The “Epidemic” of Chronic Kidney Disease-
Myths and (Inconvenient) Truths

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A Contrarian’s Lament
Chronic Kidney Disease (CKD) - THE MYTHS

One in every eight individuals in the world has (chronic) kidney damage (disease)

There is a pandemic of chronic kidney disease in the world
Proposition: The Origins of the *Myths* of CKD

NKF-KDOQI (2002) and the MDRD eGFR equations (1999) conspired (inadvertently) to create the Myths of CKD
Estimation of GFR by Formula based on Serum Creatinine

**Modification of Diet in Renal Disease**
(MDRD-eGFR) (Levey, et al, 1999)

\[
eGFR \text{ (ml/min/1.73m2)} = 186 \times (\text{Age in years})^{-0.203} \times (\text{Scr in mg/dL})^{-1.154}
\]

( x 0.742 if female and x 1.212 if Black)

(Derived by analysis of 1629 subjects with chronic kidney disease and measured GFR values; overall Bias-compared to mGFR= -9.8ml/min/1.73m2; overall Precision- one SD of total difference compared to mGFR= 20ml/min/1.73m2)
### Chronic Kidney Disease (CKD): Classification (NKF-K/DOQI-2002)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Kidney Damage</th>
<th>eGFR* (ml/min/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>NA</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>NA</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>NA</td>
<td>&lt;15 (or dialysis)</td>
</tr>
</tbody>
</table>

(*calculated from serum creatinine level by the abbreviated MDRD equation; NA= not applicable: findings must persist for ≥3 months)
Estimated GFR (eGFR) in "Healthy" Caucasian Males
(Nijmegen Biomedical Study, 2008)

![Graph showing the estimated glomerular filtration rate (eGFR) across different age groups and percentiles.](image-url)
Estimated GFR in “Healthy” Caucasian Females
(Nijmegen Biomedical Study, 2008)

![Graph showing estimated glomerular filtration rate (eGFR) in healthy Caucasian females by age. The graph includes percentile lines for 95th, 50th, and 5th percentiles. The x-axis represents age in years, and the y-axis represents eGFR in mL/min/1.73m².](image-url)
## CKD Prevalence-USA:

**NHANES (KDOQI-Based:1999-2004)**

*(Coresh et al JAMA, 2007)*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Prevalence (%)</th>
<th>Prevalence (x 10⁶)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.78</td>
<td>3.6</td>
</tr>
<tr>
<td>2</td>
<td>3.24</td>
<td>6.5</td>
</tr>
<tr>
<td>3</td>
<td>7.69</td>
<td>15.5</td>
</tr>
<tr>
<td>4</td>
<td>0.35</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Total 1-4</strong></td>
<td><strong>13.07</strong></td>
<td><strong>26.3</strong></td>
</tr>
</tbody>
</table>

*(One in every 7.6 persons over age 20)*
CKD-NHANES: Characteristics of the Staged Populations

- **Stages 1 and 2 (38% of Total)**
  * 100% had abnormal albuminuria (by definition)-88% had microalbuminuria and 12% had macroalbuminuria

- **Stage 3 (59% of Total)**
  * 67% had no abnormal proteinuria (not needed for definition)

- **Stage 4 (2.8% of Total)**
  * 23% had no abnormal proteinuria

- **Total Stage 1-4 (100% of total)**
  * M/F ratio = 0.74
  * 87% had no abnormal proteinuria
Microalbuminuria: Prevalence
(NHANES, 1999-2004)

- 4.5% of the US Adult Population (~ 8.8 Million persons) has microalbuminuria with an eGFR >60ml/min/1.73m² (Stage 1 + 2 CKD according to the KDOQI-CKD criteria)
- This represents 36% of those designated as having CKD (by KDOQI criteria)
- About 1 in every 3 individuals “diagnosed” as CKD (by KDOQI) have only microalbuminuria as a basis for this diagnosis
CKD-NHANES

Characteristics of the Staged Populations

- Stage 3 CKD (60% of the Total CKD population according to KDOQI)
  - > 67% had no proteinuria
  - > 85% over 60 years of age
CKD-NHANES-

**Summary**

- The **great majority** of **Stage 1 and 2 CKD** are so defined by having microalbuminuria **only** (85%+). Stage 1 and 2 **cannot** be reliably differentiated by eGFR (due to errors in MDRD at eGFR levels >60ml/min/1.73m²).

