GFR, Performance of Estimating Equations, Monitoring Progression of CKD

Richard J. Glassock, MD, MACP
Geffen School of Medicine at UCLA
American Society of Nephrology: Board Review and Update Course
Chicago, IL
August 10, 2013

GFR Estimating Equations: An Overview

- Purpose of GFR estimating equations (eGFR) is to permit an “approximation” of the true value for GFR (mGFR)
- GFR estimating equations are derived by comparing the estimate to a measure believed to represent “true” GFR in a reference population (ideally “representative” of the population as a whole)- a gold standard mGFR
- eGFR is based on assay of a marker whose concentration in plasma is believed to related to mGFR

eGFR Equations: Categories

- Creatinine- Based
- Cystatin C –Based
- Combination of Creatinine and Cystatin C
- Other (Beta-trace protein)
GFR Estimating Equations:  
A Partial Listing

- Cockcroft-Gault eCr- 1976 (not an estimate of GFR- an estimate of endogenous Cr)
- eGFR (MDRD- creatinine)- 1999 (Adults) (4 Variable/6 variable)
- eGFR (Mayo Clinic) (Adults) (Quadratic equation)
- eGFR (MDRD)- 2007 Re-expressed (Adults)
- eGFR (Cystatin C)- 1985 (Adults)
- eGFR (CKD-EPI- Creatinine)- 2009 (Adults)
- eGFR (CKD-EPI- Creatinine + Cystatin C (2012)
- eGFR (Berlin Initiative Study- I- creatinine; II- creatinine + Cystatin C – age over 70 years) (2012)
- eCr (Schwartz)-eGFR (Counahan-Barratt) (Pediatrics)
- eGFR- beta trace protein

mGFR – "Gold-Standards”

- Inulin Urinary Clearance (Cin; Constant Infusion, Urine Collections)
- Radioactive Iothalamate Urinary Clearance (Cio; Constant infusion or subcutaneous injection, urinary collection)
- Radioactive Iothalamate Plasma Disappearance
- Non-radioactive ("Cold’’) Cio
- Cr51 EDTA, Tc99 DTPA, Yb169, Iohexol Plasma Clearances

IOHEXOL PLASMA CLEARANCE
(? A Practical Gold Standard)  

- Infusion of ~ 5ml of Iohexol and collection of periodic plasma samples for up to 4 hours and assessing the plasma concentration of Iohexol by HPLC
- Correlation with Cin= r=0.982; Bias= -1ml/min/1.73m2; 95% agreement= -15 to +12ml/min/1.73m2 (mean mGFR-60ml/min/1.73m2)
Cockcroft-Gault (C-G) eCcr

Described in 1976 as a method to approximate endogenous (24 hr) Ccr by measurement of Scr

249 individuals (males only) ages 18-92 studied. Nearly all had CKD. No gold standard mGFR. Comparison was 24 hr endogenous Ccr.

Prediction Formula- eCcr (ml/min) = (140-age in yrs) x Weight (kg) 72 x Scr (mg/dL) x 0.85 if Female

(Conversion of eCcr (C-G) to eGFR = divide by 1.16-1.21 in normal subjects, higher in CKD)

Age, Body Weight and Gender included as “surrogates” for endogenous creatinine generation

Requires a “steady-state”

Values not corrected for BSA (weight already in numerator)

Overestimates Csin (bias; mGFR) in normal individuals (due to tubular secretion of Cr) - poor precision

Gives erroneously high values of eCcr (compared to Cio and Ccr) in “malnutrition”, nephrotic syndrome and edematous states.
Nephrotic Syndrome:
*mGFR, eGFR, eCcr*
(Branten AJW, et al NDT 20:707, 2005)

<table>
<thead>
<tr>
<th>mGFR/eGFR (ml/min/1.73m²)</th>
<th>Salb &lt;2.6gm/dL</th>
<th>Salb &gt;2.6gm/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>mGFR (Cin)</td>
<td>43</td>
<td>63</td>
</tr>
<tr>
<td>eGFR (MDRD)</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>eCcr (C-G)</td>
<td>82</td>
<td>86</td>
</tr>
<tr>
<td>eCcr (C-G)/mGFR</td>
<td>1.91</td>
<td>1.36</td>
</tr>
<tr>
<td>eGFR (MDRD)/mGFR</td>
<td>1.58</td>
<td>1.06</td>
</tr>
</tbody>
</table>

eGFR, eCcr, 24 hr Ccr:
The Intern’s Case
(Freedberg DE Kidney Int 7576:129, 2009)

