Chronic Kidney Disease Management for Primary Care Physicians

Dr. Allen Liu
Consultant Nephrologist
KTPH
21 November 2015
Incidence of Patients on Dialysis by Mode of Dialysis and Etiology, 1999 – 2012

In 2012, Prevalence patients: 5237
Age-standardised rate: 947.6pmp
Comparison of Unadjusted ESRD Prevalence Worldwide

All rates are unadjusted. Data from Japan are dialysis only.
Percentage of incident patients with ESRD due to diabetes, 2011

Data presented only for countries from which relevant information was available. All rates unadjusted. ^UK: England, Wales, & Northern Ireland (Scotland data reported separately).
*Latest data for Taiwan are from 2010. ^^ Czech Republic: Data on incident ESRD due to diabetes is an estimate. Data for France include 25 regions in 2011.

USRDS 2013 Atlas of CKD & ESRD
Rates of Death and Cardiovascular Events Rise as Renal Function Declines

• The outcomes of patients with reduced GFR are uniformly poor
• Patients with CKD are more likely to die than go onto dialysis
• Early recognition of CKD permits intervention to alter the Natural History of the disease:
  – renoprotection
  – Cardio-vascular protection
Cardiovascular Mortality Rates are Higher among Dialysis Patients

Cardiovascular Disease in CKD: Multifactorial Pathogenesis

- Elevated PTH/2'HPT
- Duration of dialysis
- Oxidative stress
- Anaemia
- Chronic inflammation
- Hyperphosphatemia
- Exogenous Ca intake
- Elevated Ca x P product
- Traditional risk factors
- Non Traditional risk factors

- High prevalence of traditional risk factors
- As renal function deteriorates, non-traditional factors play an increasing role in GFR loss and cardiovascular damage

Dyslipidemia
Hypertension
Diabetes Mellitus
Genetics
Smoking
Age
What is Your Role as a Primary Care Physician in treating CKD?

1. Know early
   - Epidemiology of CKD

2. Diagnose early
   - Diagnosis of CKD

3. Treat early
   - Mortality and Morbidity Progression of (early) CKD

4. Refer early
   - Referral to nephrologist
Chronic Kidney Disease (CKD) Nomenclature

Abnormalities of kidney structure or function, present for >3 months, with implications for health

<table>
<thead>
<tr>
<th>GFR categories (ml/min/1.73 m²)</th>
<th>Description and range</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Normal or high</td>
<td>≥90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>Mildly decreased</td>
<td>60-89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3a</td>
<td>Mildly to moderately decreased</td>
<td>45-59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3b</td>
<td>Moderately to severely decreased</td>
<td>30-44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G4</td>
<td>Severely decreased</td>
<td>15-29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G5</td>
<td>Kidney failure</td>
<td>&lt;15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Persistent albuminuria categories Description and range

<table>
<thead>
<tr>
<th>A1</th>
<th>A2</th>
<th>A3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal to mildly increased</td>
<td>Moderately increased</td>
<td>Severe increased</td>
</tr>
<tr>
<td>&lt;30 mg/q  &lt;3 mg/mmol</td>
<td>30-300 mg/q  3-30 mg/mmol</td>
<td>&gt;300 mg/q  &gt;30 mg/mmol</td>
</tr>
</tbody>
</table>
GFR MDRD Calculator

GFR (mL/min/1.73 m²) =
175 × (sCr/88.4)^{-1.154} × (Age)^{-0.203} × (0.742 if female) × (1.212 if Black)

CKD-EPI

eGFR = 141 × \min(\frac{SCr}{k,1})^a × \max(\frac{SCr}{k,1})^{-1.209} × 0.993^{\text{Age}} × [1.018 if \ Female] × [1.159 if \ Black]

Available on the
App Store

## Table 142. Laboratory Evaluation of Patients with Chronic Kidney Disease

### All Patients

- Serum creatinine to estimate GFR
- Protein-to-creatinine ratio or albumin-to-creatinine ratio in a first-morning or random untimed “spot” urine specimen
- Examination of the urine sediment or dipstick for red blood cells and white blood cells
- Imaging of the kidneys, usually by ultrasound
- Serum electrolytes (sodium, potassium, chloride and bicarbonate)

Random urine tests for
- Macroscopic/ microscopic evaluation
- Persistent WBC or RBC; cellular casts
### Definitions of Abnormalities in Albumin Excretion