- The **great majority** (85%+) of **Stage 3 CKD** are found in subjects over 60 years of age, without any concomitant abnormal albuminuria.

- The **Male/Female** ratio of **Stage 1-4 CKD** (0.74) is the **opposite** of that found in treated ESRD (1.35).

- **As defined (by K/DOQI)**, **Stages 1-4 CKD** affects primarily the elderly population and is manifested by eGFR 30-59ml/min/1.73m² or by microalbuminuria and “normal” eGFR (>60ml/min/1.73m²).
KDOQI- CKD: Fatal Flaws

- Used the eGFR (MDRD) as an absolute threshold criteria for CKD Stages 3/4 (two-thirds of total CKD), without adjustment for age and gender and without respect to other corroborating evidence of “kidney damage”.

- Conflates microalbuminuria as a disease in Stage 1/2 (one-third of total CKD), rather than a risk factor for a disease
CKD-(Inconvenient) Truths

NKF-KDOQI and eGFR (MDRD) “conspire” together to markedly overestimate the global prevalence of true CKD.
Use of eGFR to “Diagnose” CKD: Issues

- eGFR normally **declines** with age 7-8ml/min/decade after age 40)

- Appropriateness of eGFR (MDRD equation) **not verified** in various ancestries, disease states, customary diets (underestimates true GFR)

- eGFR is **inaccurate**, particularly above values of 60ml/min/1.73m²
Estimated GFR (eGFR) in "Healthy" Caucasian Males
(Nijmegen Biomedical Study, 2008)
Estimated GFR in “Healthy” Caucasian Females
(Nijmegen Biomedical Study, 2008)
Ancestry/Geography Specific eGFR Equations (Chinese)

- 684 Chinese (Beijing) patients with CKD (Stages 1-5, KDOQI) were studied with TcDPTA “true” GFR and serum creatinine based eGFR equations
- A new Chinese-specific eGFR equation was generated having greater precision and accuracy and less bias than the original MDRD equation
A co-efficient of $X \times 1.233$ was added to the original MDRD equation:

$$\text{c-eGFR} = 186 \times \text{Pcr}^{-1.154} \times \text{age}^{-0.203} \times 0.742 \times (\text{if female}) \times 1.233$$

Thus, MDRD-eGFR (186 equation, 1999) underestimated GFR by 23.3% in Chinese and overestimated the prevalence of CKD (particularly Stage 3 CKD).

Using MDRD-eGFR, 60% of subjects were re-classified as Stage 2 CKD by “true” GFR; with the new Chinese-eGFR, only 20% were erroneously classified as Stage 3 CKD when they were Stage 2 by “true” GFR.
eGFR and Measured GFR (mGFR): Accuracy and Precision

- Proper and accurate classification of CKD (according to levels of GFR) requires that eGFR affords reasonably precise estimates of actual mGFR.

- The MDRD eGFR does not meet these criteria.
eGFR (MDRD): Performance

A comparison of the precision of MDRD, Cockcroft-Gault (C-G) eGFR and $^{51}$Cr-EDTA “true” GFR (mGFR) was conducted in 2095 adult Europeans (1993 with CKD; 162 Healthy donors-average mGFR= 61±33mL/min/1.73m2)
Predicted Values
of mGFR for eGFR (MDRD)-
(Mean and 95% CI)
(Froissart, et al JASN 16:763-773, 2005)
## Classifications of CKD According to mGFR (C_{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>
Precision of MDRD eGFR  
(Froissart, et al JASN, 2005)

- The MDRD equation lacked precision in identifying the Stage of CKD

- 22% of subjects with a mGFR of >60ml/min/1.73m² were misclassified as Stage 3 or 4 CKD by MDRD eGFR

