Clinical Pearls: Chronic Kidney Disease

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Disclosures

No conflicts of interest to disclose
Learning Objectives

- Describe the most important management principles for patients with chronic kidney disease
- Describe strategies for slowing kidney disease progression
- Describe strategies for reducing cardiovascular disease in CKD
- Recognize and implement interventions to address CKD-related complications
Outline

- Cardiovascular disease (CVD) burden in chronic kidney disease (CKD)
- Strategies for slowing kidney disease progression
- Reducing cardiovascular disease in CKD
- Treating Complications
- Vaccinations
- Referral to nephrology
Case 1

- 52 year old male with CKD stage 3B (GFR 35 ml/min) secondary to DM and HTN presents for routine follow-up. No h/o CVD, quit smoking 5 years ago. No family history of CVD.
Given this patient has CKD stage 3B he should be considered:

1. Lowest risk group for CVD irrespective of his traditional CVD risk factors 0%

2. Moderate risk group for CVD irrespective of his traditional CVD risk factors 24%

3. Highest risk group for CVD irrespective of his traditional CVD risk factors 76%
CKD Population of 20M in U.S.

Stage 5
n=300,000

Stage 4
n=400,000

Stage 3
n=7,600,000

Stage 2
n=5,300,000

Stage 1
n=5,900,000

Pre-Dialysis Patients Are More Likely to Die than Progress to ESRD Dialysis Therapy

Keith D et al. *Arch Intern Med* 2004; 164: 659-663
Chronic Kidney Disease (CKD) and CVD

- Patients with CKD are at an increased risk of CVD
- CKD is an independent risk factor for CVD
  - All patients with CKD should be considered in the “highest risk” group for CVD
Rate of Death and Cardiovascular Events According to Estimated GFR

N = 1,120,295 adults.
*Age-standardized rates per 100 person-years; †CV event defined as hospitalization for coronary heart disease, heart failure, ischemic stroke, and peripheral arterial disease per 100 person-years.
Secondary Complications and Comorbidities of CKD

Complications
- Albuminuria
- Anemia
- Disordered Mineral Metabolism
  - Hyperphosphatemia
  - Secondary hyperparathyroidism
  - Vitamin D deficiency
  - Elevated FGF23
- Metabolic acidosis
- CVD

Comorbidities
- Diabetes mellitus
- Hypertension
- Dyslipidemia
- Obesity
- CVD
The most important management principles for CKD are…

- Delay CKD progression
- Treat complications of CKD
- Screen for and treat cardiovascular risk factors
Slowing Progression of Kidney Disease
Case 2

- 62 year old female with CKD stage 3B (GFR 32 ml/min) secondary to DM.
- PMH: DM, HTN, OSA
- Medications: lisinopril, furosemide, metoprolol, simvastatin, aspirin
- BP 145/90, pulse 72
- Proteinuria 2100 mg/day
- Serum bicarbonate 16 meq/L
- Serum phosphate 4.9 mg/dL
- Serum 25-hydroxyvitamin D 10 ng/mL
- Intact PTH 120 pg/mL
- Hemoglobin 10.3 g/dL
In additional blood pressure, diabetes and lipid control what other intervention with slow progression of her kidney disease?

1. Additional of an angiotensin receptor blocker (ARB)  
   - 64%

2. Treatment of her metabolic acidosis with sodium bicarbonate  
   - 23%

3. Treatment of her anemia to a hemoglobin > 12 g/dl  
   - 2%

4. No other intervention will slow progression of her kidney disease at this point  
   - 11%
Slowing Progression: Blood Pressure Control

- Over 80% of patients with CKD have HTN
- The **MOST** important factor in decreasing the progression of kidney disease
- The appropriate BP goal is unknown
  - New recommendations: <140/90 mmHg
  - Many nephrologist still do <130/80 mmHg
- BP control reduces proteinuria (another risk factor for progression of CKD)
Slowing progression: Inhibition of the Renin-Angiotensin-Aldosterone System

- RAAS has pathophysiologic role in progression of CKD
- RAAS blockade reduces proteinuria and slows progression
- Beneficial effect has been demonstrated:
  - In both diabetic and non-diabetic kidney disease
  - In advanced CKD
- Magnitude of the effect is about a 20% risk reduction
- ACEi and ARB have similar efficacy
ACE inhibitors should not be combined with ARB

- Adding ARB to ACEi is less effective than adding another agent
- Combination does not reduce cardiovascular or renal events compared to the individual agents
- Increased risk of:
  - Hyperkalemia
  - Hypotension
  - Dialysis
  - Doubling of serum creatinine
  - Death
How do we achieve BP control in CKD patients?

