Question 1: Which of these patients has chronic kidney disease?

1. Patient on dialysis
2. Patient with creatinine > 2.0 mg/dL
3. Patient with > 3g urine protein per day
4. All of the above
Introduction

- Chronic Kidney Disease (CKD):
  - Entity defined only about 10 years ago; major guideline effort by National Kidney Foundation (NKF)
  - Replaced earlier terms “chronic renal insufficiency”, “chronic renal failure”, or “high creatinine”
  - CKD stages were made up by expert panel
  - Most CKD epidemiology research has been conducted after stages defined

CKD Stages and Prevalence

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>Estimated GFR (mL/min per 1.73 m²)</th>
<th>U.S. Prevalence N (1000’s) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD Stage 1</td>
<td>90+*</td>
<td>3,200 (1.6)</td>
</tr>
<tr>
<td>CKD Stage 2</td>
<td>60-89*</td>
<td>6,500 (3.2)</td>
</tr>
<tr>
<td>CKD Stage 3</td>
<td>30–59</td>
<td>15,500 (7.7)</td>
</tr>
<tr>
<td>CKD Stage 4</td>
<td>15–29</td>
<td>700 (0.4)</td>
</tr>
<tr>
<td>CKD Stage 5</td>
<td>&lt;15 (or dialysis)</td>
<td>400 (0.2)</td>
</tr>
</tbody>
</table>

*With evidence of kidney damage, e.g. albuminuria

KDOQI Guidelines, AJKD, Feb. 2002

Problems with Current Staging

- Stages 1 and 2 are the same
- Stage 3 (30-60) is too broad; eGFR of 30-45 is very different from 45-60
- Does not address levels of albuminuria; and only uses albuminuria for Stages 1 and 2
- Designed for staging, not diagnosis of CKD (example of NYHA staging in HF)

Revised CKD Guidelines are Coming

- Guideline version 2 will begin in October 2010
- Sponsored by KDIGO, NKF
- 16 member Working Group- 3 from the U.S.
- Stages will be informed by prognosis
### Rational CKD Staging Proposal

<table>
<thead>
<tr>
<th>Albuminuria (mg/g)</th>
<th>“Normal” (&lt;30)</th>
<th>Micro (30-300)</th>
<th>Macro (&gt;300)</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (ml/min/1.72m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (&gt;60)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (45-60)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate (30-45)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe (&lt;30)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Question 2:** A 75 yr. old White male with CAD and HF has Stage 4 CKD (eGFR= 25). What is he at most risk for?

1. **Death**
2. **Dialysis**

### Outline

- Staging of CKD
- **Complications of CKD**
- Screening for CKD
- Treatment of CKD
  - ACCORD study
- Renal Artery Stenosis
- When to refer to nephrologist

### Complications of “Stage 3” CKD (eGFR<60)

- Kidney failure (end-stage renal disease)
- Death
- Atherosclerotic Cardiovascular Disease
- Heart failure
- Osteoporosis/fracture
- Cognitive impairment/dementia
- Decreased physical function
- Frailty
CKD Complications
Keith et al., Arch Int Med, 2004

- **Design:** Northwest Kaiser database
- **5 year follow-up**
- **Death and ESRD outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Stage 3 (eGFR 30-60)</th>
<th>Stage 4 (eGFR 15-30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N= 11,278</td>
<td>N= 777</td>
</tr>
<tr>
<td>Age</td>
<td>72</td>
<td>74</td>
</tr>
<tr>
<td>ESRD (%), 5 yrs</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Death (%), 5 yrs</td>
<td>24</td>
<td>45</td>
</tr>
</tbody>
</table>

Recent Meta-analysis in Lancet

- 14 studies with urine ACR measurements; 7 studies with urine protein dipstick measurements
- 1,234,182 total patients
- Categories of estimated GFR, albuminuria (ACR)
- Mortality risk

Why Do CKD Patients Have Bad Outcomes?

