New AHA Cardiovascular-Kidney-Metabolic (CKM) Staging Solves All Our Staging Problems and Should Be Applied Universally: The Nephrology Perspective

Adeera Levin MD FRCPC FCAHS OC
Professor of Medicine, Head Division of Nephrology
University of British Columbia
Vancouver, Canada
Disclosure and Perspectives

- Clinician
- Administrator
- Researcher
  - International collaborations
  - Clinical Trials: participation, execution, development and review
  - Steering Committees, Data Safety Monitoring Boards
  - Guideline methodology and development
  - CKD and CVD
  - Health systems research
  - Patient oriented research paradigms
Overview

• Perspectives
  • People living with kidney diseases
  • Nephrologists

• The purpose of staging systems
• Differentiating between Classification, Staging and Risk Prediction

• What problem are we solving?
• Towards Integrative frameworks
People with kidney disease(s) are complicated.

- Physiology
- Pathophysiology
- Drug reactions and interactions
- Differential drug binding

They have complex interactions:

- See multiple specialists
- Take many medications
- Are anxious, depressed, and overwhelmed
- Watch their numbers on the lab tests

They are afraid of needing to start dialysis and...
Nephrologists are ...

- Diverse group of specialists, interested in complex physiology
- Often Risk averse and conservative
- Worried about side effects of medications and understanding disease processes
- Accustomed to having lots of numbers
- Not accustomed to having a lot of trial data to inform decisions
Nephrologists have spent a long time...

Developing and validating eGFR equations

Developing and validating a staging system for CKD

Emphasizing need for establishing cause of CKD

Developing and validating risk prediction equations for different outcomes
The history and intention of 'staging'

- 1929 World Health Organization
  - introduced concept of describing disease by stage or extent
  - First applied to cancer
    - Cancer of cervix

- Purpose of Staging:
  - Common language to help medical professionals communicate information re: disease to others.
  - Diseases can be acute or chronic
    - Cancer, AID, CVD, RA...(CKD)
Staging Systems

• Essential tools in clinical medicine to provide valuable information for patient management and research

• Used across medicine to
  • measure disease severity,
  • estimate patient prognosis
  • determine eligibility for clinical trials and guide clinical care.

• Provide a model
  • natural history of a disease, and
  • framework to validate new biomarkers and test new interventions.

• Require ongoing efforts to standardize terminology contribute to better communication and understanding across the medical community
Definitions of Staging

• Shorthand method for describing disease.

• A coded format
  • e.g. numerical system with increasing values meaning more involvement or severity
  • Can facilitate electronic analysis of cases with similar characteristics.

• A short definition:
  • grouping of cases into broad categories based on extent of disease

• Extent of disease
  • detailed description of how far the (tumor) disease has spread from organ or site of origin (the primary site).

• Extent of disease is an anatomic categorization using descriptors to group individual cases in relation to the human body.
Classification vs Staging

• Classification
  • is the process of grouping cases based on specific criteria.
  • is an orderly arrangement showing relationships among groups.
  • does not necessarily imply a prognosis.

• Relationships b/n staging, extent of disease and classification:
  • extent of disease is a type of classification (based on human anatomy) and pertains to an individual case.
  • Staging is coded shorthand or a notation describing disease in more general terms

• By staging, characteristics about a case (precise extent of disease information) can be grouped into categories.

• Staging translates extent of disease classification about individual conditions into groups that can be studied or evaluated for prognostic significance.
Key Characteristics of Useful Clinical Staging systems

1. Clinical Relevance:
   Staging systems should be clinically relevant, providing information that directly impacts patient management and treatment decisions. Guide therapeutic strategies tailored to individual patients.

2. Customizability:
   A good staging system allows customization based on specific disease types, patient populations, and other relevant factors. Flexibility ensures applicability across diverse scenarios.

3. Comprehensive Medical Summary:
   Staging systems should offer a comprehensive summary of disease status, including relevant clinical features, prognostic indicators, and treatment implications. This aids in informed decision-making.

4. Incorporation of Pathologic Information:
   While clinical staging provides an initial assessment, combining it with pathologic data (such as histopathology or molecular markers) enhances accuracy. Pathologic staging improves precision and is crucial for modern clinical trials.

5. Periodic Revision:
   Staging systems should evolve based on new clinical and pathological data, improved understanding of biology, and other factors affecting prognosis.

