Strategies to Retard Progression of Chronic Kidney Disease

Aditi Sinha
Assistant Professor of Pediatrics
Division of Nephrology, Department of Pediatrics
All India Institute of Medical Sciences, New Delhi
# Staging Chronic kidney disease

<table>
<thead>
<tr>
<th>Glomerular filtration rate (mL/min/1.73 m$^2$) categories: Description and range</th>
<th>Dip stick</th>
<th>Persistent albuminuria categories: Description and range</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1: Normal or high</td>
<td>&gt;90</td>
<td>A1: Normal to mildly increased</td>
</tr>
<tr>
<td>G2: Mildly decreased</td>
<td>60–90</td>
<td>A2: Moderately increased</td>
</tr>
<tr>
<td>G3a: Mildly to moderately decreased</td>
<td>45–59</td>
<td>A3: Severely increased</td>
</tr>
<tr>
<td>G3b: Moderately to severely decreased</td>
<td>30–44</td>
<td></td>
</tr>
<tr>
<td>G4: Severely decreased</td>
<td>15–29</td>
<td></td>
</tr>
<tr>
<td>G5: Kidney failure</td>
<td>&lt;15</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Albumin excretion rate</th>
<th>&lt;30 mg/day</th>
<th>30–300 mg/day</th>
<th>&gt;300 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin creatinine ratio</td>
<td>&lt;30 mg/g or &lt;3 mg/mmol</td>
<td>30–300 mg/g or 3–30 mg/mmol</td>
<td>&gt;300 mg/g or &gt;30mg/mmol</td>
</tr>
<tr>
<td>Protein excretion rate</td>
<td>&lt;150 mg/day</td>
<td>150–500 mg/day</td>
<td>&gt;500 mg/day</td>
</tr>
<tr>
<td>Protein creatinine ratio</td>
<td>&lt;150 mg/g or &lt;15 mg/mmol</td>
<td>150–500 mg/g or 15–50 mg/mmol</td>
<td>&gt;500 mg/g or &gt;50 mg/mmol</td>
</tr>
</tbody>
</table>

*If no other marker of kidney disease, no CKD*
# Chief Causes of CKD (%)

<table>
<thead>
<tr>
<th>Etiology, %</th>
<th>NAPRTCS, n=3108</th>
<th>ItalKid, n=1197</th>
<th>CKiD, n=506</th>
<th>4C, n=500</th>
<th>Brazil, n=147</th>
<th>India, n=984</th>
<th>Japan, n=447</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAKUT</td>
<td>50</td>
<td>58</td>
<td>52.7</td>
<td></td>
<td>59.9</td>
<td>52</td>
<td>62.2</td>
</tr>
<tr>
<td>PUV</td>
<td>24</td>
<td>18</td>
<td>69.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reflux</td>
<td>8</td>
<td>26</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypodysplasia</td>
<td>18</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic GN</td>
<td>20</td>
<td>4</td>
<td>19</td>
<td>7.6</td>
<td>20.4</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Alport; cystic; tubular</td>
<td>8</td>
<td>15</td>
<td>12</td>
<td>13.6</td>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>AKI, HUS</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td></td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td>7</td>
<td>6.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Renal function trajectory is more important than CKD stage in managing patients with CKD.

Factors affecting trajectory:
- Proteinuria/albuninuria
- Age/race/diet
- ACE/ARB
- Protein reduction
- AKI
- Diabetes control
- Alkali therapy
- Multidisciplinary follow-up

Conventional biomarkers:
- Serum creatinine
- Urine albumin
- Sex, age, diabetes

Trajectory of >3 ml/min/1.73 m²/yr
Higher morbidity, need closer follow up

Am J Nephrol 2012;36:1–10
# Biomarkers for CKD Risk Prediction?

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Site of expression</th>
<th>Rationale</th>
<th>Physiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGF-23</td>
<td>Osteocytes, osteoblasts</td>
<td>MBD causes FGF-23 excess; early marker</td>
<td>Increases urinary PO$_4$ excretion; inhibits 1,25 (OH)$_2$ vitamin D synthesis</td>
</tr>
<tr>
<td>NGAL</td>
<td>Proximal&gt;distal tubules; neutrophils</td>
<td>Upregulated in tubular injury</td>
<td>Binds siderophores (iron trafficking); growth &amp; differentiation factor</td>
</tr>
<tr>
<td>KIM-1</td>
<td>Proximal tubules</td>
<td>Shed &amp; upregulated during tubular injury</td>
<td>Phagocytosis</td>
</tr>
<tr>
<td>suPAR</td>
<td>Immune &amp; endothelial cells, podocytes</td>
<td>Implicated in FSGS, diabetic nephropathy; interferes with podocyte migration &amp; apoptosis; also in sepsis, malignancy</td>
<td>Plasminogen-activating pathway, cell signaling, adhesion, migration, activation of podocyte β3-integrin, permeability factor</td>
</tr>
<tr>
<td>Tamm-Horsfall (UMOD)</td>
<td>Epithelial cells of thick ascending limb</td>
<td>Abundant in urine; GWAS link $UMOD$ to CKD</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

