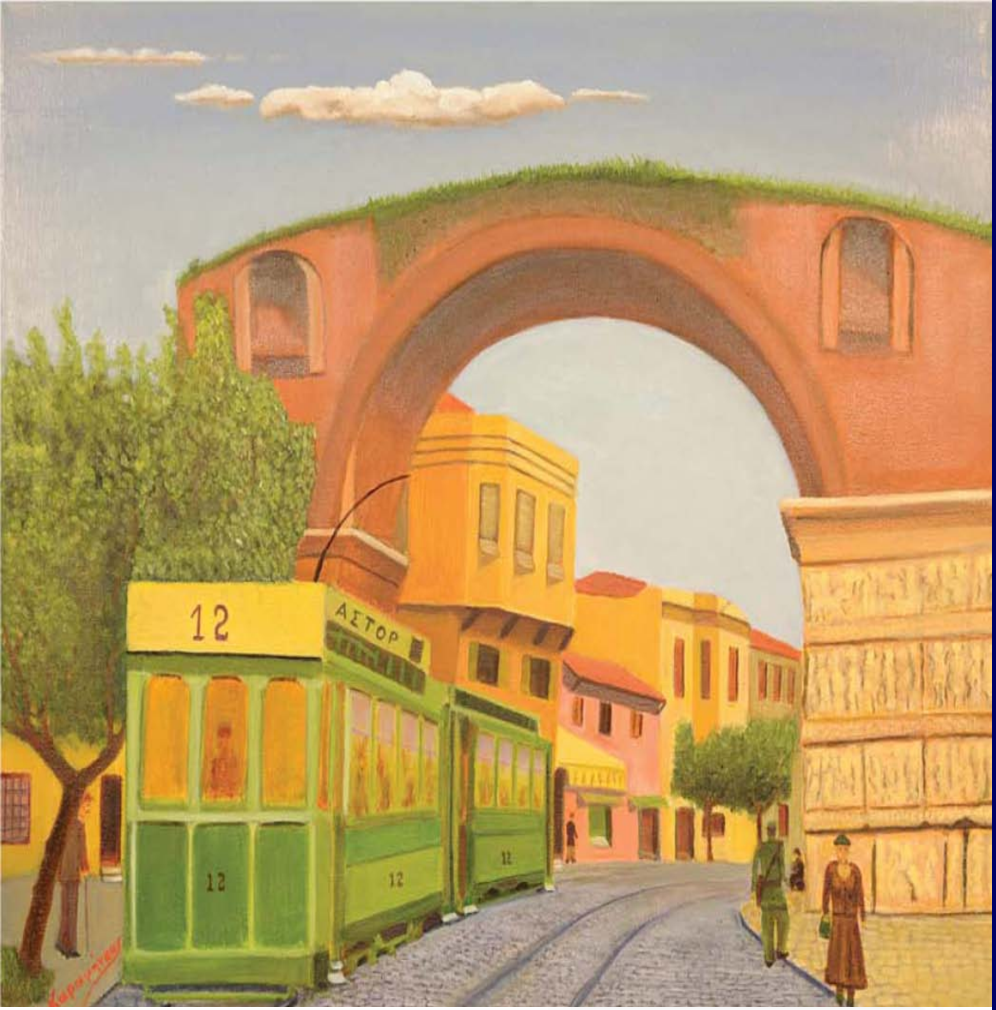


Δ.Ε.Β.Ε. Διαβητολογική Εταιρεία Βορείου Ελλάδος

24ο ΕΤΗΣΙΟ ΣΥΝΕΔΡΙΟ

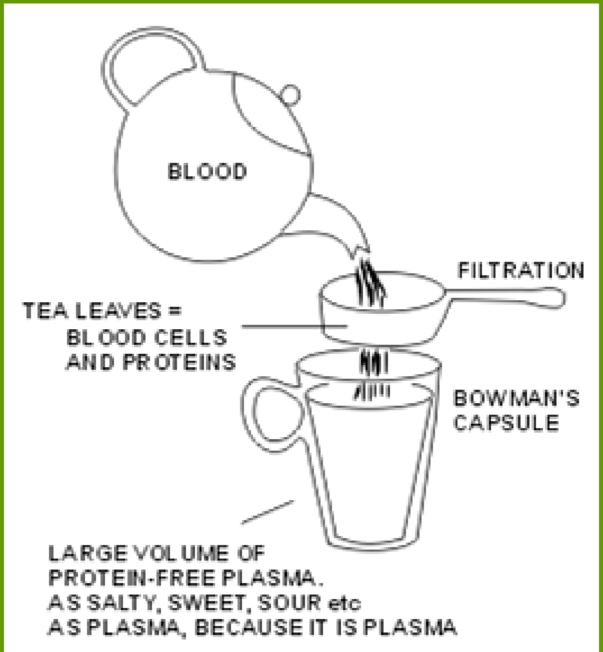
25-27 ΝΟΕΜΒΡΙΟΥ 2010 ΘΕΣΣΑΛΟΝΙΚΗ

Ξενοδοχείο Makedonia Palace

Σακχαρώδης Διαβήτης & χρόνια νεφρική νόσος

Ραδιοϊσοτοπική εκτίμηση της νεφρικής λειτουργίας

Γ. Αρσος
ΓΝΘ Ιπποκράτειο



GFR : Glomerular filtration rate

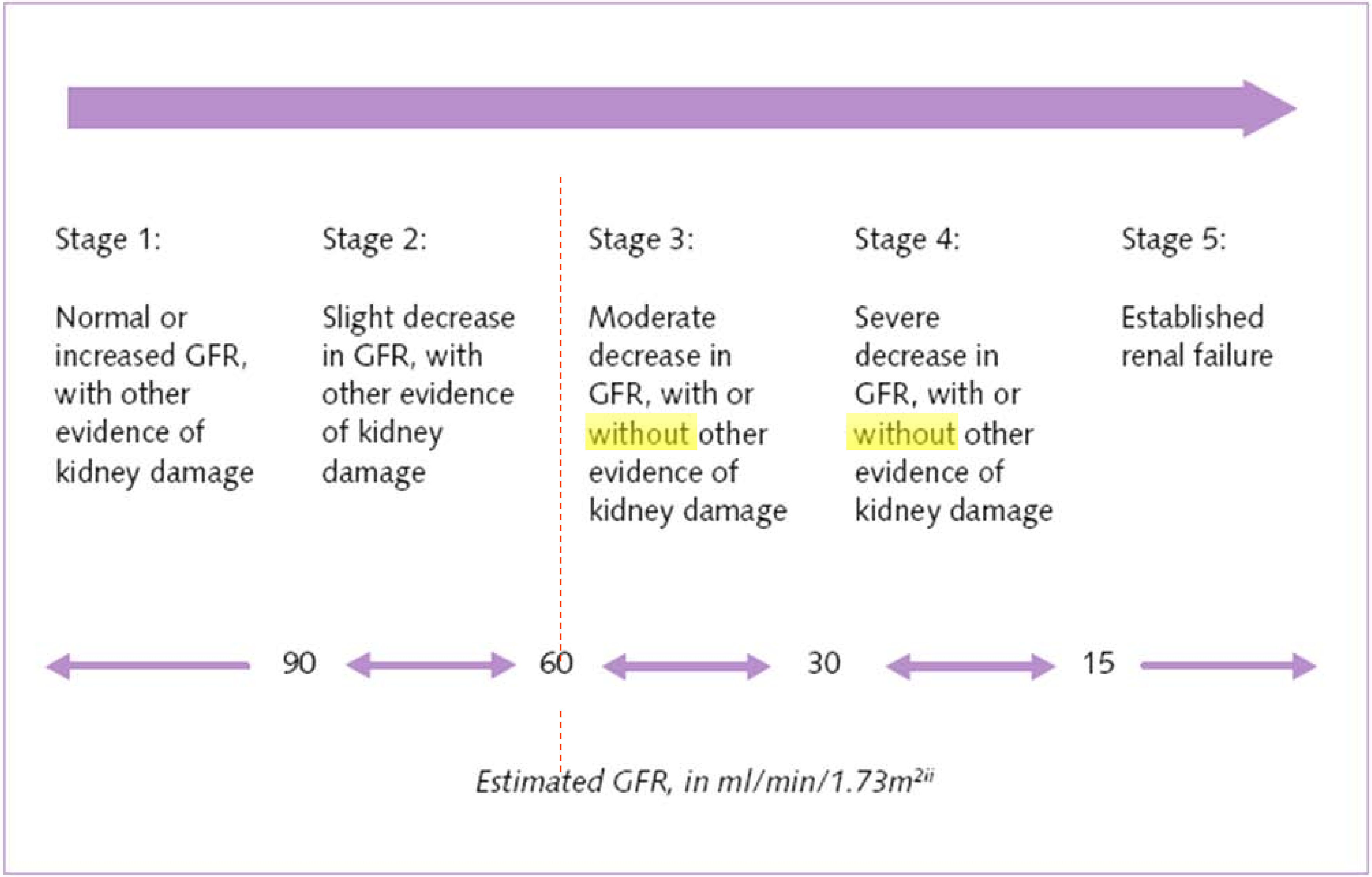
"GFR is widely accepted as *the best index* of kidney function in health and disease,

and

***accurate values* are needed for optimal decision making in many clinical settings"**

Stevens LA & Levey AS, *JASN 2009*

CKD staging (NKF – K/DOQI 1997)



