THE NKF-KDOQI (2002) CKD DEFINITION AND CLASSIFICATION SYSTEM: *Limitations and Problems*

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KDIGO Controversies Conference

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A Contrarians Lament
“A critic is a man who leaves no turn unstoned”

George Bernard Shaw
New York Times
November 5, 1950
Define chronic kidney disease (CKD) and to classify its stages, irrespective of underlying disease.

Evaluate laboratory measurements for the assessment of kidney disease.

Associate the level of kidney function with complications of CKD.

Stratify the risk of loss of kidney function (ESRD) and development of cardiovascular disease (CVD) and other complications of CKD.
Original Intent: Classification system was to be applied (unmodified) to both population analysis and to individual patient management.
# 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)*
The KDOQI-CKD Classification System

Benefits
(Real and Perceived)

- *Brought order to the chaos* of nosology of CKD
- *Increased awareness* of the “public health” problem of CKD in the general population and in general physicians
- *Galvanized research* (clinical, basic, epidemiological) on the issue of CKD
- *Stimulated interest in early detection* (population and targeted screening) of CKD
- *Minimized* untimely start of dialysis
Chronic Kidney Disease:

The KDOQI-CKD Classification System

Limitations and Problems
(Real and Perceived)

- Described as a *staging* system, it is really a *grading* system based on arbitrary bands of eGFR values
- Asserts that *normal* GFR is >90ml/min/1.73m2 and an GFR <60ml/min/1.73m2 is *pathological* across all adult ages, genders and ancestral groups
- Ignores *age- and gender*-related changes in GFR
- Linked to an *imprecise* measurement of GFR- the 4 variable eGFR (MDRD)
- Allows the “diagnosis” of CKD based on eGFR *alone*
- Conflates *isolated “microalbuminuria”* (in absence for diabetes or corroborating evidence of “kidney damage”) with “kidney disease”
- Links “*complications*” of “CKD” (e.g.CVD)to levels of eGFR, without reference to albuminuria
KDOQI-CKD (2002) Classification—Consequences of its Pitfalls

- Overestimated the global societal burden of CKD (Stages 1-4)
- Generated many unnecessary referrals from FP/GP to Nephrology (false-positive diagnosis of CKD)—leading to anxiety/expense
- Promoted screening for CKD (de facto and overt) using eGFR
- Promoted eGFR-defined CKD as a surrogate for CVD and ESRD risk—without consideration of role of albuminuria
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 10^6)</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>Total 1-4</td>
<td>13.07</td>
<td>26.3</td>
</tr>
</tbody>
</table>

*(One in every 7.6 persons over age 20-- 60% with Stage 3 CKD)*
CKD-NHANES

Prevalence of CKD (KDOQI) Stage 3 by Age
(1999-2004)
CKD Prevalence Trends:

eGFR (creatinine) v eGFR (cystatin C)

Aging and GFR
Glomerular Filtration Rate (C_{in}) and Filtration Fraction (C_{in}/RPF) in Ageing
(Davies and Shock, J Clin Invest 29:496, 1950)

![Graph showing the relationship between age and GFR (red line) and filtration fraction (blue line).]
CKD:

eGFR in “Healthy” Caucasians by Gender

Males

Females

(Wetzels, J et al; Nijmegen Biomedical Study, 2008)
CKD Prevalence: Kaiser-Permanente Age/Microalbuminuria-Adjusted and Standard KDOQI Criteria

eGFR (MDRD): Precision and Bias
eGFR (MDRD) vs mGFR (Cin)

(Botev, et al, CJASN, 2009)
Precision and Bias:

**eGFR (MDRD) vs mGFR (Cin)**


-20%  -10%  0%  10%  20%  30%  40%  50%  60%  70%

-20% -10%  0%  10%  20%  30%  40%  50%  60%  70%

-20% -10%  0%  10%  20%  30%  40%  50%  60%  70%

**mGFR (ml/min/1.73m2)**

90+  60-89  30-59  15-29  <15

**Bias (% mean difference)**

**Precision (% one SD of mean)**
Concordance of CKDStage According to mGFR (C\text{edta}) and eGFR (MDRD) (Froissart, et al. JASN, 2005) (2095 subjects; 1995 with CKD/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>
eGFR and Diagnosis of CKD: An Illustration

- A 25 year old man with an eGFR of 55 ml/min/1.73m² is 45% below the median for his age and -25 ml/min/1.73m² below the 5th percentile for age and gender

- A 75 year old man with an eGFR of 55 ml/min/1.73m² is 30% below the median for his age and +5 ml/min/1.73m² above the 5th percentile for age and gender

- WHICH ONE HAS SIGNIFICANT CKD?
CKD and Complications: 

Cardiovascular Disease (CVD)
CKD-CVD: Adjusted HR for All-Cause Mortality and CV Events
(Go et al, NEJM)
eGFR and Mortality Risk in the Elderly: *Over 70 years of age*

(ProSPER; n=5804)


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### Hazard Ratio (Fully Adjusted)

<table>
<thead>
<tr>
<th>eGFR Strata (ml/min/1.73m²)</th>
<th>All-Cause Mortality</th>
<th>Fatal/non-fatal CHD</th>
<th>Fatal/non-fatal CHF</th>
<th>Fatal/non-fatal Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-60</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-50</td>
<td>1.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-40</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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;
Lancet 2008

Hazard Ratio

<table>
<thead>
<tr>
<th>eGFR (ml/min/1.73m2)</th>
<th>Normal Proteinuria</th>
<th>Minimal Proteinuria</th>
<th>Overt Proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-104</td>
<td>1.0</td>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td>60-89</td>
<td>1.0</td>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td>45-59</td>
<td>1.0</td>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td>30-44</td>
<td>1.0</td>
<td>2.0</td>
<td>3.0</td>
</tr>
</tbody>
</table>
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)

0 0.5 1 1.5 2 2.5

CKD Stage
CVD events and CKD: 
**PREVEND Study**
(van der Velde M, et al. ASN, 2008)

![Hazard Ratio: CVD Events](chart)

- **eGFR (MDRD)-ml/min/1.73m2**
  - <60
  - 60-90
  - >90

- **Hazard Ratio**
  - Age >60; MA +
  - Age >60; MA -
  - Age <60; MA +
  - Age <60; MA -
CKD and Complications: Progression to ESRD
The HUNT-II Study-
Adjusted 10 year risk of ESRD according to eGFR and Albuminuria
(Hallan S, et al JASN 20:1069-1077, 2009)
The Problems with CKD Classification:

Conclusions-2009

- eGFR (1999) and KDOQI-CKD (2002) interacts to greatly **overestimate** the societal burden of CKD- Stages 1-4

- The “Diagnosis” of CKD by **arbitrary** eGFR thresholds (not adjusted for age and gender) leads to a significant **error** rate (false positive Stage 3 CKD)

- Risk of Complications of CKD, based on eGFR alone are **overemphasized**- neglects the multiplier effect of albuminuria

- Conflation of isolated “microalbuminuria” (without abnormal eGFR or diabetes) as a “kidney disease” lacks a firm **rationale**

- Screening for CKD based on eGFR alone cannot be **justified** as cost-effective for prevention of ESRD or CVD
What is “CKD”?  

- Is it a *Diagnosis*?--- For a population or an individual?  

- Is it a *Post-diagnostic* step to *grade* the severity and determine the risks of progression or complications?  

- Is it a *non-specific means of categorizing patients* with generic manifestations of specific kidney diseases?  

- *Or all three?*
“It ought to be remembered that there is nothing more difficult to take in hand, more perilous to conduct or more uncertain in its success than to take the lead in the introduction of a new order of things”

Niccolo Machiavelli- The Prince, 1513
THANK YOU !!!