6. Ease of Navigation and Interpretation:
   Staging systems should be straightforward and easy to use. Clinicians, researchers, and patients should find them accessible and intuitive.
What we know about CVD and CKD..., and how does the CKM Staging system help us?
CKD progression is driven by the combined effects of metabolic, haemodynamic and inflammatory and fibrotic factors (which similarly impact cardiovascular disease).

CVD is prevalent in people with CKD with high mortality

<table>
<thead>
<tr>
<th>No CKD</th>
<th>G2</th>
<th>G3</th>
<th>G4 - G5</th>
</tr>
</thead>
<tbody>
<tr>
<td>37.5%</td>
<td>63.4%</td>
<td>66.6%</td>
<td>75.3%</td>
</tr>
</tbody>
</table>

CVD mortality risk across CKD categories

<table>
<thead>
<tr>
<th>Albuminuria categories (mg/g)</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 mg/g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-29 mg/g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-299 mg/g</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≥300 mg/g</td>
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<td></td>
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</tbody>
</table>

| G1   | ≥105 | 0.93 (0.74–1.18) | 1.33 (1.04–1.72) | 2.46 (1.88–3.23) | 2.69 (1.36–5.32) |
| G2   | 90–104| 1 (reference) | 1.63 (1.20–2.19) | 1.82 (1.36–2.45) | 4.77 (3.16–7.22) |
| G3   | 75–89 | 1.03 (0.85–1.24) | 1.48 (1.23–1.78) | 1.73 (1.29–2.32) | 4.01 (2.67–6.14) |
| G4   | 60–74 | 1.09 (0.92–1.29) | 1.58 (1.31–1.91) | 2.18 (1.58–3.02) | 4.2 (2.95–6.06) |
| G5   | 45–59 | 1.52 (1.18–1.97) | 2.38 (1.91–2.96) | 3.13 (2.32–4.22) | 4.97 (3.70–6.68) |
| G6   | 30–44 | 2.40 (1.80–3.21) | 3.07 (1.73–5.44) | 4.12 (2.84–5.98) | 6.10 (4.68–9.10) |
| G7   | 15–29 | 13.51 (4.89–37.15) | 7.99 (1.95–32.81) | 5.00 (3.66–8.57) | 9.49 (4.97–18.10) |

PMID: 33720773; PMCID: PMC7969169
### Different relative risks for various CVD outcomes by eGFR and uACR

<table>
<thead>
<tr>
<th>Age &lt;65</th>
<th>eGFRcr-cys</th>
<th>ACR, mg/g</th>
<th>ACR, mg/g</th>
<th>ACR, mg/g</th>
<th>ACR, mg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>&lt;10-29</td>
<td>30-299</td>
<td>300+</td>
<td>&lt;10</td>
<td>10-29</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Myocardial infarction</td>
<td>Acute kidney injury</td>
<td>Atrial fibrillation</td>
<td>Hospitalization</td>
<td>Peripheral artery disease</td>
</tr>
<tr>
<td>105+</td>
<td>0.96</td>
<td>1.2</td>
<td>1.5</td>
<td>2.4</td>
<td>0.93</td>
</tr>
<tr>
<td>90-104</td>
<td>ref</td>
<td>1.3</td>
<td>1.5</td>
<td>2.5</td>
<td>ref</td>
</tr>
<tr>
<td>60-69</td>
<td>2.1</td>
<td>7.2</td>
<td>2.9</td>
<td>4.5</td>
<td>1.8</td>
</tr>
<tr>
<td>45-59</td>
<td>2.7</td>
<td>1.8</td>
<td>4.2</td>
<td>5.8</td>
<td>1.9</td>
</tr>
<tr>
<td>&lt;30</td>
<td>3.2</td>
<td>6.0</td>
<td>8.0</td>
<td>11.6</td>
<td>3.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiovascular mortality</th>
<th>Stroke</th>
<th>Kidney failure replacement therapy</th>
<th>Heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>105+</td>
<td>0.95</td>
<td>1.4</td>
<td>1.7</td>
</tr>
<tr>
<td>90-104</td>
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<td>&lt;30</td>
<td>6.0</td>
<td>5.5</td>
<td>9.4</td>
</tr>
</tbody>
</table>

### Heatmaps evaluated by age, eGFRcr-cys

10 outcomes, 6 cardiovascular, 2 kidney specific, 2 general
27.5 million people, 699 K with Cystatin and creatinine

Relative risks much more similar by age when using eGFRcr-cys

G3A associated with significant risk in every outcome (both optimal ACR <10; and high normal ACR 10-29)