- A 66 year old woman with urosepsis following a liver transplant. She is small and frail. Scr=1.8mg/dL
- eGFR (MDRD)= 30.0ml/min/1.73m²
  - eCcr (C-G)= 31.2ml/min
  - 24 hr Ccr= 14.6 ml/min
  - (eCcr/24 hr Ccr= 2.14)

All creatinine-based eGFR equations tend to overestimate GFR in hospitalized (especially ICU) patients due to sarcopenia and low creatinine generation.

They are not suitable for calculating dosage of toxic medications cleared by GFR (water soluble)
eGFR (MDRD)- creatinine

Described in 1999 as a method for estimating mGFR (Cio) by measurement of Scr (Jaffe method)

Derived from measurement of Scr and Cio in 1628 subjects (male and female) all with CKD (average Cio=40ml/min/1.73m2; Scr=2.3mg/dL; 6% Diabetic)

- eGFR (MDRD) ml/min/1.73m2 =
  
  186 X (Age in years)^-0.203 x (Scr in mg/dL)^-1.154
  
  ( x 0.742 if female and  x 1.212 if Black) – (4 Variable- a 6 variable equation includes BUN and Salb)

Age, Gender and Race (Black/Non-Black) (but not weight) included as “surrogates” for endogenous creatinine generation.

Requires a “steady-state”

Scr must be calibrated to a standard (Cleveland Clinic)

Values correct for BSA (to 1.73m2)

Underestimates Cio (bias) at levels of GFR >60ml/min. Poor precision.

Gives erroneously high values of eGFR (compared to Cio and Cin) in “malnutrition”, vegetarian diets and in nephrotic states
eGFR (MDRD) vs mGFR (Cin)
(Botev, et al, CJASN 2009)

Bias and Precision of eGFR (MDRD)
(Botev, R, CJASN, 2009)
eGFR (MDRD) and eCcr (C-G)
Accuracy (Values within 30% of Cin [mGFR])
(Botev R, et al CJASN 4:899, 2009)

- Can give erroneous values for GFR in:
  - Healthy people with a high or low meat diet (especially cooked meat)
  - Muscle building and deconditioning
  - Malnutrition and cachexia (sarcopenia)
  - Nephrotic syndrome (and low Salb)
  - Presence of interfering substances in the Jaffe reaction (high glucose, fructose, etc)
  - Stage 5 CKD

eGFR- Serum Creatinine-Based
(Ccr C-G, eGFR-MDRD, eGFR-Mayo Clinic)

- “mGFR” (average of 24 hour Curea and Ccr indexed for BSA) assessed in 569 patients at start of dialysis (NECOSAD Study Group) and compared to eGFR (MDRD)
- "mGFR" = 6.0ml/min/1.73m^2; eGFR (MDRD) = 6.8ml/min/1.73 (13% relative + bias for eGFR (MDRD)- range -4.1 to +5.6ml/min/1.73m^2
- P30 values (% of estimate above or below mGFR by <30% ) was 61%
- eGFR (MDRD) provides very inaccurate estimated of mGFR in Stage 5 CKD
eGFR in Stage 5 CKD

Conclusions

☐ eGFR (MDRD) is unsuitable for estimating residual renal function (mGFR) in Stage 5 CKD. Calculated GFR (Ccr+Cu/2) may be better

☐ In presence of a low GFR the muscle mass is a relatively more important determinant of serum creatinine level than mGFR

☐ Low muscle mass (and higher eGFR [MDRD]) are associated with increased mortality in Stage 5 CKD after starting HD

eGFR (MDRD-IDMS)-
Re-expressed Equation (2007)

☐ A new modification of the eGFR (MDRD) (1999) equation was introduced in 2007 to adjust for use Scr values based on a isotope dilution mass standard (IDMS)