Clinical conditions where assessment of GFR is important

Clinical Decisions	Current Level of GFR	Change in Level of GFR
Diagnosis	Detection of CKD	Detection of AKI
	Evaluation for kidney donation	Detection of CKD progression
Prognosis	Risk of CKD complications	Risk for kidney failure
	Risk for CVD	
	Risk for mortality	
Treatment	Dose and monitoring for medications cleared by the kidney	Treatment of AKI
	Determine safety of diagnostic tests or procedures	Monitoring drug toxicity
	Referral to nephrologists	
	Referral for kidney transplantation	
	Placement of dialysis access	

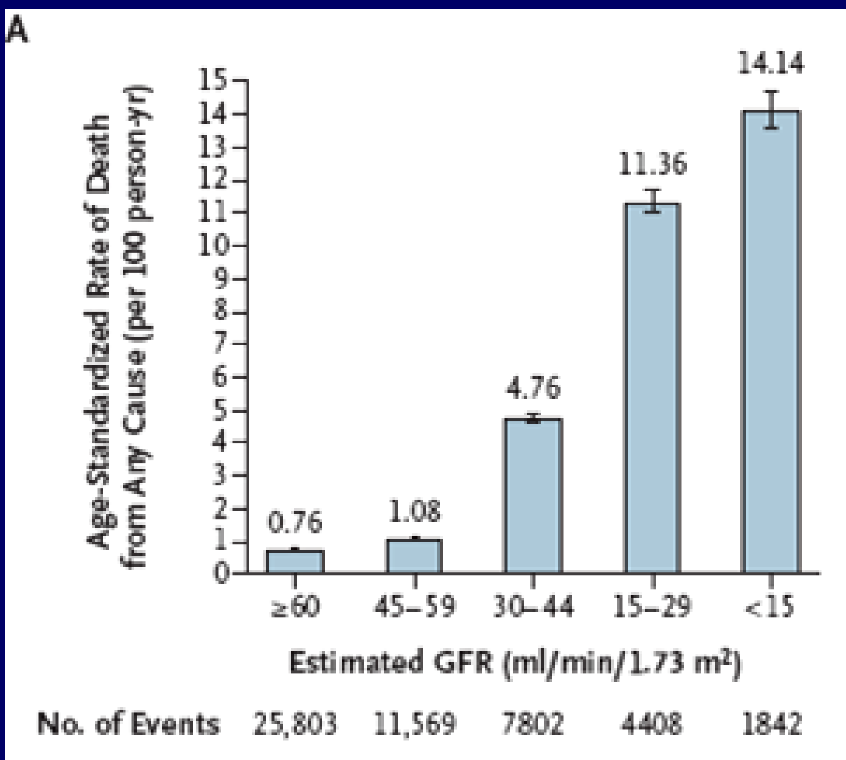
Stevens LA & Levey AS, *JASN 2009*

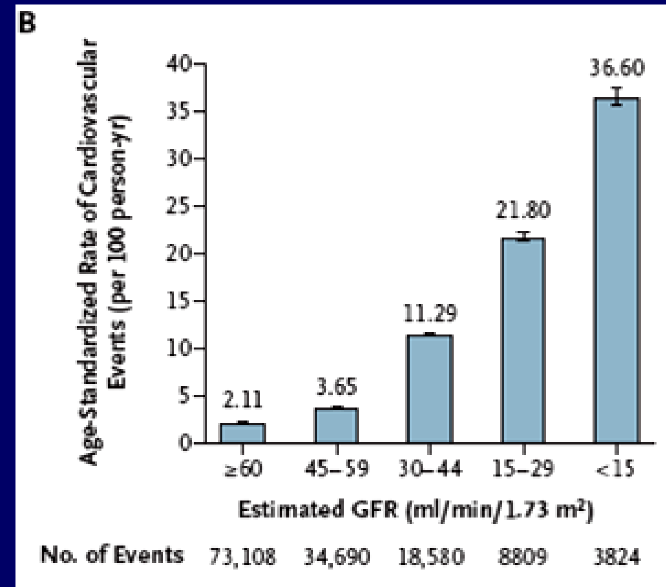
The NEW ENGLAND JOURNAL of MEDICINE

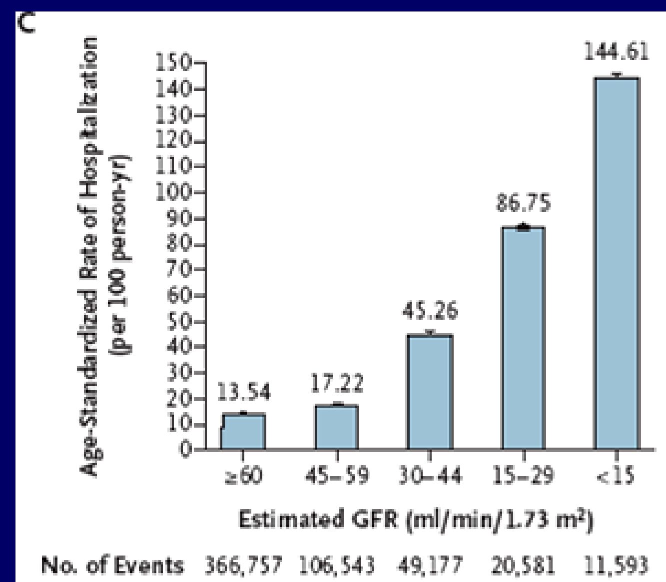
ORIGINAL ARTICLE

Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization

Alan S. Go, M.D., Glenn M. Chertow, M.D., M.P.H., Dongjie Fan, M.S.P.H., Charles E. McCulloch, Ph.D., and Chi-yuan Hsu, M.D.

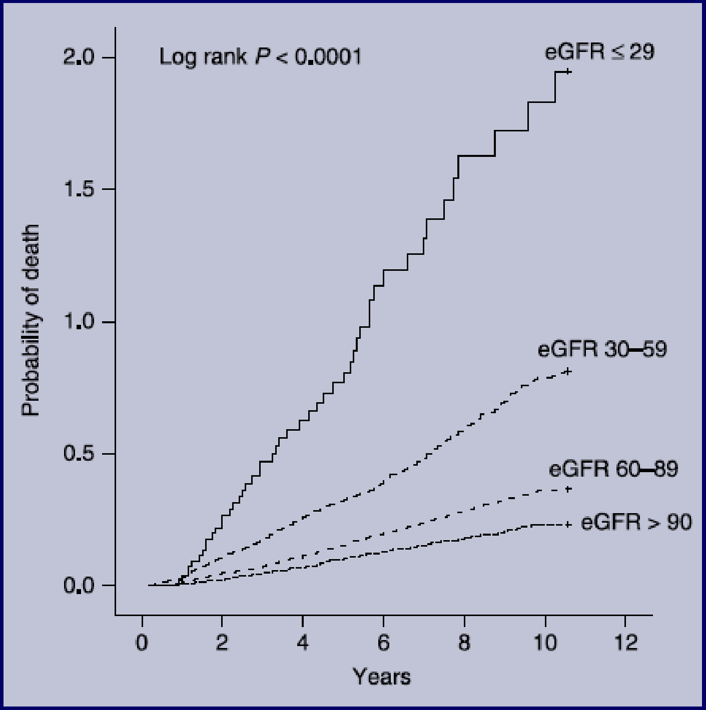






Go AS et al, *N Engl J Med 2004*

All-cause and cardiovascular mortality in diabetic subjects increases significantly with reduced estimated glomerular filtration rate (eGFR): 10 years' data from the South Tees Diabetes Mortality study



	Estimated GFR at baseline (ml/min/1.73 m^2)			
	Stage 1 (> 90)	Stage 2 (60–89)	Stage 3 (30–59)	Stage 4 and 5 combined (≤ 29)
IHD mortality†				
Adjusted HR (95% CI)	1*	1.53 (1.04, 2.26)	3.61 (2.44, 5.32)	8.08 (4.26, 15.34)
Cerebrovascular disease mortality‡				
Adjusted HR (95% CI)	1*	1.08 (0.58, 2.01)	1.86 (0.97, 3.59)	5.94 (1.88, 18.78)

Nag S et al, *Diabetic Medicine 2007*

Urea

Plasma / Serum Creatinine levels

Cystatin C

Creatinine clearance

Mean of Urea + Creatinine Clearance

endo

Inulin Clearance ex 

Radiotracer clearance

(^{51}Cr-EDTA, ^{99m}Tc-DTPA, ^{125}I-Iothalamate)

Non-radioactive contrast agent clearance (Iohexol)

exo

Imaging methods (γ-camera : Gates, MRI)

