Learning Objectives

1. Explain the correlation between CKD and hypertension
2. Describe the role of aldosterone in the renin-angiotensin-aldosterone system (RAAS) and in resistant hypertension
3. Explain the mechanism of aldosterone antagonists
4. Evaluate literature concerning the efficacy, renal protective properties, and safety of spironolactone
5. Discuss the role of spironolactone in patients with CKD and resistant hypertension
1. Chronic Kidney Disease (CKD)\textsuperscript{1-3}
   a. Associated with premature loss of life and a large economic impact
      i. 33 million American adults are diagnosed with CKD
         1. Millions more are at risk, but don’t know it
      ii. More than 46,000 (8%) of the 576,000 Americans who have end-stage renal disease (ESRD) or kidney failure are Texans
         1. Number of dialysis patients in Texas has more than tripled since 1990
      iii. Average costs of treatment with dialysis or renal transplant are $66,000 per patient per year
   b. Patients with CKD carry a larger burden of cardiovascular disease than those without
      i. More CKD patients die of heart disease or other cardiovascular complications before they reach ESRD
      ii. Awareness, treatment, and control of these conditions (e.g. hypertension, diabetes, dyslipidemia) are crucial
   c. Definition and classification of CKD
      i. Two independent criteria for chronic kidney disease:
         1. Kidney damage for 3 or more months as defined by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR)
            a. Structural damage can include pathological abnormalities (e.g. abnormal renal biopsy), or anatomical abnormalities (e.g. scarring seen on imaging or polycystic kidneys)
            b. Functional abnormalities include microalbuminuria and proteinuria
         2. GFR less than 60 mL/min/1.73m\textsuperscript{2} for three or more months, with or without kidney damage
            a. Normal GFR ≥120 mL/min/1.73m\textsuperscript{2}
      
ii. GFR is the best overall index of kidney function in health and disease
   1. Estimated from prediction equations such as the MDRD equation
      a. This equation has not been validated in children (age <18 years), pregnant women, the elderly (age >70 years), racial or ethnic subgroups other than Caucasians and African Americans, in individuals with normal kidney function who are at increased risk for CKD, or in normal individuals.

| Table 1. Classification of Chronic Kidney Disease\textsuperscript{4} |
|----------------------------------|------------------|------------------|
| Stage | Description                  | GFR mL/min/1.73m\textsuperscript{2} (Kidney Function) |
| 1     | Kidney damage with normal or ↑ GFR | ≥90              |
| 2     | Kidney damage with mild ↓ GFR | 60-89            |
| 3     | Moderate ↓ GFR               | 30-59            |
| 4     | Severe ↓ GFR                 | 15-29            |
| 5     | Kidney Failure               | <15 (or dialysis) |

Figure 1. Anatomy of the kidney and details of the nephron\textsuperscript{5}
RENAL PHYSIOLOGY