☐ eGFR (MDRD-IDMS) ml/min/1.73m² = 175 x Scr⁻¹.154 x age in yrs⁻⁰.²⁰³ x 1.212 (Black) x 0.742 (female)

(This formula can ONLY be used if the laboratory standardizes Scr to the IDMS)

Ethnic Variation in eGFR Equations
(Creatinine-based)

☐ Due to ethnic variation in non-GFR related determinant of serum creatinine the exponents and co-efficient used in the MDRD (1999 and 2007) may need to be altered

☐ Chinese, Japanese, Korean, Taiwanese, Indian versions of eGFR (creatinine) have been published and show improved accuracy for estimating mGFR in these populations
**Cystatin-C is an endogenous 13 kDa protein produced at a relatively constant rate by most nucleated cells. It is completely filtered by the glomeruli and then reabsorbed and fully catabolized in the tubule (only trace amounts are excreted in the urine) - actual production rate can only be measured if mGFR is known**

- Serum concentration is less influenced by muscle mass
- First used in 1985 to estimate GFR by Grubb, et al

**eGFR-CYC**

<table>
<thead>
<tr>
<th>eGFR (CYC) in ml/min/1.73m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>127.7 ( \times ) Scyc (mg/L)(^{-1.10}) ( \times ) age in yrs(^{-0.13}) ( \times ) 0.91</td>
</tr>
<tr>
<td>(female) ( \times ) 1.06 (Black)</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>50.52 ( \times ) Scyc (mg/L)(^{-1.26}) (if Scys&gt;2.0mg/L)</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>84.7 ( \times ) Scyc (mg/L)(^{-1.80}) ( \times ) 1.384 (if &lt;14 years)</td>
</tr>
</tbody>
</table>

**eGFR-(CYC)**

- Must be in a steady state
- Scyc influenced by non-GFR factors
  > inflammation (high CRP- cyc is in the anti-inflammatory cascade)
  > leucocytosis
  > hypoalbuminemia (negative acute-phase reaction)
  > aging
  > gender
  > diabetes
  > obesity
eGFR (CYC)
- The reciprocal of $S_{\text{CYC}}$ (in mg/L) $\times 100$ is a "reasonable" approximation of GFR
- The reciprocal of $S_{\text{CR}}$ (in mg/dL) $\times 100$ is also a "reasonable" approximation of GFR
- Is eGFR (CYC) any better than 1/Scr? Maybe, with appropriate "caveats": it adds a dimension of "inflammation", whereas Scr is influenced by sarcopenia.

eGFR- CKD-EPI (2009)
- A new Scr-based GFR estimating equation developed by the Chronic Kidney Disease Epidemiology Collaboration (EPI) in 2009
- 8254 participants (mGFR= 68ml/min/1.73m$^2$- range 2-190ml/min/1.73m$^2$; males and females, age 20-75 years.
- eGFR- CKD-EPI equation (a spine function of log Scr with gender specific knots at 0.7mg/dL in F and 0.9mg/dL in M).

eGFR- CKD-EPI
- Compared to eGFR (MDRD-IDMS) the eGFR-CKD-EPI has:
  - less bias--- -2.5 vs -5.5ml/min/1.73m$^2$ (a 54% improvement)
  - slightly better precision- inter-quartile differences 16.6 vs 18.3ml/min/1.73 (a 9% improvement)
  - marginally greater accuracy- $P_{30}$  84.1% vs 80.6% (a 4% improvement)
  - Overall performance better than eGFR (MDRD) at eGFR >60ml/min/1.73m$^2$
eGFR in an era of creatinine standardization

A Systematic Review


☐ Systematic Review of published articles using SRM-referenced Scr and estimating equations (MDRD or CKD-EPI) vs mGFR

☐ MDRD- Bias=-22 to +15; P30=71-93%

☐ CKD-EPI- Bias= -14 to +13; P30=64-95%

CKD-EPI vs MDRD eGFR

(Systematic Review)

☐ CKD-EPI is more accurate (higher P30) than MDRD in 10/12 studies but bias is more variable

☐ CKD-EPI performs better at mGFR >60ml/min/1.73m²; MDRD performs better than CKD-EPI at mGFR <60ml/min/1.73m²

