation study focused on the elderly

Anders Helldén,[1] Ingegerd Odar-Cederlöf,[1] Göran Nilsson,[2] Susanne Sjöviker,[3] Anders Söderström,[4] Mia von Euler,[1,5] Gunnar Öhlén,[6] Ulf Bergman[1,7,8]

Cockcroft MDRD



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]

A

Males

Age 70		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	-27,7	-30,3	-31,8	-32,6	-33,0	-28,5	-25,0	-22,1	-19,7	-17,8	-16,1	-14,7	-13,5	-12,4	-11,5	-10,7	-10,0	-9,3	-8,7	-8,2	-7,7	-7,3	-6,9	-6,5	-6,2	-5,9
1,30	30	-24,2	-27,9	-30,2	-31,6	-32,4	-27,9	-24,3	-21,5	-19,1	-17,1	-15,5	-14,1	-12,9	-11,8	-10,9	-10,1	-9,4	-8,7	-8,2	-7,6	-7,2	-6,8	-6,4	-6,0	-5,7	-5,4
1,39	35	-20,0	-25,0	-28,1	-30,1	-31,4	-26,9	-23,3	-20,5	-18,2	-16,2	-14,6	-13,2	-12,1	-11,0	-10,1	-9,3	-8,6	-8,0	-7,5	-7,0	-6,5	-6,1	-5,7	-5,4	-5,1	-4,8
1,47	40	-15,5	-21,7	-25,6	-28,2	-30,0	-25,6	-22,1	-19,3	-17,0	-15,1	-13,6	-12,2	-11,1	-10,1	-9,2	-8,4	-7,8	-7,2	-6,6	-6,2	-5,7	-5,3	-5,0	-4,7	-4,4	-4,1
1,54	45	-10,5	-18,0	-22,9	-26,1	-28,4	-24,0	-20,6	-17,9	-15,7	-13,9	-12,3	-11,1	-9,9	-9,0	-8,2	-7,4	-6,8	-6,2	-5,7	-5,3	-4,9	-4,5	-4,2	-3,9	-3,6	-3,4
1,62	50	-5,3	-14,1	-19,8	-23,7	-26,5	-22,3	-19,0	-16,3	-14,2	-12,5	-11,0	-9,8	-8,7	-7,8	-7,0	-6,4	-5,8	-5,2	-4,8	-4,3	-4,0	-3,6	-3,3	-3,1	-2,8	-2,6
1,68	55	0,2	-9,9	-16,6	-21,2	-24,4	-20,3	-17,2	-14,6	-12,6	-10,9	-9,6	-8,4	-7,4	-6,6	-5,8	-5,2	-4,6	-4,1	-3,7	-3,3	-3,0	-2,7	-2,4	-2,2	-1,9	-1,7
1,75	60	5,9	-5,5	-13,1	-18,4	-22,2	-18,3	-15,2	-12,8	-10,9	-9,3	-8,0	-6,9	-6,0	-5,2	-4,5	-4,0	-3,5	-3,0	-2,6	-2,3	-2,0	-1,7	-1,4	-1,2	-1,0	-0,8
