Chronic Kidney Disease for the Non-Nephrologist

Sunil Agrawal, MD
Outline

• Introduction
• Risk Factors for CKD (general)
• Calculation GFR
• Epidemiology
• Symptoms of CKD
• Overview of treatment of CKD
• Drugs in CKD
“THE BLACK BOX”
Introduction

• Why is Chronic Kidney Disease (CKD) important?
  ▫ Alone a risk factor for CAD
  ▫ Associated with non-traditional risk factors
    • Anemia
    • Increased Proteinuria
    • Uremic Toxins
    • PTH/Phosphorous/Calcium (CKDMBD)
  ▫ 1 Year Mortality of ESRD → 20-25%
  ▫ 5 Year Mortality of ESRD → 35-40%*
    • Transplant 5 Year mortality: 3%
  ▫ ESRD population increasing by 5% per year
CKD risk of Cardiovascular Disease
CKD risk of Cardiovascular Disease

Reproduced from: U.S. Renal Data System, USRDS 2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2009. The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.
Comparison of survival on dialysis between countries and between diabetic and nondiabetic patients

Five-year patient survival rates after the institution of maintenance hemodialysis in the United States (from the US Renal Data System), Europe (from the European Dialysis and Transplant Association), Japan, and Tassin, France. Survival was lowest in the United States and highest in nondiabetics and in Tassin, where the patients were more intensively dialyzed.

Data from:
## Relative risks of major complications of chronic kidney disease based upon categorical meta-analysis

### All-cause mortality

<table>
<thead>
<tr>
<th>eGFR</th>
<th>ACR &lt;10</th>
<th>ACR 10-29</th>
<th>ACR 30-299</th>
<th>ACR ≥300</th>
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</thead>
<tbody>
<tr>
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<td>1.1</td>
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<tr>
<td>90-105</td>
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<tr>
<td>75-90</td>
<td>1.0</td>
<td>1.3</td>
<td>1.7</td>
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<tr>
<td>60-75</td>
<td>1.0</td>
<td>1.4</td>
<td>1.8</td>
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<tr>
<td>45-60</td>
<td>1.3</td>
<td>1.7</td>
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<tr>
<td>30-45</td>
<td>1.9</td>
<td>2.3</td>
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<td>4.9</td>
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<td>15-30</td>
<td>5.3</td>
<td>3.6</td>
<td>4.7</td>
<td>6.6</td>
</tr>
</tbody>
</table>

Absolute risk can be computed by multiplying the RRs in each cell by the incidence rate in the reference cell.

### Cardiovascular mortality

<table>
<thead>
<tr>
<th>eGFR</th>
<th>ACR &lt;10</th>
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<tbody>
<tr>
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<td>1.3</td>
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<td>Ref</td>
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<tr>
<td>15-30</td>
<td>14</td>
<td>7.9</td>
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### Kidney failure (ESRD)

<table>
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<th>ACR &lt;10</th>
<th>ACR 10-29</th>
<th>ACR 30-299</th>
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<td>90-105</td>
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<td>30-45</td>
<td>36</td>
<td>74</td>
<td>294</td>
<td>763</td>
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<td>15-30</td>
<td>433</td>
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<td>1036</td>
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### Acute kidney injury (AKI)

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<th>ACR 10-29</th>
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<td>90-105</td>
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<td>75-90</td>
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<td>60-75</td>
<td>Ref</td>
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<td>3.3</td>
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</tr>
<tr>
<td>30-45</td>
<td>7.3</td>
<td>10</td>
<td>12</td>
<td>20</td>
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<tr>
<td>15-30</td>
<td>17</td>
<td>17</td>
<td>21</td>
<td>29</td>
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### Progressive CKD

<table>
<thead>
<tr>
<th>eGFR</th>
<th>ACR &lt;10</th>
<th>ACR 10-29</th>
<th>ACR 30-299</th>
<th>ACR ≥300</th>
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<tbody>
<tr>
<td>&gt;105</td>
<td>Ref</td>
<td>Ref</td>
<td>0.4</td>
<td>3.0</td>
</tr>
<tr>
<td>90-105</td>
<td>Ref</td>
<td>Ref</td>
<td>0.9</td>
<td>3.3</td>
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<td>22</td>
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<td>15-30</td>
<td>4.0</td>
<td>12</td>
<td>21</td>
<td>7.7</td>
</tr>
</tbody>
</table>
Introduction

