Evaluation of Assumptions in the Clinical Use of the Cockcroft-Gault Equation

KT. Baron, AK. Birnbaum, JC. Cloyd, J. St. Peter, and RC. Brundage
Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis, MN

Is the Cockcroft-Gault Equation Broken?

The Cockcroft-Gault (CG) equation[1] is the most widely used method in US clinical settings for estimating creatinine clearance (CLCR). Clinicians commonly make adjustments to CG to improve estimation, such as using an alternate body size metric (e.g. ideal body weight) and rounding serum creatinine (Scr) up to 1 mg% in elderly subjects. A 15% reduction in CLCR is also assumed in female subjects. This study aims to evaluate the appropriateness of these adjustments.

Ways We "Fix" Cockcroft-Gault

- Plug in "better" body size measure
  - Ideal Body Weight
  - Lean Body Weight
  - Dosing Weight
- Round serum creatinine in elderly patients
- Multiply by 0.85 if female

METHODS

- CLCR measured from 24-hour urine collections
- 748 measurements in 319 ambulatory subjects
- Models fit using BRugs interface to OpenBUGS (3.0.3)
  - Uninformative prior distributions except where noted
- Predictive performance of CG evaluated after plugging in different body size measures
- Body size measures:
  - WGT = Actual Body Weight
  - IBW = Ideal Body Weight
  - LW = Lean Body Weight[2]
  - DW = Dosing Weight (IBW+0.4*[WGT-IBW])
- 95% confidence intervals around predictive performance measures determined by non-parametric bootstrap
- Predictive Performance (SIZE=WGT,IBW,LW, or DW):

$$CLCR_{TRUE} = \frac{RATE_{EXCR}}{Scr} = \frac{\dot{V} \times Ucr}{Scr}$$

$$CLCR_{EST} = \frac{(140 - AGE) \times SIZE \times 0.85^{SEX}}{Scr \times 72}$$

$$pe = 100 \times \frac{(CLCR_{EST} - CLCR_{TRUE})}{CLCR_{TRUE}}$$

Patient Characteristics (N=321)	
Weight (kg)	75.6 (16.7)
Age (years)	45.5 (17.3)
Female	34%
BSA (m^2)	1.88 (0.22)
BMI	26 (5)
Collection Characteristics (N=748)	
CLCR (ml/min)	76 (37)
Duration (hr)	24 (4)
Duration > 20 hr	91%
Serum Creat (mg%)	1.1 (0.76)

median (sd)

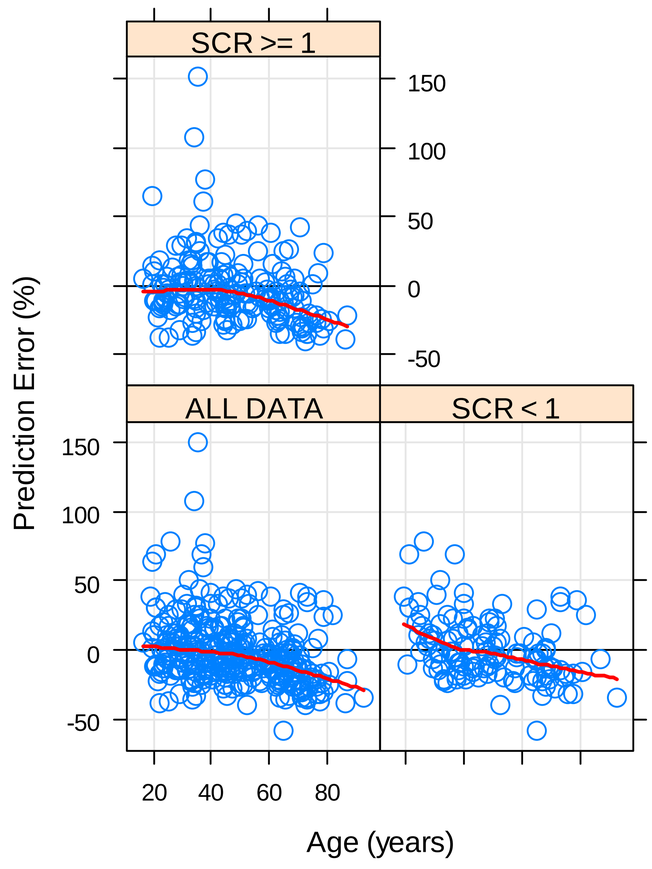
CONCLUSIONS

- Always plugging in IBW in place of WGT made the CG predictions worse
- WGT gave the best overall predictions, even in obese subjects
- Unable to model a "better" body size metric into CG
- Rounding Scr to 1 mg% in elderly decreases the CG predictive performance
- Reducing CLCR by 15% in females seems reasonable

