Validierung der GFR im Alter

Berliner DialyseSeminar

Elke Schäffner, Charité, Berlin

Stand der Dinge

- Was es bisher gibt
- Was es bisher nicht gibt
- Was wir brauchen
- Validierung anhand Berliner Initiative Studie

gemessene GFR

Methoden	+	-
Urin-Clearance		
Blasenkatheter mit kont. iv-Infusion	Goldstandard	invasiv
spontane Blasenentleerung	weniger invasiv	Restharn-Problem
Bolus-Administration	kürzere Dauer	↓ Fluß bei ↓GFR
24h-Sammelurin	ambulant mögl.	fehlerbehaftet
Plasma-Clearance	kein Urinsammeln	Überschätzung bei extrazell. Volumenexpansion
	evtl. genauer	ungenau bei Einmalwerten
Nuclear imaging	weder Urin- noch Blutproben	ungenauer

Stevens & Levey, JASN 2009: Measured GFR as a confirmatory test for estimated GFR

gemessene GFR

Marker	+	-
Creatinine	endogener Marker	Sekretion variiert inter- und intraindividuell
Cystatin C	endogener Marker	evtl. sensitiver bei leichter Einschränkung
Inulin	Goldstandard keine Nebenwirkungen	teuer komplizierte Lagerung
Iothalamate	billig, lange t1/2	wahrsch. tub. Sekretion aufwendige Lagerung, falls radioaktiv aufwendiger Assay, falls nicht radioaktiv cave bei Iodallergie
Iohexol	**nicht radioaktiv** **billig** **sensitiver Assay**	**(nur Plasma-Clearance)**
EDTA	weit verbreitet in EU	komplizierte Lagerung
DTPA	weit verbreitet in USA	komplizierte Lagerung

geschätzte Clearance / GFR, Kreatinin-basiert

- Cockcroft-Gault

$$C_{Cr} = \frac{(140 - Alter) \times Gewicht}{72 \times S_{Cr}} \times (0,85 \text{ falls weiblich})$$

- Modification of Diet in Renal Disease Study **(Alter: 50.6)**
  - ***MDRD 7:*** *GFR (mg/ml/1.73m²) =*

    170 × (SCr)-0.999 × (age)-0.176 × (BUN)-0.170 × (Alb)+0.138 × (0.762 if female) × (1.180 if African-American)
  - ***Abbreviated MDRD:***

    186 × (SCr)-1.154 × (age)-0.203 × (0.742 if female) × (1.210 if African-American)

- Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) **(Alter: 47)**

CKD-Epi: *GFR (mg/ml/1.73m²) =*

141 × min (SCr /κ)α × max(SCr /κ) 1.209 × 1.018(if female) × (1.159 if black)

κ is 0.7 for females and 0.9 for males, α is 0.329 for females ; 0.411 for male

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 = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate.

* Expressed for specified race, sex, and serum creatinine level. To convert GFR from mL/min per 1.73 m^2 to mL/s per 1.73 m^2, multiply by 0.0167. We derived equation coefficients from pooled development and internal validation data sets. The CKD-EPI equation, expressed as a single equation, is $GFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times 1.159$ [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. In this table, the multiplication factors for race and sex are incorporated into the intercept, which results in different intercepts for age and sex combinations.

geschätzte GFR, Cystatin C-basiert

$$eGFR_{(Hoek)} = -4.32 + 80.35 \times 1/CysC$$

$$eGFR_{CysC1Var} = 76 \times CysC^{-1.19}$$

$$eGFR_{CysC3Var} = 127.7 \times CysC^{-1.17} \times age^{-0.13} \times 1.06 \text{ (if black)} \times 0.91 \text{ (if female)}$$