1,81	65	11,8	-1,0	-9,5	-15,5	-19,8	-16,0	-13,2	-10,9	-9,1	-7,6	-6,4	-5,4	-4,5	-3,8	-3,2	-2,7	-2,2	-1,8	-1,5	-1,2	-0,9	-0,7	-0,4	-0,3	-0,1	0,1
1,86	70	17,8	3,7	-5,8	-12,4	-17,3	-13,7	-11,0	-8,9	-7,2	-5,8	-4,7	-3,8	-3,0	-2,4	-1,8	-1,3	-0,9	-0,6	-0,3	0,0	0,2	0,4	0,6	0,8	0,9	1,0
1,92	75	24,1	8,5	-1,9	-9,2	-14,6	-11,3	-8,8	-6,8	-5,2	-4,0	-3,0	-2,1	-1,4	-0,9	-0,4	0,0	0,4	0,7	0,9	1,2	1,4	1,5	1,7	1,8	1,9	2,0
1,97	80	30,4	13,5	2,1	-6,0	-11,9	-8,8	-6,4	-4,6	-3,2	-2,1	-1,2	-0,4	0,2	0,7	1,1	1,5	1,7	2,0	2,2	2,4	2,5	2,7	2,8	2,9	2,9	3,0
2,02	85	36,8	18,6	6,2	-2,6	-9,1	-6,2	-4,0	-2,4	-1,1	-0,1	0,7	1,3	1,9	2,3	2,6	2,9	3,1	3,3	3,5	3,6	3,7	3,8	3,9	3,9	4,0	4,0
2,07	90	43,4	23,7	10,4	0,9	-6,1	-3,5	-1,5	-0,1	1,0	1,9	2,6	3,1	3,6	3,9	4,2	4,4	4,6	4,7	4,8	4,9	4,9	5,0	5,0	5,0	5,1	5,1
2,12	95	50,1	29,0	14,7	4,5	-3,1	-0,7	1,0	2,3	3,2	4,0	4,5	5,0	5,3	5,6	5,8	5,9	6,0	6,1	6,1	6,2	6,2	6,2	6,2	6,2	6,1	6,1
2,17	100	56,8	34,4	19,0	8,1	-0,1	2,1	3,6	4,7	5,5	6,1	6,5	6,9	7,1	7,3	7,4	7,4	7,5	7,5	7,5	7,5	7,5	7,4	7,4	7,3	7,3	7,2
2,21	105	63,7	39,8	23,5	11,8	3,1	4,9	6,2	7,1	7,8	8,2	8,5	8,8	8,9	9,0	9,0	9,0	9,0	9,0	8,9	8,8	8,7	8,7	8,6	8,5	8,4	8,3
2,26	110	70,6	45,3	28,0	15,5	6,3	7,9	8,9	9,6	10,1	10,4	10,6	10,7	10,7	10,7	10,7	10,6	10,5	10,4	10,3	10,2	10,0	9,9	9,8	9,7	9,5	9,4
2,30	115	77,6	50,8	32,5	19,4	9,5	10,8	11,7	12,2	12,5	12,6	12,7	12,7	12,6	12,5	12,4	12,2	12,1	11,9	11,7	11,5	11,4	11,2	11,0	10,8	10,7	10,5
2,34	120	84,6	56,5	37,2	23,2	12,8	13,8	14,4	14,7	14,9	14,9	14,8	14,7	14,5	14,3	14,1	13,9	13,6	13,4	13,2	12,9	12,7	12,5	12,3	12,1	11,8	11,6
2,38	125	91,7	62,2	41,8	27,2	16,2	16,9	17,2	17,3	17,3	17,1	16,9	16,7	16,4	16,1	15,8	15,5	15,2	14,9	14,6	14,3	14,1	13,8	13,5	13,3	13,0	12,8