2. Renal Physiology\(^5\)\(^6\)
   a. Functions of the kidneys
      i. Regulate water and electrolyte balance
      ii. Excrete metabolic waste
      iii. Excrete bioactive substances (i.e. hormones and many foreign substances, specifically drugs)
      iv. Regulate arterial blood pressure
      v. Regulate red blood cell production (erythropoietin production)
      vi. Activate Vitamin D
      vii. Gluconeogenesis
   b. Kidneys are located in the retroperitoneal area\(^5\)
      i. Renal artery and a renal vein supply blood flow
      1. Approximately 25% of cardiac output goes to the kidney
      ii. The anatomic unit of kidney function is the nephron which consists of the glomerulus and renal tubule (see Figure 1)
      iii. Nephron processes (see Appendix A)
         a. Filtration
         b. Reabsorption
         c. Secretion
         d. Excretion
   c. Regulation of blood pressure\(^7\)\(^-\)\(^11\)
      i. Kidneys play a major role based on their effect on sodium and water balance
         1. Renin-Angiotensin-Aldosterone System (RAAS)
            a. Controls fluid and electrolyte balance through coordinated effects on the heart, blood vessels, and kidneys
            b. Angiotensin II
               i. Plays a role in the short- and long-term regulation of arterial blood pressure
               ii. Modest increases in angiotensin II acutely raise blood pressure
               iii. Has a slow pressor response and a role in altering cardiovascular structure
               iv. Signals the adrenal cortex to secrete more aldosterone
            c. Aldosterone
               i. Promotes the regulation of sodium channel activity
                  1. Effects vary with the specific cell type
                  2. Primarily promotes the reabsorption of sodium and the secretion of potassium in the distal nephron
         ii. CKD patients have a decrease in the number of functioning nephrons\(^\)\(^12\)
            1. Leads to adaptation of remaining nephrons (hyper-filtration) and increased proteinuria
               a. Initially maintains overall GFR, but has negative long-term effects
               b. Interventions that inhibit the activity of RAAS are reno-protective and may slow or even halt the progression of chronic nephropathies
   3. Hypertension and CKD\(^3\)\(^,\)\(^13\)
      a. Hypertension is one of the most common co-morbidities in CKD
         i. Approximately 80% of CKD patients develop hypertension at some point
      b. A strong relationship exists between higher blood pressure levels and increased risk of kidney failure
         i. Studies suggest that higher systolic blood pressure has a greater effect on kidney disease progression than diastolic blood pressure or pulse pressure
      c. Hypertension is often difficult to control in CKD
         i. NHANES study showed only 64% of patients with CKD achieved adequate blood pressure control \(^14\)
         ii. In CKD, multiple antihypertensive agents are usually required to reach target blood pressures of <130/80 mm Hg
TREATMENT OF HYPERTENSION IN CKD

d. Treatment Options
   i. RAAS inhibitors have been a cornerstone of antihypertensive therapy\textsuperscript{13}
      1. Guidelines recommend angiotensin converting enzyme inhibitors (ACEi) or angiotensin
         receptor blockers (ARBs) as first-line treatment for slowing the progression of kidney
         disease in hypertensive patients\textsuperscript{3, 18, 32} (See Appendix C)

e. Resistant hypertension\textsuperscript{3, 15}
   i. Defined as failure to achieve a goal BP in patients who are adhering to full doses of an
      appropriate 3-drug regimen that includes a diuretic
   ii. Exact prevalence unknown but estimated to be affect at least 20-30% of all hypertensive
      patients\textsuperscript{16}
   iii. Deterioration in blood pressure control may show progression of CKD
   iv. Treatment options
      1. KDOQI guidelines:
         a. “Treatment is beyond scope of these guidelines, see JNC 7”
      2. JNC 7:
         a. “If resistant hypertension persists after remediable causes are identified and corrected,
            then a concerted search for a cause of secondary hypertension should be conducted.
            If resistance still persists, consultation with a hypertension specialist is a logical next step”

4. Aldosterone\textsuperscript{9-10, 12}
   a. Associated with renal injury and the development of CKD
      i. Additional effects lead to cardiac injury and end-organ damage
   b. In patients with CKD aldosterone concentrations are often high due to aldosterone escape
      i. Despite treatment with ACEi/ARB, concentrations remain elevated in up to 50% of patients\textsuperscript{26}
   c. Aldosterone blockade is an important but often overlooked option in the inhibition of RAAS

Figure 2. Renal and Cardiovascular effects of Aldosterone\textsuperscript{17}
5. Aldosterone Antagonists\textsuperscript{2-11,17}  
   a. Spironolactone and eplerenone  
      i. Pharmacological properties listed in Appendix D  
   b. Competitively inhibit the binding of aldosterone to the mineralcorticoid receptor (MR)  
      i. Blocks aldosterone-induced-protein synthesis, which blocks reabsorption of sodium and the secretion of potassium in the distal nephron  
      ii. Effects on urinary excretion are a function of endogenous levels of aldosterone  
   c. Do not require adequate renal function for action\textsuperscript{1}  
      i. Do not require access to the tubular lumen to induce diuresis  
   d. Have been shown to be effective at reducing mortality and declining the rate of progression of CKD  
      i. Use of spironolactone for heart failure has been shown to significantly reduce mortality in landmark trials\textsuperscript{18}  
      ii. Meta-analysis shows spironolactone is effective for lowering blood pressure and slowing the progression of CKD\textsuperscript{19-20}  
   e. Concern for use of these agents arises from the risk for hyperkalemia\textsuperscript{1}  
      i. Increased use of spironolactone has been associated with increased rates of hyperkalemia  
         1. Causal relationship has not been shown  
      ii. Guidelines caution against the use of aldosterone antagonists in patients with baseline elevations of either serum potassium or creatinine\textsuperscript{3,15}  
6. Efficacy in heart failure  
   a. 1996-1999: RALES\textsuperscript{21}  
      i. Studied the effect of spironolactone on morbidity and mortality in patients with severe heart failure  

