The AKI to CKD Continuum: a Clinical Perspective

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THE HIDDEN EPIDEMIC: WORLDWIDE, OVER 850 MILLION PEOPLE SUFFER FROM KIDNEY DISEASES

June 27, 2018 — The global burden of kidney diseases has so far been underestimated: most people are not aware of their impaired kidney function. In general, kidney diseases are “silent diseases”, most often there are no apparent early symptoms. Many patients with kidney diseases are not aware that they have been living with high risks not only of kidney failure which may require dialysis or transplantation but also cardiovascular diseases, infections, and hospitalizations.
Kidney diseases to date have not had a major role in most health promotion and public awareness campaigns. This, however, is completely unjustified. We estimate that over 850 million people worldwide have some form of kidney disease, which is roughly double the number of people who live with diabetes (422 million, [1]) and 20 times more than the prevalence of cancer worldwide (42 million [2]) or people living with AIDS/HIV (36.7 million [3]). Thus, kidney diseases are one of the most common diseases worldwide. “It is high time to put the global spread of kidney diseases into focus”, explain Professors David Harris and Adeera Levin, President and Past-President of the International Society of Nephrology (ISN).
However, it is not only the number, which is dramatic, but also the outcome: “Even if many patients with impaired kidney function do not feel ill over a long period of time, they are at a particularly high risk of many other health outcomes due to this condition”, explains Professor Carmine Zoccali, President of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA). As he points out, the average age standardized mortality rate due to low kidney function (GFR) is 21 deaths per 100,000 [4,6]. In particular, the cardiovascular death toll from CKD is huge: In 2013, there were 1.2 million cardiovascular deaths attributed to CKD [6].
“It is time for constructive change in kidney care policy”, confirms Professor Mark D. Okusa, President of the American Society of Nephrology (ASN). “The number of kidney patients is alarmingly high, but the public is not aware of this fact. The patients have rather poor outcomes and, last but not least, kidney diseases impose a heavy financial burden on healthcare budgets.”
A CALL TO ACTION ON KIDNEY DISEASE

2018 UNITED NATIONS HIGH-LEVEL MEETING ON NCDs

13 MILLION PEOPLE AFFECTED WORLDWIDE
Acute kidney injury (AKI), an important driver of CKD, affects over 13 million people worldwide and 85% of these cases are found in low and middle-income countries (LMICs).
The Nexus of Acute Kidney Injury, Chronic Kidney Disease, and World Kidney Day 2009

Mark D. Okusa,* Glenn M. Chertow,† and Didier Portilla,‡ for the Acute Kidney Injury Advisory Group of the American Society of Nephrology

CJASN 2009
AKI is an independent risk factor for subsequent development of elevated BP

Hsu et al. JASN 2016

Cumulative incidence of elevated BP over time:

- AKI
- no AKI

Retrospective cohort study to evaluate whether AKI in the hospital is independently associated with BP elevation during the first 2 years after discharge among previously normotensive adults.
CKD after AKI: a systematic review and meta-analysis

### Hazard ratio for CKD

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Weight (%)</th>
<th>Hazard ratio IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiss et al. (13)</td>
<td>10.0</td>
<td>32.79 (4.30–249.77)</td>
</tr>
<tr>
<td>Amdur et al. (22)</td>
<td>15.5</td>
<td>6.64 (5.05–8.74)</td>
</tr>
<tr>
<td>Lo et al. (11)</td>
<td>15.5</td>
<td>28.08 (21.01–37.53)</td>
</tr>
<tr>
<td>James et al. (16)</td>
<td>15.8</td>
<td>29.99 (24.32–36.96)</td>
</tr>
<tr>
<td>James et al. (15.23)</td>
<td>15.5</td>
<td>1.60 (1.20–2.14)</td>
</tr>
<tr>
<td>Ando et al. (19)</td>
<td>12.4</td>
<td>9.91 (2.48–39.63)</td>
</tr>
<tr>
<td>Ishani et al. (21)</td>
<td>15.6</td>
<td>2.33 (1.83–2.96)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0</td>
<td>8.82 (3.05–25.48)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 1.87; \chi^2 = 446.89, \text{d.f.} = 6 (P < 0.00001); I^2 = 99\%$. Test for overall effect: $Z = 4.02 (P < 0.0001)$