REFERENCES

1. *Cockcroft DW, Gault MH (1976) Nephron 16: 31-41*
2. *Janmahasatian et. al. (2005) Clin Pharmacokinet 44(10): 1051-65*
3. *Salazar DE, Corcoran GB (1988) Am J Med 84: 1053–1060*

No Evidence that CG Over-Predicts in Elderly with Scr < 1



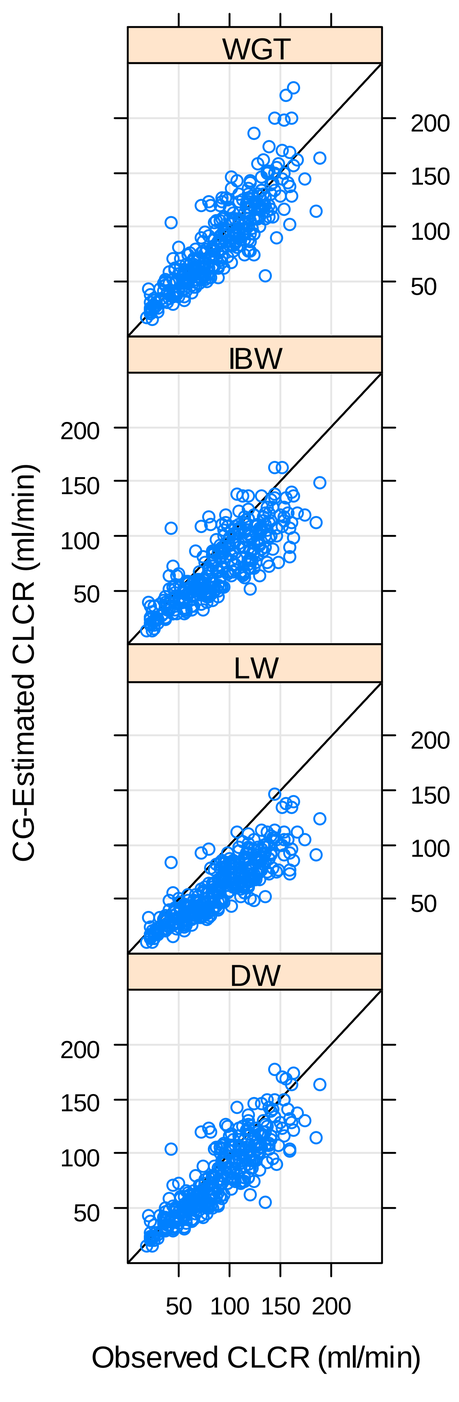
Variance Component Estimates in Model for CLCR

$$CLCR_{ij} \sim N(\theta_{ij}, \sigma_e^2) \qquad b_i \sim N(0, \sigma_b^2)$$

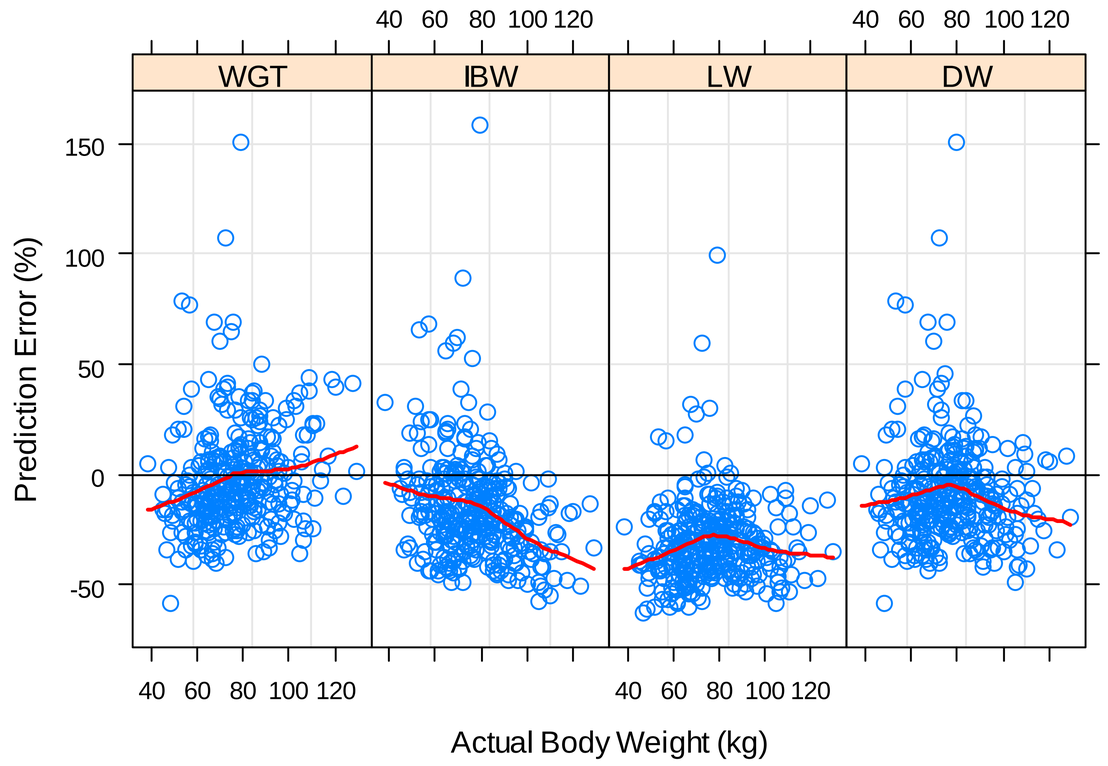
$$\theta_{ij} = \frac{(\beta_1 - AGE_{ij}) \times WGT_{ij}}{\beta_2 \times Scr_{ij}} \times (1 - \beta_3) \times e^{bi}$$