- **Financial Impact:**
  - Medicare beneficiary enrollments:
    - 10,000 (1973)
    - 86,354 (1983)
    - 547,982 (2008)
    - 661,648 (2013)
  - In dollars:
    - $66,000 per year per person
    - ESRD make up ~ 1% of population → Consume 7-10%!
Risk for Chronic Kidney Disease

- **DM**
  - 1997 to 2000 ➔ 27% number of Diabetics
  - 25 to 40% will develop nephropathy
  - 45% of new cases of ESRD

- **HTN**
  - Common cause of Kidney disease if African Americans

- Cardio-renal syndrome
- Glomerulonephritis
- Acute Kidney Injury
Introduction

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GRF (mL/min/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal GFR or increase in GFR</td>
<td>90 or above</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild decrease in GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate decrease in GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severe decrease in GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>Less than 15 or dialysis</td>
</tr>
</tbody>
</table>
Revised chronic kidney disease classification based upon glomerular filtration rate and albuminuria

<table>
<thead>
<tr>
<th>GFR stages</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>&gt;90</td>
<td>Normal or high</td>
</tr>
<tr>
<td>G2</td>
<td>60 to 89</td>
<td>Mildly decreased</td>
</tr>
<tr>
<td>G3a</td>
<td>45 to 59</td>
<td>Mildly to moderately decreased</td>
</tr>
<tr>
<td>G3b</td>
<td>30 to 44</td>
<td>Moderately to severely decreased</td>
</tr>
<tr>
<td>G4</td>
<td>15 to 29</td>
<td>Severely decreased</td>
</tr>
<tr>
<td>G5</td>
<td>&lt;15</td>
<td>Kidney failure (add D if treated by dialysis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Albuminuria stages</th>
<th>AER (mg/day)</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>&lt;30</td>
<td>Normal to mildly increased (may be subdivided for risk prediction)</td>
</tr>
<tr>
<td>A2</td>
<td>30 to 300</td>
<td>Moderately increased</td>
</tr>
<tr>
<td>A3</td>
<td>&gt;300</td>
<td>Severely increased (may be subdivided into nephrotic and non-nephrotic for differential diagnosis, management, and risk prediction)</td>
</tr>
</tbody>
</table>

The cause of CKD is also included in the KDIGO revised classification but is not included in this table.

GFR: glomerular filtration rate; AER: albumin excretion rate; CKD: chronic kidney disease; KDIGO: Kidney Disease Improving Global Outcomes.

Data from:
## Staging of patients who meet the definition of CKD

<table>
<thead>
<tr>
<th>Persistent albuminuria categories description and range</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal to mildly increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 mg/g &lt;3 mg/mmol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-300 mg/g 3-30 mg/mmol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severely increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;300 mg/g &gt;30 mg/mmol</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GFR categories (mL/min/1.73 m²) description and range</th>
<th>G1</th>
<th>G2</th>
<th>G3a</th>
<th>G3b</th>
<th>G4</th>
<th>G5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or high</td>
<td>≥90</td>
<td>60-89</td>
<td>45-59</td>
<td>30-44</td>
<td>15-29</td>
<td>&lt;15</td>
</tr>
<tr>
<td>1 if CKD</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>4+</td>
</tr>
<tr>
<td>1</td>
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<td>2</td>
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<td>3</td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
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<td></td>
<td>4+</td>
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<tr>
<td>4+</td>
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<td></td>
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</tr>
</tbody>
</table>

GFR and albuminuria grid to reflect the risk of progression by intensity of coloring (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year).


http://www.nature.com/ki/index.html.
Introduction

• Definition of CKD:
  ▫ The Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF):
    • Kidney damage
    • Abnormal urine indices
    • Abnormal imaging
    • With or without decrease glomerular filtration rate GFR
    • Decreased glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m² for 3 or more months
# Measurement of GFR