- Overall misclassification rate was 32% for MDRD eGFR
Bias and Precision of eGFR (MDRD) (Botev, R, in the press, 2008)
**eGFR (MDRD):**

*Predictive Values for Measured GFR*

(Botev, R. personal communication)

<table>
<thead>
<tr>
<th>mGFR*</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;90</td>
<td>85%</td>
<td>76%</td>
</tr>
<tr>
<td>60-89</td>
<td>40%</td>
<td>85%</td>
</tr>
<tr>
<td><strong>30-59</strong></td>
<td><strong>60%</strong></td>
<td><strong>92%</strong></td>
</tr>
<tr>
<td>15-29</td>
<td>53%</td>
<td>93%</td>
</tr>
<tr>
<td>&lt;15</td>
<td>51%</td>
<td>98%</td>
</tr>
</tbody>
</table>

(*in ml/min/1.73m²)
Classifications of CKD (KDOQI) based on MDRD-eGFR will be *WRONG* when compared to a gold-standard mGFR in *one of about every three instances*.
MDRD-eGFR: The Future?

- Ancestry- and geography-specific co-efficients—"a "universal MDRD equation is impossible"")
- Adjustments for body habitus, customary dietary intake (meat/vegetable protein)
- Calibration to a universal (global) "gold standard" creatinine
- Repeated measurements (≥3 months apart) to define chronicity in epidemiologic studies (impractical)
- Combination of eGFR (MDRD) and Cystatin C eGFR or C-G Ccr (?)
- Abandonment for diagnostic/epidemiologic purposes (?)
A threshold value of a Scr=>110µmol/L (1.25mg/dL) in men and 95µmol/L (1.08mg/dL) in women performs equally well as a threshold of an eGFR (MDRD) <60ml/min/1.73m2 for diagnosing Stage 3 and greater CKD (as assessed by true GFR ($C_{iohexol}$))

Receiver Operating Characteristics for Scr (□) and eGFR (•) (---- LOI)
Conclusions

- The K/DOQI construct using the MDRD-eGFR is fatally flawed for use as an accurate way of identifying global burden of CKD---
  - use of absolute thresholds of eGFR not adjusted for age and gender
  - inclusion of microalbuminuria with "normal" eGFR as a criteria for diagnosing CKD
  - failure to adapt eGFR equations to ancestral/geographic variables to Scr/GFR relationships
  - irrelevant for definition of CKD in children—Pediatric CKD is uncharted territory
  - Accuracy of estimates of mGFR suspect
  - Not proven to be superior to Scr alone
Global Population-based Prevalence of CKD

- Requires a population specific adaptation of MDRD and possible differing thresholds for eGFR to define CKD Stages 3-4
- Cannot be determined by examination of eGFR among hospitalized patients or those under the care of a physician for a “disease” (e.g. nursing home)
- Using K/DOQI the prevalence of CKD will “track” with the average eGFR of the population, which in turn will reflect the average age of the population AND
- Will predictably over-estimate CKD prevalence in older subjects (65 years and older; mainly females)
Estimates of the Global Prevalence of CKD
(Glassock and Winearls, Nephron: Clinical Practice, 2008)

- Estimated prevalence of CKD from 11 Countries (USA, China, Norway, Australia, Spain, Japan, Thailand UK, Taiwan, Iceland and Mexico) using K/DOQI (2002) and eGFR (MDRD)

  Stages 1-2 = 5.1% (4.0-11.7%)
  Stage 3 = 8.1% (1.8-18.5%)
  Stage 4 = 0.3% (<0.1-0.6%)

**Total Stage 1-4 = 13.3% (10.3-16.3%)**
(825,000,000 of 6.2 Billion in the World!!!)
Global Prevalence of CKD

- If one eliminates microalbuminuria from Stages 1 and 2 CKD and
- Adjusts the eGFR thresholds for Stage 3 CKD by age and gender then
- The global prevalence of CKD would decrease to about 2.0% (or about 125,000,000; 4,000,000 in the USA—one in 50 individuals over age 20 years)
How well does KDOQI-CKD and eGFR “predict” progression to ESRD?
Progression of CKD: The Tromso Study

- The change in eGFR (MDRD), patient and renal survival was measured in the municipality of Tromso, Norway (population 58,000) over a 10 year period.