Females

Age 70		Length 165																									
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
1,14	25	-23,7	-26,8	-28,7	-23,7	-20,0	-17,2	-14,9	-13,1	-11,6	-10,4	-9,4	-8,5	-7,8	-7,1	-6,5	-6,0	-5,6	-5,2	-4,8	-4,5	-4,2	-4,0	-3,7	-3,5	-3,3	-3,1
1,24	30	-20,7	-24,8	-27,5	-22,5	-18,9	-16,1	-13,9	-12,1	-10,7	-9,5	-8,5	-7,7	-6,9	-6,3	-5,8	-5,3	-4,9	-4,5	-4,1	-3,8	-3,6	-3,3	-3,1	-2,9	-2,7	-2,6
1,32	35	-17,2	-22,4	-25,8	-21,0	-17,4	-14,7	-12,6	-10,9	-9,5	-8,4	-7,4	-6,6	-6,0	-5,4	-4,9	-4,4	-4,0	-3,7	-3,4	-3,1	-2,8	-2,6	-2,4	-2,2	-2,1	-1,9
1,40	40	-13,3	-19,7	-23,8	-19,2	-15,7	-13,1	-11,1	-9,5	-8,2	-7,1	-6,2	-5,5	-4,9	-4,3	-3,9	-3,4	-3,1	-2,8	-2,5	-2,2	-2,0	-1,8	-1,7	-1,5	-1,3	-1,2
1,47	45	-9,1	-16,6	-21,6	-17,1	-13,8	-11,4	-9,5	-8,0	-6,7	-5,8	-4,9	-4,3	-3,7	-3,2	-2,8	-2,4	-2,1	-1,8	-1,6	-1,4	-1,2	-1,0	-0,8	-0,7	-0,6	-0,5
1,53	50	-4,6	-13,3	-19,1	-14,8	-11,8	-9,4	-7,7	-6,3	-5,2	-4,3	-3,5	-2,9	-2,4	-2,0	-1,6	-1,3	-1,0	-0,8	-0,6	-0,4	-0,2	-0,1	0,0	0,1	0,2	0,3
1,60	55	0,0	-9,9	-16,4	-12,4	-9,5	-7,4	-5,8	-4,5	-3,5	-2,7	-2,1	-1,5	-1,1	-0,7	-0,4	-0,1	0,1	0,3	0,4	0,6	0,7	0,8	0,9	1,0	1,1	1,1
1,66	60	4,8	-6,2	-13,6	-9,9	-7,2	-5,3	-3,8	-2,7	-1,8	-1,1	-0,5	-0,1	0,3	0,6	0,8	1,1	1,2	1,4	1,5	1,6	1,7	1,8	1,9	1,9	2,0	2,0
1,72	65	9,8	-2,4	-10,6	-7,2	-4,8	-3,0	-1,7	-0,8	0,0	0,6	1,0	1,4	1,7	2,0	2,1	2,3	2,4	2,5	2,6	2,7	2,7	2,8	2,8	2,8	2,9	2,9
1,77	70	15,0	1,6	-7,5	-4,4	-2,3	-0,7	0,4	1,2	1,8	2,3	2,7	3,0	3,2	3,4	3,5	3,6	3,7	3,7	3,8	3,8	3,8	3,8	3,8	3,8	3,8	3,8
1,82	75	20,3	5,6	-4,3	-1,5	0,4	1,7	2,6	3,3	3,8	4,1	4,4	4,6	4,7	4,8	4,9	4,9	4,9	4,9	4,9	4,9	4,9	4,8	4,8	4,8	4,7	4,7
1,87	80	25,6	9,8	-1,0	1,4	3,0	4,1	4,9	5,4	5,7	5,9	6,1	6,2	6,3	6,3	6,3	6,2	6,2	6,2	6,1	6,0	6,0	5,9	5,8	5,8	5,7	5,6
1,92	85	31,1	14,1	2,4	4,5	5,8	6,6	7,2	7,5	7,7	7,8	7,9	7,9	7,8	7,8	7,7	7,6	7,5	7,4	7,3	7,2	7,1	7,0	6,9	6,8	6,7	6,6
1,97	90	36,7	18,4	5,9	7,6	8,6	9,2	9,5	9,7	9,8	9,7	9,7	9,6	9,4	9,3	9,1	9,0	8,8	8,7	8,5	8,4	8,2	8,1	7,9	7,8	7,7	7,5
2,02	95	42,4	22,9	9,5	10,8	11,5	11,8	11,9	11,9	11,8	11,7	11,5	11,3	11,1	10,8	10,6	10,4	10,2	10,0	9,8	9,6	9,4	9,2	9,0	8,8	8,7	8,5
2,06	100	48,1	27,4	13,1	14,0	14,4	14,5	14,4	14,2	13,9	13,6	13,3	13,0	12,7	12,4	12,1	11,8	11,6	11,3	11,0	10,8	10,5	10,3	10,1	9,9	9,7	9,5
2,10	105	53,9	31,9	16,9	17,3	17,4	17,2	16,9	16,5	16,1	15,6	15,2	14,8	14,4	14,0	13,6	13,3	12,9	12,6	12,3	12,0	11,7	11,5	11,2	10,9	10,7	10,5
2,15	110	59,8	36,6	20,6	20,7	20,4	19,9	19,4	18,8	18,2	17,7	17,1	16,6	16,1	15,6	15,2	14,7	14,3	14,0	13,6	13,2	12,9	12,6	12,3	12,0	11,8	11,5
2,19	115	65,7	41,3	24,4	24,1	23,4	22,7	21,9	21,2	20,4	19,7	19,1	18,4	17,8	17,3	16,7	16,2	15,8	15,3	14,9	14,5	14,1	13,8	13,4	13,1	12,8	12,5
2,23	120	71,7	46,0	28,3	27,5	26,5	25,5	24,5	23,6	22,7	21,8	21,0	20,3	19,6	18,9	18,3	17,7	17,2	16,7	16,2	15,8	15,3	14,9	14,6	14,2	13,9	13,5
2,27	125	77,8	50,8	32,2	31,0	29,7	28,4	27,1	26,0	24,9	23,9	23,0	22,1	21,3	20,6	19,9	19,2	18,6	18,1	17,5	17,0	16,6	16,1	15,7	15,3	14,9	14,6

N=9535 serum creatinine from two different labs, in patients over 60y (hospital and private)