☐ Co-efficient used in eGFR equations cannot be generalized beyond local populations

☐ Differences in the development and validation populations explain much of the difference in performance of MDRD and CKD-EPI equations

☐ Use of CKD-EPI instead of MDRD to define CKD lowers sensitivity but increases specificity

eGFR and CKD-EPI-

Influence of BMI


![Graph showing eGFR and CKD-EPI influence of BMI]
MDRD and CKD-EPI EQUATIONS: General Population
(van den Brand, JAJo, et al. NDT, February 2011)

- 6097 Caucasians studied in the Nijmegen Biochemical Study for MDRD and CKD-EPI estimates of GFR (eGFR)
- All ambulatory, presumed healthy, ages 18-98 years (27% over 70 years of age) 45% Males.
- Stage 3-5 CKD (eGFR <60ml/min/1.73m²) determined

CKD- MDRD or CKD-EPI
(van den Brand, et al NDT, 2011)

- Graph showing distribution of CKD stages 3-5 by age group and MDRD or CKD-EPI estimates
- Graph showing difference in MDRD vs CKD-EPI for different age groups

CKD- MDRD or CKD-EPI
(van den Brand, et al NDT, 2011)

- Graph comparing MDRD vs CKD-EPI for males, females, and all genders across different age groups
CKD-EPI Equation

- Application to existing KDOQI definition of CKD (2002)
  - Reduces prevalence of CKD in those under 45 years of age
  - Increases prevalence of CKD in subjects over 65 years of age

CKD-EPI eGFR Accuracy (p30 values)
(Botev R and Delanye P - personal communication - 25 studies)

THE LATEST EQUATION ON THE BLOCK - Combined Creatinine-Cystatin C equation
(Inker LA, et al NEJM July 5, 2012 - CKD-EPI)

- CKD-EPI- Cr + CYC vs CKD-EPI Cr*
  - Bias - 5% worse (-3.9 vs -3.7)
  - Precision - 13% better (13.4 vs 15.5)
  - Accuracy (1-P30) - 33% better (8.5 vs 12.8)
  * relative to mGFR
In terms of overall accuracy, the CKD-EPI Cr + CYC equation out-performs all other GFR estimating equations and improves the correct classification of CKD GFR Categories by about 20% (in terms of mGFR).

**eGFR in the Elderly**


- None of the creatinine or Cystatin-C GFR estimating equations have been formally evaluated (vs mGFR) in the Elderly population.
- The Berlin Initiative Study (BIS) carried out such an evaluation (using Ciohexol for mGFR) in 610 all-Caucasian subjects all over age 70 years.
- Two new age-specific equations (BIS-I [cr] and BIS-II [cr + cys]) were developed and validated.

**BIS-I and BIS-II eGFR Equations**

- **BIS-I (cr)**
  
  \[
  3736 \times \text{Scr (mg/dL)}^{-0.87} \times \text{age}^{-0.95} \times 0.82 \text{ (if female)} = \text{eGFR}
  \]

- **BIS-II (cr + cys)**
  
  \[
  767 \times \text{cystatin C (mg/L)}^{-0.61} \times \text{Scr (mg/dL)}^{-0.40} \times \text{age}^{-0.57} \times 0.87 \text{ (if female)}
  \]
Bias, Precision and Accuracy: C-G, MDRD, CKD-EPI (cr), CYC, BIS-I (cr), and BIS-II (cr + cyc)

<table>
<thead>
<tr>
<th></th>
<th>Bias (ml/min/1.73m$^2$)</th>
<th>Precision (1SD)</th>
<th>Accuracy (%&lt;p30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-G</td>
<td>+2.74</td>
<td>11.7</td>
<td>87.4</td>
</tr>
<tr>
<td>MDRD</td>
<td>+11.21</td>
<td>11.4</td>
<td>70.9</td>
</tr>
<tr>
<td>CKD-EPI (cr)</td>
<td>+8.94</td>
<td>10.1</td>
<td>77.9</td>
</tr>
<tr>
<td>CYC</td>
<td>+3.22</td>
<td>10.7</td>
<td>89.1</td>
</tr>
<tr>
<td><strong>BIS-I</strong></td>
<td><strong>+0.11</strong></td>
<td><strong>9.2</strong></td>
<td><strong>95.1</strong></td>
</tr>
<tr>
<td><strong>BIS-II</strong></td>
<td><strong>+0.09</strong></td>
<td><strong>8.1</strong></td>
<td><strong>96.1</strong></td>
</tr>
</tbody>
</table>