Stevens & Levey
AJKD 2008

Cystatin C im Alter

Cystatin C ⟷ Entzündung

↓ häufig bei

chronischer Erkrankung

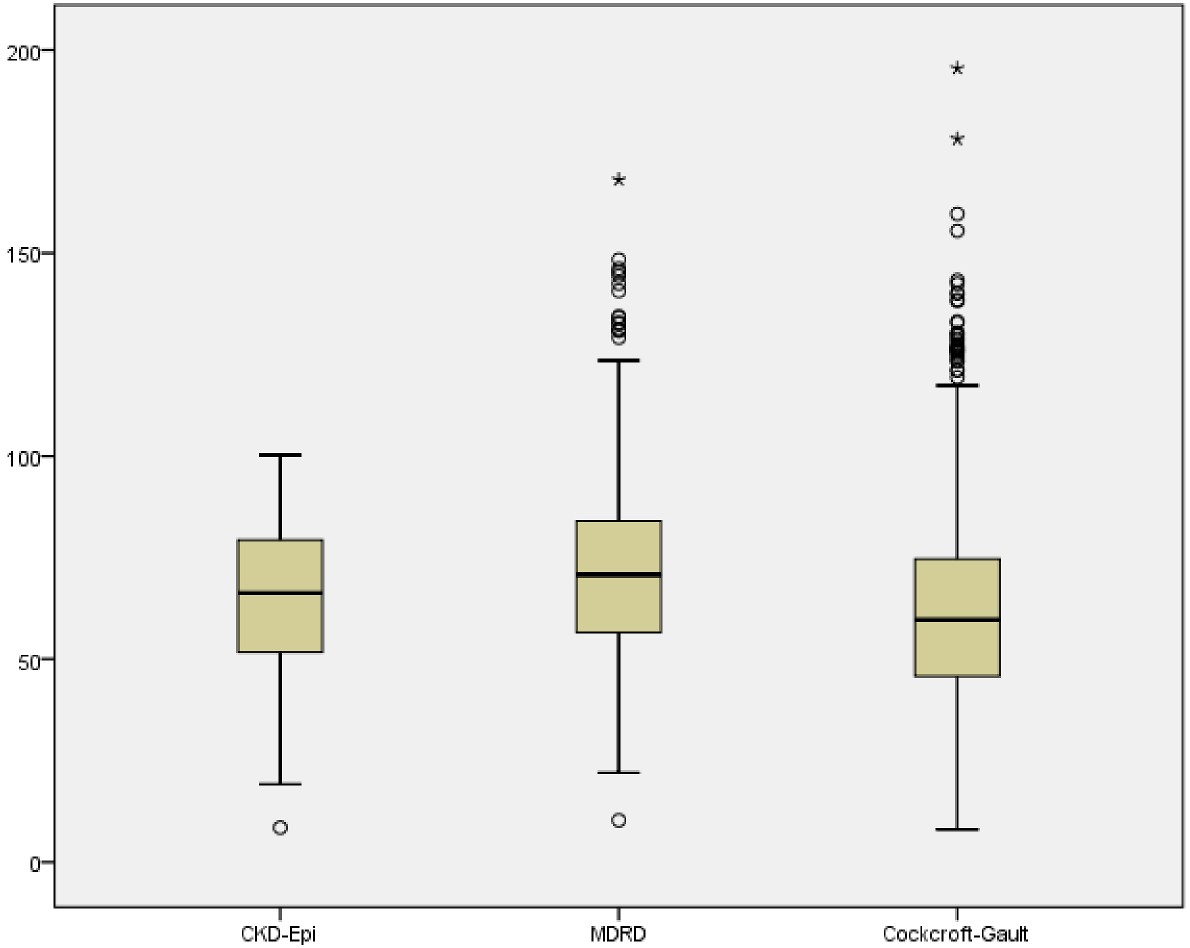
↓ häufig im

im Alter

Unterschiedliche CKD-Prävalenzen im Alter

Artikel	**Population**	**N / Alter**	**Prävalenz** GFR <60	**GFR / CrC**
Clase C, JASN 2002	NHANES III (nondiabetic)	2.610 / ≥60	40%	MDRD
Coresh J, AJKD 2003	NHANES III	2.965 / 70+ 2.945	26% **49%**	MDRD **Cockcroft-G.**
Garg A, Kidney Int 2004	87 long term care fac., Ontario	9931 / 82 (m), 85 (w)	m: 23.6%; w: 34.8% **m: 50.5%; w: 60.2%**	MDRD **Cockcroft-G.**
Hemmelgarn B., Kidney Int 2006	Community dwelling	10.184 / 78	35.5%	MDRD
Stengel B, NDT 2011	Community dwelling	8.705 / 74	13.7% 12.9%	MDRD CKD-Epi

Individuelle Unterschiede in Abh. der eGFR-Formel



CKD_{Epi}: 64.7

MDRD: 70.9

$CG_{(BSA)}$: 58.1 ml/min/1.73m^2

eGFR Verteilung der BIS-Gesamtkohorte, errechnet mit CKD-Epi, MDRD and CG, n=2068, Alter: 80.4