Predicting Equations

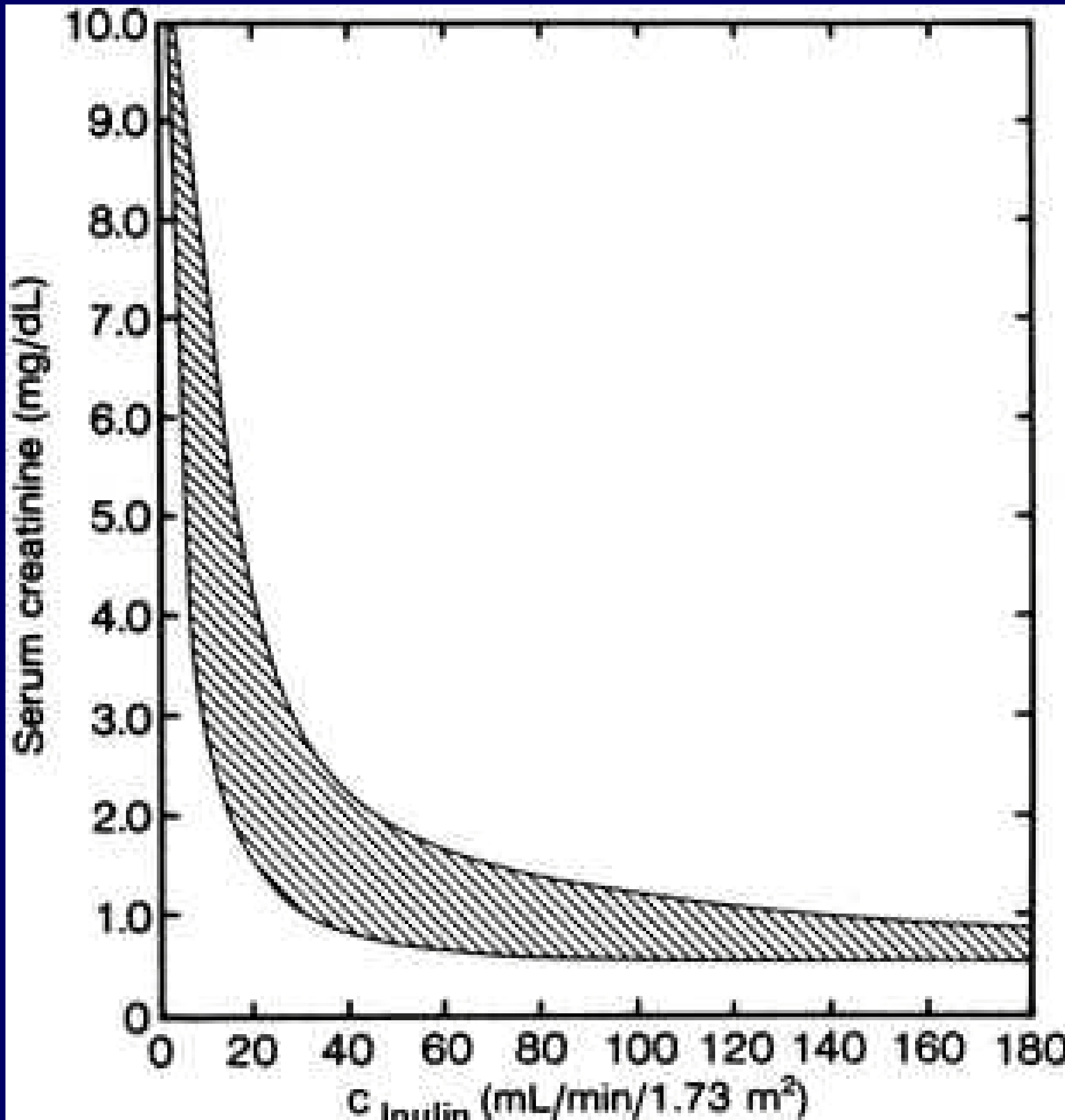
Creatinine

The closest to an ideal endogenous GRR tracer

Almost exclusively a product of the metabolism of creatine and phosphocreatine in skeletal muscle

In stable renal function : Cr levels usually constant, daily variability ≈ 8%

Renal handling : freely filtered
not reabsorbed
up to 15% actively secreted
by the tubules*



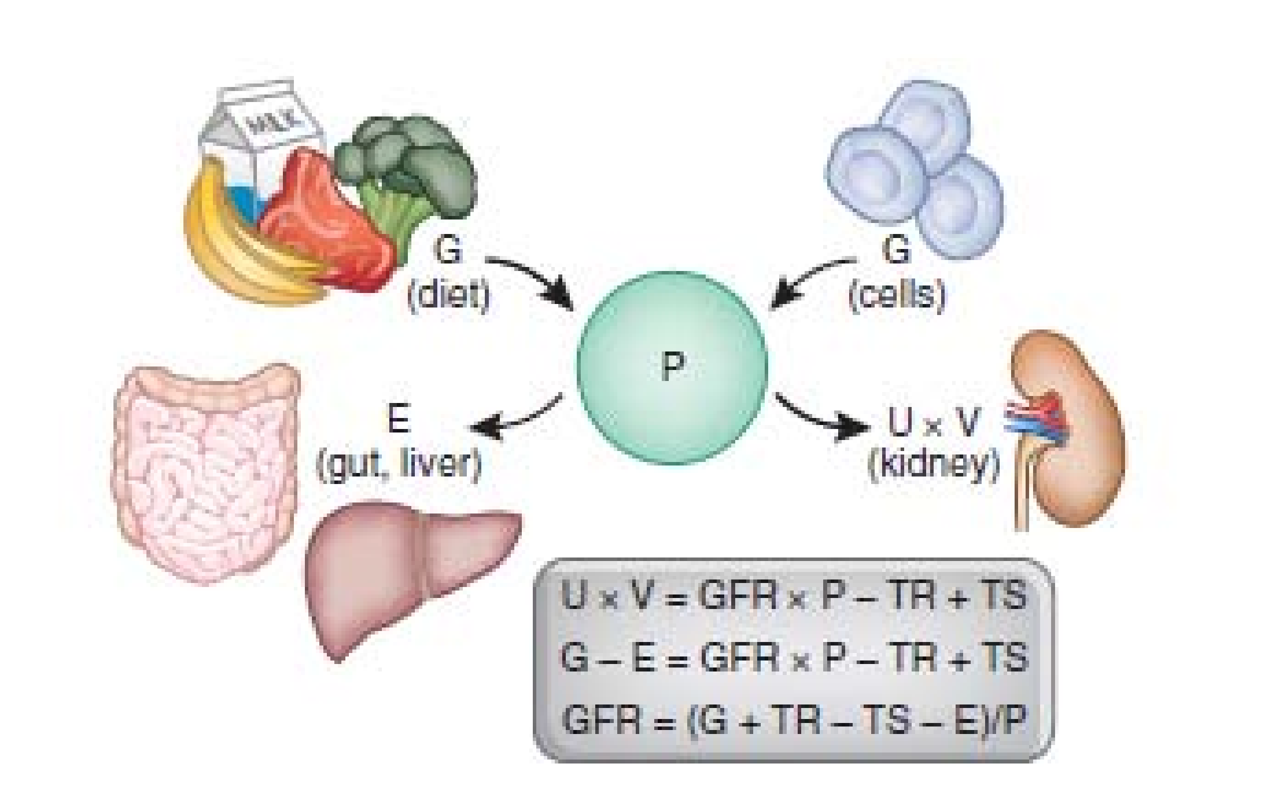
R = 0.86, P < 0.0001

* $[Cr]_{pl}$ at normal GFR greatly varies between individuals

* Cr production may not remain constant

[redacted]

Determinants of the serum level of endogenous filtration markers



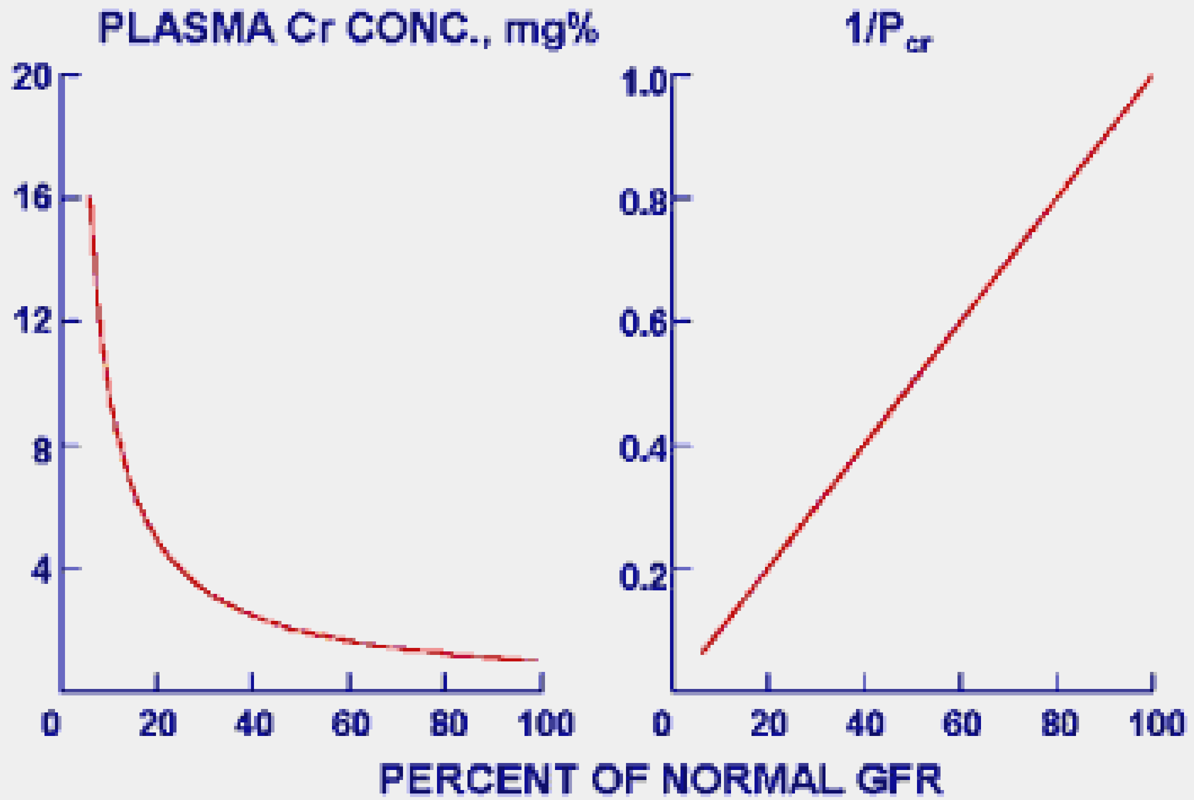
Stevens LA & Levey AS. JASN, 2009

Non-GFR determinants of creatinine

Factor	Effect on Serum Creatinine Independent of GFR		Accounted for in GFR Estimating Equations
	Direction	Mechanism	
Age	Decrease	Generation	Yes
Female gender	Decrease	Generation	Yes
Race		Generation	
African American	Increase		Yes
Hispanics	Decrease		No
Asian	Increase/Decrease		Yes
Body habitus		Generation	
Muscular	Increase		No
Amputation	Decrease		No
Obesity	No change		No
Chronic illness		Generation	
Malnutrition, inflammation, deconditioning	Decrease		No
Neuromuscular diseases	Decrease		No
Liver disease	Decrease		No
HIV	Decrease?		No
Diet		Generation	
Vegetarian diet	Decrease		No
Ingestion of cooked meat	Increase		No
Medications			
Cimetidine	Increase	Tubular secretion	No
Trimethroprim	Increase	Tubular secretion	No
Antibiotics	Increase	Extrarenal elimination	No

Stevens LA & Levey AS, *JASN 2009*

RELATIONSHIP OF P_{CR} AND I/P_{CR} TO GFR



The curvilinear relationship between P_{cr} and GFR makes it difficult to discern the degree of change in the GFR of a patient but calculation of I/P_{cr} makes it much easier.