Grams et al JAMA Oct 2023
Complex physiology of Cardiac and Vascular
diseases in CKD

Traditional risk factors:
- Lifestyle factors
- Hypertension
- Diabetes/insulin resistance
- Dyslipidemia
- Malnutrition

Novel risk factors
- Uremia
- Pro-inflammatory milieu
- Volume overload
- Disordered mineral metabolism
- Electrolyte imbalance
- Anemia
- Sympathetic hyperactivity
- RASS activation
- Endothelial dysfunction
- Protein-energy wasting
- Vitamin D deficiency
- Oxidative stress
- Increased FGF-23
- Decreased Klotho

Cardio-renal phenotype
- Dilated cardio-myopathy
- Arterial disease
- Cardiac arrythmia
- Left ventricular hypertrophy
Complex interactions of CVD and CKD over the life course of an individual
Complex physiology may explain differences in rates of different CVD conditions in CKD.

**Key Points**

**Question** How do the absolute rates and risk differences of incident heart failure, coronary heart disease, and stroke differ in participants with and without chronic kidney disease?

**Findings** This analysis of 3 community-based cohort studies found that the adjusted risk differences comparing participants with vs without chronic kidney disease (per 1000 person-years) were highest for heart failure and coronary heart disease (and lower for stroke).

**Meaning** Chronic kidney disease is associated with an excess risk of heart failure that was similar in magnitude to coronary heart disease and greater than stroke.
Traditional and non-traditional risk factors well articulated

BUT Relative contribution of each to atherosclerotic disease vs heart failure less well articulated

| Table. Traditional and Nontraditional Risk Factors for CVD in CKD |
|-----------------|-------------------------------------------------|---|
| Risk factors for CVD in CKD | Specific aspects/treatment options compared with the non-CKD population | Ref. |
| **Traditional** | | |
| Hypertension | Optimal target blood pressure has not yet been established | 41 |
| Dyslipidemia | Characteristic lipid pattern of hypertriglyceridemia and HDL cholesterol levels | 42 |
| Smoking | — | |
| Hyperglycemia | Intensive glucose control beneficial to avoid microvascular complications | 43 |
| **Nontraditional** | | |
| Vascular calcifications | Treatment of electrolyte imbalances with magnesium | 44, 45 |
| | Vitamin K administration might be beneficial | 46 |
| Inflammation | Inhibition of proinflammatory effector molecule interleukin-1β (IL-1β) with canakinumab after myocardial infarction | 47 |
| Increased proteinuria | RAS blockade | 48 |

CKD indicates chronic kidney disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; and RAS, renin-angiotensin system.
Disproportional incidence of Sudden cardiac death on HD may be due to combination of electrolyte disturbances leading to dysrhythmia +/- fibrosis +/- Atherosclerotic disease.

Figure 7. Cause-specific mortality according to varying levels of kidney dysfunction. For the 3 categories of kidney dysfunction, cause-specific mortality is depicted. Sudden cardiac death was the major cause of death in patients with end-stage renal disease (ESRD) on dialysis (50.0% vs 10.1% [glomerular filtration rate (GFR) <60 mL/min] vs 10.3% [GFR ≥60 mL/min], χ² P=0.010). Number at the top of each bar is the mortality rate; number within the bar is the n per group. The unknown category was reserved for those patients whose cause of death could not be determined. Adapted from Cheema et al.115
Attempts at understanding contributions to atherosclerotic processes and events

Table 2. Association of Biochemical and Vascular Ultrasound Parameters With Outcomes in CKD G3-G5D Patients