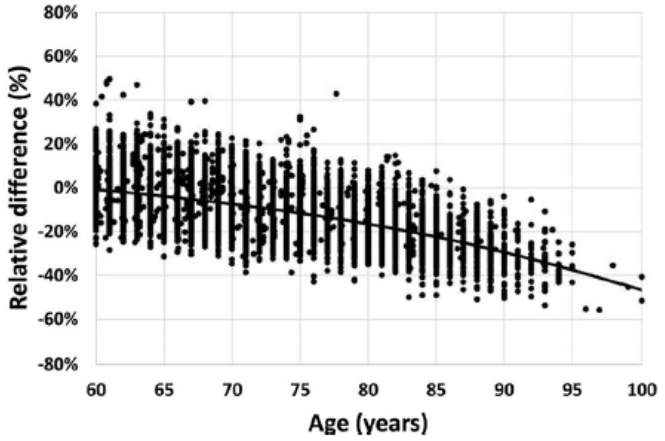


Fig. 4 Effect of age on relative difference between CG and CKD-EPI (clinical data). *CG* Cockcroft–Gault, *CKD-EPI* Chronic Kidney Disease Epidemiology

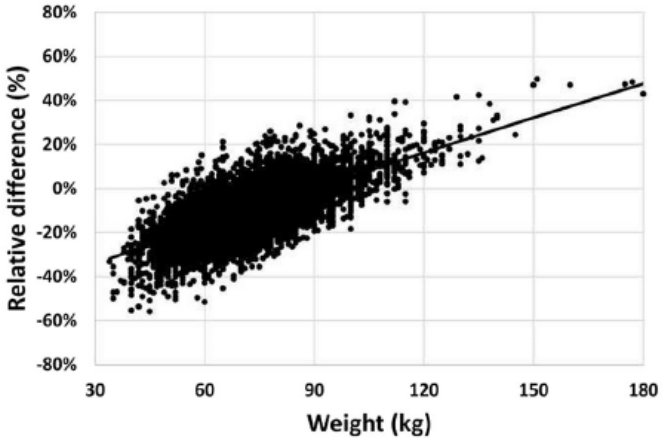
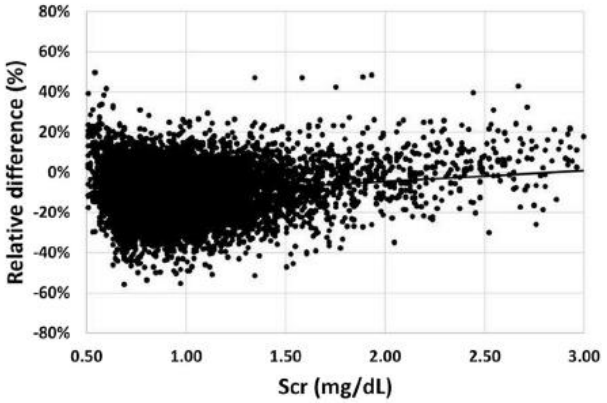


Fig. 5 Effect of weight on relative difference between CG and CKD-EPI (clinical data). *CG* Cockcroft–Gault, *CKD-EPI* Chronic Kidney Disease Epidemiology



Conclusions

- Several studies illustrate the discrepancies between Cockcroft and MDRD/CKDEPI
- …and between these equations and measured GFR

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Performance of formulae based estimates of glomerular filtration rate for carboplatin dosing in stage 1 seminoma

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Available online 17 January 2014

Calvert: Target AUC x (GFR + 25)
N=115
GFR = CrEDTA
Target AUC: 7 mg/ml/min
Same dose = +/- 10%

