Lessons learned from AASK (African-American Study of Kidney Disease and Hypertension)

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ASH Clinical Specialist in Hypertension
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Stage 5 CKD Incidence Rates per Million Vary by Race/Ethnicity

Odds ratios: 1 3.89 2.74 1.56 1 1.45

*P<0.0001
†Reference population.

Hypertension: The 2nd Most Common Cause of ESRD

Primary Diagnosis For Patients Who Start Dialysis

- Diabetes: 50.1%
- Hypertension: 27%
- Glomerulonephritis: 13%
- Other: 10%


No of Patients Projected 95% CI

- 1984: 243,524
- 1986: 281,355
- 1988: 520,240

R² = 99.8%
Hypertension in African Americans

• Prevalence, severity, and impact of hypertension are increased in African Americans

• Lower achievement rate of BP control
• As monotherapy, β-blockers, ACE inhibitors or ARBs may produce less blood pressure lowering effects than in whites
  – Diuretics and CCBs may have greater BP efficacy
• Differential responses are minimized by drug combinations that include adequate doses of diuretics

AASK Study Questions

• Does very aggressive lowering of blood pressure result in slower decline in renal function?

• Does the type of antihypertensive agent used to initiate blood pressure lowering matter with regard to renal outcomes?
African American Study of Kidney Disease and Hypertension (AASK)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Usual</th>
<th>Aggressive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goal MAP:</td>
<td>102-107 mm Hg</td>
<td>≤92 mm Hg</td>
</tr>
<tr>
<td>N = 217</td>
<td>Amlodipine</td>
<td>Amlodipine</td>
</tr>
<tr>
<td>N = 436</td>
<td>Ramipril</td>
<td>Ramipril</td>
</tr>
<tr>
<td>N = 441</td>
<td>Metoprolol</td>
<td>Metoprolol</td>
</tr>
</tbody>
</table>

- 1094 patients with HTN and CKD, 4 yr f/u
  GFR = 20-65 mL/min/1.73 m², Subsequent 10 yr f/u
- Excluded DBP <95 mm Hg, DM, UP/Cr >2.5

MAP = mean arterial pressure; DBP = diastolic blood pressure; UP/Cr = urinary protein to creatinine ratio. Wright et al for the AASK Study Group. JAMA. 2002;288:2421-2431.
Mean Arterial Pressure During Follow-up

Lower BP Goal (Achieved: 128/78)
Usual BP Goal (Achieved: 141/85)
Composite Clinical Outcome
Declining GFR Event, ESRD or Death

Lower BP (Achieved: 128/78)
Usual BP (Achieved: 141/85)

Low vs. Usual:
RR=2%, (p=0.85)

Follow-Up Time (Months)

% with Events

0 5 10 15 20 25 30 35 40

Follow-Up Time (Months)
Clinical Evidence for Risk Reduction With ACE Inhibitor or β Blockade: AASK

Composite risk of rapid GFR decline—decrease from baseline of 50% or 25 mL/min/1.73 m², kidney failure, or death

- Ramipril vs Amlodipine: $P = 0.004$
- Ramipril vs Metoprolol: $P = 0.04$
- Metoprolol vs Amlodipine: $P = 0.17$

Patients with existing kidney damage (baseline UP/Cr > 0.22).
Geometric mean urine protein/creatinine ratio declined faster in ramipril and metoprolol groups than amlodipine group (p < 0.001)
% of Patients Reached Urine Protein/Creatinine Ratio > 0.22 During Follow-up by Drug Group

Ramipril vs. Metoprolol: p=0.014
Amlodipine vs. Metoprolol: p=0.009
Ramipril vs. Amlodipine: p<0.001

Analysis of patients with UP/Cr < 0.22 at baseline
Albuminuria is mediated by efferent arteriolar constriction - Angiotensin II (Ang II)

Hypertension

Afferent arteriolar dilation

Glomerular hypertension

Efferent arteriolar constriction

Afferent arteriolar constriction

Albiminaruria
Association of Main Clinical Composite Outcome (GFR Event, ESRD, or Death) With Baseline Proteinuria