### Hazard ratio for ESRD

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Weight (%)</th>
<th>Hazard ratio IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newsome et al. (14)</td>
<td>15.0</td>
<td>3.26 (2.87–3.70)</td>
</tr>
<tr>
<td>Ishani et al. (20)</td>
<td>14.8</td>
<td>12.99 (10.57–15.96)</td>
</tr>
<tr>
<td>Wald et al. (17)</td>
<td>14.9</td>
<td>3.22 (2.70–3.85)</td>
</tr>
<tr>
<td>Hsu et al. (10)</td>
<td>13.5</td>
<td>1.47 (0.95–2.28)</td>
</tr>
<tr>
<td>James et al. (15.23)</td>
<td>12.5</td>
<td>4.15 (2.32–7.41)</td>
</tr>
<tr>
<td>Lafrance et al. (18)</td>
<td>15.0</td>
<td>2.33 (2.09–2.61)</td>
</tr>
<tr>
<td>Choi et al. (12)</td>
<td>14.4</td>
<td>1.37 (1.02–1.84)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0</td>
<td>3.10 (1.91–5.03)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.40; \chi^2 = 252.85, \text{d.f.} = 6 (P < 0.00001); I^2 = 96\%$. Test for overall effect: $Z = 4.58 (P < 0.00001)$

Coca, Singanamala, & Parikh. Kidney Int 2012
3.4.1: We recommend **not** using diuretics to prevent AKI. (1B)
3.4.2: We suggest **not** using diuretics to treat AKI, except in the management of volume overload. (2C)
3.5.1: We recommend **not** using low dose dopamine to prevent or treat AKI. (1A)
3.5.2: We suggest **not** using fenoldopam to prevent or treat AKI. (2C)
3.5.3: We suggest **not** using atrial natriuretic peptide (ANP) to prevent (2C) or treat (2B) AKI.
3.6.1: We recommend **not** using recombinant human (rh)IGF-1 to prevent or treat AKI. (1B)

What can we do ??
Electronic alerts for AKI did not provide benefit, only leading to alert fatigue

Wilson et al. Lancet 2015
Secondary analysis: personalized alert targeting to identify patients expected to benefit from electronic alerts for AKI

Conclusion: Data-driven targeting of AKI alerts has the potential to successfully identify patients most likely to benefit
the effect of a "KDIGO bundle" consisting of optimization of volume status and hemodynamics, avoidance of nephrotoxic drugs, and preventing hyperglycemia

Meersch et al. Intensive Care Med 2017
the overall mortality in the early versus the delayed RRT initiation group

Log–rank test, $P=0.005$; HR=0.617 (95% CI, 0.439–0.866)

Early Versus Delayed Initiation of RRT in Critically Ill Patients with AKI (ELAIN) Trial

Meersch et al. JASN 2018
Vagus nerve stimulation protects the kidney against IRI through α7nAChR+ splenocytes

Inoue, Okusa et al.
J Clin Invest 2016
The excess risk after AKI persisted over ten years of study, irrespective of AKI severity, or post-episode proteinuria.

14,651 hospital survivors (1,966 with AKI, 12,685 no AKI)
25.7% of AKI patients had non-recovery

30% renal decline during follow-up

- no AKI, post-episode eGFR≥60
- AKI, post-episode eGFR≥60
- no AKI, post-episode eGFR 45-59
- AKI, post-episode eGFR 45-59
- no AKI, post-episode eGFR 30-44
- AKI, post-episode eGFR 30-44
- no AKI, post-episode eGFR<30
- AKI, post-episode eGFR<30

Sawhney et al. Kidney Int 2017
Interventions that affect risk of acute, mild to moderate, elevation in serum Cr showed no effect on CKD later.