BIS Berliner Initiative Studie

Vergleich: van den Brand et al., NDT 2011

CKD-EPI and its effect on CKD prevalence

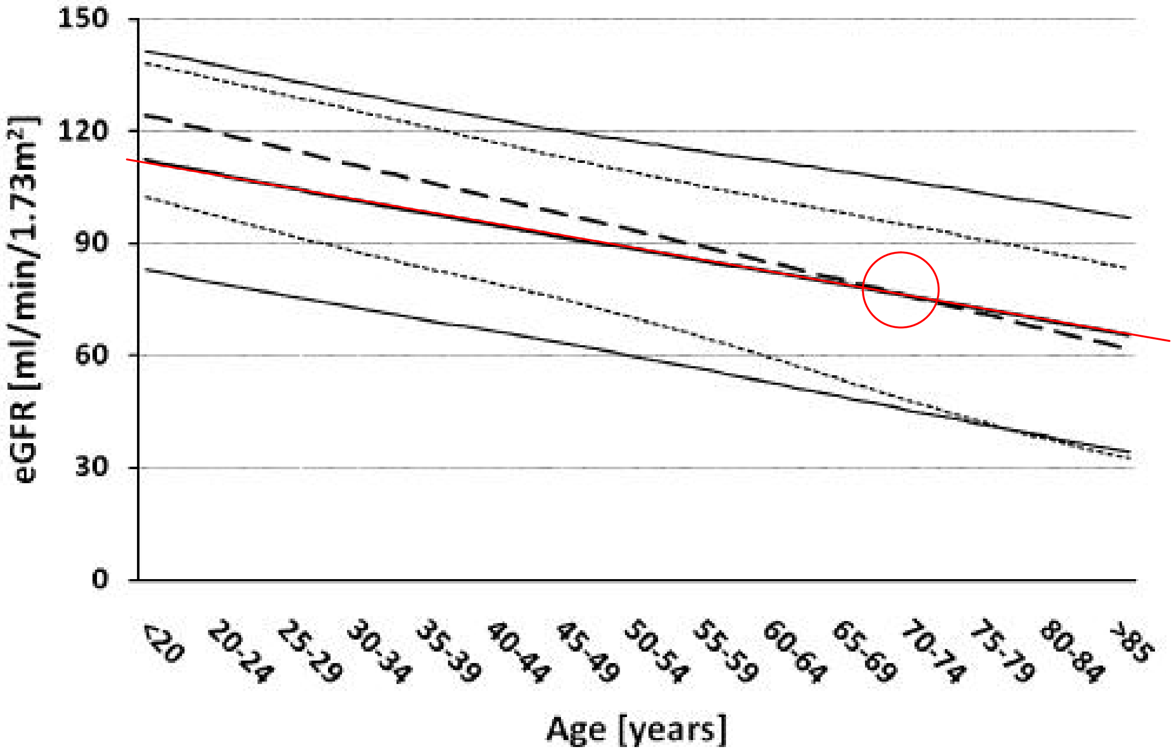


Fig. 1. Smoothed eGFR by age for Caucasian males (total population) in the Nijmegen Biomedical Study. The interrupted lines represent the $eGFR_{CKD\text{-}EPI}$ and the connected lines the $eGFR_{MDRD4}$. Data are presented as the p95, median and p5.

Kreatinin im Alter

Kreatinin ⟷ Muskelmasse

↓ abhängig von

Alter

Geschlecht

Rasse

chron. Krankheit

körperl. Aktivität

Medikation

Assays

- **Kreatinin**
  - kinetisch (Jaffe)
  - enzymatisch (Roche), IDMS-traceable

- **Cystatin C**
  - PENIA – particle enhanced nephelometrisch (Siemens, ehem. Dade-Behring)
  - PETIA – particle enhanced turbidimetrisch (Roche)