<table>
<thead>
<tr>
<th>Creatinine based formulas (reference)</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MDRD Study 4 variable equation traceable to IDMS standardized creatinine (31)</strong></td>
<td>( 175^* \times (\text{Scr in mg/dl})^{-1.154} \times (\text{age in years})^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black}) )</td>
</tr>
<tr>
<td>*186 if non-IDMS creatinine</td>
<td></td>
</tr>
<tr>
<td><strong>CKD-EPI (2)</strong></td>
<td>( 141 \times \min(\text{Scr}/\kappa, 1)^{\alpha} \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993 \text{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]} )</td>
</tr>
<tr>
<td>( \kappa ) is 0.7 for females and 0.9 for males, ( \alpha ) is (-0.329) for females and (-0.411) for males, min indicates the minimum of ( \text{Scr}/\kappa ) or 1, and max indicates the maximum of ( \text{Scr}/\kappa ) or 1.</td>
<td></td>
</tr>
<tr>
<td><strong>Cockcroft-Gault (32)</strong></td>
<td>( (140 - \text{age}) \times (\text{Wt in kg}) \times (0.85 \text{ if female}) / (72 \times \text{Scr}) )</td>
</tr>
<tr>
<td><strong>Schwartz (8)</strong></td>
<td>( K \times \text{height} = \text{Scr} )</td>
</tr>
<tr>
<td><strong>Mayo Clinic (33)</strong></td>
<td>( \exp[1.911 + 5.249/\text{SCr} - 2.114/\text{SCr}^2 - 0.00686 \times \text{age (years)} - 0.205 \text{ if female}] )</td>
</tr>
<tr>
<td><strong>Cystatin C-based formulas</strong></td>
<td><strong>Equation</strong></td>
</tr>
<tr>
<td><strong>Cystatin C alone (34)</strong></td>
<td>( 76.7 \times (\text{cystatin C in mg/L})^{-1.19} )</td>
</tr>
<tr>
<td><strong>Cystatin C-demographics (34)</strong></td>
<td>( 127.7 \times (\text{cystatin C in mg/L})^{-1.17} \times (\text{age in years})^{-0.13} \times (0.91 \text{ if female}) \times (1.06 \text{ if black}) )</td>
</tr>
<tr>
<td><strong>eGFR Cr-Cys C combined (34)</strong></td>
<td>( 177.6 \times (\text{serum creatinine in mg/dl})^{-0.65} \times (\text{cystatin C in mg/L})^{-0.57} \times (\text{age in years})^{-0.20} \times (0.82 \text{ if female}) \times (111 \text{ if black}) )</td>
</tr>
</tbody>
</table>
Measurement of GFR

- **Normal GFR:**
  - 130 ml/min/1.73 m² (men)
  - 120 mL/min/1.73 m² (women)
- **24 hour collection and calculation of creatinine clearance**
  - Cumbersome and difficult to collect
- **Cockcroft-Gault equation**
  - Traditionally used by FDA for drug dosing
- **MDRD equations**
  - More accurate in estimating GFR (recalibrated four variable: MDRD4)
Measurement of GFR

• “Weakness” of MDRD and Cockcroft-Gault equation:
  ▫ Can only be used in stable kidney function
  ▫ Inaccurate to predict near normal GFR(s)
    • CKD-EPI equation better for near normal/mild function
  ▫ Inaccurate in malnourished or low muscle mass patients
  ▫ Renal allografts → variable results related to the accuracy
  ▫ Less accurate in obese individuals
  ▫ Less accurate in populations of different ethnicities and from outside of the United States
Measurement of GFR

- Cystatin C
  - may correlate more closely with the GFR than the serum creatinine concentration
  - low-molecular-weight protein
  - member of the cystatin superfamily of cysteine protease inhibitors.
  - filtered at the glomerulus and not reabsorbed.
  - metabolized in the tubules
    - prevents use of cystatin C to directly measure clearance.
  - Produced by all nucleated cells.
  - Gender, Lean muscle mass, weight may effect level
  - Hypothyroidism, Hyperthyroidism, DM also can affect secretion

- Estimation of GFR:
  - Equations with both Creatinine and Cystatin C are better than alone
Measurement of GFR

- Which Equation to use??
  - MDRD is most widely used
  - Best Equation: CKD-EPI equation
    - More accurate at mild and near normal function
    - As accurate as MDRD in eGFR <60 ml/min
    - Less Bias
    - Improve precision
  - Holy Grail Equation: CKD-EPI creatinine-cystatin C equation
Measurement of GFR