- 6863 of 38242 (18%) patients had “Stage 3 CKD” on single Scr measurement—88 (1.3%) had a subsequent measure of Scr giving an eGFR <30ml/min/1.73m2 and 2175 (32%) had a subsequent measure of Scr giving an eGFR of >59ml/min/1.73m2—(33% “false positive” rate for a single Scr)
Progression of CKD: 
*The Tromso Study*

- **3074/38,242 (9.2%)** patients with at least **2** measures of Scr within a 3 month period and eGFR of 30-59ml/min/1.73m² *(Stage 3 CKD)* were followed for a mean of 50 months (up to 10 years)

- *Mortality, development of (treated) Stage 5 CKD and change in eGFR over* time were determined according to age and gender
Progression of 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>
Ratio of CKD Stage 3-4 Prevalence to Treated ESRD (CKD Stage 5D) Incidence in Males and Females (NEOERICA, 2008)
Relationships of Global Burden of CKD and Treated ESRD

- Based on prevalence rates of CKD Stage 3 only about **0.15%** of patients will enter ESRD treatment programs (in developed countries) each year (transition rate-Stage 3 to RRT-Stage 5D or T)

- Ratio of Stage 3-4 Prevalence to Treated ESRD Incidence (per million population) at any point in time *varies by age and gender* (NEOERICA, 2005 and CG analysis)
Conclusions

- Global prevalence rates of CKD have been **greatly overestimated due to inherent flaws in the K/DOQI construct and the eGFR (MDRD) formula**.

- Even with "bona-fide" Stage 3 CKD the **risk** of surviving and receiving ESRD treatment (in developed countries) is **very low** and inversely related to age (0.2-0.4% per year; greater in males than females), despite higher mortality in males from CVD.

- The combination of **reduced eGFR and dipstick positive proteinuria greatly increases** the risk of progression to ESRD (proteinuria more predictive than eGFR). eGFR and proteinuria are poorly correlated with each other.
Does a “low” eGFR predict CVD (events or deaths)?– An analysis of Stage 3 CKD.
**CKD-CVD:**

*Adjusted HR for All-Cause Mortality and CV Events*  
*(Go et al, NEJM)*

![Bar chart showing adjusted hazard ratios for mortality and CV events across different eGFR categories.](image-url)
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)

Hazard Ratio

<table>
<thead>
<tr>
<th>eGFR (ml/min/1.73m²)</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;135</td>
<td>1.0</td>
</tr>
<tr>
<td>120-134</td>
<td>2.0</td>
</tr>
<tr>
<td>105-119</td>
<td>3.0</td>
</tr>
<tr>
<td>90-104</td>
<td>4.0</td>
</tr>
<tr>
<td>60-89</td>
<td>5.0</td>
</tr>
<tr>
<td>45-59</td>
<td>6.0</td>
</tr>
<tr>
<td>30-44</td>
<td>7.0</td>
</tr>
<tr>
<td>15-29</td>
<td>8.0</td>
</tr>
<tr>
<td>&lt;15</td>
<td>9.0</td>
</tr>
</tbody>
</table>
All-Cause Mortality and Proteinuria

*(At same eGFR strata)*

Taiwan Health Management Institution Study

![Graph showing hazard ratio for different eGFR strata and proteinuria categories.](image-url)
## CVD and CKD: Cross-Classification of eGFR and Microalbuminurinaria: Effect on CV Event Risk

- **CV Events** (Hazard Ratio after adjustment for co-morbidity-95% CI)