**A. Event: AKI (Acute Increase in Serum Creatinine)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CORONARY</td>
<td>257</td>
<td>1472</td>
<td>0.09</td>
<td>0.94 [0.72, 0.97]</td>
</tr>
<tr>
<td>Miner</td>
<td>9</td>
<td>95</td>
<td>0.01</td>
<td>0.42 [0.20, 0.89]</td>
</tr>
<tr>
<td>NU-HIT CKD</td>
<td>36</td>
<td>141</td>
<td>0.03</td>
<td>0.43 [0.32, 0.59]</td>
</tr>
<tr>
<td>NU-HIT LVD</td>
<td>7</td>
<td>68</td>
<td>0.01</td>
<td>0.26 [0.12, 0.56]</td>
</tr>
<tr>
<td>POSEIDON</td>
<td>12</td>
<td>176</td>
<td>0.02</td>
<td>0.41 [0.22, 0.76]</td>
</tr>
<tr>
<td>SEPSIS/PAM</td>
<td>53</td>
<td>167</td>
<td>0.07</td>
<td>0.75 [0.57, 1.00]</td>
</tr>
<tr>
<td>Yunos</td>
<td>122</td>
<td>773</td>
<td>0.12</td>
<td>0.68 [0.55, 0.84]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>2894</strong></td>
<td><strong>2859</strong></td>
<td></td>
<td><strong>0.57 [0.44, 0.74]</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>496</td>
<td>711</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.08; Chi² = 25.57, df = 6 (P = 0.0002); I² = 77%
Test for overall effect: Z = 4.24 (P < 0.0001)

**B. Event: CKD**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CORONARY</td>
<td>252</td>
<td>1472</td>
<td>0.09</td>
<td>1.12 [0.95, 1.32]</td>
</tr>
<tr>
<td>Miner</td>
<td>1</td>
<td>95</td>
<td>0.01</td>
<td>0.89 [0.65, 1.20]</td>
</tr>
<tr>
<td>NU-HIT CKD</td>
<td>1</td>
<td>141</td>
<td>0.03</td>
<td>0.20 [0.02, 1.73]</td>
</tr>
<tr>
<td>NU-HIT LVD</td>
<td>1</td>
<td>144</td>
<td>0.03</td>
<td>0.24 [0.03, 2.06]</td>
</tr>
<tr>
<td>POSEIDON</td>
<td>1</td>
<td>196</td>
<td>0.05</td>
<td>0.26 [0.03, 2.26]</td>
</tr>
<tr>
<td>Yunos</td>
<td>6</td>
<td>773</td>
<td>0.12</td>
<td>1.18 [0.36, 3.85]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>2745</strong></td>
<td><strong>2714</strong></td>
<td></td>
<td><strong>0.87 [0.52, 1.46]</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>262</td>
<td>243</td>
<td></td>
<td></td>
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</tbody>
</table>

Heterogeneity: Tau² = 0.10; Chi² = 6.11, df = 5 (P = 0.30); I² = 18%
Test for overall effect: Z = 0.63 (P = 0.86)

Coca et al. JASN 2016
Tubular epithelial cells?  
Vascular endothelial cells?
Caspase-3 deficiency aggravates tubular injury but attenuates microvascular injury in IRI.

Yang et al. JASN 2018

KIM-1 IHC

rouleaux formation

KO

WT

WT 1d

KO 1d

KO

WT

WT 3d

KO 3d

Yang et al. JASN 2018
microvascular injury, not tubular injury, determines fibrosis of the kidney after IRI

α-SMA IHC

sirius red staining

Yang et al. JASN 2018
How does AKI progress to CKD?

hypoxia

Association between indices of urinary hypoxia and risk of post-surgical AKI

Intraoperative urinary PO$_2$ measurement via a fiber optic probe in the tip of the urinary catheter

Zhu et al. Nephrol Dial Transplant 2018
Measurement of oxygen tension in the kidney utilizing a novel phosphorescence probe

Hirakawa, Nangaku et al. Sci Rep 2015
S1 segment has higher oxygen tension compared with S2 segment.