- **Biological Reasons**—poor clearance by kidney of endogenous toxins (ex. Inflammation, thrombosis)
- **Worsening Risk Factors**—blood pressure, diabetes, Vitamin D conversion, anemia
- **Marker of Cumulative Aging**—“biological integrator”
- **Less aggressive treatment**
**Outline**

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**Who and When to Check Creatinine?**

- **Begin screening:**
  - Age >40 lower-risk populations
  - Age >30 Blacks, Native Americans

- More frequent monitoring (1-3 years):
  - Hypertension, diabetes, cardiovascular disease, heart failure, age >65, family history

**GFR Estimation from Creatinine**

- Cockroft-Gault (Nephron, 1976)
  - Still method generally used by FDA and pharmacies

- MDRD (Annals, 1999)

- CKD-EPI is most recent (Annals, 2009)

- Estimated GFR:
  - Automatic reporting by most labs
  - Equations are rough
  - <60 concerning for kidney disease, but not diagnostic of kidney disease

**Pros and Cons of Estimated GFR**

- **Pros:**
  - Indexes creatinine for demographic characteristics
  - Forces us to think in terms of GFR and kidney function

- **Cons:**
  - Mostly validated in younger patients with kidney disease
  - Huge assumption that demographic characteristics alone can define muscle mass
  - Only developed in Whites and Blacks
  - Rough approximation; “>60”
Who to Screen with Urine Albumin?

- Primary prevention screens:
  - Diabetes - annual
  - Hypertension
  - Elderly

- CKD Staging:
  - Albumin is growing as important part of CKD staging
  - Should be measured and documented in all CKD patients; repeat every 2-3 years

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Question 4: Which of the following treatment options will not slow the progression of kidney disease?

1. ACE/ARB treatments
2. Blood pressure control
3. Glucose control
4. Statins

CKD Treatment

- Is focused on prevention of progression to ESRD and control of complications
- We will review the following topics:
  - ACE/ARB therapy
  - Blood Pressure Control
  - Glucose Control in Diabetes
  - Statins
Are ACE/ARB’s for All CKD Patients?

- Diabetic CKD- ACE/ARB essential for all disease categories:
  - Type I or II
  - Early disease (microalbuminuria)
  - Late disease (macroalbuminuria)

  Shlipak, Clinical Evidence 2009

- Non-diabetic CKD- may vary by proteinuria status (Jafer TH, Ann Intern Med, 2008)
- Meta-analysis- 1,860 CKD patients in RCTs of ACE vs. other blood pressure control
- Overall RR 0.67 (0.53-0.84) on ACE-I
- Subgroup analysis:
  - No benefit in group without proteinuria (< 500 mg/g)

ACE-I/ARB in CKD patients

- ALLHAT Hypertension Trial – Compared lisinopril, amlodipine, and hctz for multiple outcomes
- ACE not different from thiazides or CCB’s for kidney decline or ESRD (Rahman, Arch Intern Med, 2005)
- Suggests that the unique advantage of ACE-inhibitors for kidney health may be limited to persons with albuminuria or advanced CKD

ACE-I in Advanced CKD

- Hou FF et al. NEJM 2006;354:131-140
- 224 patients with creatinine 3.1-5.0 mg/dL
- Mean eGFR 25; mean urine prot – 1.6g/day
- Benazepril 20 mg daily vs. placebo
- primary end point: doubling of creatinine, ESRD, death

  Findings:
  - 43% reduction in primary end point
  - 52% reduction in proteinuria
  - Effects independent of blood pressure
  - Adverse events rare
**ACE/ARB Combination?**

- Proteinuria reduction from ACE inhibitors and ARBs is similar.
- In short term studies, combination of ACE inhibitors and ARBs has additional reductions in proteinuria.
- Uncertainty about outcomes and adverse effects.
- Given added risk of hyper-kalemia and uncertain benefit, I do NOT recommend combination therapy.

**Blood Pressure Treatment in CKD**

- Extremely important to treat SBP for diabetic and non-diabetic CKD
- Typically, requires 3-4 meds at full dose
- Since CKD often in older patients with stiff arteries, an SBP<130 may not be attainable.