Parameter		Estimate	95% CI
σ_e	IOV+RUV	12.5 (ml/min)	[11.7 , 13.3]
σ_b	BSV	15%	[13 , 16]

CG Predictions vs Observations



CG Predictions Are Worse at Higher Actual Weights When Ideal, Lean, or Dosing Weight is Used



Summary: Median Prediction Error By Actual Body Weight (kg)	ALL	<60	60-80	80-100	>100
WGT	**-5.8** [-8.8 , -3.3]	**-12.8** [-16.9 , -8.2]	**-7.2** [-10.9 , -4.4]	**-0.8** [-4.94 , 4.35]	**2.03** [-8.6 , 20.8]
IBW	**-18.5** [-20.5 , -16.6]	**-8.29** [-17.2 , -3.6]	**-16.8** [-19.8 , -12.5]	**-21.9** [-24.8 , -18.7]	**-35.1** [-41.6 , -30.3]
LW	**-33.5** [-34.8 , -31.2]	**-39.1** [-42.2 , -34.9]	**-31.9** [-34.3 , -29.5]	**-30.2** [-33.7 , -26.9]	**-37.8** [-41.6 , -30.3]
DW	**-11.6** [-14.2 , -9.1]	**-13.9** [-17.2 , -7.4]	**-10.9** [-14.5 , -6.0]	**-9.6** [-14.2 , -5.3]	**-19.4** [-25.2 , -10.4]
SC*	**-2.7** [-5.8 , 0.33]	**3.9** [-3.9 , 7.7]	**-2.4** [-7.3 , 2.9]	**-3.6** [-9.1 , 0.56]	**-13.3** [-18.5 , -0.34]

** Salazar Corcoran equation for estimating CLCR in morbidly obese patients[3]*

Re-estimating CG model parameters

$$\frac{EXCR_{ij}}{WGT_{ij}} \sim N(\theta_{ij}, \sigma_e^2) \qquad b_i \sim N(0, \sigma_b^2)$$

$$\theta_{ij} = (\beta_1 + \beta_2 \times AGE_{ij}) \times (1 - \beta_3)^{SEXi} \times e^{bi}$$

	Current Estimate	95% CI	CG Estimate	95% CI
β_1	26.1	[24.9 , 27.5]	28	[26.3 , 29.2]
β_2	-0.13	[-0.16 , -0.11]	-0.2	[-0.22 , -0.17]
β_3	0.19	[0.15 , 0.23]	0.15*	NA

Modeling A New Body Size for CG

$$EXCR_{ij} \sim N(\theta_{ij}, \sigma_e^2) \qquad b_i \sim N(0, \sigma_b^2)$$

$$\theta_{ij} = \frac{1}{72} \times (140 - AGE_{ij}) \times SIZE_{ij} \times e^{bi}$$

$$SIZE_{ij} = IBW_{ij} + (\beta_1^{WGT_{ij} < \beta_3} \times \beta_2^{WGT_{ij} >= \beta_3}) \times (WGT_{ij} - IBW_{ij})$$

	MODEL 1	MODEL 2	MODEL 3 *
β_1	1 [FIXED]	1 [FIXED]	1.0 [0.87 , 1.2]
β_2	1 [FIXED]	0.95 [0.84 , 1.1]	0.89 [0.72 , 1.0]
β_3	0 [FIXED]	0 [FIXED]	87 [71 , 99]
DIC	6278	6278	6277

** Prior β**3** is uniform(70,130)*