- **DRUG DOSING**
- FDA uses Cockcroft-Gault equation
  - Most pharmacokinetic studies use CG equation for renal function
  - Highly variable creatinine assays (past)
  - Studies may not translate reliably to clinical practice
- Consensus: can use either MDRD or CG equations.
- BE CONSISTENT!
- 24 hour clearance for drugs with narrow therapeutic window
Introduction

- Ethnicity/Race
- US higher incidence of ESRD exists in blacks than in whites; the incidence rate for blacks is nearly 4 times than for whites
- Native Americans are 1.5 times more likely than whites for ESRD
- Hispanics are 1.5 times more likely than whites for ESRD
- Cause by ethnicity/Race:
  - Diabetic Nephropathy #1 cause (all races)
  - African Americans → 33% secondary to hypertensive nephropathy (compared to 25%)
  - African Americans versus Caucasians
    - Much younger with ESRD → why????
Apolipoprotein L1 (APOL1)
Apolipoprotein L1 (APOL1) 
Trypanosoma brucei
Apolipoprotein L1 (APOL1)

**Interesting Overlap**

- Chromosome overlap of 22q with APOL1
- APOL1 may contribute to increase risk of DN
- May be involved in: HTN/HIV/FSGS
- Favored gene in African Americans: resistance to trypanosomiasis (Trypanosoma brucei)
- APOL1 associated with early onset of CKD

**“African Sleeping Sickness”**

![Diagram of Tsetse fly stages and human stages related to trypanosomiasis](https://www.cdc.gov/trypanosomiasis/)

1. Epimastigotes multiply in salivary gland. They transform into metacyclic trypomastigotes.
2. Metacyclic trypanosomes transform into bloodstream trypanosomes, which are carried to other sites.
3. Bloodstream trypanosomes multiply by binary fission in various body fluids, e.g., blood, lymph, and spinal fluid.
4. Trypanosoma multiply by binary fission into bloodstream trypanosomes, which are carried to other sites.
5. Tsetse fly takes a blood meal (bloodstream trypanosomes are ingested).
7. Tsetse fly takes a blood meal.
8. Procylic trypomastigotes leave the midgut and transform into epimastigotes.

Packman HealthCare

http://www.cdc.gov/trypanosomiasis/
Apolipoprotein L1 (APOL1)

APOL1 protects from T. brucei
Apolipoprotein L1 (APOL1)

- Circulates systemically
- Two variants discovered:
  - G1
  - G2
- Risk of CKD passed autosomal recessive
  - Two G1 alleles
  - Two G2 alleles
- More Prevalent in Western Africa
  - Absent in Ethiopia
  - These areas have higher rates of Trypanosoma brucei
Introduction

- Epidemiology
- Worldwide:
  - Effects 10-16% of adult population
- The Third National Health and Examination Survey (NHANES III)
- Chronic Kidney Disease in adults in the United States:
  - CKD STAGE I: 3.3% (5.9 million)
  - CKD STAGE II: 3% (5.3 million)
  - CKD STAGE III: 4.3% (7.6 million)
  - CKD STAGE IV: 0.2% (400,000)
  - CKD STAGE V: 0.2% (300,000)
Introduction

- **NHANES III:**
  - ~6.2 million people >12 years had a serum creatinine value above 1.5 mg/dL
    - 3% of the total US population
  - ~8 million people had a GFR <60 mL/min
    - Majority Medicare senior population: 5.9 million people
Symptoms of CKD

• Silent disease processes
• Metabolic symptoms usually seen GFR < 40 ml/min
• Uremic Symptoms:
  ▫ Anorexia
  ▫ Myoclonic Jerking/Seizures
  ▫ Nausea and vomiting
  ▫ Pericarditis
  ▫ Peripheral neuropathy
When to refer to the Consultant?
Referral to a Nephrologists

- **When to refer to a Nephrologist?**
  - Typically GFR <60 ml/min/1.73 m² or CKD STAGE III
    - Some sources recommend <30 ml/min/1.73 m²
  - Referrals up due to automatic eGFR reporting