\textbf{ALDOSTERONE ANTAGONISTS}  

\textbf{Figure 3. Effects of aldosterone and diuretic mechanism of aldosterone antagonists}\textsuperscript{7}
Patients received spironolactone (25 mg/day) or placebo as add-on therapy

Results
1. 0.70 relative risk of death (95% CI 0.60-0.82; p<0.001)
2. 0.65 relative risk of hospitalization (95% CI 0.54-0.77; p<0.001)
3. Spironolactone group also had significant improvement in symptoms of heart failure
4. Incidence of serious hyperkalemia was minimal in both groups

Concluded that spironolactone substantially reduces the risk of both morbidity and death in patients with severe heart failure

Excluded patients with serum creatinine >2.5 mg/dL and/or serum potassium > 5.0 mEq/L

June 1999: FDA updates safety labeling on spironolactone

- “Warnings: Hyperkalemia in patients with severe heart failure. Hyperkalemia may be fatal.”

2004: Juurlink et al.

- Population-based time-series analysis to examine trends in the rate of spironolactone prescriptions and the rate of hospitalizations for hyperkalemia

Results
1. Following the publication of the RALES study, spironolactone prescription rate increased from 34 per 1000 patients to 149 per 1000 patients in Canada
2. Rate of hospitalization for hyperkalemia rose from 2.4 per 1000 patients to 11.0 per 1000 patients

Conclusion
1. Publication of RALES was associated with abrupt increases in the rate of prescriptions for spironolactone and in hyperkalemia-associated morbidity and mortality
2. Did not actually show causal relationship, instead demonstrated a temporal relationship

Three questions to consider
1. Is spironolactone effective in treating hypertension and resistant hypertension?
2. Does spironolactone have reno-protective properties?
3. Is spironolactone safe in CKD patients?
ii. **ASPIRANT**: Vaclavik et al.\(^6\)
   1. Effect of adding spironolactone to patients with resistant hypertension
   2. Results
      a. Significantly greater reduction of SBP
         i. 5.4 mm Hg decrease in daytime SBP (p = 0.024); 9.8 mm Hg decrease in 24H SBP (p = 0.004)
      b. Mean serum potassium increased from 4.15 to 4.52 during 8 weeks of treatment
         i. 0.3 median increase in serum potassium (p < 0.001)
         ii. Highest serum potassium was 5.53 mEq/L
   3. Conclusion
      a. Spironolactone is an effective drug to lower SBP in patients with resistant hypertension
      b. Risk of hyperkalemia would be higher if spironolactone was used in CKD patients

b. **Renal Protection: Does spironolactone have reno-protective properties?**
   i. Bianchi et al.\(^23\)
      1. Uncontrolled pilot study evaluating the short-term effects of spironolactone on proteinuria in CKD patients already treated with ACEi and/or ARB
      2. Results
         a. Spironolactone (25mg/day) decreased proteinuria from 2.09 ± 0.16 to 1.32 ± 0.08g/24 h after 2 weeks
         b. Four weeks after discontinuation of spironolactone, proteinuria levels returned to baseline
   3. Conclusions
      a. Spironolactone may effectively reduce proteinuria in patients with CKD
      b. Concern still remains for the risk of hyperkalemia
      c. Prospective, randomized trials necessary to confirm safety and efficacy

ii. **Cochrane review\(^20\)**
   1. Meta-analysis for the benefits and harms of adding spironolactone or eplerenone in patients with CKD currently treated with ACEI and/or ARB
   2. Key findings
      a. Aldosterone antagonists administered over RAAS inhibition in patients with CKD reduces end-of-treatment 24 hour proteinuria and BP but have no significant impact on end-of-treatment GFR
      b. Significantly higher incidence of hyperkalemia (>5.5 mEq/L) with aldosterone antagonists compared to RAAS inhibition alone
   3. Implications