Panel of biomarkers (IL-6, TNF-α, OPN, OPG, and FGF-23) predicted severity of vascular changes and progression of CKD

## Risk prediction models for adults

<table>
<thead>
<tr>
<th>Prediction Model</th>
<th>Predicted Outcome</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney Failure Risk Equation</td>
<td>2- and 5-y risk for kidney failure in patients with CKD 3-5</td>
<td>3,449 patients (2001-2008)</td>
</tr>
<tr>
<td>Prediction of Contrast Induced Nephropathy after Percutaneous Coronary Intervention</td>
<td>Risk for contrast-induced nephropathy</td>
<td>Prospective database in 1990s</td>
</tr>
<tr>
<td>Hemodialysis Mortality Risk</td>
<td>6-mo mortality risk in maintenance hemodialysis patients</td>
<td>512 MHD patients in 2006-2007</td>
</tr>
<tr>
<td>iChoose Kidney</td>
<td>1- and 3-y risk for mortality in ESRD patients on dialysis vs transplantation</td>
<td>US Renal Data System (2005-2011)</td>
</tr>
</tbody>
</table>

Excellent discrimination for kidney failure
Modest prediction of all-cause mortality
Poor prediction of cardiovascular morbidity
Predictive Model of Progression of Pediatric CKD

Retrospective cohort, Brazil
147 with CKD 2-4; 1990-2008
Follow up 4.5 yr
60% CAKUT
Median eGFR 37 ml/min/1.73 m²
Proteinuria 53%

Time to CKD5: 8.1 (5.7-10.8) yr
52% probability of CKD5 @ 10 yr

Glomerular diseases fare worse

Model, risk score
Baseline eGFR
Baseline proteinuria
Primary renal disease

Chances of CKD5 @10-yr by risk category

Predicting progression of kidney disease

Chronic Kidney Disease in Children (CKiD) Cohort

Prospective cohort: 496 children & adolescents

End point: Renal replacement therapy, 50% decline in GFR

29% of 398 non-glomerular & 41% of 98 glomerular progressed

@ Risk

Up/Uc >2 g/g
Hypoalbuminemia
Hypertension
Dyslipidemia
Boys
Anemia

Am J Kidney Dis 2015; 65: 878-88
Survival curves for composite event (50% GFR, RRT)

10-yr F GFR 30-45

Non-glomerular Diagnosis

10-yr F GFR <45

Glomerular Diagnosis

Incident proteinuria

Persistent proteinuria, hypertension, incident anemia

Persistent proteinuria, hypertension, persistent anemia, hypoalbuminemia, dyslipidemia

Incident proteinuria & hypertension

Persistent proteinuria, hypertension, incident anemia, hypoalbuminemia

Progression of CKD in Japanese children
Nationwide prospective cohort study

447 Japanese children with pre-dialysis CKD in 2010
52 (12.5%) progressed to ESKD over median 1.5 yr
Risk factors: Advanced CKD (HR 11-27); Up/Uc >2 g/g (HR 7.6);
age <2 yr (HR 9); after starting puberty (HR 4.9)

Ishikura, et al. NDT 2014; 29: 878

KNOW-Ped CKD (KoreaN cohort study for outcomes in patients with pediatric CKD)

7 centers, 450 patients <20-yr-old with CKD I - V; 2011 Phenotype, structured follow-up, biorepository

Kang, et al. BMC Nephrol 2016; 17: 35
Cardiovascular Comorbidity in Children with Chronic Kidney Disease (4C) Study

Long-term prospective observational study
Causes, consequences of CV comorbidity in children
6-17 yr-old with eGFR 10-60 ml/min/1.73 m²
737 patients in 55 participating centers in 12 European countries

Morphology, function of heart & large arteries
Clinical, anthropometric, biochemical & pharmacological risk factors
Whole genome association study for variants linked to CVS disease
Arterial (4C-A) & peritoneal (4C-P) histology, gene & protein expression

## Risk factors for progression

<table>
<thead>
<tr>
<th>Non-modifiable</th>
<th>Modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal programming</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Proteinuria</td>
</tr>
<tr>
<td>Age</td>
<td>Mineral homeostasis</td>
</tr>
<tr>
<td>Gender</td>
<td>Diet (protein, salt)</td>
</tr>
<tr>
<td>Genetic polymorphisms</td>
<td>Dyslipidemia</td>
</tr>
<tr>
<td></td>
<td>Hyperuricemia</td>
</tr>
<tr>
<td></td>
<td>Anemia; folate deficiency</td>
</tr>
<tr>
<td></td>
<td>Acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Rates of progression vary by underlying cause