Systematischer Review: 12 Artikel mit Populationen 65+

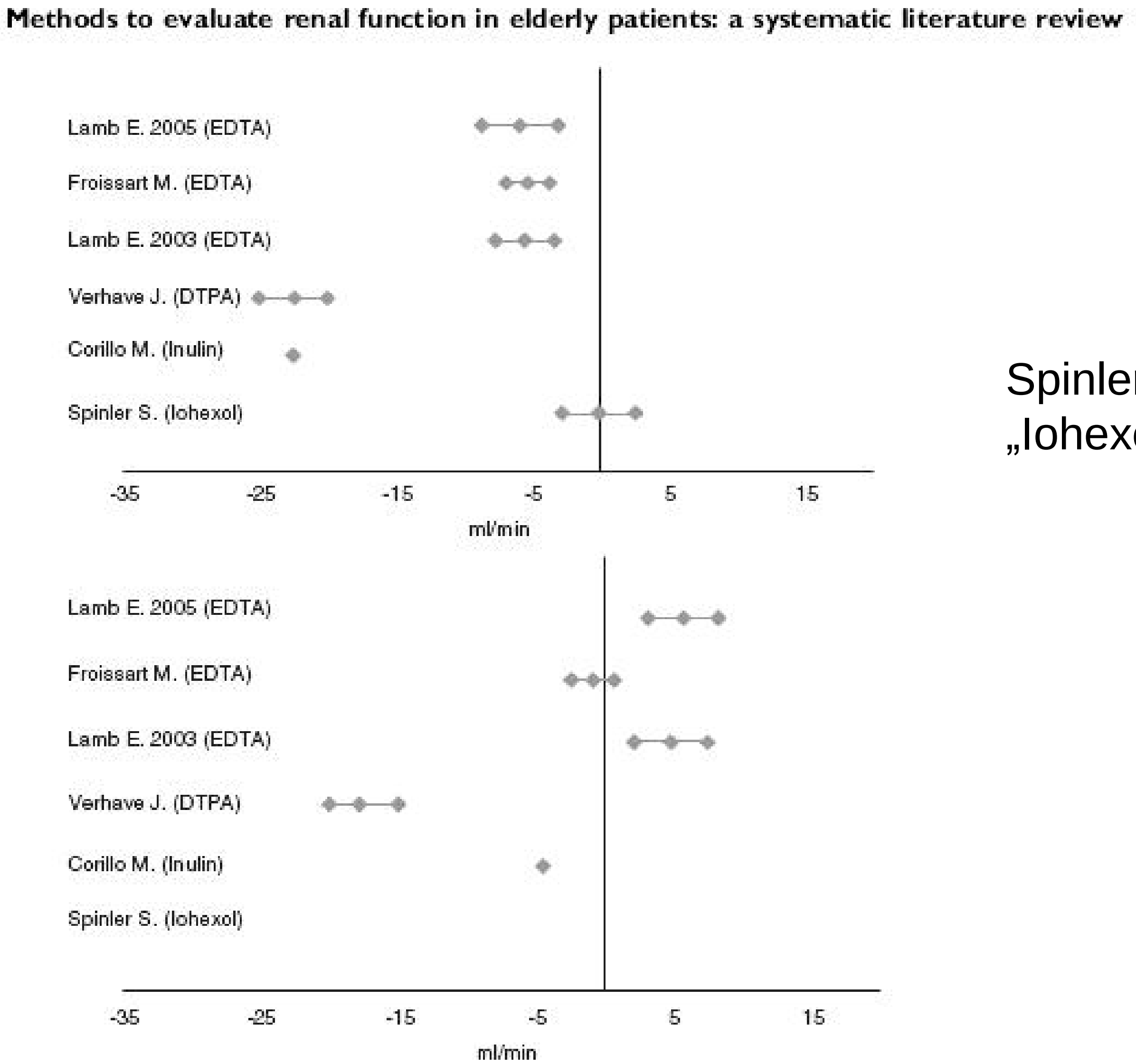


Figure 1. Mean difference between the gold standard and the formula to calculate the GFR (with 95% CIs) for the separate studies. Top: GFR calculated with the CG formula. Bottom: GFR calculated with the MDRD formula.

Spinler et al: 222 elderly (>65) 71.5 J
„Iohexol Cooperative Study“

Van Pottelbergh et al. Age Ageing 2010:39:542-548

Literatur

- Gijs van Pottelbergh: „…The large differences in GFR estimates for individual patients show that there is an urgent need for further research on methods for estimating GFR in elderly patients. Such research should compare existing equations and new equations based on creatinine or cystatin C levels with true GFRs measured using the (?) gold standard method and a representative sample of the oldest old….“

  Age and Ageing, 2011, 40: 401-5

- Rossini Botev: „…Obviously, large studies to establish the boundaries of normal mGFR according to a wide range of ages in different genders and races are needed to resolve recent debates [….] about overdiagnosing CKD in the elderly, [..]. Hopefully, the ongoing **Berlin Initiative Study** in the elderly would provide some answers for proper CKD diagnosing in this population [..]….“