---

**Our analysis of existing studies of selective and non-selective aldosterone antagonists administered over RAS inhibition in patients with CKD found that both reduce end of treatment 24 hour proteinuria and BP but have no significant impact on end of treatment GFR. There was, however, a significantly higher incidence of hyperkalaemia (> 5.5 mEq/L) with non-selective antagonists compared to RAS inhibition only. This was not found with selective antagonists compared to RAS inhibition only, but direct comparison studies of selective versus non selective aldosterone antagonists are not available. The impact of adding aldosterone blocking agents to RAS blockers on mortality and long-term renal outcomes has not been evaluated in existing studies.**
c. Safety: Is spironolactone safe to use in patients with CKD and resistant hypertension?
   i. EPHESUS: Pitt et al.\textsuperscript{25}
      1. Evaluation of serum potassium and clinical outcomes of eplerenone in heart failure patients following an acute myocardial infarction (MI)
      2. Patients randomized 3 to 14 days after the acute MI to receive additional treatment with eplerenone or placebo
      3. Results
         a. Eplerenone resulted in a 4.4% absolute increase in the incidence of serum potassium >5.5 mEq/L; a 1.6% increase of >6.0 mEq/L; and a 4.7% absolute decrease in hypokalemia (<3.5 mEq/L) versus placebo
         b. Determined four independent baseline predictors of hyperkalemia: potassium (>4.3 mEq/L), estimated GFR (≤60 mL/min/1.73m\textsuperscript{2}), diabetes, and prior use of antiarrhythmic agents
      4. Concluded that use of eplerenone in heart failure patients post-acute MI improves outcomes without an excess of risk of hyperkalemia when periodic monitoring of potassium is instituted
      5. Patients were excluded if baseline potassium was >5.0 mEq/L or if serum creatinine was >2.5 mg/dL
   ii. CRIB II: Edwards et al.\textsuperscript{26}
      1. Safety and tolerability of spironolactone in early CKD (stage 2-3)
      2. Results
         a. After 40 weeks of treatment, incidence of serious hyperkalemia (K\textsuperscript{+} >6.0 mEq/L) was <1%
         b. Mean [K\textsuperscript{+}] were persistently higher with spironolactone (p < 0.05) but remained stable over 35 weeks of follow-up
         c. At 40 weeks, spironolactone significantly reduced SBP (-6 mm Hg; 95% CI -8 to 3, p < 0.01)
      3. Conclusion
         a. Spironolactone is well tolerated in early CKD
         b. Strict monitoring over the first month followed by standard monitoring recommended

Conclusions of literature evaluation
• Spironolactone is effective in hypertension and resistant hypertension
• Spironolactone has been shown to have renal protective properties
• Limited efficacy data of spironolactone use in CKD patients
• Safety data is conflicting/inconclusive
8. Spironolactone efficacy and safety in resistant hypertension for patients with CKD
   a. 2010: Heshka et al\textsuperscript{27}
      i. Retrospective cohort analysis to determine the safety and efficacy of empiric use of spironolactone in patients with difficult-to-control hypertension and CKD
      ii. Results

<table>
<thead>
<tr>
<th>Table 2. Heshka et. al.: Blood pressure and laboratory parameters by CKD status\textsuperscript{27}</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CKD</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>ΔSBP (mm Hg)</td>
</tr>
<tr>
<td>ΔDBP (mm Hg)</td>
</tr>
<tr>
<td>ΔK (mEq/L)</td>
</tr>
<tr>
<td>Significant K increase (%)</td>
</tr>
<tr>
<td>K&gt;5.5 mEq/L (%)</td>
</tr>
</tbody>
</table>
   iii. Concluded spironolactone was associated with a significant fall in BP among those patients with CKD and difficult-to-control blood pressure.
         1. Associated with a modest rise in serum potassium, which was more pronounced in those with a GFR < 45 mL/min