<table>
<thead>
<tr>
<th></th>
<th>Plaque Progression</th>
<th>IMT Progression</th>
<th>Cardiovascular Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full cohort</td>
<td>Lower FGF2</td>
<td>Higher phosphate</td>
<td>Atheromatous plaque</td>
</tr>
<tr>
<td></td>
<td>rs495392 Klotho polymorphism</td>
<td>Higher potassium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lower TWEAK</td>
<td></td>
<td>Lower 25(OH)D</td>
</tr>
<tr>
<td>G3</td>
<td>Atheromatous plaque at baseline</td>
<td>Higher phosphate</td>
<td>Atheromatous plaque</td>
</tr>
<tr>
<td></td>
<td>Higher phosphate</td>
<td></td>
<td>Higher potassium</td>
</tr>
<tr>
<td></td>
<td>Lower 25(OH)D</td>
<td></td>
<td>Lower 25(OH)D</td>
</tr>
<tr>
<td>G4</td>
<td>Atheromatous plaque at baseline</td>
<td>Lower 25(OH)D</td>
<td>Atheromatous plaque</td>
</tr>
<tr>
<td></td>
<td>Higher ferritin</td>
<td>PTH over recommended level</td>
<td>Higher potassium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower 25(OH)D</td>
</tr>
<tr>
<td>G5</td>
<td>Lower 25(OH)D</td>
<td>Higher phosphate</td>
<td>Atheromatous plaque</td>
</tr>
<tr>
<td></td>
<td>Higher ferritin</td>
<td>PTH outside the recommended level</td>
<td>Higher phosphate</td>
</tr>
<tr>
<td></td>
<td>Higher uric acid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Novel factors found in the NEFRONA study (Observatorio Nacional de Aterosclerosis en NEFRona) being independently associated with progression of subclinical atherosclerosis and cardiovascular events in CKD patients. CKD indicates chronic kidney disease; FGF, fibroblast growth factor; IMT, intima-media thickness; PTH, parathyroid hormone; and TWEAK, TNF-related weak inducer of apoptosis.

New paradigms and models for risk prediction

Changes in care pattern

Wide spread use of antiHTN

Integrating new models

Incorporating new risk predictors

Novel Prediction Equations for Absolute Risk Assessment of Total Cardiovascular Disease Incorporating Cardiovascular-Kidney-Metabolic Health: A Scientific Statement From the American Heart Association

AHA SCIENTIFIC STATEMENT
A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic (CKM) Syndrome: A Scientific Statement From the American Heart Association

Chadi E. Naboulsi, MD, PhD, FAHA; Chair; Jan J. Neufeld, MD, FAHA; Katherine R. Tuttle, MD; Sheehy L. Chow, PhD, FAHA; Vice Chair; Roy D. Matin, MD, Saffia S. Khan, MD, MSC, FAHA; Joseph C. Cottrell, MD, PhD; Carissa M. Baker-Smith, MD, MPH, FAHA; Mercedes R. Cartenhofer, PhD, FAHA; Jean-Francois Després, PhD, FAHA; Jennifer E. Hs, MD, FAHA; Joshua J. Joseph, MD, MPH, FAHA; Walter N. Kaufer, MD, Anil Khosla, MD, MSC, FAHA; Michael H. Kostis, MD, Carolyn L. Laskasch, PhD, Elin F. Lewis, MD, MPH, FAHA; Kevin B. Liu, MD, Biyo Oktan, MD, STL; Luqma F. Alansari, MD, MS, FAHA, Sofia S. Patel, MD, PhD, Michael J. Pescina, PhD, Tiffany M. Powell-Wiley, MD, MPH, FAHA; Laurence S. Sperling, MD, FAHA; Selin S. Yonis, MD, PhD, FAHA; Jackson T. Wright, MD, PhD; Radhika Raghav Singh, PhD, FAHA; Michael D. Bluemke, MD, FAHA; Jason Bergeron, MD, FAHA; Vice Chair, on behalf of the American Heart Association

Acknowledging the complexity of interactions

Figure 1. Conceptual diagram for CKM syndrome.

The image displays the pathophysiology underlying cardiovascular-kidney-metabolic (CKM) syndrome. CKM syndrome most commonly originates from excess adipose tissue, dysfunctional adipose tissue, or both. Multiple pathological processes related to dysfunctional adipose tissue result in insulin resistance and eventual hyperglycemia. Inflammation, oxidative stress, insulin resistance, and vascular dysfunction are highlighted as central processes leading to the development of metabolic risk factors, to the progression of kidney disease, to the potentiation of heart-kidney interactions, and to the development of cardiovascular diseases. Metabolic risk factors and chronic kidney disease further predispose to cardiovascular diseases through multiple direct and indirect pathways. MASLD indicates metabolic dysfunction–associated steatotic liver disease.
‘Stages’ of CKM: Describing processes and syndromes (in linear manner)
CKM Health Stages

- Describe characteristics of different risks
- Uses multiple types of information
  - Imaging
  - History
  - Laboratory data (specialized and common)
  - Risks and risk equivalents
  - Events
  - And/or