eCcr/eGFR-Pediatrics

Schwartz/ Counahan-Barratt Equations

- **eCcr (Schwartz)**
  
  \[
  eCcr \text{ ml/min} = 0.55 \times \text{Height (cm)} \,
  \text{Scr (mg/dL)}
  \]

- **eGFR (Counahan-Barratt)**
  
  \[
  eGFR \text{ ml/min/1.73m}^2 = 0.43 \times \text{Height (cm)} \,
  \text{Scr (mg/dL)}
  \]

GFR Estimating Equations: The Bottom Line

- All GFR estimating equations are *imprecise* and potentially *biased* relative to measured GFR (although not always in the same direction)
- The estimating equations perform best when applied to the subjects having the *same* characteristics of the group from which they were derived
- The eGFR (MDRD), (CKD-EPI) or (CYC) equations are not optimal across all population and mGFR ranges; The new CKD-EPI- Scr +CYC may be superior for to estimation of mGFR. Special equations are needed in the elderly and in certain ethnic groups
CKD-Diagnosis/Staging:

**MDRD or CKD-EPI EQUATION**

GFR-Estimating Equations:  
**Issues**

- **Scr-derived**
  > overestimates GFR in malnutrition, muscle wasting, nephrotic syndrome, vegetarians, ESRD
  > underestimates GFR in high meat diets, muscle building
  > confounded by interfering substances in plasma

- **Cystatin-C derived**
  > values influenced by gender, race, diabetes
  > bias introduced by inflammation, hypoaalbuminemia, leukocytosis

eGFR- Correction for BSA:  
**Is it appropriate?**

- The eGFR (MDRD), eGFR (Re-expressed), eGFR (CKD-EPI), and Counahan-Barratt eGFR (Pediatrics) give eGFR standardized to a BSA of 1.73m²; the eCcr (C-G) does not.

- Example of potential errors:
  Two 75 year old men with identical Scr=1.2mg/dL and BMI 27kg/m². Subject A- BSA= 1.95m²; Subject B- BSA= 1.40m²
  eGFR (MDRD)
  Subject A= 63ml/min/1.73m²  
  Subject B= 63ml/min/1.73m²

  Uncorrected eGFR:
  Subject A= 71ml/min  
  Subject B= 51ml/min

**Which value for GFR is correct? (for drug dosing or diagnosis of CKD)**

**eGFR and Diagnosis of CKD**

**CKD:**
*KDIGO-2012 Definition/Classification (CGA)*
*(Kidney International Supplements; January 2013)*

<table>
<thead>
<tr>
<th>Category</th>
<th>Description and range</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
<th>G1</th>
<th>G2</th>
<th>G3e</th>
<th>G3d</th>
<th>G4</th>
<th>G5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or high</td>
<td>≥90</td>
<td>90.0</td>
<td>1.9</td>
<td>0.2</td>
<td>97.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mildly decreased</td>
<td>60-89</td>
<td>90.8</td>
<td>2.0</td>
<td>0.3</td>
<td>95.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately to moderately decreased</td>
<td>45-59</td>
<td>9.6</td>
<td>0.9</td>
<td>27</td>
<td>4.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe decreased</td>
<td>15-29</td>
<td>1.0</td>
<td>1.1</td>
<td>31</td>
<td>1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney failure</td>
<td>&lt;15</td>
<td>5.3</td>
<td>5.4</td>
<td>1.3</td>
<td>100.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CKD (G3/4) Prevalence Depends on eGFR Equation
(Pattaro, et al, 2013)

According to mGFR ($C_{\text{edta}}$) and eGFR (MDRD)
(Froissart, et al. JASN, 2005-2095 subjects; 1995 with
CKD and 162 normal donors)