<table>
<thead>
<tr>
<th>Microalbuminurinaria</th>
<th>Absent</th>
<th>Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Reduced</td>
<td>1.00</td>
<td>1.20</td>
</tr>
<tr>
<td></td>
<td>(ref)</td>
<td>(0.8-1.8)</td>
</tr>
<tr>
<td>Reduced*</td>
<td>0.90</td>
<td><strong>1.60</strong></td>
</tr>
<tr>
<td></td>
<td>(0.6-1.4)</td>
<td>(1.0-2.5)</td>
</tr>
</tbody>
</table>

(*<64ml/min/1.73m2 in males; <59ml/min/1.73m2 in females)
CKD Stage 3

Risk of Cardiovascular Disease

(Brantsma AH, et al and PREVEND. NDT, 2008)
(n=8495-1590 with CKD)

Hazard Ratio for CV Events (no CKD=1.00)

Stage 1  Stage 2  Stage 3 (All)  Stage 3 (UAE <30mg/d)  Stage 3 (UAE >30mg/d)

CKD Stage
CKD-CVD Associations

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

- Concomitant proteinuria magnifies the increased risk of CV events. *In the absence of proteinuria risk of CVD is not increased in Stage 3 CKD*
What can (should) be done?
Recommendations for Redesigning the Staging System for Chronic Kidney Disease (Winearls and Glassock, Kidney Int, in-the-press, 2008)

- Eliminate microalbuminuria as a criteria for defining CKD (a risk factor is not a disease)

- Compress CKD Stages 1-2 into a single Stage based on evidence of overt kidney damage (e.g. macroalbuminuria) with a “normal” eGFR

- Use age and gender appropriate values for eGFR to diagnose CKD (in the absence of other corroborative evidence of kidney damage)

- Use ancestry/geography specific equations for estimating eGFR from serum creatinine concentrations
A Proposed Revised Staging System for CKD
*(Winearls and Glassock, Kidney Int. In the press 2008)*

<table>
<thead>
<tr>
<th>Stage</th>
<th>eGFR</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;5&lt;sup&gt;th&lt;/sup&gt; percentile of healthy age/sex matched subjects</td>
<td>Macroalbuminuria or Glomerular hematuria or Abnormal histology or Imaging</td>
</tr>
<tr>
<td>2</td>
<td>&lt;5&lt;sup&gt;th&lt;/sup&gt; percentile of healthy age/sex matched subjects, but &gt;30ml/min/1.73m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>As in Stage 1</td>
</tr>
<tr>
<td>3</td>
<td>15-30ml/min/1.73m&lt;sup&gt;2&lt;/sup&gt;, (regardless of age/sex)</td>
<td>Kidney damage assumed</td>
</tr>
<tr>
<td>4</td>
<td>&lt;15ml/min/1.73m&lt;sup&gt;2&lt;/sup&gt;, (regardless of age/sex)</td>
<td>Kidney damage assumed</td>
</tr>
<tr>
<td>5</td>
<td>Dialysis dependent</td>
<td>Kidney damage assumed</td>
</tr>
</tbody>
</table>

*(Suffix T added for kidney transplant recipients)*
Subjects (of any age) with eGFR* <5th percentile for age/sex but without any corroborating evidence of kidney damage (macroalbuminuria, glomerular hematuria, imaging or histology) would be labeled as:

“RedUced Renal Function of Uncertain Significance” (RUFUS) NOT Chronic Kidney Disease

(*Ancestry/Geography specific)
Conclusions

- Global prevalence rates of CKD have been *greatly overestimated due to inherent flaws in the K/DOQI construct and the eGFR (MDRD) formula*.

- Even with “bona-fide” Stage 3 CKD the **risk** of surviving and receiving ESRD treatment (in developed countries) is **very low** and inversely related to age (0.2-0.4% per year; greater in males than females), despite higher mortality in males from CVD.