- Clinical utility of the staging system

<table>
<thead>
<tr>
<th>CKM health stages</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0: No CKM health risk factors</td>
<td>Individuals without overweight/obesity, metabolic risk factors (hypertension, hypertriglyceridemia, MetS, diabetes), CKD, or subclinical/clinical CVD</td>
</tr>
<tr>
<td>Stage 1: Excess and/or dysfunctional adiposity</td>
<td>Individuals with overweight/obesity, abdominal obesity, or dysfunctional adipose tissue, without the presence of other metabolic risk factors or CKD BMI ≥25 kg/m² (or ≥23 kg/m² if Asian ancestry) Waist circumference ≥88/102 cm in women/men (or if Asian ancestry, ≥80/90 cm in women/men) and/or Fasting blood glucose ≥100–124 mg/dL or HbA1c between 5.7% and 6.4%*</td>
</tr>
<tr>
<td>Stage 2: Metabolic risk factors and CKD</td>
<td>Individuals with metabolic risk factors (hypertriglyceridemia ≥135 mg/dL), hypertension, MetS†, diabetes) or CKD</td>
</tr>
<tr>
<td>Stage 3: Subclinical CVD in CKM</td>
<td>Subclinical ASCVD or subclinical HF among individuals with excess/dysfunctional adiposity, other metabolic risk factors, or CKD Subclinical ASCVD to be principally diagnosed by coronary artery calcification (subclinical atherosclerosis by coronary catheterization/CT angiography also meets criteria) Subclinical HF diagnosed by elevated cardiac biomarkers (NT-proBNP ≥125 pg/mL, high-sensitivity troponin T ≥14 ng/L for women and ≥22 ng/L for men, high-sensitivity troponin I ≥10 ng/L for women and ≥12 ng/L for men) or by echocardiographic parameters, with combination indicating highest HF risk. Risk equivalents of subclinical CVD Very high-risk CKD (G4 or G5 CKD or very high risk per KDIGO classification) High predicted 10-yr CVD risk</td>
</tr>
<tr>
<td>Stage 4: Clinical CVD in CKM</td>
<td>Clinical CVD (coronary heart disease, heart failure, stroke, peripheral artery disease, AFib) among individuals with excess/dysfunctional adiposity, other metabolic risk factors, or CKD Stage 4a: no kidney failure Stage 4b: kidney failure present</td>
</tr>
</tbody>
</table>
New AHA Cardiovascular-Kidney-Metabolic (CKM) Staging Solves All Our Staging Problems and Should Be Applied Universally

- What problem are we trying to solve?
- Do we have a staging problem?

- Does the proposed CKM staging foster awareness of complex physiology and identify gaps in knowledge?

- Does the proposed CKD staging foster integration of strategies for identification and care, and enrolment into clinical studies?
What we do not know.....

• Relative importance of different risk factors / biomarkers
  • in different kidney diseases and by CKD stage

• Relative importance of constellations of risk factors/ biomarkers within different people with different phenotypes

• Best value for therapeutic options at different time points
  • Stages of disease vs disease(s)
Our common goal is to prevent CV and kidney outcomes through identifying triggers for early intervention

Approaches are multidisciplinary... ...
...multifactorial and guideline recommended¹⁻⁷

ADA, American Diabetes Association; ERA, European Renal Association; ERBP, European Renal Best Practice; ESC, European Society of Cardiology; ESH, European Society of Hypertension; KDIGO, Kidney Disease Improving Global Outcomes; nsMRA, nonsteroidal mineralocorticoïd receptor antagonist; PCP, primary care physician; RASi, renin-angiotensin system inhibitor; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

Its actually about the care, and the people.
“New AHA Cardiovascular-Kidney-Metabolic (CKM) Staging Solves All Our Staging Problems and Should Be Applied Universally”…

• Not really

• The concept of Cardiovascular Kidney Metabolic syndrome
  • Recognizes the complexity of disease processes currently impacting a lot of people worldwide
  • Offers opportunities for collaboration in research and care paradigms

• The staging system
  • Ignores etiologies of different kidney and CV diseases
  • Is not simple to use for clinicians or researchers yet
  • May inadvertently thwart research and validation efforts

• Is better as a ‘framework’ for education and needs to be tested in terms of utility
Ongoing tensions between Inclusive frameworks and GDMT and Precision Medicine

Timing and individualization

Identifying phenotypes within classification systems
  Lean
  Overweight
  Diabetes
  No Diabetes
  Age/ Sex
One nephrologist’s perspective...
Thank you and looking forward to the Discussion