Dysplasia: Change in GFR
- Improvement after birth (till 3-yr)
- Pre-pubertal: stable renal function
- Pubertal: faster decline (start 11-yr)

Faster progression in glomerulonephritis
Non-modifiable risk factors

Underlying disease
Early age @ CKD
Acceleration of GFR loss @ puberty

Gender
Men fare less well: ADPKD, IgA nephropathy, MGN

Genetic basis..
Genetic polymorphisms influence risk of disease, progression, response

DD polymorphism of ACE gene
Disease progression: IgA nephropathy, VUR, dysplasia
Predicts renoprotection in non-diabetic proteinuria

Chronic Renal Insufficiency Cohort Study:
Genome Wide Association for CKD progression

1331 blacks & 1476 whites with CKD; stratified by race; diabetes
Single-nucleotide polymorphisms (in blacks; 6 in whites) with P<1×10^{-6} associated with eGFR slope; 8 validated in cohorts

LINC00923: RNA gene expressed in kidneys
rs653747 in blacks and rs931891 in whites, without diabetes
Pediatric Investigation for Genetic Factors Linked with Renal Progression (PediGFR) Consortium

1136 patients; 3 pediatric CKD cohorts: CKiD, ESCAPE & 4C

GWAS to relate SNPs to eGFR & proteinuria in European-ancestry patients; compared to 1347 similar controls

SNPs with suggestive association: 10 regions for eGFR, 4 regions for proteinuria, 6 regions for CKD

No SNP associated at genome-wide significance


Chronic Kidney Disease in Children (CKiD) cohort

419 children with CKD vs. 21575 children/adults without

Copy number disorders in 31 (7.4%) children

HNF1 homeobox B (HNF1B)

Triple X syndromes

12 likely pathogenic genomic imbalances

J Clin Invest 2015;125:2171-8
Which of the following interventions has basis in pediatric RCTs to decrease risk of progression of CKD?

1. Control of hypertension
2. Control of serum phosphate
3. Management of hypoalbuminemia
4. Management of acidosis
Hypertension & proteinuria in CKD
Proteinuria: a marker and mechanism of progressive kidney disease

For each 1 g/d proteinuria decline

**MDRD trial**: GFR decline reduced by 1 ml/min/yr

**REIN study**: GFR decline reduced by 2 ml/min/yr

Reduce proteinuria; <300 mg/m^2^/d

Proteinuria: chief predictor of outcome in IgA nephropathy

542 patients; Toronto GN Registry
Proteinuria & hypertension predict loss of GFR >10 ml/min/1.73 m²

European Study Group. Lancet 1997

Children; 349: 1117–23

Albuminuria in Childhood CKD Associated with Mortality & ESRD


## Pediatric studies on proteinuria & progression

<table>
<thead>
<tr>
<th>Study (Type)</th>
<th>N; patients</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effects of Low Protein Diet on Progression of CKD</strong> (Prospective multicenter cohort)</td>
<td>191 patients 2-18 yr-old with GFR 15-60 ml</td>
<td>Proteinuria &gt;50 mg/kg/day associated with greater decrease in GFR</td>
</tr>
<tr>
<td><strong>Japanese Nationwide Trial</strong> (2 surveys of 1190 centers)</td>
<td>429 patients 3 mo-15 yr-old with CKD 3-5</td>
<td>Up/Uc &gt;2 predicts progression to ESKD (HR 7.6)</td>
</tr>
<tr>
<td><strong>ESCAPE</strong> (Multi-center RCT)</td>
<td>468 patients 3–18 yr-old with GFR 15-80 ml</td>
<td>Proteinuria associated with an risk of reaching ESRD or 50% reduction of GFR (HR 1.5)</td>
</tr>
<tr>
<td><strong>CKiD</strong> (Ongoing multi-center prospective cohort)</td>
<td>891 patients 1-16 yr-old with GFR 30-90 ml</td>
<td>Baseline proteinuria linked to GFR; elevated or nephrotic-range proteinuria predict progression to ESKD or 50% reduction of GFR; CKD in nonglomerular cohort progressed faster if elevated Up/Uc, elevated BP or both</td>
</tr>
</tbody>
</table>
Strict Blood-Pressure Control and Progression of Renal Failure in Children

ESCAPE Trial

Achieving blood pressure targets, reduced proteinuria predict delayed progression

Intensified blood pressure control (N = 189): 24-hr MAP <50th C

Conventional blood pressure control (N = 196): 24-hr MAP 50-95th C

30% in Intensive gr. & 42% conventional group reached end point of Time to 50% decline in GFR; ESRD); HR 0.7; 95% CI 0.4-0.9

Similar adverse events, withdrawal (28%, 27%)

Reappearance of proteinuria common with long-term ACE inhibition
Effects of enalapril on GFR & proteinuria in children with CKD