9. Is spironolactone a safe and efficacious option for difficult-to-control hypertension in patients with CKD?
   a. 2011: Smith et al. (Abstract for ASHP Midyear Clinical Meeting)\textsuperscript{28}
      i. Retrospective analysis to answer remaining questions
         1. Primary objective: determine the efficacy and safety of spironolactone in patients with difficult-to-control hypertension and stage 3-5 CKD
         2. Methods
             a. Identified patients with stage 3-5 CKD prescribed spironolactone for hypertension from patient records from three clinic sites of Kidney Treatment Centers of San Antonio
             b. Exclusion Criteria
                i. Patients without a follow-up visit within six months of spironolactone initiation, a GFR>59, an undetermined stage of CKD, or a baseline SBP <130 mmHg
             c. Demographic data included gender, age, BMI, and current anti-hypertensive medications
                i. SBP and DBP values at initiation of spironolactone and follow-up were recorded
             d. Data were analyzed as two separate cohorts
                i. Efficacy was measured by the change in SBP/DBP after initiation of spironolactone
                   1. The efficacy cohort excluded patients with an initial SBP >180 mmHg
                ii. Safety measurements included the change in serum potassium, incidence of hyperkalemia, and incidence of severe hyperkalemia.
                   1. To be included patient must have had a recorded serum potassium measurement within three months prior to spironolactone initiation and an additional measurement within six months after initiation
      3. Results
         a. Patient demographics (Table 4)
         b. Pre/post measurements for SBP/DBP (Figure 6)
            i. Median difference was -16.5 (95% CI -20 to -12; p < 0.0001) for SBP
            ii. Median difference for DBP was -6 (95%CI -8 to -3; p < 0.001)
         c. Pre/post measurements for serum potassium (Figure 7)
            i. Median difference of +0.3 (95% CI 0.2 to 0.4; p < 0.0001)
         d. 3.6% incidence of hyperkalemia and no incidence of severe hyperkalemia (Table 4)
**Table 3.** Patient demographics for retrospective analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (Q1-Q3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>75 (66-81)</td>
</tr>
<tr>
<td>Gender %</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>59</td>
</tr>
<tr>
<td>Male</td>
<td>41</td>
</tr>
<tr>
<td>SCr</td>
<td>1.67 (1.3-2.2)</td>
</tr>
<tr>
<td>CKD stage</td>
<td>3 (3-4)</td>
</tr>
<tr>
<td>Incidence of diabetes %</td>
<td>68.9</td>
</tr>
<tr>
<td># of anti-hypertensives prior to initiation</td>
<td>3 (2.4)</td>
</tr>
</tbody>
</table>

**Figure 6.** Median SBP/DBP before and after spironolactone initiation

**Table 4.** Incidence of hyperkalemia following spironolactone initiation

<table>
<thead>
<tr>
<th>Incidence of hyperkalemia</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[K⁺] &gt; 5.5</td>
<td>3/83 (3.6%)</td>
</tr>
<tr>
<td>[K⁺] &gt; 6.0</td>
<td>0/83 (0%)</td>
</tr>
</tbody>
</table>
4. Study conclusion  
   a. Spironolactone may be an effective option to reduce blood pressure in patients with stage 3-5 CKD  
   b. Overall incidence of hyperkalemia was low  
   c. Results suggest the use of spironolactone in this population may be advantageous and warrants further investigation  

10. Conclusions  
   a. Spironolactone has been shown to be effective in reducing blood pressure in hypertension and resistant hypertension  
   b. Studies show that spironolactone has renoprotective properties and may delay progression in CKD  
   c. Serum potassium appears to have a median increase of 0.3 mEq/L when spironolactone is added to antihypertensive regimens  
   d. Large scale outcome trials needed  
      i. Confirm efficacy and safety in this patient population  
      ii. Provide morbidity and mortality data  
   e. Use of spironolactone appears to be safe and effective in patients with CKD and resistant hypertension  
      i. Strict monitoring is required in these patients  
      ii. Suggested algorithm (Appendix E)
REFERENCES