- Combination of 3 or more drugs are usually needed
- All diabetics with CKD should be treated with an ACEi or ARB
- All patients with proteinuria should be treated with an ACEi or ARB
Other “Traditional” Risk Factors for Kidney Disease Progression and CVD

- Hyperlipidemia
- Smoking
- Obesity
- Diabetes
- Genetics
- Race and socioeconomic status
**Slowing Progression: Treating Metabolic Acidosis**

- **Metabolic Acidosis**
  - Reduction in serum HCO$_3^-$ concentration
  - Common complication of CKD
  - Major consequences:
    - Degradation of muscle protein and muscle wasting
    - Reduced albumin synthesis
    - Production or exacerbation of bone disease
    - Impairment in glucose tolerance
  - Traditionally treatment of metabolic acidosis was for these consequences

Kraut J. Am J Physiol Renal Physiol 2011;300:F828-829
Metabolic Acidosis is also a Risk Factor for Kidney Disease Progression

Bicarbonate Administration Slows Progression of Kidney Disease

- 134 patients with CKD stage 4 with serum HCO3⁻ 16-20 mmol/L
- Randomized to supplementation with sodium bicarbonate or placebo for 2 years

![Graph showing dialysis-free survival over 2 years for intervention and control groups.]

Alkali Therapy Slows CKD Progression

- 59 CKD stage 3 patients treated with sodium citrate (1 mEq/kg/day) or standard care for 24 months
- Mean serum bicarbonate of 20 meq/L

| Table 2 | SBP, Pcr, and eGFR before (0 months) and after 24 months of No-NaCit vs NaCit |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | No-NaCit (n=29) | NaCit (n=30)    |
|                | Month 6         | Month 30        | P-value,         | Month 6         | Month 30        |
|                | 30 vs 6 months  | 30 vs 6 months  | P-value,         | 30 vs 6 months  | 30 vs 6 months  |
|                |                 |                 | NaCit vs No-NaCit |                 | 0.839           | 0.490           |
| SBP             | 132.1 ± 6.3     | 131.9 ± 3.8     | 0.870            | 132.4 ± 6.2     | 132.7 ± 5.7     | 0.761            | 0.839           | 0.490           |
| Pcr (mg/dl)     | 3.30 ± 0.91     | 4.24 ± 1.55     | <0.0001          | 3.31 ± 0.69     | 3.61 ± 0.78     | <0.0001          | 0.954           | 0.057           |
| eGFRcr (ml/min) | 32.5 ± 8.3      | 24.9 ± 9.7      | <0.0001          | 32.7 ± 8.2      | 29.5 ± 8.8      | <0.0001          | 0.945           | 0.066           |
| Pcs (mg/l)      | 3.94 ± 1.10     | 5.24 ± 1.41     | <0.0001          | 3.93 ± 0.80     | 4.33 ± 0.89     | <0.0001          | 0.952           | 0.005           |
| eGFRcys (ml/min)| 31.7 ± 7.9      | 23.0 ± 6.05     | <0.0001          | 31.4 ± 8.2      | 27.8 ± 7.4      | <0.0001          | 0.885           | 0.008           |

Abbreviations: eGFR, estimated glomerular filtration rate; Pcr, plasma creatinine; Pcs, plasma cystatin; SBP, systolic blood pressure.
Bicarbonate Therapy is Safe

- Sodium bicarbonate therapy is not associated with a higher likelihood of increasing or starting antihypertensive therapies
  - No detrimental effect as far as hypertension from the sodium load
Recommendations for Bicarbonate Therapy

- Bicarbonate therapy appears to slow the rate of progression in patients with moderate to severe CKD with acidosis
- Bicarbonate therapy should be started in patients with serum bicarbonate levels < 22 meq/L
- Target bicarbonate level is > 22 meq/L
- At this time, unclear if we should be treating earlier CKD patients with serum HCO3 > 23 meq/L
Slowing Progression: Treating Vitamin D Deficiency

- 25(OH)D status throughout the spectrum of CKD

Vitamin D Metabolism

Holik MF. Seminars in Dialysis 2005; 18:266-275
**Vitamin D**

**Endocrine**
- 25(OH)D
- 1,25(OH)₂D
- 1-α-OHylase
- 1,24,25(OH)₃D

**Kidney Cell**
- 1,25(OH)₂D
- PTH
- Serum Pi
- FGF23

**Autocrine**
- 25(OH)D
- 1-α-OHylase
- 1,25(OH)₂D
- 1,24,25(OH)₃D
- 24-OHylase

**Calcemic Effects**

**Non-Calcemic Effects**
Non-Calcemic Effects of Vitamin D

- Inhibition of the renin angiotensin aldosterone system
- Anti-inflammatory properties
- Reduces podocyte injury
- Results in cardiomyocyte remodeling
Low 25-vitamin D Levels are a Risk Factor for Kidney Disease Progression