- The combination of **reduced eGFR and dipstick positive proteinuria increases** the risk of progression to ESRD and risk of CV events (proteinuria more predictive than eGFR). eGFR and proteinuria are poorly correlated with each other.
Final Comments

The purported global “epidemic” of CKD is a myth------ it does not now and probably never has existed---- it is/was an artifact of a flawed definition and methodology for defining CKD

The truth is now being appreciated--- this will require a complete and thorough re-assessment of strategies for the control of CKD as a public health issue
“Modern medicine is a negation of health– It is not organized to serve human health, but only itself, as an institution. \textit{It makes more people sick than it heals.}”

\textbf{Ivan Illich}

\textbf{Medical Nemesis (1974)}

(20\textsuperscript{th} Century Philosopher and Social Critic)
CKD-USA (K/DOQI):
NHANES (1999-2004)

- Composite results of estimating the prevalence of CKD (K/DOQI definition) in non-institutionalized adults (>20 years) by surveys involving volunteers and single estimates of eGFR (MDRD equation) and measurements of albumin excretion (microalbuminuria and macroalbuminuria).

- Findings adjusted to be “representative” of the USA non-institutionalized adult population.
CKD-NHANES

Over 70 years of age-% in Stage

- Stage 1/2
- Stage 3
- Stage 4
- Stage 1-4
MDRD-eGFR Equation

- Originally derived from a group of subjects all of whom had CKD—designated to evaluate the extent and severity of CKD—not for diagnosis of CKD.
- Values of 60-89 ml/min/1.73 m² were regarded as mildly reduced eGFR, yet these values incorporated the majority of values in normal, healthy subjects 45-65 years of age.
- Adjusting for BSA (automatic in the MDRD) can give rise to errors in estimating eGFR in obese and very lean subjects.
Glomerular Filtration Rate (Cin) and Filtration Fraction (Cin/RPF) in Ageing (Davies and Shock, J Clin Invest 29:496, 1950)

![Graph showing the decline of GFR and filtration fraction with age](image-url)
GFR (Cin) According to Age-
(Wesson, LG, 1983)
Percentiles of Estimated GFR (eGFR) according to Age
(from Coresh, et al and NHANES, 2002)
Two subjects, both 60 years of age, male and white have identical serum creatinine values (1.35mg/d), and BMI (27.4Kg/m²) but different BSA values:

> Subject A- BSA= 1.73m²
> Subject B- BSA= 2.28m²

**MDRD eGFR:**

> Subject A= 57ml/min/1.73m²
> Subject B= 57ml/min/1.73m²

(Both have stage 3 CKD)

**Absolute eGFR:**

> Subject A= 57ml/min
> Subject B= 75ml/min

Absolute eGFR is 32% higher in the larger man than the smaller man– which is the correct value for classification of CKD and also for dosing with a nephrotoxic drug??
Estimated GFR (eGFR) in “Healthy” Caucasian Males
(Nijmegen Biomedical Study, 2008)
## Classification of CKD According to mGFR ($C_{io}$) and eGFR (MRDD)-KDOQI
(from Poggio E, et al JASN 16:459-466, 2005- 828 CKD subjects only)

<table>
<thead>
<tr>
<th>mGFR</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4/5</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;90</td>
<td>79%</td>
<td>16%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>60-89</td>
<td>14%</td>
<td>72%</td>
<td>15%</td>
<td>0%</td>
</tr>
<tr>
<td>30-59</td>
<td>&lt;1%</td>
<td>23%</td>
<td>59%</td>
<td>18%</td>
</tr>
<tr>
<td>&lt;30</td>
<td>0%</td>
<td>&lt;1%</td>
<td>3%</td>
<td>96%</td>
</tr>
</tbody>
</table>
Estimated GFR in "Healthy" Caucasian Females
(Nijmegen Biomedical Study, 2008)
CKD Progression: The Tromso Study

Ratio of Death to ESRD in 5 years
CKD: Progression-
The MRFIT Study*

☐ 12,866 men at “high-risk” for CVD were enrolled in 1973-1974 and followed thru 1999 (25 years)

☐ Rate (25 year cumulative) of treated ESRD determined (USRDS)

☐ Single measurement of dipstick protein and eGFR (MDRD) at baseline related to cumulative (25 yr) risk of treated ESRD

