Case presentation

• 54 yo woman with Type 2 DM for 20 years presents with hypertension and proteinuria. She has long-standing microalbuminuria and is taking losartan 25 mg daily. Her BP is 145/90, 24 hour urine protein is 2 grams, and serum creatinine is 1.5 mg/dL (eGFR 39 mL/min). Losartan is increased to 100 mg daily. Follow-up BP is 138/78 and 24 hour urine protein is 0.8 grams.

Question 1

Which of the following is true of her kidney disease?
A. Treatment with angiotensin receptor blocker (ARB) will decrease risk of end-stage renal disease (ESRD) by 80%.
B. Improved glycemic control at this stage of disease (HbA1c < 7%) has been shown to decrease risk of developing ESRD
C. She is more likely to have a cardiovascular complication than develop ESRD
D. A blood pressure of 120/70 has been shown to decrease risk of developing ESRD
Question 2
Which is the most appropriate next step?
A. Add lisinopril 5 mg daily to decrease proteinuria further
B. Add aliskiren 150 mg daily
C. Add ezetimibe/simvastatin combination
D. Add amlodipine 10 mg daily

Outline
• Update in diabetic kidney disease
  – Dual RAAS Blockade
  – Goal BP
  – Glycemic Control
  – Statins
• Update in hypertension
  – Resistant Hypertension

Cases of Incident ESRD from Diabetes

Inhibition of Renin Angiotensin Aldosterone System (RAAS) in Type 2 DM

- Two large RCTs (n > 1500 pts) in patients with T2DM and overt nephropathy
  - IDNT
  - RENAAL
- Both trials used a composite endpoint (death, doubling serum creatinine, dialysis) as the primary endpoint
- ARBs associated with a 15-20% risk reduction in primary endpoint
  - 20-30% reduction in ESRD

Should we use dual blockade of RAAS?

- Rationale for dual blockade
  - Reduction in proteinuria appears to correlate with prevention of renal progression
  - Dual blockade of RAAS (ACE inhibitor + ARB, ACE Inhibitor + renin inhibitor, ACE inhibitor + aldosterone antagonist) leads to greater reduction in proteinuria than single agent alone
  - AVOID trial – RCT of 599 patients with T2DM and nephropathy. Short term study showed aliskerin + losartan further decreased proteinuria.
Addition of Renin Inhibitor to ARB in Type 2 DM

**ALTITUDE trial**
8561 patients with either diabetic kidney disease or T2DM and cardiovascular disease
Received aliskiren (300 mg daily) or placebo in addition to ACE or ARB
Primary endpoint—time to cardiovascular death, nonfatal MI, nonfatal stroke, unplanned hospitalization, ESRD, death from kidney failure, or doubling serum creatinine

Parving HH et al., NEJM, 2012.

ALTITUDE trial
- Terminated early
- Median follow up of 33 months
- Primary endpoint
  - 18.3% aliskiren
  - 17.1% placebo
  - P=0.12
- Hyperkalemia more common in aliskerin group
  - 11.2% vs. 7.2%
- Hypotension more common in aliskiren group
  - 12.1% vs. 8.3%

Addition of ACE Inhibitor to ARB in Diabetic Kidney Disease

**VA NEPHRON-D**
1448 patients with T2DM and overt kidney disease
All taking losartan 100 mg daily
Randomized to lisinopril or placebo
Primary end point—1st occurrence change in GFR, ESRD, or death