Randomized controlled trial, 2006-2008

Children 2-18 yr; eGFR 15-60 ml/min/1.73 m²

<table>
<thead>
<tr>
<th>Enalapril @ 0.4 mg/kg/day + standard therapy*</th>
<th>Standard therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non ACE-I/ARB allowed; target BP &lt;90th C</td>
<td></td>
</tr>
</tbody>
</table>

Therapy, follow up 1-yr: Renal function, potassium, BP; DTPA
GFR @ 6 and 12 months

Enalapril reduces proteinuria compared to standard therapy
70.7% vs. -12.7% at 6-mo (P<0.001)
80.8% vs. -11% at 12-mo (P=0.01)

Similar GFR at 1-yr
22.6±5.8 vs. 25.3±10.7 ml/min/1.73 m²

Similar rate of decline in GFR
4.0±7.6 vs. 3.5±1.4 ml/min/1.73 m²/ year

* Correction of anemia, mineral bone disease, malnutrition
**CCBs NOT as renoprotective as ACE-I/ARB**

8 RCTs, 25647 participants

**CCBs vs. ACE-I and/or ARB**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurrence of ESRD</td>
<td>1.25 [1.05-1.48]</td>
</tr>
<tr>
<td>Control of hypertension</td>
<td>1.10 [0.78-1.23]</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.96 [0.89-1.03]</td>
</tr>
</tbody>
</table>

Ren Fail. 2016;38:849-56

**CCB add on to ACE-I/ARB**

17 RCTs, 1905 patients

- No additional lowering effect on blood pressure
- Further decrease in proteinuria
- Further improvement in kidney function

Hypertens Res 2015; 38: 847-55
# Renin-Angiotensin system blockade in CKD

119 RCTs; 564768 participants; **Bayesian network meta-analysis**

## Odds ratio [95% credible interval]

<table>
<thead>
<tr>
<th></th>
<th>ACE inhibitors</th>
<th>ARB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kidney failure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>versus placebo</em></td>
<td>0.61 [0.47-0.79]</td>
<td>0.70 [0.52-0.89]</td>
</tr>
<tr>
<td>vs active comparator</td>
<td>0.65 [0.51-0.80]</td>
<td>0.75 [0.54-0.97]</td>
</tr>
<tr>
<td><strong>All cause mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>versus placebo</em></td>
<td>0.72 [0.53-0.92]</td>
<td>Not significant</td>
</tr>
<tr>
<td><strong>Mortality by cardiovascular causes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>versus placebo</em></td>
<td>0.82 [0.71-0.92]]</td>
<td>0.81 [0.62-0.90]</td>
</tr>
</tbody>
</table>

ACE inhibitors more effective than ARB

Renin–Angiotensin system blockade in Diabetes

71 RCTs; 103120 participants

Odds ratio [95% credible interval] versus ACE inhibitor alone

<table>
<thead>
<tr>
<th></th>
<th>ARB alone</th>
<th>ACE + ARB</th>
<th>DR inhibitor + ACE inhibitor</th>
<th>DR inhibitor + ARB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced cardiovascular outcomes</td>
<td>1.02 0.90-1.18</td>
<td>0.97 0.79-1.19</td>
<td>1.32 0.96-1.81</td>
<td>1.0 0.73-1.38</td>
</tr>
<tr>
<td>Progression of CKD</td>
<td>1.1 0.90-1.40</td>
<td>0.97 0.72-1.29</td>
<td>0.99 0.65-1.57</td>
<td>1.18 0.78-1.84</td>
</tr>
</tbody>
</table>

No differences in all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, ESRD or doubling of serum creatinine

Dual blockade: significant adverse events
Single RAS inhibition preferred

Dual blockade of RAAS

33 RCT; n=68405

No benefit for mortality (RR 0.97; 0.9-1.1)
18% reduced admissions for heart failure (0.82; 0.7-0.9)
55% increased hyperkalemia
66% increased hypotension
41% increased renal failure
27% increased withdrawal

Proteinuria
Modest benefit of 20%
Definite benefit on decline in renal function unclear

Aldosterone antagonists add-on to ACE-I &/or ARB
Reduced proteinuria and blood pressure
Increase hyperkalemia & gynaecomastia
Unclear effect on cardiovascular events or ESKD

Cochrane Database Syst Rev. 2014; 29:CD007004
Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis

19 RCT (n=44989); mean 3.8 (range 1-8.4) yr follow-up
133/76 mm Hg vs. 140/81 mm Hg

- Reduced risk of MI, all-cause mortality, stroke; **albuminuria**
- No effect on heart failure, cardiac death, total mortality, or **ESRD**
- No difference in SAE

Esp. useful if CKD, DM

Control of hypertension & proteinuria

ACE inhibitors, ARBs
30-40% reduction in proteinuria; doubling of creatinine; ESRD