# MRFIT Study

## Cumulative Prevalence of Treated ESRD

<table>
<thead>
<tr>
<th>Proteinuria</th>
<th>10y</th>
<th>25y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neg/Tr</td>
<td>&lt;0.5%</td>
<td>1.4%</td>
</tr>
<tr>
<td>1+</td>
<td>&lt;0.5%</td>
<td>5.0%</td>
</tr>
<tr>
<td>2+</td>
<td>3.1%</td>
<td><strong>20.1%</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>eGFR (ml/min/1.73m²)</th>
<th>10y</th>
<th>25y</th>
</tr>
</thead>
<tbody>
<tr>
<td>75+</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>60-75</td>
<td>&lt;0.5%</td>
<td>2.1%</td>
</tr>
<tr>
<td>&lt;60</td>
<td>1.0%</td>
<td><strong>5.2%</strong></td>
</tr>
</tbody>
</table>
CKD Progression:  
*The Tromso Study*-  
Conclusions

- Progression of CKD Stage 3 to treated Stage 5 CKD is uncommon (*about 0.4% per year*), in significant part due to the competing influence of “early” mortality” (mostly CVD)

- Deaths within 10 years of Stage 3 CKD are **13 X** more common than ESRD

- **Age and gender** have important influences on both risk of ESRD and death among patients with Stage 3 CKD. **Risk of developing treated ESRD varies inversely with age**
MRFIT Study

True Positive rate (sensitivity) for development of treated ESRD within 25 yrs of initial screening

- **Proteinuria** - 1+ or greater = 19%
  (FN rate = 81%)

- **eGFR** - <60ml/min/1.73m2 = 13%
  (FN rate = 87%)

- **Proteinuria or eGFR** - = 27%
  (FN rate = 73%)
### MRFIT Study -
**Relative Risk of Treated ESRD by 25 y**

<table>
<thead>
<tr>
<th>Proteinuria</th>
<th>Neg/Tr</th>
<th>1+</th>
<th>2+</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (ml/min/1.73m2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥75</td>
<td>1.0</td>
<td>1.9</td>
<td>11.4</td>
</tr>
<tr>
<td>60-75</td>
<td>0.8</td>
<td>2.8</td>
<td>12.9</td>
</tr>
<tr>
<td>&lt;60</td>
<td><strong>2.4</strong></td>
<td><strong>3.1</strong></td>
<td><strong>32.9</strong></td>
</tr>
<tr>
<td></td>
<td>(0.1%/yr)</td>
<td>(1.3%/yr)</td>
<td></td>
</tr>
</tbody>
</table>
CKD and CVD
Association of eGFR and CVD

PEACE Trial – CVD-HR (Adjusted)
10 year CV event free-survival: eGFR and Albuminuria Status

Gubbio Population Study

CVD and CKD - Cross Classification of eGFR and Microalbuminuria - Effect on CVD Events + All-Cause Mortality


- 5 year Event Rate (CVD + All-Cause Mortality in %) after adjustment for co-morbidity-

<table>
<thead>
<tr>
<th>Microalbuminuria</th>
<th>Absent</th>
<th>Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Reduced</td>
<td>5%</td>
<td>11%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>eGFR</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced*</td>
<td>14%</td>
<td>32%</td>
</tr>
</tbody>
</table>

(* <64 ml/min/1.73m² in males and <59 ml/min/1.73m² in females)
CVD in CKD

(Tonelli, et al, 2006)

- Unadjusted RR of CVD mortality in subjects with CKD (Stages 3, 4, 5 – no dialysis)

> mean age 50 years = RR of 3.4 (CI=2.1-5.5)
> mean age 70 years = RR of 1.5 (CI=0.96-2.3)

(Adjusted RR about 20% lower)
eGFR and All-Cause Mortality by Age
(O’Hare et al, 2006)
CVD and CKD-

The Framingham Risk Score in CKD
Final Comments

- The K/DOQI (2002) and eGFR-MDRD constructs have been very useful in galvanizing interest in a largely neglected area of study.