<table>
<thead>
<tr>
<th>mGFR</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
<th>Stage 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;90</td>
<td>67%</td>
<td>32%</td>
<td>0.6%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>60-89</td>
<td>16%</td>
<td>64%</td>
<td>21%</td>
<td>0.2%</td>
<td>0</td>
</tr>
<tr>
<td>30-59</td>
<td>0.5%</td>
<td>12%</td>
<td>78%</td>
<td>10%</td>
<td>0</td>
</tr>
<tr>
<td>15-29</td>
<td>0</td>
<td>0</td>
<td>17%</td>
<td>79%</td>
<td>4.2%</td>
</tr>
<tr>
<td>&lt;15</td>
<td>0</td>
<td>0</td>
<td>3.1%</td>
<td>32%</td>
<td>65%</td>
</tr>
</tbody>
</table>
Classification of CKD Stages by $eCcr$ (c-G)
eGFR (MDRD) and eGFR (CKD-EPI):

*Performance relative to mGFR*

**Correct classification of CKD Stage**
- C-G $eCcr/1.73m^2 = 64\%$ (55-72%)
- $eGFR$ (MDRD) = 63\% (53-71%)
- $eGFR$ (CKD-EPI) = 69\%

Classification of CKD Stage (Category) by Scr based formulae will be *incorrect* (relative to mGFR) in about 1 of 3 patients

CKD Prevalence Trends:

*eGFR (creatinine) v eGFR (cystatin C)*
The prevalence rates of CKD by estimated GFR will vary according to the method for determining eGFR.


- Using the enzymatic, IDMS-traceable values for Scr compared to eGFR (MDRD) and eGFR (Mayo Clinic)—
- 97.5% of subjects could be correctly classified as having Stage 3-5 CKD (KDOQI-2002)
- eGFR equations have no added value over IDMS-Scr in classifying CKD (Stage 3-5)

Receiver Operating Characteristics for Scr (□) and eGFR (●) (--- LOI) in Diagnosis of Stage 3 CKD (Kallner A, Khatami Z, Scand J Clin Lab Invest. 68:39, 2008)
Use of eGFR (alone) to Diagnose CKD has significant limitations

- Issues of bias, precision and accuracy
- Issues of what is “normal” eGFR according to age and gender
**KDIGO-CKD-2012:**

*Recommendations for evaluation of GFR*

(Kidney International Supplements 3: 2013 (January))

- **Initial Assessment** - use Scr standardized to IDMS reported in 2 decimal places (mg/dL or μM/L) and an estimating equation (CKD-EPI [cr] preferred) for eGFR adjusted to 1.73m²

- **Confirmatory Testing** - use eGFR (cyc) or CKD-EPI (cr + cyc) or a clearance method (endogenous Ccr or mGFR [e.g. iohexol or iothalamate]) when eGFR (cr) is *less accurate* or when eGFR (cr) is 45-59ml/min/1.73m² and markers of kidney damage are absent (e.g. CGA Class G3A/A1)

---

When using eGFR to evaluate renal function in diagnosis and treatment, it is crucial that one clearly understand the clinical situations where eGFR is so inaccurate as to be rendered unsuitable. Direct measurement of GFR (mGFR) may be needed in these circumstances depending on the impact of the results on decision making.

---

*eGFR and Assessment of Progression*
eGFR and GFR Renal Function Trajectories

Renal Function Trajectory (eGFR-creat) in the AASK Trial
(Li L, et al AJKD 2012; 59:504-512)

- Non-linear or prolonged non-progression – 42%
- Linear progression – 58%
  (At >0.9 Probability- baseline eGFR= 50.2ml/min/1.73m²
   (40-59ml/min/1.73m² = 25th and 75th percentile)
- Baseline eGFR >40ml/min/1.73m² and/or a UACR <220mg/gm associated with higher probability of non-progression
eGFR- Assessing Progression (Longitudinal Studies)

- eGFR (MDRD) and eCcr (c-G) underestimates mGFR at higher values of GFR (>60ml/min/1.73m²) and overestimates mGFR at lower values of GFR (particularly in Stage 4 (malnutrition, loss of LBM))