For example, the degree of fall in GFR necessary to produce a rise in P_{cr} from 1 to 1.5 mg%is difficult to assess in graph A but a calculation of 1/P_{cr} indicates that GFR has fallen to 67% of normal (graph B).

- **GFR is the best overall index of kidney function**
- **Gold-standard GFR techniques are not practical for the entire CKD population**
- **Estimates of GFR are better/more practical than creatinine clearance**
- **Estimates of GFR are more sensitive for CKD than creatinine alone**

estimated GFR :
how to construct a GFR prediction equation

PCr (±U) or Cys C or both

+

age

+

sex

+

ethnicity

±

body size

⇄

GFR measured with an exogenus marker

Cockroft and Gault equation

Estimated creatinine clearance (Cl_{Cr}) = $\frac{(140\text{-age}) \times \text{weight} \times 1.2}{SCr}$ x (0.85 if female)

where age is expressed in years, SCr in µmol/l, and weight in kg[10]

6-variable MDRD[15]

$170 \times (S_{Cr}/88.4)^{-0.999} \times \text{age}^{-0.176} \times (SU/0.357)^{-0.170} \times (SAlb \times 10)^{+0.318} \times (0.762 \text{ if female}) \times (1.180 \text{ if black})$

where S_{Cr} = serum creatinine in µmol/l, SU = serum urea in mmol/l, SAlb = serum albumin in g/l, and age is expressed in years

4-variable MDRD[16]

$186.3 \times (S_{Cr}/88.4)^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$

where S_{Cr} = serum creatinine in µmol/l, and age is expressed in years

Modified 4-variable MDRD (traceable by isotope dilution mass spectrometry)[19]

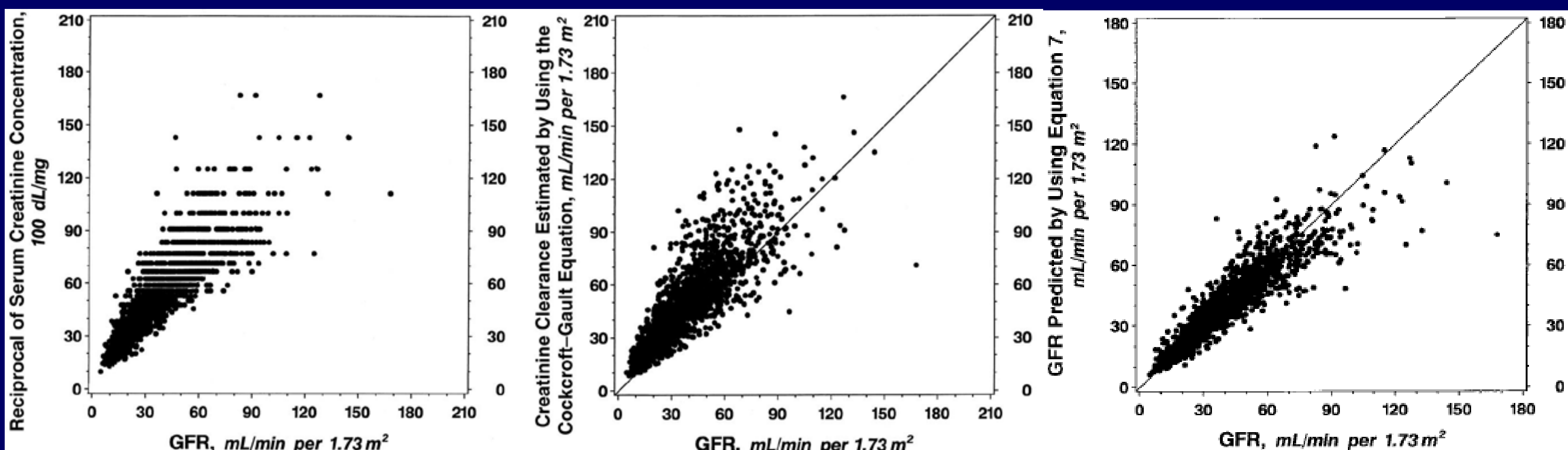
$F \times 175 \times (S_{Cr}/88.4)^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$

where F = correction factor, S_{Cr} = serum creatinine in µmol/l, and age is expressed in years

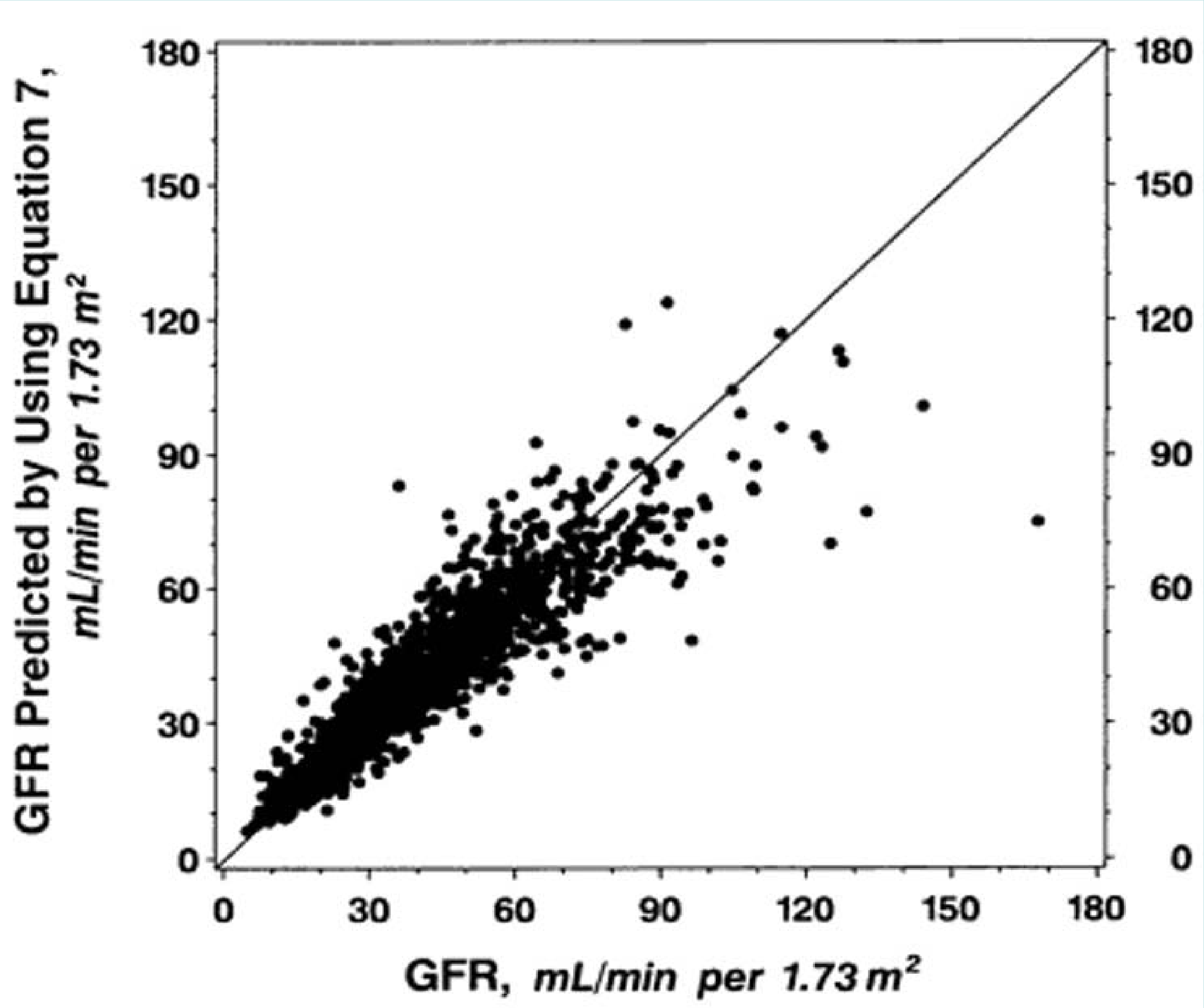
16 March 1999 Volume 130 Number 6

Annals of Internal Medicine

A More Accurate Method To Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation



Levey AS et al . *Ann Intern Med, 1999*

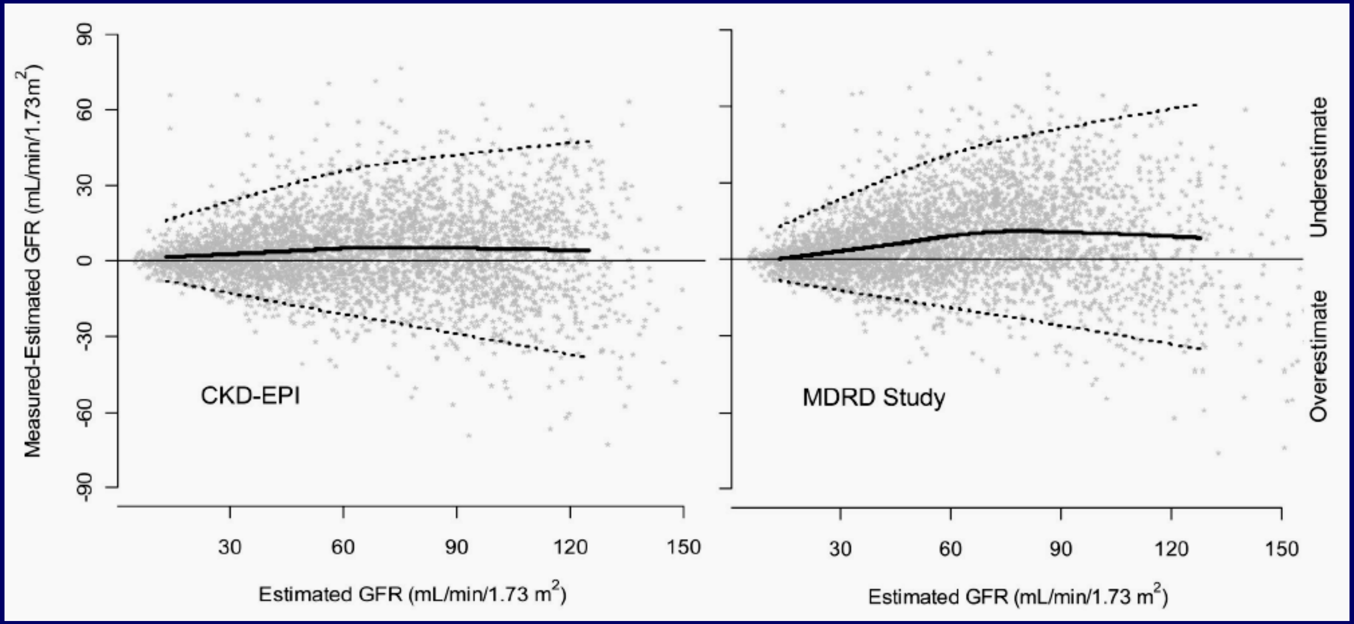


> ± 30% scatter using results from one instrument

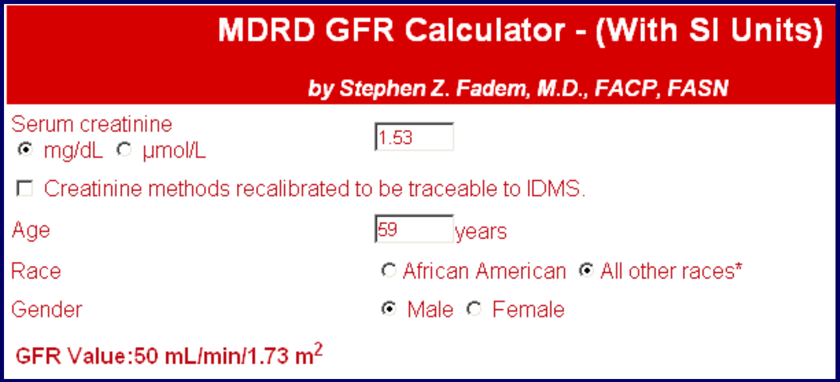
Levey AS et al . *Ann Intern Med, 1999*

A New Equation to Estimate Glomerular Filtration Rate

Race and Sex	Serum Creatinine 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)	$GFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$



Levey AS et al. *Ann Intern Med*, *2009*


MDRD GFR Calculator - (With SI Units)

by Stephen Z. Fadem, M.D., FACP, FASN

Serum creatinine 1.53
(•) mg/dL ( ) µmol/L

☐ Creatinine methods recalibrated to be traceable to IDMS.

Age 59 years

Race ( ) African American (•) All other races*

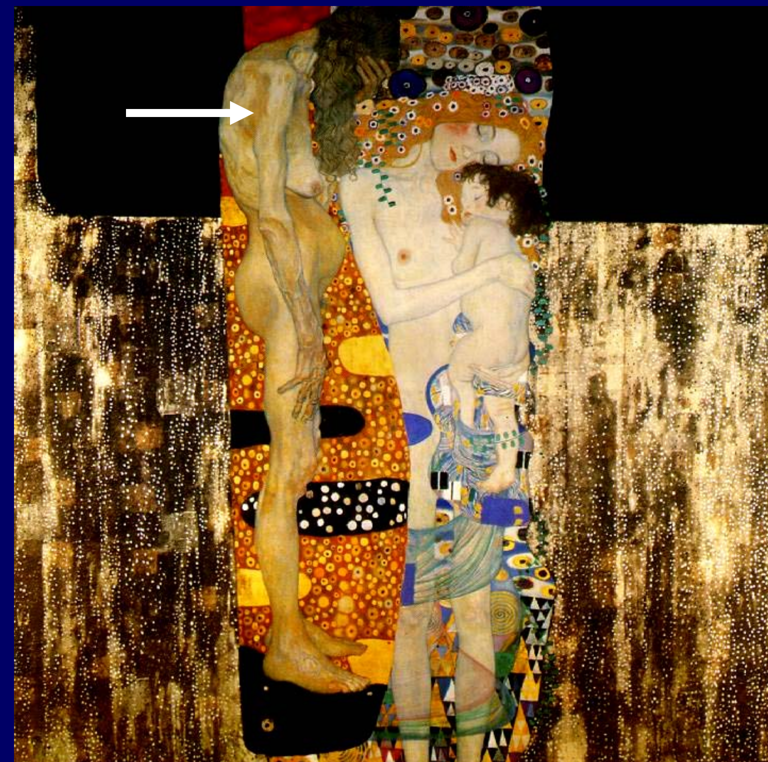
Gender (•) Male ( ) Female

GFR Value:50 mL/min/1.73 m^2

[redacted]

^{51}Cr EDTA GFR = 57 ml/min/1,73 m^2

Role of age, sex, ethnicity, muscularity on *PCr* levels & eGFR



MDRD GFR Calculator - (With SI Units)

by Stephen Z. Fadem, M.D., FACP, FASN

Serum creatinine: 1.2
◉ mg/dL ○ µmol/L

☐ Creatinine methods recalibrated to be traceable to IDMS.

Age: 18 years

Race: ◉ African American ○ All other races*

Gender: ◉ Male ○ Female

GFR Value:102 mL/min/1.73 m^2

MDRD GFR Calculator - (With SI Units)

by Stephen Z. Fadem, M.D., FACP, FASN

Serum creatinine: 1.2
◉ mg/dL ○ µmol/L

☐ Creatinine methods recalibrated to be traceable to IDMS.