  CJASN, 2011, 6: 937-950

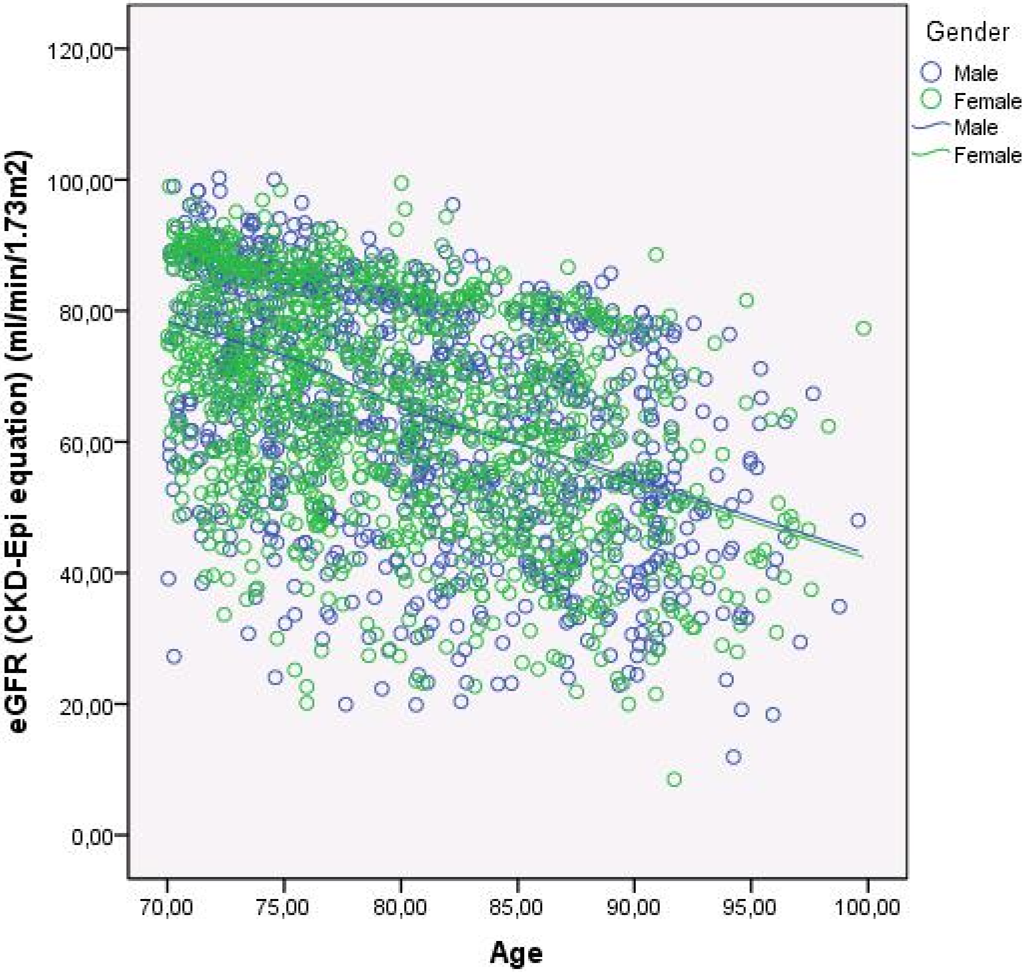
BIS

Berliner Initiative Studie

GFR-Validierung bei Personen ≥70

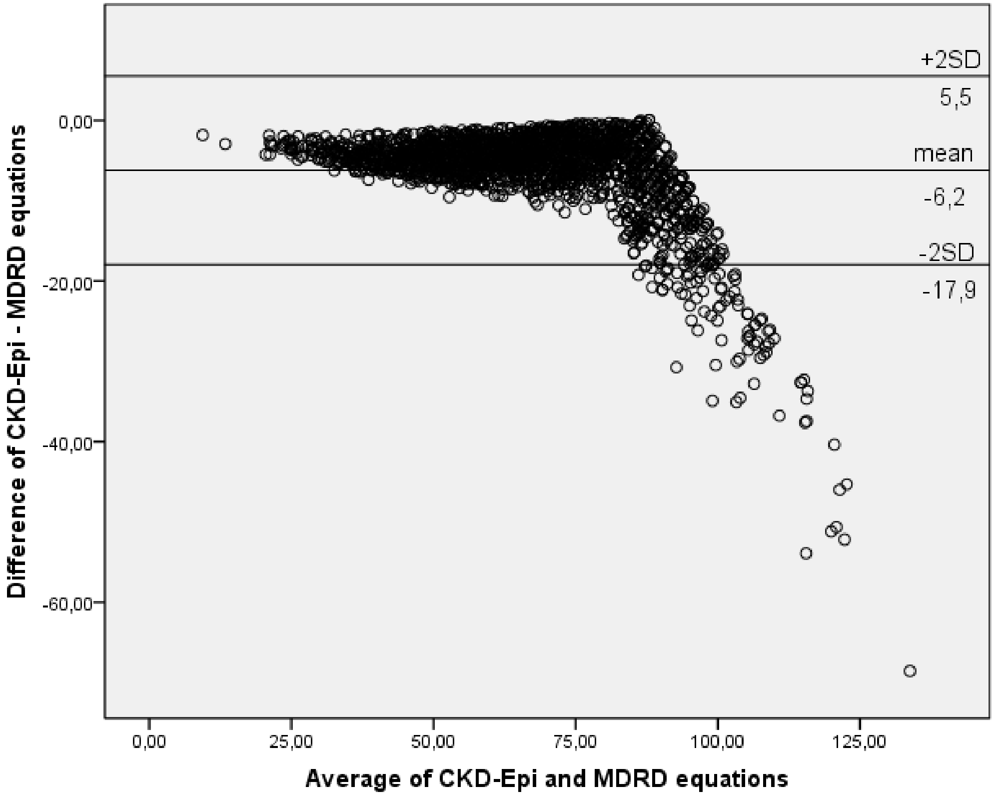
http://bis.charite.de