- Slope of eGFR and mGFR vs time may show systemic (unexplained) variances

Variation of mGFR and eGFR (MDRD) slopes in CKD
(Xie D, et al JASN 3:1332, 2008)

Use of mGFR and eGFR in assessing progression and treatment effects in ADPKD

- Iohexol mGFR and eGFR (MDRD)/(CKD-EPI) assessed simultaneously in a cohort (n=111) of ADPKD studied in interventional trials (SIRENA; EUDRACT)

- Changes in mGFR and eGFR changes at one year compared
eGFR vs mGFR in estimating “progression” in ADPKD

- Current eGFR equations may not be adequate for accurate assessment progression rates in interventional trials
- The assumption that co-efficients used in eGFR equations remain constant with follow-up may not be correct

Reciprocal of Scr: A tool for following progression
Use of eGFR to evaluate Living Donors

eGFR/mGFR-
Living Donor Evaluation

- eGFR (MDRD; Re-expressed) imprecise and biased in the normal range of GFR
- Many potential donors will be rejected (eGFR <80ml/min/1.73m2)
- mGFR (Cio) or 24 hour Ccr are recommended for evaluation of GFR in LD

eGFR is inadequate for evaluation of Living Donors

- eGFR (MDRD; Re-expressed) imprecise and biased in the normal range of GFR
- Many potential donors will be rejected (eGFR <80ml/min/1.73m2)
- mGFR (Cio) or 24 hour Ccr are recommended for evaluation of GFR in LD
eGFR and Assessment of Complications

- eGFR and Cardiovascular Risk in CKD
- eGFR and risk of Progression to ESRD
- eGFR and Metabolic Complications

---

**CKD-CVD:**

Adjusted HR for All-Cause Mortality and CV Events

*Go et al, NEJM*

---

**All-Cause Mortality and eGFR**

Taiwan Health Management Institution Study

(462,293 Adults-No abnormal proteinuria)

*Wen, CP et al. The Lancet 371:2173, 2008*
All-Cause Mortality and Proteinuria
(At same eGFR strata)
Taiwan Health Management Institution Study

CV Events (Hazard Ratio after adjustment for co-morbidity-95% CI)
Microalbuminuria
Absent          Present
Not Reduced     1.00          1.20 (ref) (0.8-1.8)
Reduced*       0.90          1.60 (0.6-1.4) (1.0-2.5)
(*<64ml/min/1.73m2 in males; <59ml/min/1.73m2 in females)

CVD and CKD:
Cross-Classification of eGFR and Microalbuminuria: Effect on CV Event Risk

CKD Stage 3
Risk of Cardiovascular Disease
(Brantsma AH, et al and PREVEND. NDT, 2008)
(n=8495-1590 with CKD)
**eGFR and CVD Risk in Women:**
*The Women’s Health Study*
(Kurth T, et al BMJ 338:[July], 2009: 27939 “healthy women >45y old, followed for 12 years)

![Graph showing eGFR and CVD risk across different age groups.]

**Fully Adjusted Mortality Risk by eGFR in Various Age Groups**
(O’Hare AM, et al. JASN 17:846-863, 2006)

![Graph showing fully adjusted mortality risk by eGFR across different age groups.]

**Mechanisms of “Attenuation” of Mortality Risk with Aging in eGFR Strata**

- “Survivor” bias
- More subjects with “normal for age” eGFR

HR for All-Cause and CV Mortality according to eGFR and UACR or Dipstick Proteinuria (CKD Prognosis Collaboration Lancet May 18, 2010)

eGFR and UACR-
A-Risk of fatal or non-fatal CVD events; B- Risk of 2xScr or ESRD (Clase CM, et al Ann Intern Med 154:310-318, 2011)
**eGFR and Prognosis:**

**The French 3 Cities Study**

(Stengel B, et al NDT June, 2011)

- 8705 community living adults >65 years of age studied for all-cause and CV mortality over 6 years according to eGFR (MDRD) and eGFR (CKD-EPI)
- Median eGFR (MDRD) - men = 78; women 74 ml/min/1.73
- Median eGFR (CKD-EPI) - men = 79; women 77 ml/min/1.73 m²
- Stage 3,4,5 = 13.7% for eGFR (MDRD) and 12.7% for eGFR (CKD-EPI)

