Kidney Disease, Hypertension and Cardiovascular Risk

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Chronic Kidney Disease

Definition

Kidney damage for $\geq 3$ months
- Structural or functional abnormalities with or without decreased GFR
  - Pathological abnormalities
  - Abnormal blood or urine tests
  - Abnormal imaging

GFR $< 60$ mL/min/1.73m² for $\geq 3$ months

NKF 2002
The Five Stages of CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney Damage with Normal or ↑ GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney Damage with Mild ↓ GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney Failure or &lt;15 or dialysis</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

GFR represents Glomerular Filtration Rate.
## Awareness of CKD per CKD Stage

<table>
<thead>
<tr>
<th></th>
<th>Stage 1 and ACR 30 mg/g</th>
<th>Stage 2 and ACR 30 mg/g</th>
<th>Stage 3</th>
<th>Stage 4</th>
<th>Stage 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2000–2002</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%)</td>
<td>190</td>
<td>313</td>
<td>2113</td>
<td>112</td>
<td>25</td>
</tr>
<tr>
<td>(% aware)</td>
<td>3.16 (0.66–5.65)</td>
<td>2.56 (0.80–4.31)</td>
<td>4.45 (3.57–5.33)</td>
<td>15.18 (8.50–21.85)</td>
<td>40.00 (20.40–60.74)</td>
</tr>
<tr>
<td><strong>2003–2005</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%)</td>
<td>1,187</td>
<td>1,846</td>
<td>6,753</td>
<td>315</td>
<td>53</td>
</tr>
<tr>
<td>(% aware)</td>
<td>4.55 (3.36–5.74)</td>
<td>5.25 (4.24–6.27)</td>
<td>5.69 (5.13–6.24)</td>
<td>38.10 (32.72–43.47)</td>
<td>47.10 (33.60–60.74)</td>
</tr>
</tbody>
</table>

Values shown are number or percent (95% confidence interval); awareness defined as a positive response to the question: *Have you ever been told you have kidney disease?* Albumin-creatinine ratio in mg/g may be converted to mg/mmol by dividing by 8.84.

Incidence of Kidney Failure
per million population, 1990, by HSA, unadjusted
Incidence of Kidney Failure
per million population, 2000, by HSA, unadjusted

USRDS, 2000
Cardiovascular Comorbidities,
5% Medicare Sample, by Diabetes and CKD Status 1999-2000

% Stroke/TIA

% Heart Failure

% ASHD

% Amputation/PVD

Table 2. Adjusted Hazard Ratio for Death from Any Cause, Cardiovascular Events, and Hospitalization among 1,120,295 Ambulatory Adults, According to the Estimated GFR.*

<table>
<thead>
<tr>
<th>Estimated GFR</th>
<th>Death from Any Cause</th>
<th>Any Cardiovascular Event</th>
<th>Any Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60 ml/min/1.73 m²†</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>45–59 ml/min/1.73 m²</td>
<td>1.2 (1.1–1.2)</td>
<td>1.4 (1.4–1.5)</td>
<td>1.1 (1.1–1.1)</td>
</tr>
<tr>
<td>30–44 ml/min/1.73 m²</td>
<td>1.8 (1.7–1.9)</td>
<td>2.0 (1.9–2.1)</td>
<td>1.5 (1.5–1.5)</td>
</tr>
<tr>
<td>15–29 ml/min/1.73 m²</td>
<td>3.2 (3.1–3.4)</td>
<td>2.8 (2.6–2.9)</td>
<td>2.1 (2.0–2.2)</td>
</tr>
<tr>
<td>&lt;15 ml/min/1.73 m²</td>
<td>5.9 (5.4–6.5)</td>
<td>3.4 (3.1–3.8)</td>
<td>3.1 (3.0–3.3)</td>
</tr>
</tbody>
</table>

* The analyses were adjusted for age, sex, income, education, use or nonuse of dialysis, and the presence or absence of prior coronary heart disease, prior chronic heart failure, prior ischemic stroke or transient ischemic attack, prior peripheral arterial disease, diabetes mellitus, hypertension, dyslipidemia, cancer, a serum albumin level of 3.5 g per deciliter or less, dementia, cirrhosis or chronic liver disease, chronic lung disease, documented proteinuria, and prior hospitalizations.