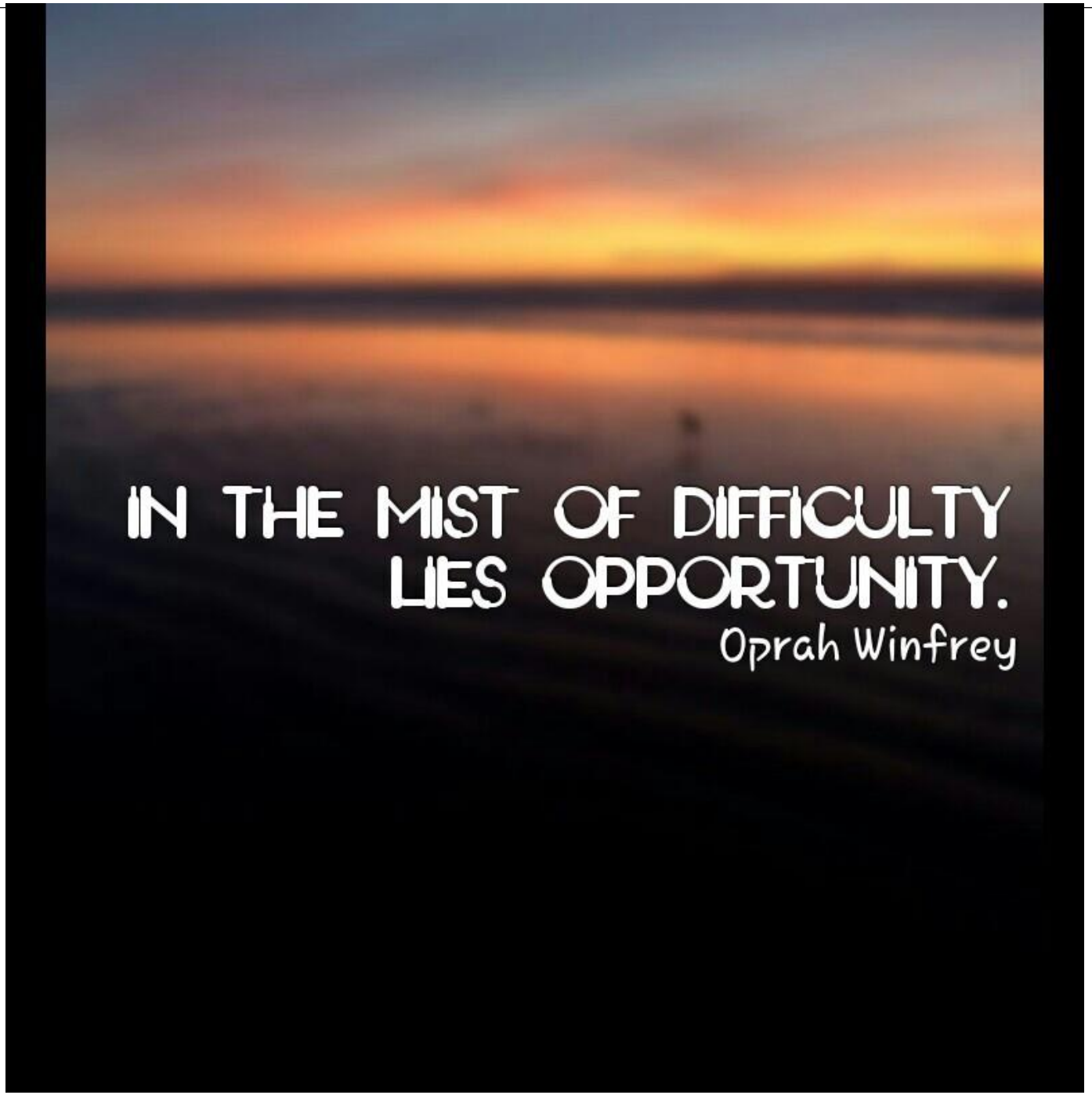
Comparison of carboplatin doses calculated using eGFR formulae versus 51Cr-EDTA, demonstrating the number of patients who would receive the same, higher or lower dose of carboplatin using a 10% and 20% margin of acceptability.

Estimating formula	Same dose *n* (%)		Overdosed *n* (%)		Underdosed *n* (%)	
	10% error	20% error	10% error	20% error	10% error	20% error
Cockcroft–Gault $(CG)_{ABW}$ (ml/min)	45 (40.5)	73 (66.3)	61 (55.0)	37 (33.4)	5 (4.5)	1 (0.9)
CG_{ABW}/1.73 m^2 (ml/min/1.73 m^2)	46 (41.4)	87 (78.4)	28 (25.2)	12 (9.5)	37 (33.3)	12 (9.5)
CG_{IBW} (ml/min)	49 (44.5)	74 (66.7)	42 (37.8)	23 (20.7)	20 (18.0)	14 (12.6)
CG_{IBW}/1.73 m^2 (ml/min/1.73 m^2)	19 (17.1)	53 (47.7)	15 (13.5)	8 (6.6)	77 (69.4)	50 (45)
Management of Diet in Renal Disease (MDRD) (ml/min/1.73 m^2)	27 (24.1)	61 (54.0)	10 (8.9)	5 (4.4)	75 (67.0)	48 (42.5)
Chronic Kidney Disease-Epidemiology $(CKD\text{-}EPI)_{UNCORR}$ (ml/min)	51 (45.9)	96 (86.4)	45 (40.5)	12 (10.8)	15 (13.5)	4 (3.6)
CKD-EPI (ml/min/1.73 m^2)	44 (39.6)	80 (72.0)	11 (10.0)	7 (6.3)	60 (54.0)	24 (21.6)