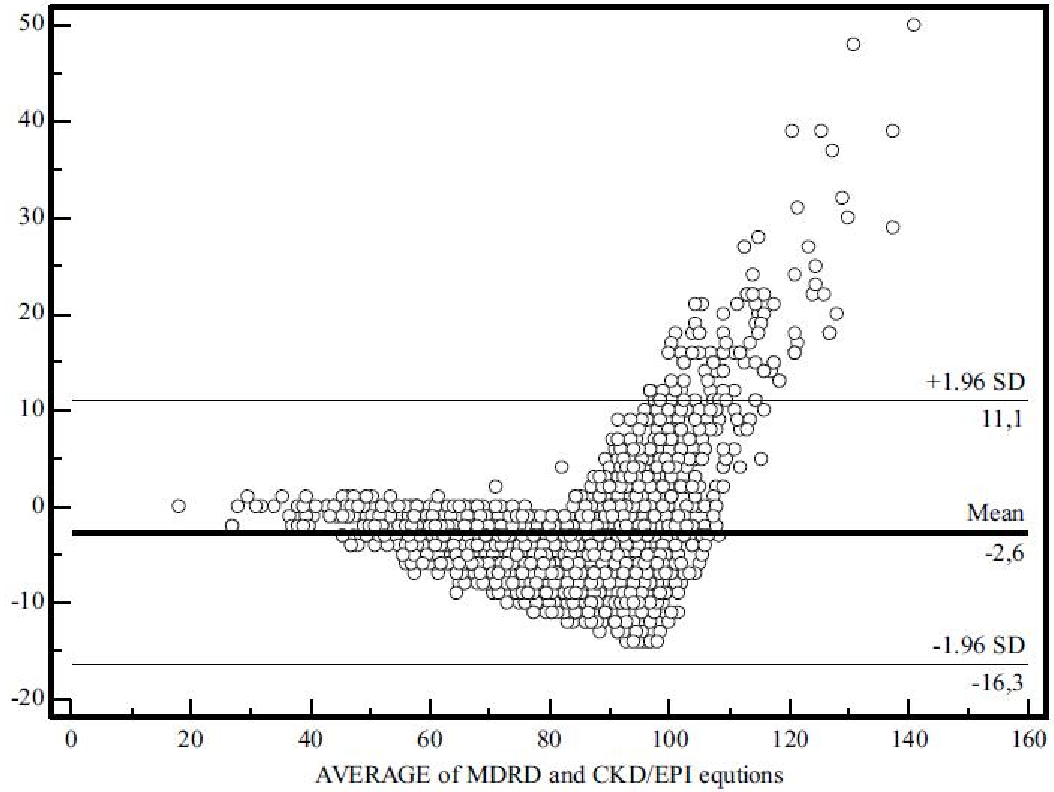
eGFR-Verteilung (eGFR $_{\text{CKD Epi}}$)



N=2070, Alter: 80.4
eGFR <60: 37.9% (784)

Übereinstimmung zwischen CKD-Epi und MDRD besser im niedrigeren als im hohen eGFR-Bereich