- But, they have inadvertently introduced myths and serious misconceptions regarding the definition and epidemiology of CKD that now require clarification and revision.

- Much more research is needed— better methods for simply and accurately assessing GFR- that is geography/ancestry specific; better markers for defining CKD and the risk of its progression to ESRD progression.
Tromso-II- Predictors of rate of decline in eGFR-over 7 years

In individuals without Diabetes or Cardiovascular Disease

> Age
> Systolic BP
> Urinary Albumin/Creatinine Ratio
> Smoking (women only)
> Physical inactivity (women only)

(Total and HDL Cholesterol, waist circumference, alcohol consumption not predictive)
Global Prevalence of CKD

A recent example of a country-wide epidemiological study from Asia
The Taiwan Health Management Institution Cohort Study

- A prospective cohort study of 462,293 adults (>20 years) in Taiwan (1994-2006)
- Cohort recruited by payment incentives (with discounts for those with large families)—**not representative of the population at-large and biased towards detecting familial disease**
A single initial Scr ( uncompensated Jaffe Kinetic method, non-calibrated to MDRD) and the original MDRD eGFR equation used to determine eGFR (unadjusted for a Chinese population or for use of an uncalibrated Scr).

Urine protein concentration (unadjusted for S.G.) measured by the Roche Miditron M (semi-quantitative, automated) method: negative=normal; trace-1+= minimal/microalbuminuria; 2+ or more= overt/macroalbuminuria
Subjects classified according to NKF-KDOQI into 5 stages of CKD or no CKD* and subdivided into minimal or overt proteinuria and/or by level of eGFR

**Stage 1**- eGFR ≥90ml/min/1.73m²
   1a= minimal proteinuria
   1b= overt proteinuria

**Stage 2**- eGFR 60-89ml/min/1.73m²
   2a= minimal proteinuria
   2b= overt proteinuria

**Stage 3**- eGFR 30-59ml/min/1,73m²
   3a= eGFR= 45-59ml/min/1.73m²
   3b= eGFR= 30-44ml/min/1.73m²

**Stage 4**- eGFR 15-29ml/min/1.73m²

**Stage 5**- eGFR <15ml/min/1.73m² (not on dialysis)
(*no CKD= eGFR >60ml/min/1.73m² and No Proteinuria)
Taiwan Health Management Institution Study

Stage of CKD

Prevalence (%)
Taiwan Health Management Institution Study

Prevalence of Stage 1-5 CKD (%)

Age (years):
- 20-24
- 25-29
- 30-34
- 35-39
- 40-44
- 45-49
- 50-54
- 55-59
- 60-64
- 65+

Percentage:
- 0%
- 5%
- 10%
- 15%
- 20%
- 25%
- 30%
- 35%
- 40%
Taiwan Health Management Institution Study

Flaws

- Not a population study—*biased* by selection forces (familial disease)

- eGFR threshold for defining CKD (Stage 3) not adjusted for age- or gender-effects on “normal” eGFR—*overestimates* CKD in the elderly

- Scr not adjusted for creatinine method; no calibration to MDRD standard; no adjustment of eGFR equation of Chinese population; single Scr—*no proof of chronicity*

- Proteinuria method (UAC semi-quantitative, not SG adjusted) subject to *false-positive error for minimal proteinuria*

- Portion of all-cause and CVD mortality attributable to CKD *greatly overstated*
Taiwan Health Management Institution Study
Adjustment of CKD Prevalence Estimates

☐ If minimal proteinuria reduced by 50% (for false positives) in both Stage 1a and 2a and

☐ If only 33% of subjects categorized as Stage 3a have eGFR below an age- and gender adjusted standard reference value (5th percentile) and

☐ If 50% of Stage 3a without abnormal proteinuria were not categorized as CKD and 30% were false positive due to single values of Scr used to define CKD then

☐ The estimated prevalence of CKD Stage 1-5 in Taiwan would fall to about 3% (a 65% decrease)