Baseline proteinuria determines benefit

Aldosterone escape: combined therapy

Calcium channel blockers
Achieve blood pressure goals
Dihydropyridine CCB: do not reduce proteinuria

Beta blockers useful
Metoprolol reduces blood pressure, proteinuria
Carvedilol, atenolol

Aliskrein: direct renin inhibitor
Recommendations for hypertension in CKD

**JNC4 guidelines.** Use 2 or more agents for severe hypertension [add diuretic or CCB]

Hypertension, proteinuria independent risk factors

Long-term benefits of agents affecting the RAAS

Lower targets for hypertension

Administering medication/s at night; restore nocturnal dipping; increased day-to-night blood pressure ratio
Multiple actions of Vitamin D

- Increase in 1,25-D
- Activation of VDR

Traditional:
- Increase in Ca
- Decrease in PTH
- Increase in Bone mineralization

Nontraditional:
- Decrease in Hepcidin
- Decrease in Inflammation
- Decrease in Anemia

Nontraditional:
- Decrease in RAAS
- Decrease in BP and CV disease
- Decrease in Left atrial volume
- Decrease in Albuminuria

Decrease in TGF-β, hs-CRP in various RCTs
Vitamin D inhibits multiple pathogenic pathways* in renal fibrosis
**Vitamin D deficiency common in children with CKD**

<table>
<thead>
<tr>
<th></th>
<th>CKD 2 (n=14)</th>
<th>CKD 3 (n=18)</th>
<th>CKD 4 (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-OH D₃, ng/ml</td>
<td>15.5 (10-20)</td>
<td>22 (18-37)</td>
<td>21 (9-55)</td>
</tr>
<tr>
<td>Insufficient, &lt;30</td>
<td>14 (100%)</td>
<td>13 (72%)</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>Deficient, &lt;15</td>
<td>8</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

Significant increase in serum PTH and 25(OH) vitamin D₃ 6 weeks after supplementation

**CKiD cohort**

- 506 children

**Deficiency in 28%**

**Determinants**

- Older age
- Higher BMI
- <1/day milk intake
- Proteinuria
- Non-white race
- Assessed in winter
- Non-use of supplement

Pediatr Nephrol 2016; 31: 121–129
Post-hoc analysis: ESCAPE cohort

167 children with median eGFR 51 ml/min/1.73 m²

Normal vitamin D levels linked to less proteinuria

Patients with lower 25(OH)₂ D levels had higher Up/Uc at baseline (P=0.03) and at follow-up (P=0.006)

Normal vitamin D linked to attenuated CKD progression

Annualized loss of eGFR was inversely associated with baseline 25(OH)₂ D level (r=0.32; P<0.001)

5-yr renal survival: 75% in those with baseline levels ≥50 nmol/L
50% in those with lower levels (P<0.001)

Effect remained significant but attenuated with ACEi therapy (P=0.05)

Vitamin D/analogs cut residual proteinuria

6 studies (paricalcitol 4, calcitriol 2) 688 patients; 84% ACEI/ARB

Analogs reduced proteinuria (WMD -16%; 95% CI -13, -18%)

>15% proteinuria reduction analogs vs. controls; OR 2.7 (1.8, 4.1) \( P < 0.001 \)
**Vitamin D/analogs in CKD: Meta-analysis**

**Paracalcitol in 9 RCTs; 832 patients with CKD 2-5**

<table>
<thead>
<tr>
<th>Versus placebo</th>
<th>Relative risk [95% CI]</th>
<th>Trend to hypercalcemia (NS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in serum PTH</td>
<td>6.37 [4.64-8.74]</td>
<td></td>
</tr>
<tr>
<td>Decrease in proteinuria</td>
<td>1.68 [1.25, 2.25]</td>
<td></td>
</tr>
</tbody>
</table>


**Conventional vitamin D and newer analogs: 18 RCTS**

**Reduced proteinuria** to similar extent (RR 2.00; 95% CI 1.42-2.81)  
**Stable renal function**; similar risk of dialysis initiation  
**Increased risk of hypercalcemia** (RR 4.78; 95% CI 2.20-10.37)

Phosphate associated with CKD progression, attenuates renoprotective effect of ACE inhibition

Cumulative incidence of ESRD (+/-doubling serum creatinine)

Efficacy of ramipril in reducing incidence of ESRD, by PO₄ quartile

Ramipril Efficacy In Nephropathy (REIN) trial

331 with proteinuric nephropathies

Serum phosphate associated with risk of ESRD, mortality

Meta-analysis of 12 cohorts with 25546 patients
1442 (8.8%) developed ESRD, 3089 (13.6%) died

Every 1-mg/dL increase in serum phosphorus was associated independently with increased risk of

Kidney failure  HR 1.36; 95% CI, 1.20-1.55
Mortality  HR 1.20; 95% CI, 1.05-1.37
High FGF23 levels associate with progression of CKD in adults