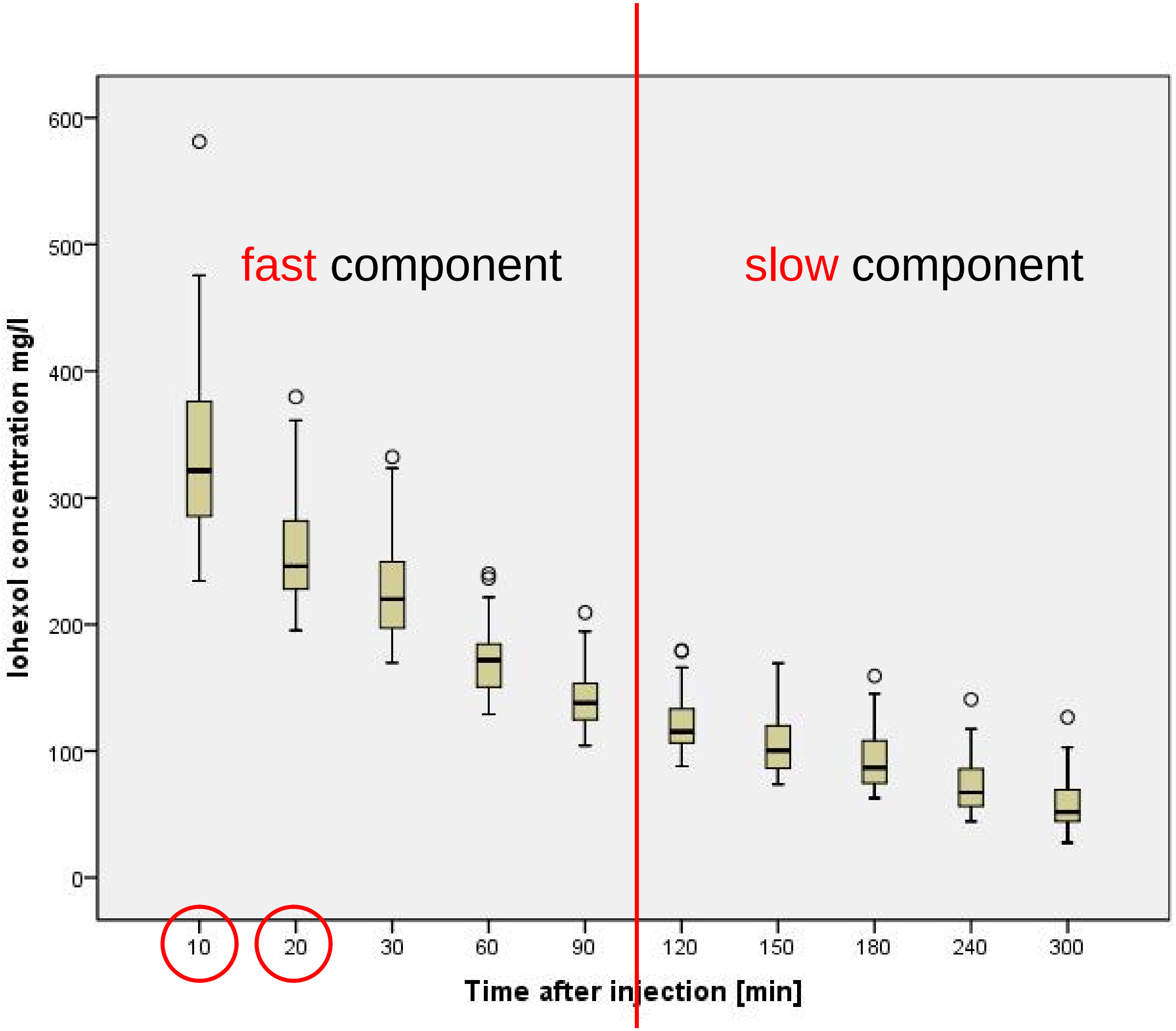




Ebert et al. Abstract, ASN 2011

Delanaye et al., BMC Nephrology 2010

Goldstandard:
Iohexolkonzentration im Serum über die Zeit (N=607)



Bei 50/607 Probanden zusätzliche 10 und 20 Minuten-Werte.

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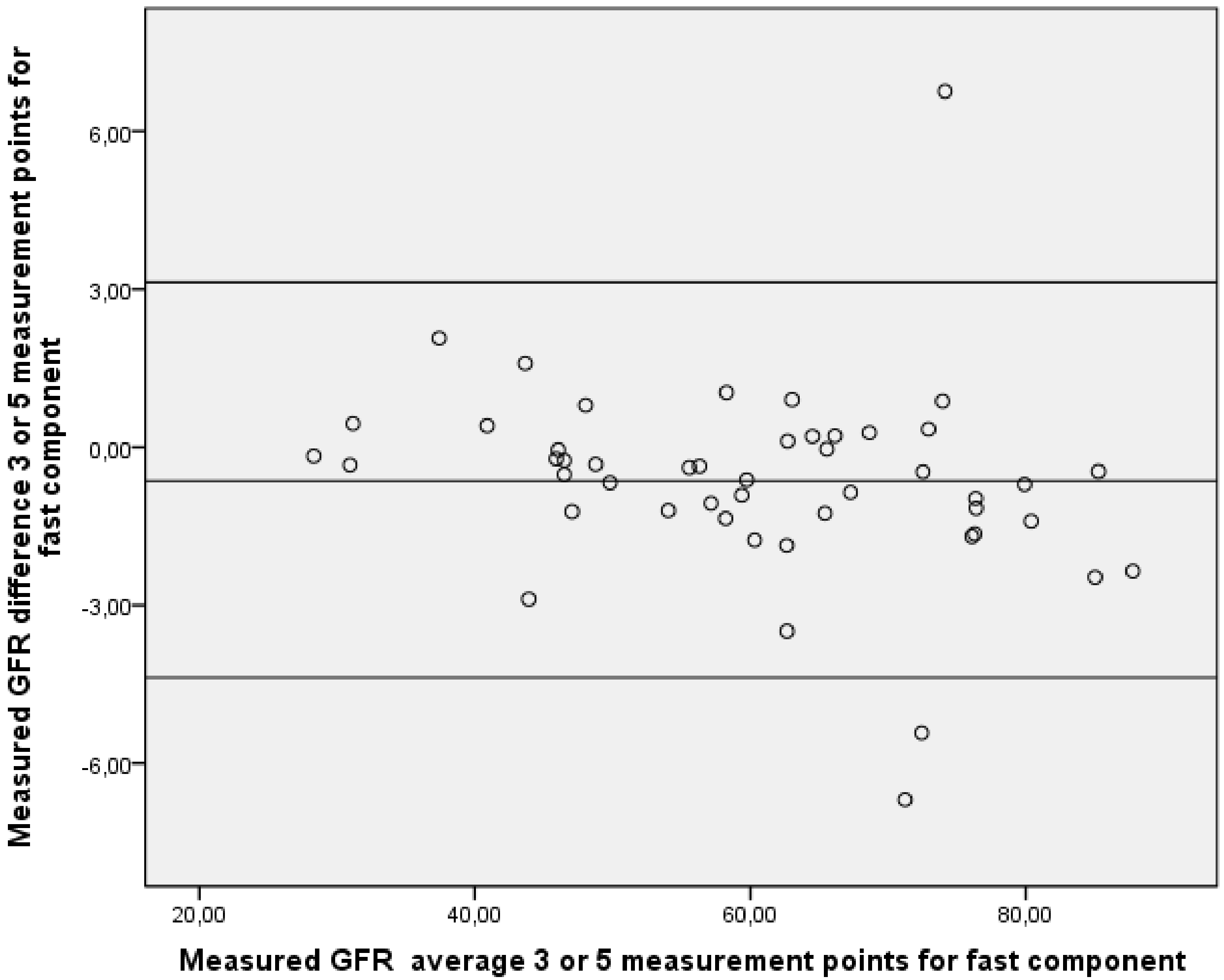
Keine verbesserte Präzision durch Hinzunahme von 10- und 20-Minutenwerten