<table>
<thead>
<tr>
<th>Category</th>
<th>Older Terms</th>
<th>Spot Collection (mg/g Creatinine)</th>
<th>24-h collection (mg/24h)</th>
<th>Timed collection (mcg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal To Mildly Increased</td>
<td>(Normoalbuminuria)</td>
<td>&lt;30</td>
<td>&lt;30</td>
<td>&lt;20</td>
</tr>
<tr>
<td>(Increase UAE)</td>
<td></td>
<td>&gt;=30</td>
<td></td>
<td>&gt;=30</td>
</tr>
<tr>
<td>Moderately Increased</td>
<td>(Microalbuminuria)</td>
<td>30-299</td>
<td>30-299</td>
<td>30-299</td>
</tr>
<tr>
<td>Severely Increased</td>
<td>(Macroalbuminuria)</td>
<td>&gt;300</td>
<td>&gt;300</td>
<td>&gt;300</td>
</tr>
</tbody>
</table>

Diagnosis of moderately increased albuminuria based of **2 out of 3 urine samples** in the absence of UTI.

**After 5 years of diagnosis** in T1DM and than annually.

**At the time of diagnosis** in T2DM.

Cardiovascular Disease in CKD: Multifactorial Pathogenesis

- High prevalence of traditional risk factors
- As renal function deteriorates, non-traditional factors play an increasing role in GFR loss and cardiovascular damage
Strategies on Reduction of Progression of Early CKD – Role of A Primary Physician

1. Control of blood pressure
2. Use of ACEI/ARB
3. Glycaemic control in DM
4. Control of dyslipidaemia
5. Protein restriction
6. Management of anaemia (CKD3 or above)
7. Control of CaPO4 (CKD 3 or above)
Strategies on reduction of progression of CKD

1. Control of blood pressure
Goal of BP control in CKD

- Reduction of Proteinuria
- Retardation of CKD progression
- Reduction of Mortality
- Reduction of CVD
Evaluation of BP

Pre-HD CKD and PD
• Clinic BP (standard vs nonstandard)
• Home BP
• Ambulatory BP monitoring (ABPM)

Haemodialysis patients
• Pre-HD
• Post-HD
• Home BP
• ABPM
Role of ABPM

- White coat ↑BP: Clinic SBP > 140 but normal home BP or ABPM without target organ damage (TOD)
- Masked ↑BP: Clinic SBP < 140 but home SBP or ABPM > 140 ± TOD
- Nocturnal BP > 125/75
- Nondipper: DBP and SBP ↓ by < 10 and 20% during sleep respectively
- Reverse dipper: no drop in SBP or DBP during sleep
- BP load: < 25% above normal over 24h
Is home BP any better?

<table>
<thead>
<tr>
<th>SBP monitoring method</th>
<th>ESRD or death HR (95% CI)</th>
<th>Composite CV outcomes (MI, CVA or death) HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine clinic SBP</td>
<td>1.27 (1.01-1.60)</td>
<td>1.07 (0.60-1.93)</td>
</tr>
<tr>
<td>Standardised clinic SBP</td>
<td>1.69 (1.32-2.17)</td>
<td>1.08 (0.53-2.21)</td>
</tr>
<tr>
<td>Home BP</td>
<td>1.84 (1.46-2.32)</td>
<td>1.36 (0.66-2.76)</td>
</tr>
<tr>
<td>ABPM</td>
<td>—</td>
<td>2.22 (1.23-4.01)</td>
</tr>
</tbody>
</table>

n=217 CKD FU 3.5y

DBP did not consistently correlate with outcomes across all BP assessment methods

B Agarwal, KI, 65: 406-411
Meta Analysis: Lower Mean BP Results in Slower Rates of Decline in GFR in Diabetics and Non-Diabetics

\[ r = 0.69; \, P < 0.05 \]