APPENDIX A. Nephron Physiology

Renal physiology & diuretics

Cortex
Medulla

PCT
Osmotic

NaCl 67-90
H2O
HCO3
Glucone, AA

Creatinine, Antibiotics, Diuretics, Uric acid

Proximal part
Thiazides

DCT
Distal part
Osmotic, K-sparing

K
H2O

NaCl 10
Ca

"PTN"

"Aldosterone"

K-sparing

Collecting duct and tubules
Osmotic

NaCl 25

H2O

"ADH"

Why all these colors?
Segment name in violet
Diuretic name in pink
Reabsorption in red
Secretion in green
Percentage in blue
Hormone in orange

Loop of Henle
Loop diuretics
APPENDIX B. Renin-Angiotension-Aldosterone System


Cardiovascular system → Vasoconstriction → ↑ Blood pressure

Aldosterone → Kidney → Salt and H₂O retention

Liver
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Spironolactone</th>
<th>Eplerenone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical indication</td>
<td>Severe (NYHA class III-IV) CHF with LV systolic dysfunction</td>
<td>Severe (NYHA class III-IV) CHF after myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Essential hypertension</td>
<td>Essential hypertension</td>
</tr>
<tr>
<td></td>
<td>Primary hyperaldosteronism</td>
<td></td>
</tr>
<tr>
<td>Receptor binding affinity</td>
<td>(1.1 \times 10^{-1})</td>
<td>(5.1 \times 10^{-3})</td>
</tr>
<tr>
<td>(aldosterone=1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex-steroid receptor cross-reactivity</td>
<td>Yes</td>
<td>Minimal</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic</td>
<td>Cytochrome P450, isoenzyme CYP3A4</td>
</tr>
<tr>
<td>Conversion to metabolites for effect</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Half-life, h</td>
<td>1.4</td>
<td>4–6</td>
</tr>
<tr>
<td>Excretion</td>
<td>Renal and bile</td>
<td>Renal and GI</td>
</tr>
<tr>
<td>Administration</td>
<td>With food to maximize absorption</td>
<td>With or without food</td>
</tr>
<tr>
<td>Recommended dose, mg/d</td>
<td>Hypertension, 50–100; CHF, 25–200</td>
<td>Hypertension, 50–100; CHF, 25–50</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Potentiate hyperkalemia ACE-I</td>
<td>Potentiate hyperkalemia ACE-I</td>
</tr>
<tr>
<td></td>
<td>NSAIDs</td>
<td>NSAIDs</td>
</tr>
<tr>
<td></td>
<td>Potentiate hypotension</td>
<td>CYP3A4 inhibitors increase eplerenone: itraconazole, ribonavir, clarithromycin</td>
</tr>
<tr>
<td>Narcotics</td>
<td>Increase digoxin levels</td>
<td>CYP3A4 inducers decrease eplerenone: St John’s wort</td>
</tr>
<tr>
<td>Side effects</td>
<td>Hyperkalemia</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td></td>
<td>Gynecomastia, breast tenderness</td>
<td>Abdominal pain, diarrhea</td>
</tr>
<tr>
<td></td>
<td>Erectile dysfunction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dysmenorrhea, amenorrhea</td>
<td></td>
</tr>
</tbody>
</table>

***GI indicates gastrointestinal; NSAIDs, non-steroidal anti-inflammatory drugs.**
APPENDIX E. Clinical Algorithm for the Initiation of Spironolactone

1. **Aldosterone Antagonist Eligibility**

2. **Identify Clinical Indication**
   - Moderate to Severe CHF + LV dysfunction
   - Moderate to Severe CHF Early Following Acute MI
   - Essential or Resistant Hypertension on Combination Therapy

3. **Assess Safety Profile**
   - Measure Serum K⁺, Creatinine
   - Is K⁺ ≤ 5.0 mEq/L?
     - No
     - Yes
       - Is serum Creatinine < 2.0 mg/dL (Women) < 2.5 mg/dL (Men)?
         - No
         - Yes

4. **Therapy Initiation**
   - Maximize Standard Therapy
   - Consider Therapy Initiation
   - Assess Additional Hyperkalemia Risk Factors: Diabetes, Drug Interactions

5. **Laboratory Monitoring Frequency per Hyperkalemia Risk**