**Fibroblast Growth Factor 23 independently associated with CKD Progression in Children**

Chronic Kidney Disease in Children (CKiD)

419 children, 1-16 yr  
GFR: 44 (IQR 33-57) ml/min/1.73 m²

**Composite end point**: Start of dialysis or kidney transplantation or 50% decline from baseline GFR

Seen in 32.5% children at median 5.5 (IQR 3.5-6.6) yr

**Adjusted hazard ratio of composite outcome**

Highest *versus* lowest FGF23 tertile  
2.52 [95%CI 1.44-4.39; P=0.002]

Per doubling of FGF23  
1.33 [95%CI 1.13-1.56; P=0.001]

40% shorter time to progress for those with highest vs. lowest tertile

**Serum phosphate**, PTH and vitamin D not associated with risk of progression
FGF23 & Klotho: The holy grail in CKD?

**FGF23**
- Biomarker of MBD in early CKD
- Elevated levels predict mortality

**Klotho**
- Transmembrane co-receptor for FGF23
- Deficient in CKD
- **Biomarker** for early detection of CKD
- Potential future therapeutic tool

Loss of Klotho, decreased phosphate excretion, FGF23 elevation occur early in CKD and contribute to disease progression and complications.

RAAS activation & proteinuria decrease Klotho expression leading to phosphate retention and FGF23 elevation.

RAAS blockade may reverse Klotho loss during CKD.

Which of the following interventions, practiced in adults with CKD, has been demonstrated to be NOT beneficial in preventing progression in pediatric CKD?

1. Control of hypertension
2. Control of proteinuria
3. Use of low protein diet
4. Management of anemia
Does dietary protein restriction impact the progression of CKD?

Brenner’s hypothesis

Modification of Diet in Renal Disease Study

1585 patients with GFR 25-55 ml/min/1.73 m²

Low protein diet slows progression in non-diabetic CKD & type 1 DM, not type 2 DM

Meta-analysis: 15 RCTs, 1965 patients

0.83±0.15 g/kg/day vs. 1.07±0.17 g/kg/day

Change in mean GFR, ml/min/1.73 m²/yr

All patients  
-0.95 [95% CI -1.79, -0.11]  P=0.03

Non-diabetic, type 1 DM  
-1.50 [95% CI -2.73, -0.26]  P=0.02

Type 2 DM  
-0.17 [95% CI: -1.88, 1.55]  P=0.85

PLoS One 10: e0145505
Protein restriction not recommended in children

RCTs: Unrestricted vs. protein restricted diet (0.8-1.1 g/kg/d)
2 trials; 124 protein restricted, 126 control diet

No significant differences

- renal deaths (RR 1.1; 95% CI 0.5, 2.3)
- GFR (MD 1.5; -1.2, 4.1)
- weight (MD -0.13; -1.1, 0.8)
- height (MD -2.0; -4.8, 0.9)

Low protein intake does not delay progression to ESRD

Concern regarding adverse effects on growth
Salt restriction in people with CKD

8 RCTs (5 cross-over); 258 participants
Duration: 1-26 weeks

Lower urinary Na excretion (52-141 mEq/day)

Reduced blood pressure
Systolic: Mean difference (MD) -8.75 [95% CI -11.33, -6.16] mm Hg
Diastolic: MD -3.70 [95% CI -5.09, -2.30] mm Hg
Reduced antihypertensive dose RR 5.48 [95% CI 1.27, 23.66]

Reduced proteinuria consistently (not meta-analysed)

No change in serum creatinine/eGFR; cholesterol; weight

Effect on ESKD incidence & cardiovascular events not studied

Cochrane Database of Systematic Reviews 2015; 2: CD010070
Dyslipidemia parallels renal dysfunction

Multiple causes: insulin resistance, high PTH, malnutrition, acidosis, low lipoprotein lipase

Hypercholesterolemia: macrophages form foam cells; endothelial & mesangial cell dysfunction

Adults with type 1 diabetes & high cholesterol: faster decline in GFR, nephropathy

Non-diabetics with low HDL cholesterol, high TG: increased risk
Arterial stiffness is associated with steeper decline in kidney function

Rotterdam Study
Incident CKD in 601 of 3666 participants
**Pulse pressure, carotid stiffness** associated with
Steeper annual eGFR decline, risk of incident CKD


Lipophilic index (LI) associated with GFR decline

Prospective Investigation of Vasculature in Uppsala Seniors
198 of 975 elderly adults: eGFR reduction ≥30%) after 5-yr

Lipophilic index = \( \Sigma \) (fatty acid proportion \( \times \) FA melting point)
Reflects membrane fatty acids; linked to
Lower GFR -3 ml/min/1.73 m\(^2\) per 1 SD
Decline in GFR Adjusted OR 1.32 [95% CI 1.05-1.65]

Does therapy with statins delay CKD progression?