- **Late Referral?**
  - Patient started of Renal Replacement Therapy (RRT) 6 months after referral
    - 25-50% start dialysis with in one month
  - Associated with greater health care costs
  - Longer Hospitalizations
  - Loss of “early” protective measures:
    - Institution of ACEi
  - **Lower Mortality**
    - Department of Veteran's Health Affairs system study
    - 39,000 patients/retrospective cohort study
Referral to a Nephrologists

- Urine albumin-to-creatinine ratio (ACR) ≥300 mg/g (34 mg/mmol)
- Hematuria not secondary to urological condition
- Inability to identify a presumed cause of CKD
- eGFR decline of more than 30% < 4 months without an obvious explanation
- Anemia requiring erythropoietin therapy, and abnormalities of bone and mineral metabolism requiring phosphorus binders or vitamin D preparations
- Serum potassium > than 5.5 meq/L
- Difficult to manage drug complication
- Patients under the age of 18 years
- Resistant hypertension
- Recurrent or extensive nephrolithiasis
- Confirmed hereditary kidney disease
Referral to a Nephrologists

- Management of metabolic derangements
  - Typically seen at \( \text{GFR} < 40 \text{ ml/min/1.73m}^2 \)
  - Acidosis
    - 39% of patients with GFR < 20 ml/min
  - Hyperkalemia
    - 42% of patients with GFR < 20 ml/min
  - Hyperphosphotemia
    - 30% of patients with GFR < 20 ml/min
  - Secondary Hyperparathyroidism
    - 85% of patients with GFR < 20 ml/min
  - Anemia Management
    - 41% of patients with GFR < 20 ml/min

- Dialysis Planning (Renal Replacement Therapy)
- Preemptive Transplantation
- Renal Dosed medications
Referral to a Nephrologists

• Why are patients referred late?
  ▫ Acute Kidney Injury (Unavoidable)
  ▫ Accesses to Health Care
    • Geographic
    • Socioeconomic
  ▫ Denial/Fear by the patient
  ▫ Fear of loss of income by physician
  ▫ Poor Communication
Referral to a Nephrologists

- Patients typically referred least:
  - Older patients
  - Women
  - Non-white patient
  - Residing in a zip code with a higher percentage of African Americans


Intervention of CKD

Continuous Risk Reduction

- Demonstrate continuous risk reduction
- Aim standard - mostly frequency reduction
- Risk reduction measures - mostly consequence reduction

No accidents
No harm to people
No damage to the environment
Interventions in CKD patients

- Good Blood Pressure Control
- Good glycemic control
- Low Protein Diets
- Avoiding Nephrotoxic Drugs
- Preventing Nephrolithiasis
- Weight loss
- Statin Therapy
- Vitamin D
- Metabolic Acidosis
Hypertension Control

- **Initial Monotherapy (JNC8)**
  - Nonblack populations
    - Thiazide type
    - Calcium Channel Blockers
    - ACEi/ARB
  - Black populations
    - Thiazide type
    - Calcium Channel Blockers
- **Initial Monotherapy (JNC8)**
  - >18 yo with CKD
    - ACEI or ARB
    - Initial or add on therapy

- **Goal BP (JNC-8)**
  - BP goal Age > 60 : <150/90*
  - BP goal Age < 60: <140/90
From: 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)


2014 Hypertension Guideline Management Algorithm

- SBP indicates systolic blood pressure; DBP, diastolic blood pressure; ACEI, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; and CCB, calcium channel blocker. aACEIs and ARBs should not be used in combination. bIf blood pressure fails to be maintained at goal, reenter the algorithm where appropriate based on the current individual therapeutic plan.

Figure Legend:
Table 6: Guideline Comparisons of Goal BP and Initial Drug Therapy for Adults With Hypertension