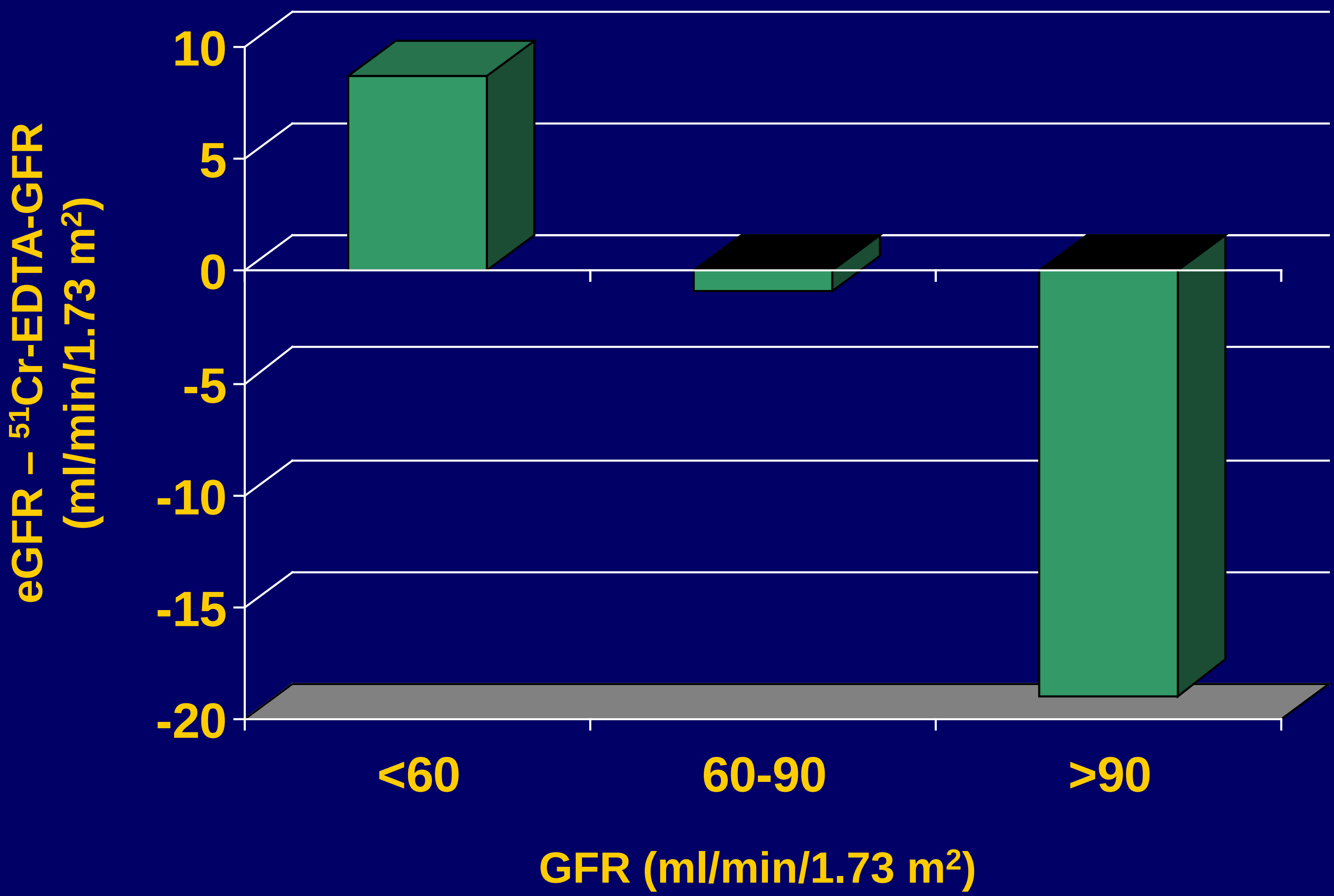
Age: 80 years

Race: ○ African American ◉ All other races*

Gender: ○ Male ◉ Female

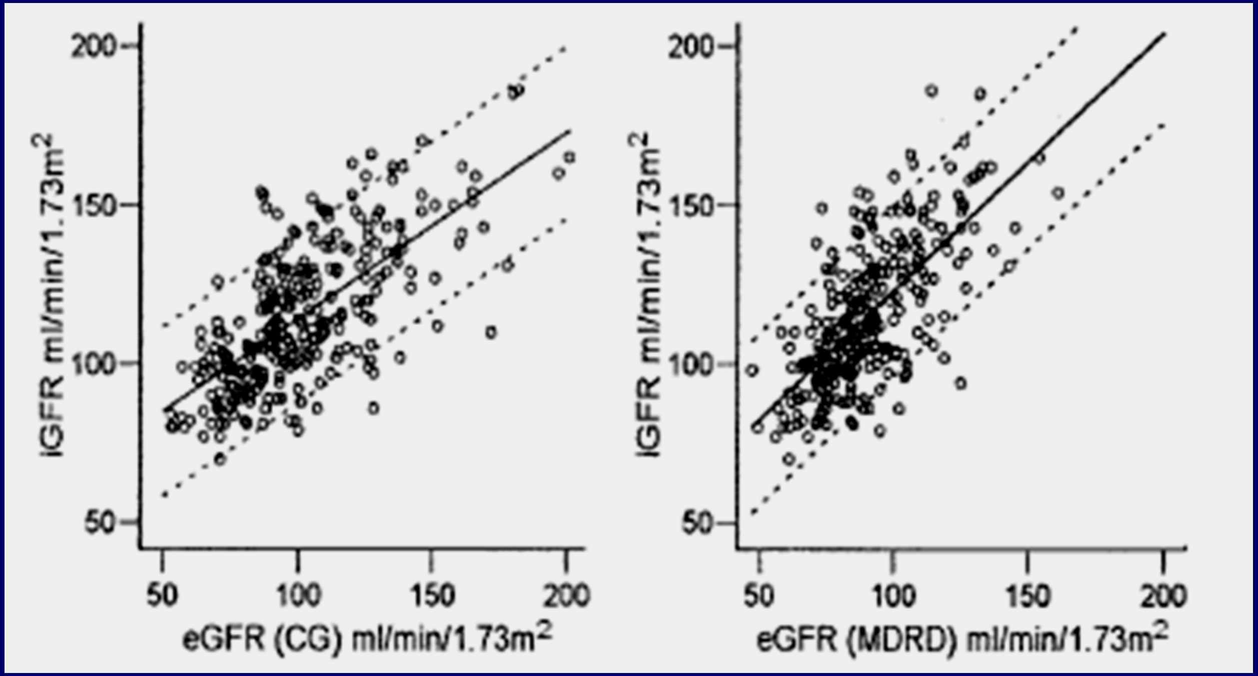
GFR Value:46 mL/min/1.73 m^2

Mean MDRD-eGFR – ^{51}Cr-EDTA-GFR differences



G Arsos et al. *EJNMMI, S2006*

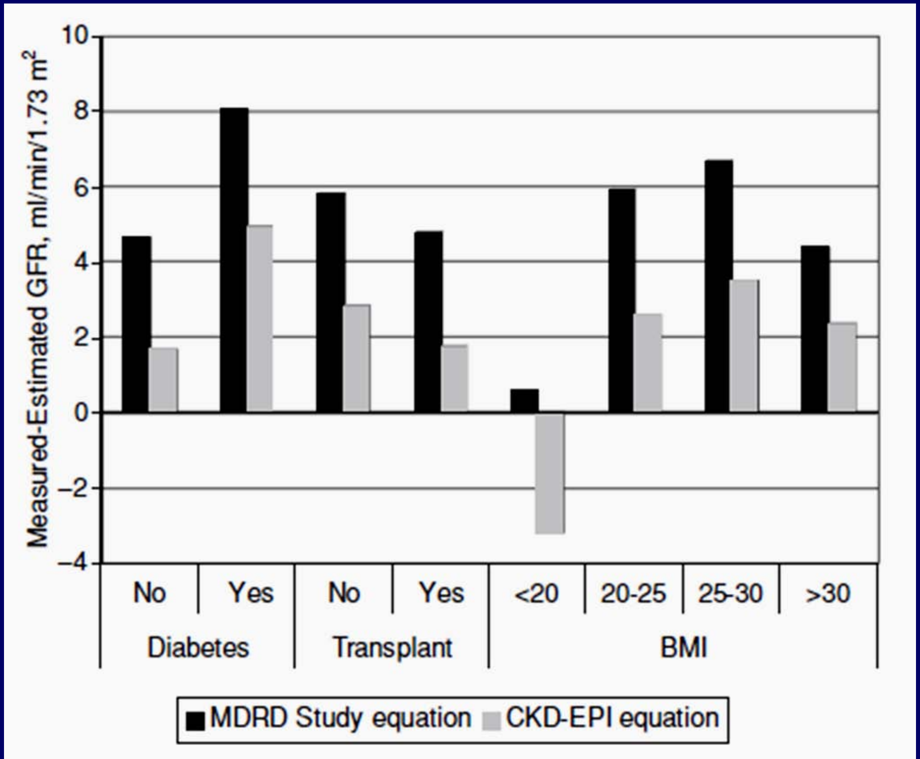
How Reliable Is Estimation of Glomerular Filtration Rate at Diagnosis of Type 2 Diabetes?



"In newly diagnosed type 2 diabetic patients, particularly those with a GFR >90 ml/min per 1.73m^2, both CG and MDRD equations significantly underestimate iGFR.
This highlights a limitation in the use of eGFR in the majority of diabetic subjects outside the setting of chronic kidney disease."

Chudleigh RA et al. *Diabetes Care,* 2007

Development and validation of GFR-estimating equations using diabetes, transplant and weight



"The CKD-EPI equation, based on creatinine, age, sex and race, has been validated and is more accurate than theMDRDstudy equation. The addition of weight, diabetes and transplant does not significantly improve equation performance."

Stevens LA et al. Nephrol Dial Transplant, 2010

Diagnostic accuracy of various glomerular filtration rates estimating equations in patients with chronic kidney disease and diabetes

References	Proposed formulae
Levey et al[2]	$MDRD=186\times(Scr/88.4)^{-1.154}\times age^{-0.203}\times(0.742 \text{ if female})$
Perkins et al[8]	$eGFR=100/(\text{cystatin C})$
Macisaac et al[9]	$eGFR=(86.7/\text{cystatin C})-4.2$
Rule et al[10]	$eGFR=66.8\times(\text{cystatin C}^{-1.30})$
Stevens et al[12]	$eGFR=177.6\times(Scr/88.4)^{-0.65}\times \text{cystatin C}^{-0.57}\times age^{-0.20}\times(0.82 \text{ if female})$
Ma et al[13]	$eGFR=169\times(Scr/88.4)^{-0.608}\times \text{cystatin C}^{-0.63}\times age^{-0.157}\times(0.83 \text{ if female})$

Estimated formulae	GFR ($ml\cdot min^{-1}\cdot 1.73\ m^{-2}$)	Bland-Altman bias ($ml\cdot min^{-1}\cdot 1.73\ m^{-2}$)	Accuracy within		
			15%	30%	50%
MDRD	$76.35\pm18.10^*$	–10.4	37.36	69.23	96.70
Stevens	83.29 ± 22.62	–3.6	35.16	70.33	86.81‡
Ma	$95.81\pm26.79^*$	9.0	36.26	61.54	81.32‡
Rule	87.83 ± 36.21	1.0	27.47	47.25§	75.82§
Macisaac	$101.16\pm34.47^*$	14.3	31.87	54.95	72.53§
Perkins	$121.46\pm39.96^†$	34.6	21.98‡	43.96§	60.44§

Li H et al. *Chin Med J, 2010*

BRIEF REVIEW www.jasn.org

Measured GFR as a Confirmatory Test for Estimated GFR

Lesley A. Stevens and Andrew S. Levey

Tufts Medical Center, Boston, Massachusetts

Extremes of age and body size
Severe malnutrition or obesity
Disease of skeletal muscle
Paraplegia or quadriplegia
Evaluation for kidney donation
Vegetarian diet
Before administration of prolonged courses of toxic medications

Stevens LA & Levey AS. JASN, 2009

Property	Inulin	Creatinine	Iothalamate
M.M. (Da)	5,200	113	636
Elim. half-life (min)	70	200	120
Protein binding (%)	0	0	<5
Space distribution	ECW	TBW	ECW