† This group served as the reference group.
Risk Factors for CKD

- Diabetes
- Hypertension
- Older age
- Family history of kidney disease or diabetes
- Male gender

Racial/Ethnic Background:
- African American
- Native American
- Asian-American
- Pacific Islander
- Latin American

Tobacco Use
The Spectrum of Albuminuria

- Microalbuminuria
- Albuminuria (Proteinuria)

\[ \text{mg/day} \]

- \( \uparrow \) CV Risk and Presence of Renal Dysfunction and Vascular Dysfunction

Normal

Microalbuminuria

(Proteinuria)
Use of MAU, CRP, and BNP as Predictors of Mortality and CV Events

Mortality

- **MAU**: Hazard Ratio (HR) 1.7, 95% CI (1.1, 2.6), p = .008
- **CRP**: HR 1.5, 95% CI (1.1, 2.0), p = .014
- **NT-proBNP**: HR 1.3, 95% CI (1.0, 1.7), p = .007

First Major CV Event

- **MAU**: HR 1.9, 95% CI (1.1, 3.2), p = .003
- **CRP**: HR 1.1, 95% CI (0.7, 1.8), p = .96
- **NT-proBNP**: HR 1.7, 95% CI (1.2, 2.6), p < .001

Adjusted for age, sex, smoking, DM, HTN, Afib, LVEF<50%, LVH, total cholesterol, serum creatinine. Mortality analysis based on 91 deaths, and CV event data based on 63 events due to missing covariates. The 80th percentile corresponds to values more than 5.85 pg/mL for NT-proBNP, 5.76 mg/L for CRP, and 18.4 mg/g for MAU.

VOLUME FRACTION OF THE MESANGIUM (Vv Mes) IN THREE GROUPS OF DIABETIC PATIENTS

The Early Natural History of Nephropathy in Type 1 Diabetes: Predictors of 5-Year Urinary Albumin Excretion Rate Patterns in Initially Normoalbuminuric Patients

Steinke J et.al. Diabetes 2005;54:2164

All Groups had mesangial expansion and stable GFR at 5 years
Clinical Trials and Renal Outcomes Based on Proteinuria Reduction

Increased Time to Dialysis (30-35% proteinuria reduction)
- Captopril Trial - N Engl J Med, 1993
- AASK Trial - JAMA, 2001

No Change in Time to Dialysis (NO proteinuria reduction)
- DHPCCB arm - IDNT
- DHPCCB arm - AASK

Hart P & Bakris GL Managing Hypertension in the Diabetic Patient.
IN: Egan BM, Basile JN, and Lackland DT (eds.) Hot Topics in Hypertension
Meta-analysis of Trials on Proteinuria Reduction with RAS Blockade—Ratio of means (95% CI)* for change in proteinuria, by randomized therapy, over two follow-up intervals

<table>
<thead>
<tr>
<th>Randomized Therapy</th>
<th>1-4 Months</th>
<th>5-12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARBs vs placebo</td>
<td>0.57 (0.47–0.68)</td>
<td>0.66 (0.63–0.69)</td>
</tr>
<tr>
<td>ARBs vs ACE-I</td>
<td>0.99 (0.92–1.05)</td>
<td>1.08 (0.96–1.22)</td>
</tr>
<tr>
<td>ARBs vs CCBs</td>
<td>0.69 (0.62–0.77)</td>
<td>0.62 (0.55–0.70)</td>
</tr>
<tr>
<td>ARB+ACE-I vs ARBs</td>
<td>0.76 (0.68–0.85)</td>
<td>0.75 (0.61–0.92)</td>
</tr>
<tr>
<td>ARB+ACE-I vs ACE-I</td>
<td>0.78 (0.72–0.84)</td>
<td>0.82 (0.67–1.01)</td>
</tr>
</tbody>
</table>