Fried L et al. NEJM, 2013.
VA NEPHRON-D Primary Outcome

Table 1. Efficacy End Points and Mortality

<table>
<thead>
<tr>
<th>End Point</th>
<th>Isoniazid plus Placebo (N=114)</th>
<th>Isoniazid plus Lisinopril (N=114)</th>
<th>Hazards Ratio with Isoniazid plus Lisinopril (HR 95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>6 (5.3)</td>
<td>8 (7.0)</td>
<td>1.04 (0.75-1.45)</td>
<td>0.75</td>
</tr>
<tr>
<td>Myocardial infarction, heart failure, or stroke</td>
<td>15 (20.9)</td>
<td>15 (19.7)</td>
<td>0.97 (0.66-1.43)</td>
<td>0.78</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7 (5.9)</td>
<td>10 (8.8)</td>
<td>1.60 (0.87-3.03)</td>
<td>0.18</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>15 (12.9)</td>
<td>19 (16.6)</td>
<td>0.90 (0.56-1.43)</td>
<td>0.77</td>
</tr>
<tr>
<td>Stroke</td>
<td>48 (23.8)</td>
<td>63 (32.9)</td>
<td>1.04 (0.75-1.45)</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Fried L et al. NEJM, 2013.

VA NEPHRON-D Results

- Trial terminated early – median follow-up of 2.2 years
- Increased risk of hyperkalemia with combination therapy (two to three fold)
- Increased risk of acute kidney injury (2 fold)
Take-home points from ALTITUDE and VA NEPHRON-D study

- Monotherapy with losartan is preferred to combination therapy with ACE inhibitor or direct renin inhibitor
- Patients with hyperkalemia were excluded from both trials
  - In non-research settings, rates of hyperkalemia may be higher
  - New oral potassium-binding resins that are currently being studied may allow trials testing these strategies to be performed in the future.

What is the Goal BP for Patients with Diabetes and Kidney Disease?

- UKPDS established benefits of blood pressure control in diabetics
- Steno-2 trial compared 2 BP targets in diabetics with kidney disease
  - In addition to BP control, trial compared multifactorial interventions including a low BP target and found a reduction in mortality
- Appropriate Blood Pressure Control in Diabetes (ABCDO): Compared DBP <80 mm Hg to DBP 80-90 mm Hg
  - Lower BP had fewer strokes, less retinopathy, and reduced incidence of overt albuminuria
- Action to Control Cardiovascular Risk in Diabetes (ACCORD): SBP <120 mm Hg vs. SBP <140 mm Hg
  - Low BP group with fewer strokes but more episodes of acute kidney injury and hyperkalemia
- Post-hoc analysis of other studies in CKD (MDRD and AASK)
  - In patients with significant proteinuria, BP less than 130/80 mm Hg associated with improved renal prognosis

What is the Goal BP for Patients with Diabetes and Kidney Disease?

  - Patients with DM or CKD – 130/80 mm Hg
- JNC 8 – JAMA, 2014.
  - All patients 140/90 mm Hg
  - Diabetes with urine alb < 30 mg – 140/90 mm Hg
  - Diabetes with urine alb > 30 mg – 130/80 mm Hg
  - Patients with DM and CKD – 130/80 mm Hg
Glycemic control

- Data regarding different HbA1c targets mainly comes from patients with normal kidney function or early kidney damage
- Control of blood sugar in advanced kidney disease is complicated due to:
  - Inability to use some oral agents such as glyburide and metformin
  - Higher incidence of hypoglycemia

Metformin therapy in CKD

- Since metformin is renally cleared, risk of accumulation and lactic acidosis in CKD
  - True risk of lactic acidosis unknown
- Current FDA guidelines
  - Avoid in renal disease (serum creatinine > 1.5 mg/dL in men or > 1.4 mg/dL in women)
- No RCTs have examined metformin use and risk of lactic acidosis in CKD

Meta-analysis of Metformin in CKD

[Table 1. Retrospective Studies Examining the Frequency of Metformin Use in Patients With Active Renal Disease]

Meta-analysis of Metformin in CKD

- Risk of lactic acidosis is unclear in CKD
- Clearance is significantly reduced in CKD but serum metformin levels remain therapeutic
- Authors suggest another approach to metformin in CKD
  - Avoid use when eGFR < 30 mL/min
  - Reduce dose to 1000 mg daily in patients with GFR 30-45 mL/min who are already taking metformin

Are Statins Helpful in CKD?