Property	DTPA	EDTA	Iohexol
M.M. (Da)	393	292	821
Elim. half-life (min)	110	120	90
Protein binding (%)	5	0	<2
Space distribution	ECW	ECW	ECW

Schwartz G et al. *Pediatr Nephrol 2007*

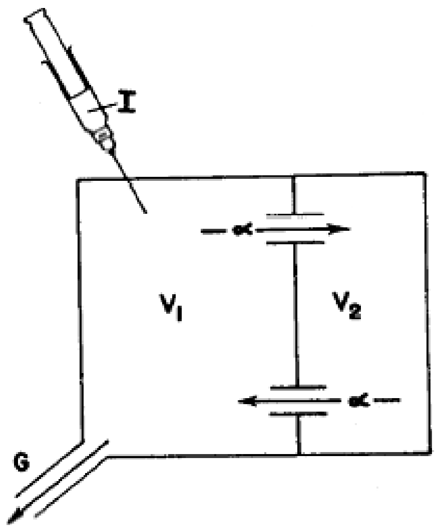


FIG. 2. System for which the equations of the appendix are derived. The excretory clearance is designated G, and is the virtual (not the actual) volume leaving V_1 for the outside.

$$G = \frac{I\gamma_1\gamma_2}{A\gamma_2 + B\gamma_1} \qquad (1)$$

where G is the glomerular filtration rate in milliliters per minute, I is the dose of creatinine in milligrams injected and the other terms have the significance already noted.

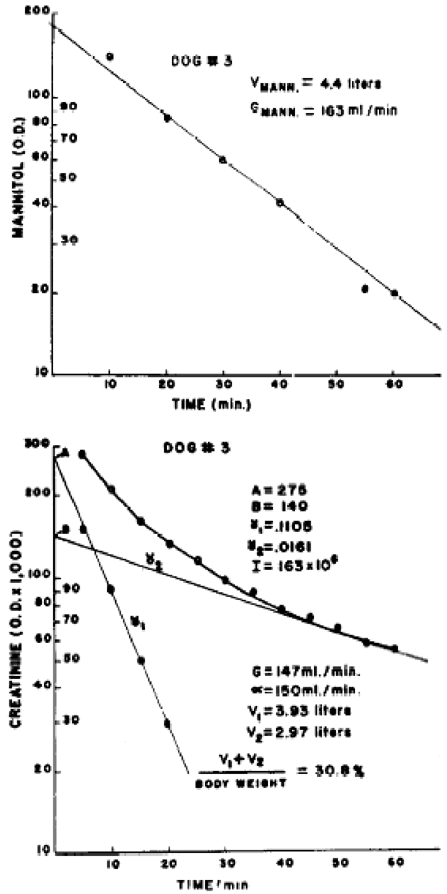


FIG. 1. Disappearance curves for mannitol and creatinine after single injection in a dog. A, B, γ_1, γ_2, V_1, V_2, $V_{mann.}$, $G_{cr.}$, $G_{mann.}$, and α have the significance given in the text. See also fig. 2.

Sapirstein LA, Vidt DC, Mandel MJ, Hanusek G. Volumes of distribution and clearances of intravenously injected creatinine in the dog. *Am J Physiol* 1955;181:330-6.

Measurement of glomerular filtration-rate in man using a ^{51}Cr-edetic-acid complex

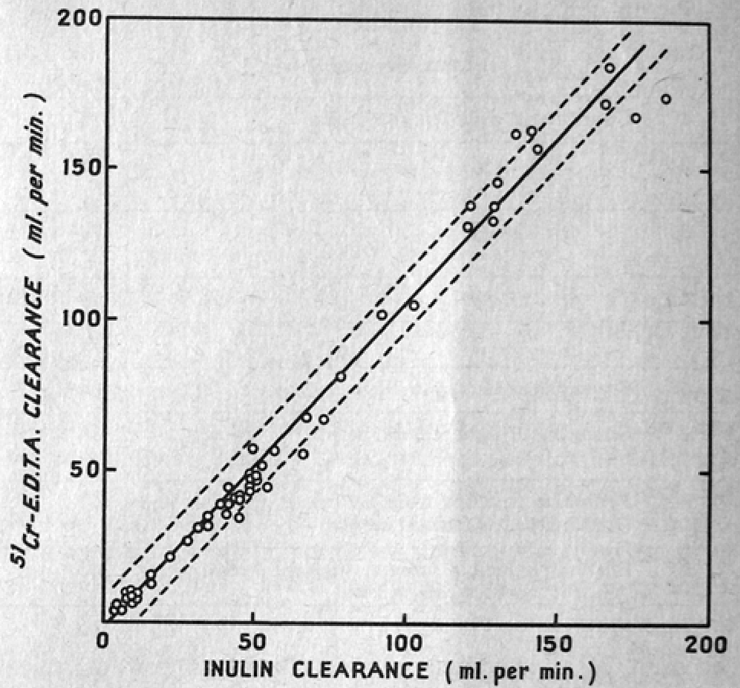
Preliminary Communications

MEASUREMENT OF GLOMERULAR FILTRATION-RATE IN MAN USING A ^{51}Cr/EDETIC-ACID COMPLEX

Summary ^{51}Cr complexed with edetic acid (^{51}Cr-E.D.T.A.) can be prepared in a form which is stable when autoclaved and in vivo. It does not bind to protein or enter red blood-cells and excretion via the gut is insignificant. The renal clearance, as measured by the continuous-infusion technique, is the same as that of inulin. Equilibration with interstitial fluid in non-œdematous patients takes less than 2 hours and there is no detectable extrarenal uptake so that the " slope " method based on 2–4-hour plasma-activity measurements can be used as a simple routine procedure. Results obtained in this way accord well with 24-hour endogenous creatinine-clearance data, but the technique is not applicable to œdematous patients where equilibration is delayed. ^{51}Cr-E.D.T.A. seems to be eminently suitable for clinical use.

INTRODUCTION

THE preparation of ^{51}Cr complexed with edetic acid (E.D.T.A.) and its use as an inert rumen marker have been described by Downes and McDonald.[1] Subsequently



Comparison between ^{51}Cr-E.D.T.A. and inulin clearance data from continuous-infusion measurements.

Inulin clearance (ml. per minute) $= 1{\cdot}075 \times$ ^{51}Cr-E.D.T.A. clearance (ml. per minute) $- 3{\cdot}06$.

Standard error $\pm 5{\cdot}1$ ml. per minute; $r = 0{\cdot}995$. The 95% confidence limits are indicated by dashed lines.

Garnett ES et al. *Lancet, 1967*

^{51}Cr-EDTA :

a common GFR tracer in Europe

^{51}Cr-EDTA GFR determination (BSNM protocol)

1) Bolus i.v injection of 3.7 MBq ^{51}Cr-EDTA

2) 10 ml blood sampling at 2 and 4 hours p.i. from a different vein

3) Activity counting of 1 ml plasma samples (x2)

4) Clearance calculation (with fast component correction)

5) Normalization for body surface area

Fleming S et al, *Nucl Med Commun 2005*

^{51}Cr-EDTA GFR determination (“Hippokration” protocol)

1) Bolus i.v injection of 3.7 MBq ^{51}Cr-EDTA

2) 5 ml blood sampling at 2 and 4 hours p.i. from the same vein route

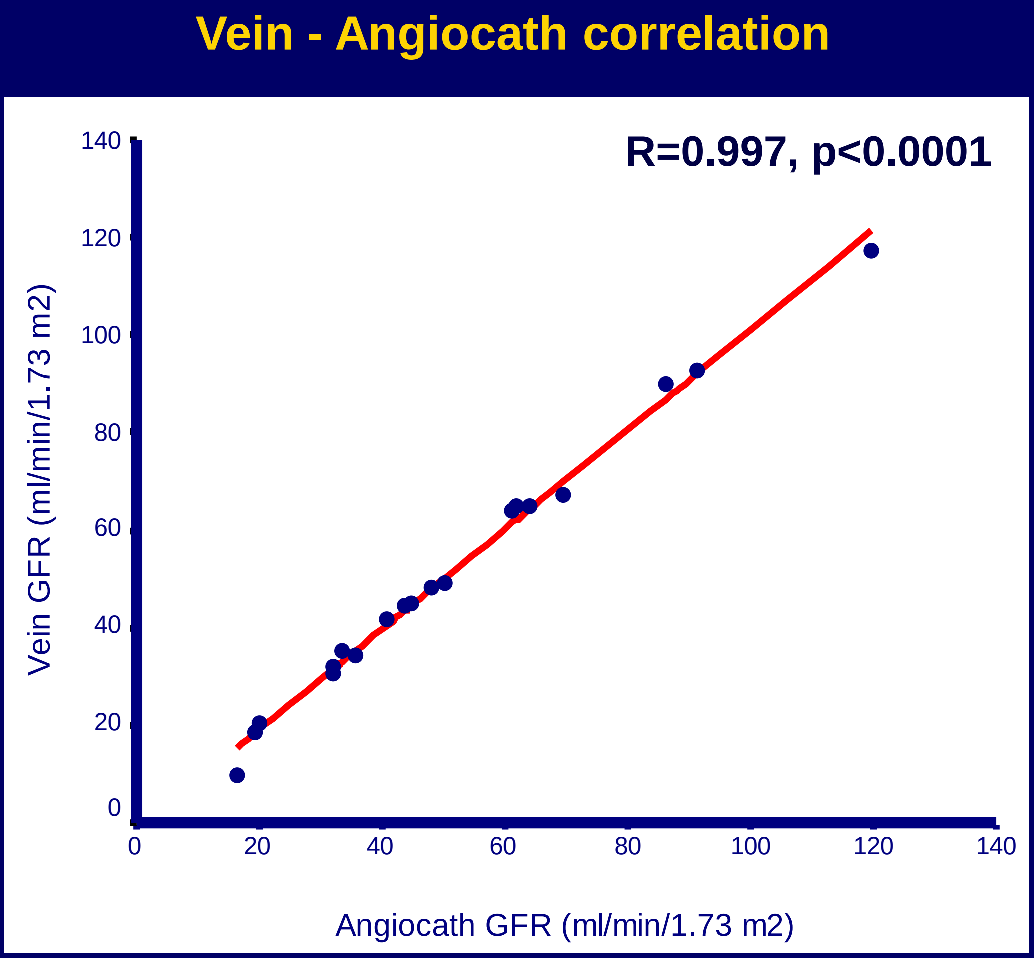
3) Activity counting of 1 ml plasma samples (x1)