---

**Three Cities Study:**

**Relative Risk of All-Cause and CV Mortality (over 6 years)**

![Graph showing relative risk of mortality over 6 years according to eGFR (MDRD) for all causes and cardiovascular causes.](image)

- RR of event over 6 years
- eGFR (MDRD) - ml/min/1.73 m²
- □ All Cause - Men □ All Cause - Women
- □ CV - Men □ CV - Women

---

**eGFR/UACR and HR for All-Cause Mortality according to Age**

(Hallan S, et al JAMA, 2012)

![Graph showing HR for all-cause mortality according to age and eGFR/UACR.](image)
eGFR/UACR and HR for ESRD

According to Age

(Hallan S, et al. JAMA, 2012)

**Some Under-appreciated Facts**

- The risk of CVD in Stage 3 CKD is not increased unless proteinuria is also present.

- The relationship of eGFR to CVD risk may have a "U" or "J" shape (higher eGFR spuriously associates with higher risk of CVD due to overestimation of mGFR).

- The risk of CVD increases below an eGFR of about 45-50 ml/min/1.73 m², particularly in males. CV Risk is mainly CHF.

- The risk of mortality (principally CVD) is attenuated by advancing age for all levels of eGFR <50 ml/min/1.73 m². The threshold level of eGFR below which mortality rate exceeds a referent category is much lower than in younger patients.

---

Adding eGFR and UACR to "Traditional Risk Factors". ONTARGET and TRANSCEND (n=27,620)

(Clase, C. Ann Intern Med 154:310. 2011)
CKD-CVD Associations

- The risk of CVD only begins to increase significantly at eGFR values <45ml/min/1.73m2.

- Concomitant proteinuria (albuminuria) magnifies the increased risk of CV events. In the absence of proteinuria (albuminuria) risk of CVD is not (greatly) increased in Stage 3A CKD.

- Hazard Ratio
- Quintiles of eGFR
- eGFR (CKD-EPI) vs eGFR (CYC)


- Hazard Ratio
- Quintiles of eGFR
- eGFR (CKD-EPI) vs eGFR (CYC)

eGFR (CYC) and CRP in the very Elderly (Shastri S, et al J Am Geri Soc, July, 2012)

- eGFR (CYC)-ml/min/1.73m²
- CRP (mg/L x 10)
Progression of Stage 3 CKD: 
The Tromso Study

- Cumulative 10 year incidence of treated Stage 5 CKD or Death (CVD)

<table>
<thead>
<tr>
<th>Age</th>
<th>Stage 5 CKD</th>
<th>Death</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;69 y</td>
<td>7%</td>
<td>17%</td>
<td>2.4</td>
</tr>
<tr>
<td>&lt;70-79 y</td>
<td>4%</td>
<td>49%</td>
<td>12.3</td>
</tr>
<tr>
<td>&gt;79 y</td>
<td>3%</td>
<td>84%</td>
<td>28.0</td>
</tr>
<tr>
<td>All</td>
<td>4%</td>
<td>51%</td>
<td>12.8</td>
</tr>
</tbody>
</table>

Albuminuria and Progression of CKD

(Hallan SI, et al JASN 20:1069-1077, 2009)

- Adjusted 10 year risk of ESRD according to eGFR and Albuminuria

<table>
<thead>
<tr>
<th>eGFR (ml/min/1.73m²)</th>
<th>Normal UACR</th>
<th>Microalbuminuria</th>
<th>Macroalbuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>1.00</td>
<td>27.3</td>
<td>196.3</td>
</tr>
<tr>
<td>45-59</td>
<td>23.4</td>
<td>146.5</td>
<td>641.1</td>
</tr>
<tr>
<td>30-44</td>
<td>51.9</td>
<td>448.9</td>
<td>2036.0</td>
</tr>
<tr>
<td>15-29</td>
<td>368.7</td>
<td>2202.0</td>
<td>4146.0</td>
</tr>
</tbody>
</table>
In the elderly with "Stage 3 CKD" the risk of dying (often of CVD) is much higher than the risk of developing treated ESRD. This risk is attenuated with advancing age.
Metabolic Abnormalities in CKD