- Baseline UP/Cr < 0.22
- Baseline UP/Cr > 0.22

Follow-up Month

% with Events

Follow-up Month

P < 0.001
Percent Change in Proteinuria from Baseline

<table>
<thead>
<tr>
<th>Follow-up Month</th>
<th>Lower BP Goal</th>
<th>Usual BP Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-18 (SE)</td>
<td>0 (SE)</td>
</tr>
<tr>
<td>6</td>
<td>22 (SE)</td>
<td>49 (SE)</td>
</tr>
<tr>
<td>12</td>
<td>82 (SE)</td>
<td>122 (SE)</td>
</tr>
<tr>
<td>24</td>
<td>172 (SE)</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

% change in geometric mean urine protein/creatinine ratio
Conclusion: AASK Blood Pressure Control Study

• Pharmacological lowering of blood pressure to levels known to protect against cardiovascular events are achievable in patients with hypertensive nephrosclerosis

• Aggressive lowering of BP
  – did not result in a significantly slower rate of decline in GFR (primary endpoint)
  – did not result in significant difference in composite endpoint of rapid decline in GFR or ESRD or death (secondary endpoint)
  – did result in significant reduction in proteinuria
The Relationship Between Magnitude of Proteinuria Reduction and Risk of End-stage Renal Disease

Results of the African American Study of Kidney Disease and Hypertension

Janice Lea, MD; Tom Greene, PhD; Lee Hebert, MD; Michael Lipkowitz, MD; Shaul Massry, MD; John Middleton, MD; Stephen G. Rostand, MD; Edgar Miller, MD, PhD; Winifred Smith, MPH; George L. Bakris, MD; for the African American Study of Kidney Disease and Hypertension Study Group

Lea et al, Arch. Int. Med. 2005
Six Month Change in Proteinuria from Baseline Predicts Outcome of Kidney Disease: Results from the AASK trial


• The baseline level and change at 6 months in proteinuria were strong predictors of subsequent progression of hypertensive kidney disease.

• The relationship extended to participants with normo- to micro-albuminuria.
Intensive Blood-Pressure Control in Hypertensive Chronic Kidney Disease


Figure 2. Cumulative Incidence of the Composite Primary Outcome, According to Baseline Proteinuria Status.

Among patients with baseline proteinuria, which was defined as a urinary protein-to-creatinine ratio (P:C) of more than 0.22, those who received intensive blood-pressure control had a significantly lower cumulative incidence of the composite primary outcome (a doubling of the serum creatinine level, end-stage renal disease, or death) than those who received standard blood-pressure control (hazard ratio in the intensive-control group, 0.73; 95% confidence interval [CI], 0.58 to 0.93; P=0.01). However, the between-group difference was not significant among patients with a P:C of 0.22 or less (hazard ratio, 1.18; 95% CI, 0.93 to 1.50; P=0.16). The values at the bottom of the graph are numbers of patients.
Prevalence and Correlates of LVH in AASK (Peterson et al, HTN 2007)

• LVH present in 66.7% of men and 73.9% of women; this contrasts with most series ~ 30%.

• 24 hr ABPM- SBP, lower GFR, younger age in MV analyses predicted LVH.
Cumulative Incidence Based on Competing Risk Analysis

- ESRD
- All-Cause Death
- CV Death

Follow-Up Year
Metabolic Syndrome in CKD (Cardiorenal)

• The tendency for cardiovascular disease risk factors to occur in clusters has lead to the description of metabolic syndrome.

• The impact of the different components of the syndrome on the relative risk of CV death in the general population is not clearly established.