1. 2014: 38 studies, 37274 participants: Uncertain effect

2. 10 RCT or cohort studies
   Statin vs. placebo
   Difference in change of eGFR 0.10 [95%CI 0.09-0.12] ml/min/1.73 m²
   Difference in reduction of proteinuria 0.19 [95%CI -0.02 to 0.40] g/day
   Favors statin use with use of higher dose
   No difference in eGFR in studies using low or moderate doses

High intensity cholesterol lowering therapy may improve renal outcomes


3. 30 RCTs; 45688 participants

Improves GFR or delays reduction of GFR; esp. atorvastatin; high dose
Does not prevent ESRD or risk of doubling of serum creatinine

Nan Fang Yi Ke Da Xue Xue Bao 2016; 36:445-54
## Hyperuricemia indicates CKD progression?

<table>
<thead>
<tr>
<th>Reference</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsu, 2009</td>
<td>Increased risk of ESRD 2.14-fold</td>
</tr>
<tr>
<td>Obermayr, ‘08</td>
<td>Increased risk of CKD 1.74-fold (men) or 3.12-fold (women)</td>
</tr>
<tr>
<td>Weiner, 2008</td>
<td>1 mg/dL rise increases risk of CKD by 7-11%</td>
</tr>
<tr>
<td>Iseki, 2001</td>
<td>Level &gt;8 mg/dl increases CKD risk 3-fold (men) or 10-fold (women)</td>
</tr>
<tr>
<td>Borges, 2009</td>
<td>Increased risk of CKD in hypertensive women 2.63-fold</td>
</tr>
<tr>
<td>Chen, 2009</td>
<td>Associated with prevalent CKD in elderly</td>
</tr>
<tr>
<td>Park, 2009</td>
<td>Correlates with rapid decline in residual renal function in PD patients</td>
</tr>
<tr>
<td>Sturm, 2008</td>
<td>Predicts progression of CKD only in unadjusted sample</td>
</tr>
<tr>
<td>See, 2009</td>
<td>Level &gt;7.7 mg/dL (men) or &gt;6.6 mg/dL (women) associated with CKD</td>
</tr>
<tr>
<td>Madero, 2009</td>
<td>Correlates with death but not to ESRD in patients with CKD 3-4</td>
</tr>
</tbody>
</table>
Hyperuricemia in pediatric CKD

AIIMS, 2001-2010; n=110, CKD stage 2-5
Uric acid >5.5 mg/dl: 70 (63.6%)
Lower eGFR (24.2±16.7 vs. 30.8 ±22.4 ml/min; P=0.08)
Higher serum phosphate (5.3±1.4 vs. 4.9±0.7 mg/dl; P=0.07)

Chronic Kidney Disease in Children (CKiD) Cohort

678 children and adolescents
Uric acid 5.5-7.5 mg/dl in 294 (43%); >7.5 mg/dl in 175 (26%)

Decline of eGFR >30% from baseline or need for RRT

Relative risk (95% CI)

- Uric acid 5.5-7.5 mg/dl: 0.83 (0.62-1.11)
- Uric acid >7.5 mg/dl: 0.62 (0.45-0.85)

Other determinants: Hypertension, lower GFR, glomerular cause and proteinuria

Urate lowering therapy to improve renal outcomes in patients with chronic kidney disease: systematic review and meta-analysis

19 RCT (n=992); allopurinol vs. inactive control for >3 months
Pooled eGFR favors allopurinol; mean difference **3.2 (0.2-6.2)** ml/min/1.73 m²
Reduced systolic & diastolic blood pressure; uric acid

Correction of anemia has no impact on CKD progression

**Retrospective observational studies**
ESA therapy slows progression of CKD
ESA have direct renoprotective effect

**5 RCTs using C.E.R.A.:** Response at 12 weeks
Group with lower hemoglobin had lower eGFR; lower renal survival

19 RCTs; 8129 participants CKD 1-4; ≥2 months

<table>
<thead>
<tr>
<th>Versus placebo, another agent</th>
<th>Relative risk/mean difference [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of end-stage kidney disease</td>
<td>0.97 [0.83-1.20]</td>
</tr>
<tr>
<td>Change in estimated GFR</td>
<td>−0.45 [−2.21, 1.31] ml/min/1.73 m²</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>1.10 [0.90– 1.35]</td>
</tr>
<tr>
<td>Treatment withdrawal for AE</td>
<td>1.18 [0.77– 1.81]</td>
</tr>
</tbody>
</table>

Can folic acid delay CKD progression?