Conclusions

- Several studies illustrate the discrepancies between Cockcroft and MDRD/CKDEPI
- …and between these equations and measured GFR
- Many methodological limitations
- **NO prospective trial having compared the impact of using measured GFR, Cockcroft or CKDEPI in the efficacy/safety profile (carboplatin, aminosides etc)**

So, yes…we are still in the mist


IN THE MIST OF DIFFICULTY
LIES OPPORTUNITY.
Oprah Winfrey

No improvement? Yes, A great one…

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

Adopted by CHMP	17 December 2015
Date for coming into effect	1 July 2016

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. This may be particularly important for drugs that are expected to be affected by renal impairment to such an extent that dose adjustments will be needed and where it, e.g. due to a relatively narrow therapeutic index, is critical that dose adjustments are made at a certain GFR cut-off. In other cases, e.g. in a reduced-design study of a hepatically eliminated drug or if the dose can be individually titrated based on clinical monitoring, it may be less critical to have an accurate measure of GFR in the pharmacokinetic study, and the use of estimation methods may be sufficient.

As discussed in the Introduction, renal elimination capacity is related to absolute GFR. When presenting the results of the pharmacokinetic study and developing dose recommendations (see section 6.2), GFR should therefore be expressed as ml/min. If a formula providing BSA-normalised GFR (ml/min/1.73 m^2) has been used to estimate renal function in study subjects, this should be recalculated to the absolute GFR in ml/min in each individual.

If assessment of renal function is based on creatinine concentration in plasma, creatinine should be measured with a method, preferably an enzymatic method, with results that are traceable to a reference measurement procedure.

Some (personal) advices…
but always a personalized approach

- Nephrotoxic agent with narrow therapeutic window and/or extreme age or body size

  I still recommend measuring GFR (iohexol plasma clearance)

- Cystatin C: maybe… Frazee E, Am J Kidney Dis, 2017, p658

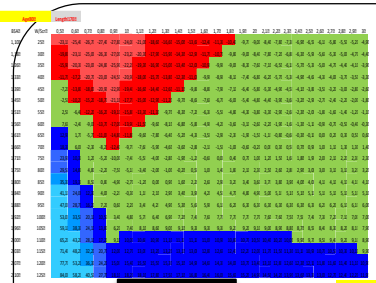
- I would recommend to calculate both Cockcroft and CKDEPI (desindexed)

- If no significant difference => dosage adaptation if needed

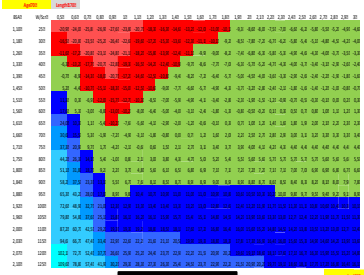
- If differences: consider THE PATIENT (age, body size, frailty) and the DRUG (balance between efficacy and safety)

- CKD is always a good reason for drug monitoring (direct or indirect)

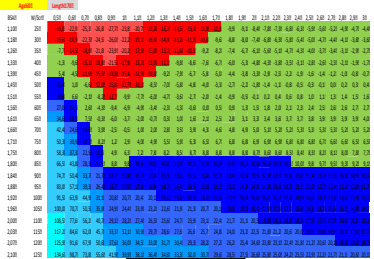
Thank you for your attention



80 y



70 y



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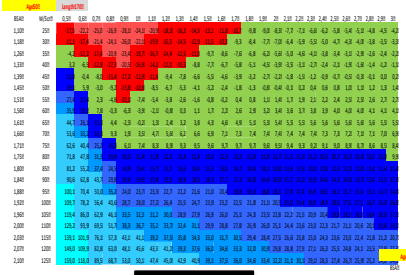
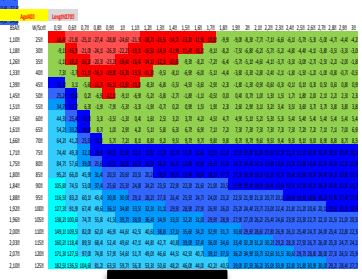


50 y



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