• CKD has recently emerged as a CV mortality risk factor
# Clinical Identification of the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>Waist circumference:</td>
</tr>
<tr>
<td></td>
<td><strong>Men</strong></td>
</tr>
<tr>
<td></td>
<td>&gt;40 in (&gt;102 cm)</td>
</tr>
<tr>
<td></td>
<td><strong>Women</strong></td>
</tr>
<tr>
<td></td>
<td>&gt;35 in (&gt;88 cm)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL-C Men</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>HDL-C Women</td>
<td>&lt;50 mg/dL</td>
</tr>
</tbody>
</table>

≥3 Risk factors comprise the metabolic syndrome. ICD-9 Code 277.7

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS unadjusted</td>
<td>1.31</td>
<td>1.03-1.68</td>
<td>.03</td>
</tr>
<tr>
<td>MS adjusted for</td>
<td>1.37</td>
<td>1.07-1.77</td>
<td>.01</td>
</tr>
<tr>
<td>other covariates,</td>
<td>1.23</td>
<td>.95-1.58</td>
<td>.11</td>
</tr>
<tr>
<td>+ uprot/cr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>By BP goal</td>
<td>1.37</td>
<td>1.05-1.8</td>
<td>.02</td>
</tr>
<tr>
<td>By Drug group</td>
<td>1.35</td>
<td>1.03-1.78</td>
<td>.03</td>
</tr>
</tbody>
</table>
Key Points for Optimal Hypertension Management

JNC 7 recommends:
If SBP >20 mm Hg, DBP >10 mm Hg over goal, consider initiating with 2-drug combination

JNC 7 BP Goals

<140/90 mm Hg

<130/80 mm Hg in diabetes or renal disease

## Recommendations for BP and RAS Management in CKD

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Goal BP (mm Hg)</th>
<th>First Line</th>
<th>Adjunctive</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ Diabetes</td>
<td>&lt;130/80</td>
<td>ACE-I or ARB</td>
<td>Diuretics then CCB or BB</td>
</tr>
<tr>
<td>− Diabetes</td>
<td>&lt;130/80</td>
<td>ACE-I or ARB</td>
<td>Diuretics then CCB or BB</td>
</tr>
<tr>
<td>+ Proteinuria</td>
<td>&lt;130/80</td>
<td>ACE-I or ARB</td>
<td>Diuretics then CCB or BB</td>
</tr>
<tr>
<td>− Diabetes</td>
<td>&lt;130/80</td>
<td>No specific preference: Diuretics then ACE-I, ARB, CCB, or BB</td>
<td></td>
</tr>
<tr>
<td>− Proteinuria</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**EXPECT TO NEED TO USE 3+ AGENTS TO ACHIEVE GOALS**

Recommendations largely consistent across JNC 7, ADA, and K/DOQI

Average Number of Antihypertensive Agents Needed Per Patient to Achieve Diastolic BP Goals

- UKPDS (<85 mm Hg Diastolic)
- ABCD (<75 mm Hg Diastolic)
- MDRD (<92 mm Hg MAP)
- HOT (<80 mm Hg Diastolic)
- AASK (<92 mm Hg MAP)

No. of BP medications

Clinical Implications of AASK

- These results support the use of ACEI as initial therapy to control BP in a multidrug regime over DHP-CCB or β-blockers in CRF due to HTN.
- AASK documents renoprotective effects of ACEI in African-Americans, a population thought previously less responsive to ACEI.
- It is not known whether the addition of a CCB or β-blocker to an ACEI will blunt renoprotection.
- Aggressive lowering of BP to <140/90 in <1 gm proteinuria does not slow GFR decline or delay ESRD, findings c/w MDRD study.
Summary

• Lower BP goals mostly benefit hypertensive CKD pts with > 300 mg/g proteinuria.

• Degree of proteinuria predicts progression to ESRD in those with and without Metabolic syndrome.

• Future randomized prospective trials needed to evaluate racial disparities in CVD and mortality in CKD patients.
Reducing Risks of Kidney Disease in African-Americans

• Education
• Early detection of kidney disease
• Adequate treatment of hypertension and diabetes
• Adequate access to healthcare
• Proper dietary habits
• More clinical research in African-Americans to better understand the increased risks