Hirakawa, Nangaku et al. Kidney Int 2018

pseudocolored PLIM image
(phosphorescence lifetime imaging microscopy)

U: upstream tubules
D: downstream tubules

\( \tau_p (\mu s) \)

Hirakawa, Nangaku et al. Kidney Int 2018
Measurement of kidney oxygenation by a novel phosphorescence probe

Hirakawa, Nangaku et al. Sci Rep 2015
Direct correlations between fibrosis and hypoxia in the kidney of folic acid-induced AKI

Jiang et al. Am J Physiol Renal Physiol 2018
Weekly averages of radiotelemetrically measured systolic BP of uninephrectomized IRI rats

![Graph showing changes in systolic BP over weeks post IR.](image)

- IR (n=22)
- Sham IR (n=8)

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**RVR**  
Renal Vascular Resistance

**RBF**  
Renal Blood Flow

- at 4 wk Post IR

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Picken et al. Hypertension 2016
Decrease of blood flow after ischemia reperfusion

Ehling et al. JASN 2016
The microvascular perfusion decreased in the outer medulla during the post-IR period.

contrast-enhanced ultrasonogrophy

Fischer et al. Kidney Int 2016
Rouleaux formation causing occlusion within the renal microvasculature after renal I/R

aggregate of red blood cells occluding the capillary lumen

Collett et al. JASN 2017
Hydrodynamic isotonic fluid delivery improves post-AKI vascular occlusion and kidney function

Collett et al. JASN 2017
Hypertonic saline protects the kidney by promoting renal microcirculatory oxygenation in a model of IRI

Ergin et al. Shock 2018
How does AKI progress to CKD?

Epigenetic modification of expression of glucose transporter 3 (GLUT3) by hypoxia

H3K4me1 normoxia
H3K4me1 hypoxia

H3K27ac normoxia
H3K27ac hypoxia

H3K4me3 normoxia
H3K4me3 hypoxia

HIF1α normoxia
HIF1α hypoxia
HIF1α Hypoxia

ENHancer mark

active mark

Mimura, Nangaku et al. Mol Cell Biol 2012
Regulation of GLUT3 expression by hypoxia

Mimura, Nangaku et al. Mol Cell Biol 2012
Cross-enhancement of ANGPTL4 transcription by HIF1 and PPAR β/δ

Inoue, Nangaku et al. Genome Biol 2014
Inoue, Nangaku et al. Genome Biol 2014
RNA-seq revealed DARS-AS1 as a HIF-induced long non-coding RNA with anti-apoptotic function

Mimura, Nangaku et al. Physiol Rep 2017
HDAC inhibition protects against fibrosis after ischemia-reperfusion injury

trichostatin (TSA): pan-HDAC inhibitor
MS-275: class I-specific HDAC inhibitor

Levine et al. Am J Transplant 2015
Amelioration of AKI-to-CKD transition by Dznep

Dznep: inhibitor of EZH2

EZH2 (Enhancer of zeste homolog 2): histone methyltransferase of H3K27me

Mimura, Nangaku et al. Sci Rep 2018
RNA-seq of the tubules isolated by laser capture microdissection

Dznep suppressed TIMP2 expression in the kidney

Timp2

Mimura, Nangaku et al. Sci Rep 2018
Dznep attenuates renal fibrosis in obstructed kidneys

Zhou et al. JASN 2016
AKI-to-CKD transition mediated by hypoxic memory

Nangaku et al. Nephron 2017
Clinical AKI with Maladaptive Repair

Improvement of oxygenation
Intervention of epigenetic changes

Hypoxic memory

Functional marker level higher than at start

Fibrosis

Functional Marker Threshold

Damage Marker Threshold

Duration

Marker Level

Basile, Nangaku et al. for the ADQI XIII Work Group. JASN 2016
Unraveling the Secrets of Kidney Disease
organized by Katalin Susztak, Caroline Fox, and Masaomi Nangaku

joint with the meeting on Diabetes:
Innovations, Outcomes and Personalized Therapies
President: David Harris
President-elect: Vivek Jha
Program chair: Masaomi Nangaku
Program deputy chair: Marcello Tonelli
LOC chair: Peter Kerr
Diabetes Complications and Comorbidities
Peter Rossing
Masaomi Nangaku
Ammar Ibrahim
Sam Dagogo-Jack
Dario Rahelic