N=168
Low 1,25-vitamin D (calcitriol) Levels are a Risk Factor for CKD Progression

Treatment with Active Vitamin D (Calcitriol) Reduces Proteinuria

De Zeeuw D et al. *Lancet* 2010;376:1543-1551
Recommendations for Vitamin D Replacement

- No randomized trials showing vitamin D slows progression
- All CKD patients with 25-vitamin D levels < 30 ng/mL should receive repletion with nutritional vitamin D
- The use of active vitamin D analogues (e.g. calcitriol) in CKD patients not yet on dialysis is controversial
Reducing Cardiovascular Risk Factors in CKD
“Traditional” Risk Factors for CVD in CKD

- Hypertension
- Hyperlipidemia
- Smoking
- Obesity
- Diabetes
- Genetics
- Race and socioeconomic status
Case 3

- 60 year old male with CKD stage 4 (GFR 25 ml/min) secondary to DM and HTN.
- PMH: DM, HTN, gout
- SH: non-smoker
- BP 135/80, pulse 65
- A1C 7.2%, LDL 80 mg/dL
- Proteinuria 1200 mg/day
- Serum phosphate 5.1 mg/dL
- Serum 25-hydroxyvitamin D 15 ng/mL
- Intact PTH 130 pg/mL
- Hemoglobin 9.2 g/dL
In addition to his traditional CVD risk factors what kidney disease-related (nontraditional) CVD risk factors does this patient have?

1. Vitamin D deficiency
   - 3%

2. Hyperphosphatemia
   - 3%

3. Secondary hyperparathyroidism
   - 3%

4. Proteinuria
   - 5%

5. All of the above
   - 88%
Nontraditional Risk Factors: Vitamin D Deficiency


N=825
Treatment with Active Vitamin D is Associated with a Lower Risk of Death in CKD Patients

Kovesdy et al. *Arch Intern Med* 2008;168:397-403

N=520
Treatment with paricalcitol does not improve LVMI in patients with CKD

- 220 patients with CKD stage 3-4
- Randomized to treatment with paricalcitol or placebo for 48 weeks
- Number of CVD hospitalizations was lower in paricalcitol group

Thadhani et al. JAMA 2012;307:674-684
Recommendations for Vitamin D Replacement in CKD

- All CKD patients with 25-vitamin D levels < 30 ng/mL should receive repletion with nutritional vitamin D

- The use of active vitamin D analogues (e.g. calcitriol) in CKD patients not yet on dialysis is controversial
  - Currently only recommended for treating secondary hyperparathyroidism
Nontraditional Risk Factors for CVD: Serum Phosphate

- As GFR declines, serum phosphate levels increase
- Overt hyperphosphatemia is rare until the GFR is less than 20 ml/min
- Phosphate is associated with all-cause and cardiovascular mortality in patients with CKD
- Even serum phosphate within normal range is associated with adverse events in CKD
Serum Phosphate is Associated with an Increased Risk of Death and Myocardial Infarction in Patients with CKD

Hazard Ratio of Death or Myocardial Infarction per 1mg/dL Increase in Serum Phosphate

Higher Serum Phosphate is Associated with Vascular and Cardiac Valve Calcification in CKD

Proportion of calcified sites by serum phosphate group.

Treatment of Serum Phosphate and Outcomes

- Currently there is no evidence from randomized trials that lowering serum phosphate within a target range improves clinical outcomes.
- All recommendations are based on observational data.
- Randomized trials have been done in CKD patients but they have only compared two different binders:
  - Data is conflicting
  - No placebo controlled trials
Recommendations for Treatment of Serum Phosphate in CKD

- Current recommendations are to initiate treatment once serum phosphate levels exceed normal range
- Goal is to keep serum phosphate within the normal laboratory range
  - Limit amount of dietary phosphate in diet
  - Use of phosphate binders
- Insufficient evidence to recommend one phosphate binder over another
Treating Complications of CKD
Case 4

- 47 yo female with CKD stage 4, eGFR 20 ml/min.
- Hb 9.8 g/dL
- Ferritin 50 ng/mL
- Tsat 15%
How should her anemia be treated?