- Most large RCTs have excluded patients with advanced CKD
- Post-hoc analyses of RCTs have shown that statins are beneficial in patients with mild-moderate CKD (eGFR >45 mL/min)
- As compared to the general population, the relationship with LDL cholesterol and cardiovascular events is less pronounced

Relationship Between LDL-C and CV Events Depends on eGFR

CKD Alone Significantly Increases Risk of CV Events

The SHARP Trial
- RCT of patients with CKD
  - Age > 40
  - Creatinine < 1.7 mg/dL in men and 1.5 mg/dL in women
- Enrolled 9270 patients (33% dialysis, 23% with DM)
- Baseline LDL 2.77 mmol/L

Simvastatin/Ezetimibe Decreases CV Events in Patients with CKD
SHARP-Further Analysis

- Benefit seen in treatment group was driven by a reduction in stroke and vascular interventions
- In the dialysis subgroup, simvastatin/ezetimibe was not beneficial
  - Similar to 4D and AURORA trial
- Benefit was largest in patients with LDL-C < 3 mmol/L
- Treatment well-tolerated

Take-away from SHARP

- CKD patients have a significantly elevated risk of cardiovascular events
- Simvastatin/ezetimibe combination significantly reduced major cardiovascular events
- K-DIGO guidelines

A Patient With Hard to Control Hypertension

- 55 yo man with Type 2 DM and CKD (creatinine 1.6 mg/dL) returns with elevated blood pressure. Exam normal except for 1+ edema.
  - Current regimen: losartan 100 mg daily, amlodipine 10 mg daily, HCTZ 25 mg daily
- What next?
Resistant Hypertension

- Persistent hypertension despite treatment with 3 anti-hypertensives (including 1 diuretic) at full doses
- First steps
  - Medication compliance
  - Dietary sodium (24 hour urine collection for Na)
  - Interfering substances (NSAIDs, OCPs)
  - Evaluate for white-coat hypertension
    - Control blood pressure measured correctly

Resistant Hypertension-Management

- Our strategy is usually to increase diuretics
  - (increase dose of HCTZ, switch to chlorthalidone, switch to furosemide, add aldosterone antagonist)
- Few trials in patients with resistant hypertension
- Endothelin antagonists are effective but cause edema
- New strategies (carotid baroreflex stimulator and renal sympathetic denervation) are under study and have had mixed results

**Original Investigation**

Effect of Home Blood Pressure Telemonitoring and Pharmacist Management on Blood Pressure Control

A Cluster Randomized Clinical Trial

JAMA, 2013
Trial design

- 450 primary care patients with uncontrolled BP
  - BP > 140/90 mm Hg or 130/80 mm Hg in patients with diabetes or chronic kidney disease
- Clinics were randomly assigned to an active pharmacist-managed program or usual care
  - Patients given home BP monitors, check BP 6 times per week, and meet with pharmacist every 2 weeks
  - Pharmacists could increase medication dosages and change medications within a given set of parameters

Active Pharmacist Involvement Improves BP Control

<table>
<thead>
<tr>
<th>Table 2: Composite and Blood Pressure (BP) Control</th>
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<tbody>
<tr>
<td><strong>Table 3: Blood Pressure (BP) Reduction From Baseline</strong></td>
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<tr>
<td><strong>Diastolic BP, mm Hg</strong></td>
<td></td>
</tr>
<tr>
<td>At 18 mo</td>
<td>135</td>
</tr>
<tr>
<td>At 12 mo</td>
<td>141</td>
</tr>
<tr>
<td>At 6 mo</td>
<td>148</td>
</tr>
<tr>
<td>At 6, 12, and 18 mo</td>
<td>96</td>
</tr>
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</table>

Mean (95% CI)

Conclusions

- Frequent home BP monitoring and pharmacist-led management improve blood pressure in patients with uncontrolled hypertension
- The beneficial effect was seen for at least 18 months after starting the intervention
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