Folate deficiency → Hyperhomocysteinemia → Albuminuria → CKD progression

Supplementation reduces progression of CIMT

Homocysteinemia in Kidney & ESRD (HOST)
FA 40 mg (+ B6, B12)

Diabetic Intervention with Vitamins to Improve Nephropathy (DIVINE)
FA 2.5 mg (+ B6, B12)

China Stroke Primary Prevention Trial (Substudy)
15104 adults with hypertension and eGFR >30 ml/min/1.73 m²

Enalapril 10 mg vs. Enalapril 10 mg + folic acid 0.8 mg
Primary event: eGFR <60 ml/min/1.73 m² with 30-50% decline
Odds ratio: 0.79 [95% CI 0.62-1.00] No. needed to treat: 29
Rate of GFR decline: 1.28% vs 1.42% per year; P=0.02
Mean serum folate: 7.7 vs 15-16.6 ng/mL

Metabolic Acidosis: Linked to CKD progression, cardiovascular disease & mortality

Recommendations
- Calculate bicarbonate requirement: (desired serum bicarbonate concentration – actual serum bicarbonate concentration) × 50% body weight (in kg)
- Administer sufficient base to increase serum bicarbonate concentration close to mean reference value of 24 mEq/L
- Administer dose over 3-4 days while monitoring serum bicarbonate concentration
- When serum bicarbonate concentration reaches target (~24 mEq/L), reduce dose of base with goal of maintaining serum bicarbonate concentration at ≤24 mEq/L
- Consider more aggressive base replacement in chronic kidney disease patients with disorders associated with base loss, such as profuse diarrhea, or generation of large acid loads, such as ketoacidosis

Study | Patients | Outcome
--- | --- | ---
De Brito-Ashurst et al\textsuperscript{58} | 134 with GFRs 15-30 | Decrease in slope of decline in GFR with base
Phisitkul et al\textsuperscript{68} | 59 with GFRs of 20-60 | Less GFR decline with base
Mahajan et al\textsuperscript{67} | 120 with GFRs of 75 ± 6 | Less GFR decline with base

Preventing progression in ADPKD

Cyst expansion impairs renal function; hyperfiltration preserves GFR

**Interventions:** Slowing vs. restoration

*PKD1* vs. *PKD2*
Truncating vs. missense mutations
In utero cysts vs. adolescence onset

**Total kidney volume (TKV)**
Increases by 3-13% per year

MRI/CT (not USG; height adjusted)

**Rate of increase in TKV 1/α**
Rate of fall in eGFR

TKV at baseline predicts the development of CKD stage 3

\[
GFR_t = (GFR_{t-1}) - \left(\frac{TKV_t}{400}\right) \quad t=\text{age}
\]

RCTS on retarding progression in ADPKD: Target TKV, not eGFR?

<table>
<thead>
<tr>
<th>Agent</th>
<th>Increase in TKV</th>
<th>Decrease in eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>mTOR inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>Inconsistent</td>
<td>No effect</td>
</tr>
<tr>
<td>Rapamycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressin receptor 2 antagonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolvaptan (TEMPO3:4; REPRISE)</td>
<td>49% slower; awaited</td>
<td>31% slower; awaited</td>
</tr>
<tr>
<td>ACE inhibitors +/- ARB (HALT-PKD: low vs. standard BP target)</td>
<td>Slower</td>
<td>(Insignificantly) slower</td>
</tr>
<tr>
<td>Somatostatin analogs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Octreotide (ALADIN)</td>
<td>Slower; awaited</td>
<td>+/-; awaited</td>
</tr>
<tr>
<td>Lanreotide (ongoing)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins*</td>
<td>Slower</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Pravastatin (in children)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Inhibits vasopressin activated MAP kinase stimulation of cyst growth

Prevent & correct acute decline in GFR

Volume depletion
Intravenous radiographic contrast
Drugs
  - Aminoglycosides, amphotericin B
  - NSAIDS, COX-2 inhibitors
  - ACE inhibitors, Ang2 R blockers
  - Cyclosporine, tacrolimus
Obstruction of the urinary tract
Acute Kidney Injury: Gateway to CKD

CKD in 3-28 per 1000 person-yr; CKD stage 3 in 10-15%

Identified risk factors
- Recurrent episodes of AKI
- Higher AKI stage, need for RRT
- Old age; hypoalbuminemia
- Multiple causes (vs. pure ATN)
- Biomarkers: inflammation, recovery

Children with congenital heart disease may progress to CKD after AKI

Clinical and experimental evidence
- Biomarkers may help predict CKD progression

Therapies for slowing progression

Hypertension, proteinuria independent risk factors

Agents affecting the RAAS very useful

Lower targets for hypertension in CKD

Correct vitamin D deficiency; consider analogs for therapy of residual proteinuria

Manage dyslipidemia with statins

High serum phosphate & uric acid; acidosis; low folic acid and anemia: Linked to progression; unclear efficacy of therapy
What was the theme of WKD 2016?

(1) Kidneys for Life – Stop Kidney Attack!
(2) Protect your kidneys: Keep your pressure down
(3) Kidney Health for All
(4) Act early to prevent it

Averting the legacy of kidney disease - Focus on childhood