1. An erythropoetin stimulating agent (ESA) should be stated
   - 12%

2. Iron supplementation should be started
   - 12%

3. ESA + iron supplementation should be started
   - 49%

4. No treatment is required
   - 27%
Anemia


Prevalence of Anemia by GFR

N=94,000
Presence of Anemia in CKD Portends a Worse Prognosis


N=13,329
Treatment of Anemia with ESAs does not Improve Outcomes

N=4038

Treatment of Anemia with ESAs Resulted in an Increased Risk of Stroke

Recommendations for Treatment of Anemia in CKD

- Goal Hemoglobin is 10-11 g/dL
- Use of ESAs is not recommended unless used as rescue therapy for Hemoglobin < 9 g/dL
- All CKD patients with anemia should be screened for iron deficiency anemia
- Check CBC and iron studies at least once a year
- Targets for iron therapy in CKD
  - Transferrin saturation > 20%
  - Serum Ferritin > 100 ng/mL
Secondary Hyperparathyroidism

Bone Disease
- osteitis fibrosa
- demineralization
- fractures
- bone pain

\[ \uparrow \text{PTH} \]

\[ \downarrow \text{Ca}^{++} \]

\[ \uparrow \text{Pi} \]

\[ \uparrow \text{FGF-23} \]

\[ \downarrow \text{1,25 D} \]

\[ \downarrow 25 \text{ (OH)D} \]

Renal Failure

Systemic Toxicity
- nervous system
- cardiac
- endocrine
- immunologic
- cutaneous

Early

\[ \uparrow \text{PTH} \]
Treatment of Secondary Hyperparathyroidism

- The optimal PTH levels for patients not on dialysis is not known
- Correct serum calcium, phosphorus and 25-vitamin D levels first
- If PTH remains elevated then treat with active vitamin D (e.g. calcitriol)
  - Active vitamin D can result in hyperphosphatemia and hypercalcemia
- Very reasonable to refer to nephrology for treatment of elevated PTH
## Recommended Monitoring Intervals

<table>
<thead>
<tr>
<th>Test</th>
<th>GFR 30-60 ml/min/1.73m²</th>
<th>GFR &lt; 30 ml/min/1.73m²</th>
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<tbody>
<tr>
<td>25-hydroxyvitamin D</td>
<td>Q 6 months</td>
<td>Q 6 months</td>
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<tr>
<td>Parathyroid Hormone</td>
<td>Q 6 months</td>
<td>Q 3 months</td>
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<tr>
<td>Phosphorus</td>
<td>Q 6 months</td>
<td>Q 3 months</td>
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<tr>
<td>Calcium</td>
<td>Q 6 months</td>
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<td>Bicarbonate Level</td>
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<tr>
<td>CBC</td>
<td>Yearly</td>
<td>Q 6 months</td>
</tr>
<tr>
<td>Iron studies</td>
<td>Yearly</td>
<td>Yearly</td>
</tr>
</tbody>
</table>
Immunizations

- Rates of infection are 3 to 4 times that of general population
- Second leading cause of death in patients with CKD
- Most common infections are: UTI, pneumonia and sepsis
- Vaccines are underused in CKD population
Vaccine Recommendations in CKD

- Influenza for all adults unless contraindicated

- Pneumococcal vaccine (unless contraindicated in):
  - All adults with eGFR < 30 ml/min
  - Those at high risk of infection (nephrotic syndrome, diabetes, immunosuppression)

- Hepatitis B immunization:
  - All adults with eGFR <30 ml/min
  - Adults with rapid progression of CKD
Referral to Nephrology

- 1/3 of patients with CKD do not see a nephrologist before initiation of RRT
- >80% of patients who do not see a nephrologist before RRT start dialysis with a catheter
- Only 13% of patients see a dietician before initiation of RRT
Refer to Nephrology When:

- GFR < 30 ml/min/1.73m²
- GFR decrease >30% in 4 months without explanation
- Resistant hypertension
- Persistent hyperkalemia
- Persistent proteinuria despite ACEi/ARB use
- Unclear etiology of CKD
What will the nephrologist do?

- Delay progression
- Treat complications of CKD
- Educate patients early and frequently about CKD
- Dialysis and transplant education
- Referral for permanent vascular access
- Referral for transplantation early
- Dietary education
Conclusions

- Patients with CKD have an increased risk of CVD
- Management of CKD must focus on all risk factors for CVD and kidney disease progression
- Continue ACEi/ARB as long as possible
- Treat complications of CKD
- Early referral to nephrology
- Multidisciplinary approach to management is needed