BIS
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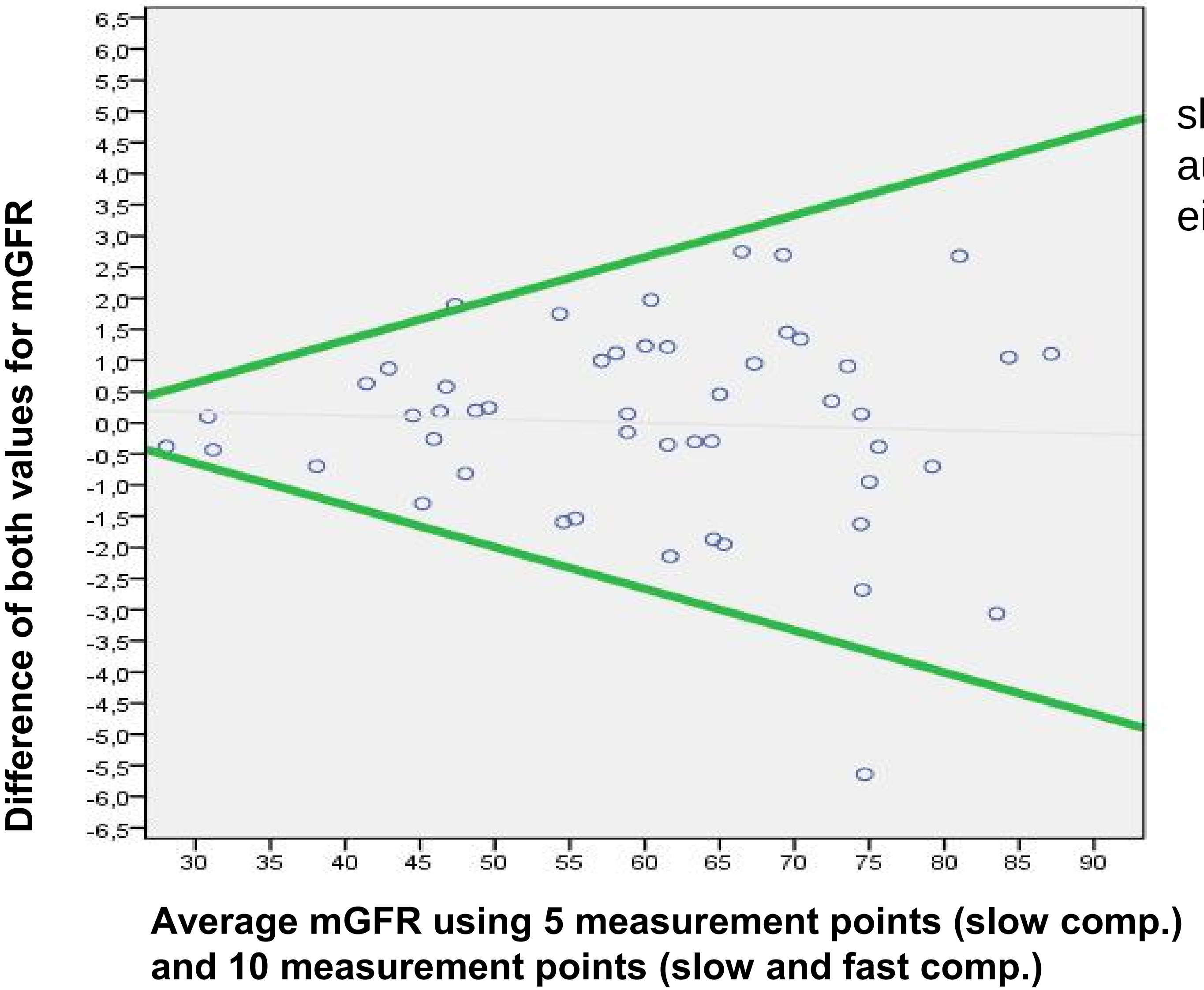
Übereinstimmung der GFR durch slow component und slow + fast component



slow component ausreichend v.a. im eingeschränkten GFR-Bereich

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Zusammenfassung

- Kreatinin- od. Cystatin C-basierte eGFR hängt ab von
  - Gleichung
  - Assay
  - Population (Alter, Nierenerkrankung, Komorbiditäten)

- große Unterschiede zwischen den momentan gebrauchten Schätzgleichungen bei älteren Personen

- Derzeit (noch) keine validierte eGFR-Formel für Personen 70+

- Benötigt wird:
  - der Vergleich bestehender Schätzformeln (eGFR) mit einem Goldstandard (mGFR)
  - die Entwicklung einer neuen GFR-Schätzformel anhand eines Goldstandards