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Population</th>
<th>Goal BP, mm Hg</th>
<th>Initial Drug Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014 Hypertension guideline</td>
<td>General ≥60 y</td>
<td>&lt;150/90</td>
<td>Nonblack: thiazide-type diuretic, ACEI, ARB, or CCB; Black: thiazide-type diuretic or CCB</td>
</tr>
<tr>
<td></td>
<td>General &lt;60 y</td>
<td>&lt;140/90</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>&lt;140/90</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td></td>
<td>CKD</td>
<td>&lt;140/90</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td>ESH/ESC 2013</td>
<td>General nonelderly</td>
<td>&lt;140/90</td>
<td>Diuretic, β-blocker, CCB, ACEI, or ARB</td>
</tr>
<tr>
<td></td>
<td>General elderly &lt;80 y</td>
<td>&lt;150/90</td>
<td>Diuretic, β-blocker, CCB, ACEI, or ARB</td>
</tr>
<tr>
<td></td>
<td>General ≥80 y</td>
<td>&lt;150/90</td>
<td>Diuretic, β-blocker, CCB, ACEI, or ARB</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>&lt;140/85</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td></td>
<td>CKD without proteinuria</td>
<td>&lt;140/90</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td></td>
<td>CKD + proteinuria</td>
<td>&lt;130/90</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td>CHEP 2013</td>
<td>General &lt;80 y</td>
<td>&lt;140/90</td>
<td>Thiazide, β-blocker (age &lt;60y), ACEI (nonblack), or ARB</td>
</tr>
<tr>
<td></td>
<td>General ≥80 y</td>
<td>&lt;150/90</td>
<td>Thiazide, β-blocker (age &lt;60y), ACEI (nonblack), or ARB</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>&lt;130/80</td>
<td>ACEI or ARB with additional CVD risk</td>
</tr>
<tr>
<td></td>
<td>CKD</td>
<td>&lt;140/90</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td>ADA 2013</td>
<td>Diabetes</td>
<td>&lt;140/80</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td>KDIGO 2012</td>
<td>CKD without proteinuria</td>
<td>≤140/90</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td></td>
<td>CKD + proteinuria</td>
<td>≤130/80</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td>NICE 2011</td>
<td>General &lt;80 y</td>
<td>&lt;140/90</td>
<td>&lt;55 y: ACEI or ARB</td>
</tr>
<tr>
<td></td>
<td>General ≥80 y</td>
<td>&lt;150/90</td>
<td>≤55 y or black: CCB</td>
</tr>
<tr>
<td>ISHIB 2010</td>
<td>Black, lower-risk</td>
<td>&lt;130/85</td>
<td>Diuretic or CCB</td>
</tr>
<tr>
<td></td>
<td>Target organ damage</td>
<td>≤130/80</td>
<td>Diuretic or CCB</td>
</tr>
<tr>
<td></td>
<td>or CVD risk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ADA, American Diabetes Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CHEP, Canadian Hypertension Education Program; CKD, chronic kidney disease; CVD, cardiovascular disease; DHPRCCB, dihydropyridine calcium channel blocker; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ISHIB, International Society for Hypertension in Blacks; JNC, Joint National Committee; KDIGO, Kidney Disease: Improving Global Outcome; NICE, National Institute for Health and Clinical Excellence.

Table Title:
Guideline Comparisons of Goal BP and Initial Drug Therapy for Adults With Hypertension
Proteinuria and Chronic Kidney Disease

- Independent risk factor for cardiovascular disease
  - Protein/creatinine: >150 (200)
  - Albumin/creatinine > 30
- Example of progression of CKD (Membranous GN):
  - Low risk: <4 gm normal GFR
  - Moderate risk: 4 to 8 gm normal GFR (50% CKD $\rightarrow$ 5 years)
  - High risk: > 8 gm declining GFR +/- (75% CKD $\rightarrow$ 5 years)
Relative risks of major complications of chronic kidney disease based upon a continuous meta-analysis

- Urine ACR >300 mg/g or dipstick >2+ positive
- Urine ACR 30-299 mg/g or dipstick 1+ positive
- Urine ACR of <30 mg/g or dipstick negative and trace

**All-cause mortality**

**Cardiovascular mortality**

**End stage renal disease**

**Acute kidney injury**

**Progressive CKD**

Adjusted HR vs eGFR, mL/min per 1.73 m²
DM control in CKD

• A1C target <7 (vs. 6.5?)
  ▫ ACCORD trial?
  ▫ ADVANCE trial?
  ▫ VADT trial?
  ▫ No more reduction in cardiovascular disease

• Choice of Medications:
• Insulin
  ▫ Cleared by the kidney
  ▫ Longer half-life in renal failure (Acute and Chronic)
  ▫ Can occur at any CKD Stage
    • More prevalent in GFR <30 ml/min
  ▫ Leads to frequent hypoglycemic episodes
DM control in CKD