4) Clearance calculation (with fast component correction)

5) Normalization for body surface area

Fleming S et al, *Nucl Med Commun 2005*

Separate injection–sampling vs single route method



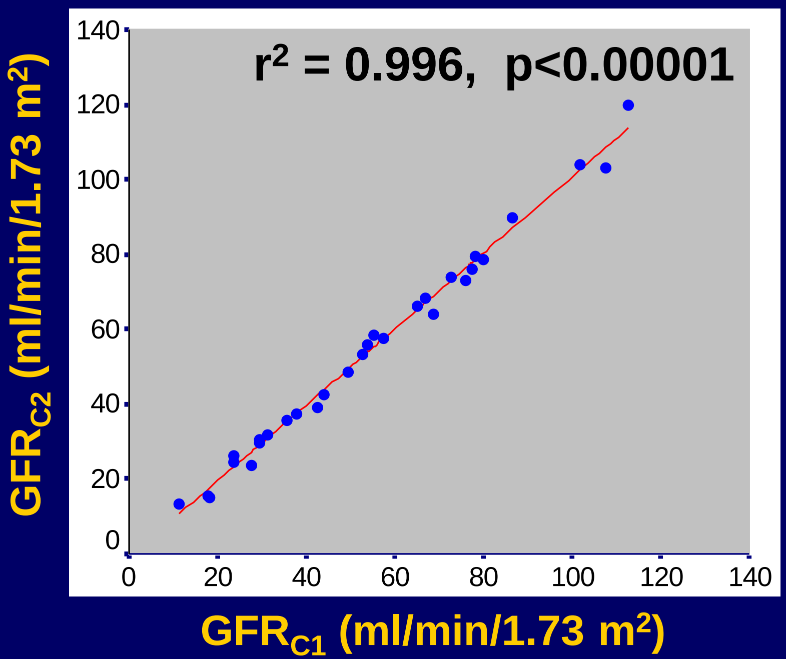
Vein GFR = 1.02 Angiocath GFR -1.25

Arsos G et al, *EJNMMI S2008*

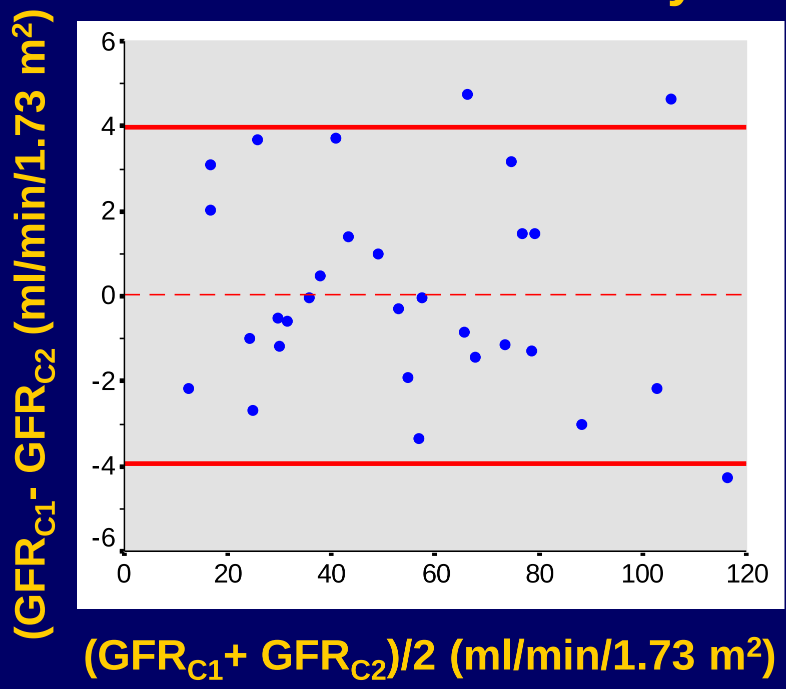
Repeatability of a simplified GFR measurement method based on a single vein route and simple plasma samples determinations

C1, C2 first and second counting

C1 - C2 correlation



C1 - C2 difference analysis

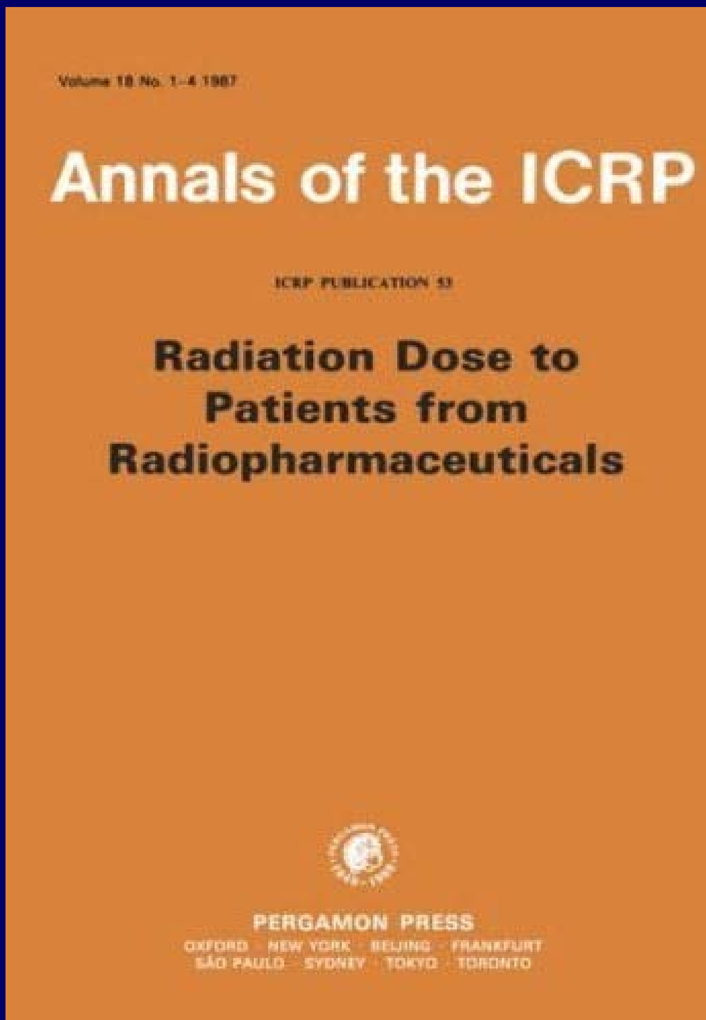


bias (- - -) : 0.0 ml/min/1.73 m²

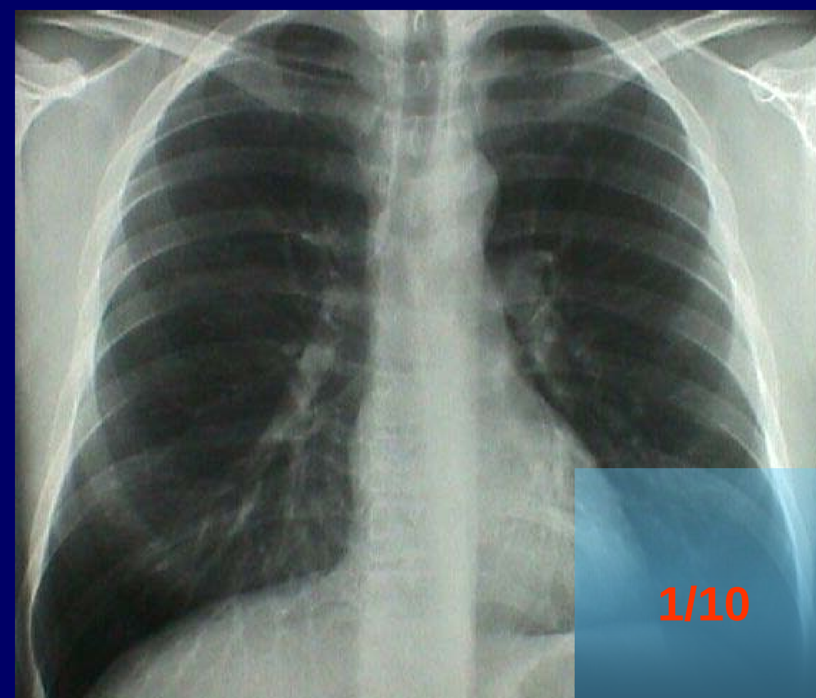
95% CI (—) : - ± 4.0 ml/min/1.73 m²

Arsos G et al, *EJNMMI S2010*

Radiation dose to the patient from GFR determination with ^{51}Cr-EDTA



Normal GFR : 0.01 mSv
Reduced GFR : 0.02 mSv



ACR : effective dose = 0.1 mSv


The Village Doctor
Musees Royaux des Beaux Arts de Belgique, Brussels
David Teniers the Younger, 1610 - 1690