# Blood Pressure Targets and Treatment Recommendations in CKD

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Blood pressure target in CKD without proteinuria</th>
<th>Blood pressure target in CKD with proteinuria*</th>
<th>Recommended first line medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA JNC8</td>
<td>&lt;140/&lt;90 mmHg</td>
<td>&lt;140/&lt;90 mmHg</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td>KDIGO</td>
<td>&lt;140/&lt;90 mmHg</td>
<td>&lt;130/&lt;80 mmHg</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td>NICE</td>
<td>&lt;140/&lt;90 mmHg</td>
<td>&lt;130/&lt;80 mmHg</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td>CHEP</td>
<td>&lt;140/&lt;90 mmHg</td>
<td>&lt;140/&lt;90 mmHg</td>
<td>ACEI; ARB if ACEI intolerant</td>
</tr>
<tr>
<td>ESC/ESH</td>
<td>&lt;140 mmHg</td>
<td>&lt;130 mmHg</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td>ASH/ISH</td>
<td>&lt;140/&lt;90 mmHg</td>
<td>&lt;140/&lt;90 mmHg</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td>ISHIB</td>
<td>&lt;130/&lt;80 mmHg</td>
<td>&lt;130/&lt;80 mmHg</td>
<td>Diuretic or CCB</td>
</tr>
</tbody>
</table>
Strategies on reduction of progression of CKD

2. Use of ACEI/ARB
### RAAS blockade- GFR decline at the expense of improvement in proteinuria

<table>
<thead>
<tr>
<th></th>
<th>Without RAAS blockade BP &gt;140/90</th>
<th>Without RAAS blockade but BP 130/80</th>
<th>With RAAS blockade BP 130/80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline GFR</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Baseline proteinuria (g/day)</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Expected GFR decline/year</td>
<td>5-10mL/min/yr</td>
<td>4-6mmL/min/yr</td>
<td>2-3mL/min/yr</td>
</tr>
<tr>
<td>(normal decline 1mL/min/yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR after 2 years</td>
<td>20</td>
<td>28</td>
<td>34</td>
</tr>
<tr>
<td>Proteinuria after 2 years</td>
<td>6</td>
<td>2.8</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

# Renin angiotensin aldosterone blocking trials

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>DM number</th>
<th>Protocol</th>
<th>FU</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Captopril trial</strong> — Lewis EJ et al NEJM 1993</td>
<td>Type 1DM</td>
<td>Captopril 25mg tds vs placebo</td>
<td>3y</td>
<td>Doubling of Crt ↓48%</td>
</tr>
<tr>
<td></td>
<td>N=490</td>
<td></td>
<td></td>
<td>Cct ↓11±21 vs 17±20ml/min/y</td>
</tr>
<tr>
<td></td>
<td>BP 135/86</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UACR&gt;0.5g/d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Crt 220</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No CV pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RENAAL</strong> — Reduction Endpoints in NIDDM with Angiogen II Antagonist Losartan Brenner BM et al NEJM 2001</td>
<td>Type 2DM</td>
<td>Losartan 50-100mg vs placebo</td>
<td>3.5y</td>
<td>UTP↓ 36%</td>
</tr>
<tr>
<td></td>
<td>N=1513</td>
<td></td>
<td></td>
<td>Doubling of Crt ↓26%</td>
</tr>
<tr>
<td></td>
<td>BP 150/80</td>
<td></td>
<td></td>
<td>ESRD↓ 28%</td>
</tr>
<tr>
<td></td>
<td>UACR 1.2g/d</td>
<td></td>
<td></td>
<td>GFR↓ 4.4 vs 5.2ml/min/y</td>
</tr>
<tr>
<td></td>
<td>Crt 170</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No CV pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Irbesartan in Patients with DM2Nephropathy Diabetes trial</strong> Lewis EJ, NEJM 2001</td>
<td>Type 2DM</td>
<td>Irbesartan 75-300mg/d vs Amlodipine 10mg vs Placebo</td>
<td>2.6y</td>
<td>UTP↓ 33%</td>
</tr>
<tr>
<td></td>
<td>N=1715</td>
<td></td>
<td></td>
<td>Doubling of Crt↓ 33-37%</td>
</tr>
<tr>
<td></td>
<td>BP 160/85</td>
<td></td>
<td></td>
<td>ESRD↓ 23%</td>
</tr>
<tr>
<td></td>
<td>UACR 1.9g/d</td>
<td></td>
<td></td>
<td>Cct 5.5 vs 6.5-6.8ml/min/y</td>
</tr>
<tr>
<td></td>
<td>Crt 141</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No CV pts</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Monotherapy with RAAS blockers slows progression of proteinuric DM nephropathy. ARB preferable in type 2 DM CKD.