• Choice of Medications:
  • Metformin
    ▫ **NOT NEPHROTOXIC**
    ▫ FDA recommendation:
      • Contraindicated in creat >1.5 in men, >1.4 women
      • Contraindicated in GFR < 30 ml/min
      • Need to monitor kidney function between 45 to 60 ml/min
    ▫ Decreased clearance and life threatening Lactic Acidosis
DM control in CKD

• Choice of Drugs:
  • Thiazolidinediones
    ▫ Actos and Avandia
      • Good for glucose control
      • Caution: volume control
      • Retention of Na and Water
  • Sulfonylureas
    ▫ First and Second Generations
      • Glyburide
      • Should be avoided due to accumulation
        • Risk of Hypoglycemia
    ▫ Exceptions:
      • Glipizide and gliclazide (not available in US)
DM control in CKD

• DPP-4 inhibitors
  ▫ Sitagliptin (Januvia)
  ▫ Can be used in CKD with dose adjustment
  ▫ Typically not first-line agents
Low Protein Diets

- Conflicting Data
- No restriction >60 ml/min
- 0.8* to 0.6 g/kg (<60 ml/min)
- <0.6 g/kg (low protein)
- High protein diets → theoretically should worsen kidney function
- Thought to slow the progression of CKD
- Multiple Studies have shown no real reno-protection
  - MDRD trial
  - PREVEND
- Showed higher mortality in low protein arm
Metabolic Acidosis

- Still debated
- Can activate the alternative complement $\rightarrow$ tubulointerstitial fibrosis
- Marker of decreased GFR
- Demineralization of Bone $\rightarrow$ buffer
- Better nutrition
  - Decrease albumin synthesis
  - Increase skeletal muscle breakdown
- Goal treatment $>22$ meq/dl
- Drug of Choice: Sodium Bicarbonate
Vitamin D and CKD

- Benefit in the management secondary hyperparathyroidism
- Inhibition of renin angiotensin system?
- Anti-inflammatory
- May help with reduction of proteinuria
  - In conjunction with ACEi and ARB
Obesity in CKD

- Increased risk for CKD
  - BMI
  - Waist size
- Many patients have metabolic syndromes
  - DM
  - HTN
- Causes hyperfiltration $\Rightarrow$ secondary FSGS
DRUGS!
Drugs and CKD

- **NSAIDS**
  - Hyperkalemia
  - Volume overload/HTN
  - Vasomotor injury
  - Proteinuria
  - AIN

- **Tylenol**
  - Analgesic nephropathy? → insufficient evidence
  - Safe to use in advanced CKD

- **Demerol (meperidine)**
  - Normeperidine → metabolite
  - Very potent neuroexcitatory agent → seizures
  - Should be avoided
Drugs and CKD

• Phosphate Laxatives
  ▫ Acute phosphate nephropathy → acute kidney injury
  ▫ Try to avoid

• Bactrim
  ▫ Trimethoprim
    • Benign blocking of secretion of creatinine
    • Potassium retention
  ▫ Sulfamethoxazole
    • AIN
    • Kidney Stones
Drugs and CKD

- **Thiazide**
  - Not really effective at GFR <40 ml/min

- **Fibrates**
  - **Example:** Tricor
  - Cause reversible rise in creatinine
    - Controversial → real vs. benign
    - 30% increase is acceptable
  - **Gemfibrozil (lopid)** is the preferred agent
ACEi and CKD

- Diabetic nephropathy and non-diabetic chronic kidney diseases
  - Clear evidence in multiple studies → help slow progression
  - Down regulate TGF-Beta
  - Decrease of GFR ~30 % acceptable
  - Vasomotor injury in pre-renal states
    - Dilation of Efferent Arteriol
  - Reduction of proteinuria
  - Watch for Hyperkalemia!
  - On Target Trial → be careful in combination with ARB
Conclusion

• Upshot of risk in CKD:
  ▫ Progression to ESRD
  ▫ Increase risk of cardiovascular disease
  ▫ Increased risk of death
  ▫ Need to practice risk reduction
    • Good control of HTN
    • Reduction of proteinuria
  ▫ Early referral may lead to better outcomes
The End