**Glycemic Control in Diabetic CKD**

- **Type I Diabetes** - tight glucose control slows kidney disease progression: OR= 0.34 (0.20-0.58)
- **Type II Diabetes** - ADVANCE trial (NEJM, 2008, 2560-72)
  - Tight glucose control (Hb, A1c 6.5 vs. 7.3) led to 20% lower risk of "new or worsening nephropathy"; 4.1 vs. 5.2% (p = 0.006)
- In Type II Diabetes, risk of hypoglycemia and other adverse risks of glucose control may offset kidney benefits- tailor to individual.

**Statins in CKD- beneficial for CVD**

- 26 studies comparing statin with placebo in CKD
- Statins decreased both the risk of
  - all-cause mortality (21 RCTs, 18,781 patients, RR 0.81, 95% CI 0.74, 0.89) and
  - cardiovascular deaths (20 studies, 18,746 patients: RR 0.80, 95% CI 0.70 to 0.90).
- No change in renal function!
- Surprisingly, in dialysis patients statins have no CVD or mortality compared with placebo in 2 large RCTs.
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My Patient

- 75 yr. old white woman with severe PAD, refractory hypertension, prior hyper-K, and bradycardia (Wenckebach rhythm, HR 50)
- Meds: Lasix 40, Amlod 10
- BP: 160/70, HR= 48
- Labs: Creatinine = 1.4 (eGFR 50), K = 4.8; ACR 100
- My treatment: Lisinopril 10mg; f/u in 2 weeks

Case continued....

- Patient returns and “feels great”
- BP: 130/60, HR= 48
- K= 5.9; creatinine= 2.0 (eGFR 40)
- Clinical diagnosis– atherosclerotic RAS

Question 5: Management of the Patient with Suspected Atherosclerotic RAS.

What should I do next?

1. MRI to diagnose RAS
2. Angiography for ideal views of arteries
3. Control of BP without ACE/ARB
Clinical Profile of RAS

- Older patients, multiple vascular risk factors, often with co-existing vascular diseases
- Etiology: atherosclerosis, rarely FMD
- Extremely high risk for CVD
- As a consequence, these patients often have poor prognosis and low tolerance for procedures.

When to Suspect Atherosclerotic RAS

- Refractory HTN: ≥ 3 drugs at target dose
- ↑ creatinine after ACE/ARB
- Hyper-K after ACE/ARB

Imaging to Confirm Diagnosis?

- Whether or not to image is controversial.
- Nephrologists more likely to want imaging
- Options
  - Ultrasound- may not get adequate views
  - MRA- great images; concern of gadolinium in CKD patients for nephrogenic systemic sclerosis
  - CT Angio- risk of contrast nephropathy in CKD
  - Angiography- best images, but invasive, contrast

Treatment

- Medical Therapy is the cornerstone:
  - ACE are ideal therapy, if tolerated
  - Monitor K
  - Expect creatinine to rise up by up to 50%
  - Creatinine likely will return close to baseline over time
- May require many agents if ACE-intolerant
  - Minoxidil, hydralazine used as 4th/5th agents
Procedures for RAS

- Options include surgery, angioplasty, stenting
- Stenting is now favored procedure
- However, recent trials indicate no benefit on BP or kidney function for stenting vs. medical therapy
- ASTRAL trial
  - Largest ARAS study (N=806)
  - Procedure vs. medical treatment
  - 5 year follow-up

ASTRAL Trial

- A Reciprocal of Event-Curves
  - 2005: Medical Therapy vs. Revascularization
  - 2006: Medical Therapy vs. Revascularization

- B Serum Creatinin
  - Medical Therapy vs. Revascularization

ASTRAL Investigators, NEJM 2009

Summary of RAS

- Patients typically have vascular disease and other conditions.
- Procedures no better than medical therapy
- No reason for imaging, unless:
  - Diagnostic challenge
  - Frequent acute heart failure episodes
**Outline**

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**Reasons to Consider Referral to Nephrologist**

- Combined hematuria and proteinuria
- Estimated GFR < 30
- Nephrotic proteinuria
- Mineral metabolism management:
  - High phosphate
  - Anemia of CKD

Thank you

**Questions?**