Cct= creatinine clearance
Combinations and SAE (ONTARGET)

- 25620 patients
- Telmisartan vs. Ramipril vs. combinations
- Temisartan (16.7%) noninferior; combination (16.3%) not superior to ramipril (16.5%) for primary endpoints (CV death, MI, stroke, heart failure)
- Combination groups
  - Increased risk of hypotensive symptoms, syncope and renal dysfunction (13.5% vs. 10.2%, P<0.001)
- Combination drugs more adverse events without an increase in benefit

## Double RAAS combination trials

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>DM number</th>
<th>Protocol</th>
<th>FU</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONTARGET</td>
<td>N=25,620</td>
<td>Ramipril 2.5-10mg/d vs Telmisartan 40-80mg/d vs combo</td>
<td>2.2y</td>
<td>AKI 10.2 vs 10.6 vs 13.5%</td>
</tr>
<tr>
<td>Yusuf et al, NEJM 2008</td>
<td>CV pts 85%</td>
<td>DM 38%</td>
<td>↑BP 69%</td>
<td>Microalb 13%</td>
</tr>
<tr>
<td>VA-NEPHRON</td>
<td>N=1448</td>
<td>ΔUACR 128 vs 269 mg/g</td>
<td>2.2y</td>
<td>ESRD 5.9 vs 3.7%</td>
</tr>
<tr>
<td>Friend LF et al, NEJM 2013</td>
<td>UACR 0.9g/d</td>
<td>BP 137/72</td>
<td>ΔUACR 128 vs 269 mg/g</td>
<td>GFR 2.7 vs 2.9ml/min/yr</td>
</tr>
<tr>
<td>ALTITUDE</td>
<td>N= 8561</td>
<td>ACE-I/ARB vs Alikirein 150-300mg/d + ACE-I/ARB</td>
<td>32.9m</td>
<td>↑Crt 5.1 vs 4.9</td>
</tr>
<tr>
<td>Parving HH et al, NEJM 2012</td>
<td>Type 2 DM</td>
<td>CV pts 42.3%</td>
<td>UACR 0.2g/d</td>
<td>BP 137/74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑K 2.6vs 4.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓BP 8.3vs 9.8%</td>
</tr>
</tbody>
</table>

*Dual therapy with RAAS blockers aggravates renal function in mildly to moderately proteinuric CKD patients with high CV burden. No evidence it is harmful in severely proteinuric CKD.*
RAAS Inhibition: What we know

• Decrease risk of progression from
  – Normoalbuminuria to microalbuminuria
  – Microalbuminuria to overt nephropathy
  – Overt nephropathy to ESRD
• ACEI comparable to ARB
• GFR drops by 10% before plateauing
• Combination therapy is effective in reducing proteinuria; effects on slowing progression is questionable
Hyperkalaemia (K>5.5)

• Dietary indiscretion - eg bananas, potatoes, coconut and Nyoni juice
• Or NSAIDs, dehydration, absence of a kalliuretic diuretic (thiazide or frusemide)
• If K 5.5-6, review diet, K binding resins ± hold of RAAS blocker temporarily
• Longterm K binding resins - Resonium/Kayalexate/ Partiromer/Zirconium cyclosilicate
Rising creatinine

- Always check creatinine 1-2 weeks after starting or changing RAAS blocker
- <30% ↑ is acceptable
- ≥30% - dehydration, recent hypotension, ischaemia, NSAID, interstitial nephritis
- Screening for renal artery stenosis
- Hold off agent and review in 2-4 weeks and ↓ thiazide dose to 12.5mg
Strategies on reduction of progression of CKD

3. Glycaemic control in DM
Intensive Diabetes Management

- 1441 IDDM patients
- 2-3x increase in hypoglycaemia
- Reduced microalbuminuria by 39% for both groups
- Reduced macroalbuminuria by 54% for retinopathy group
- 60% reduction in clinical nephropathy

Randomised prospective trial of treatment strategies in T2DM

• 5102 patients
• 53000 patient years follow-up

<table>
<thead>
<tr>
<th></th>
<th>Intensive</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>7%</td>
<td>7.9%</td>
</tr>
</tbody>
</table>

• Each 1% decrease in HbA1c decreases microvascular complications by 35%
• Strict BP control decreases microvascular complications

(1998) Lancet
Intensive Insulin/OHA Therapy

- Partially reverse the glomerular hypertrophy and hyperfiltration
- Delay the development of elevated albumin excretion
- Stabilize or decrease protein excretion in patients with increased albumin excretion
- Slow the progression of glomerular filtration rate decline

Recommendation (KDIGO 2012)
- A target hemoglobin A1c (HbA1c) of about 7.0% to prevent or delay progression of the microvascular complications of diabetes, including diabetic kidney disease. (1A)