Bold=significant P<0.01 at 5-12 Months

Design of Combination Angiotensin Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy (VA NEPHRON-D)

Linda F. Fried,* William Duckworth,† Jane Hongyuan Zhang,‡ Theresa O’Connor,§ Mary Brophy,‖ Nicholas Emanuele,* Grant D. Huang,§ Peter A. McCullough,∗∗ Paul M. Palevsky,* Stephen Seliger,** Stuart R. Warren,** and Peter Peduzzi,† for VA NEPHRON-D Investigators

∗Veterans Affairs (VA) Pittsburgh Healthcare System and Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; †Carl T. Hayden VA Medical Center, School of Life Sciences, Arizona State University, and Department of Medicine, University of Arizona, Phoenix, Arizona; ‡West Haven VA Cooperative Studies Program Coordinating Center, West Haven, Connecticut; ∗VA Boston Healthcare System and Department of Medicine, Boston University School of Medicine, Boston, Massachusetts; ‖Hines VA and Department of Medicine, Loyola University Medical Center, Hines Illinois; †Cooperative Studies Program Headquarters, VA Office Research and Development, Washington, District of Columbia; ∗∗Department of Medicine, William Beaumont Hospital, Royal Oak, Michigan; ‡‡VA Maryland Medical Center and Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland; ‡VA Cooperative Studies Program Research Pharmacy and University of New Mexico College of Pharmacy, Albuquerque, New Mexico

Both angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) can slow the progression of diabetic nephropathy. Even with ACEI or ARB treatment, the proportion of patients who progress to end-stage renal disease (ESRD) remains high. Interventions that achieve more complete blockade of the renin–angiotensin system, such as combination ACEI and ARB, might be beneficial. This approach may slow progression of nondiabetic kidney disease as well. In diabetic nephropathy, combination therapy decreases proteinuria, but its effect in slowing progression is unknown. In addition, the potential for hyperkalemia may limit the utility of combined therapy in this population. VA NEPHRON-D is a randomized, double-blind, multicenter clinical trial to assess the effect of combination losartan and lisinopril, compared with losartan alone, on the progression of kidney disease in 1850 patients with diabetes and overt proteinuria. The primary endpoints are time to (D) reduction in estimated GFR of >50% (if baseline < 60 ml/min/1.73 m²); (2) reduction in eGFR of 30 ml/min/1.73 m² (if baseline ≥ 60 ml/min/1.73 m²); (3) progression to ESRD (need for dialysis, renal transplant, or eGFR <15 ml/min/1.73 m²); or (4) death. The secondary endpoint is time to change in eGFR or ESRD. Tertiary endpoints are cardiovascular events, slope of change in eGFR, and change in albuminuria at 1 yr. Specific safety endpoints are serious hyperkalemia (potassium >6 mEq/L, requiring admission, emergency room visit, or dialysis), all-cause mortality, and other serious adverse events.

This paper discusses the design and key methodological issues that arose during the planning of the study.


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Aldosterone Blockade

- EPHESUS -K(Pitt B et.al. Circulation, 2008)
- Meta-analysis-antiproteinuric effects (Bomback A Am J Kidney Dis 2008)
## Odd Ratio of Hyperkalemia Development following Aldosterone Antagonism in Nephropathy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline eGFR (\leq45) ml/min/1.73m(^2) + serum potassium (&gt;4.5) mEq/L</td>
<td>8.71 (2.89-24.8)</td>
<td>(&lt;0.0001)</td>
</tr>
<tr>
<td>Baseline eGFR (\leq45) ml/min/1.73m(^2) + (&gt;30% ) reduction in eGFR</td>
<td>7.76 (2.13-29.8)</td>
<td>(&lt;0.0001)</td>
</tr>
<tr>
<td>Baseline eGFR (\leq45) ml/min/1.73m(^2)</td>
<td>2.97 (1.14-21.3)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Baseline eGFR (\leq45) ml/min/1.73m(^2) + (&gt;15) mmHg in systolic BP</td>
<td>3.98 (0.89-27.1)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Major Factor Limiting Antiproteinuric Effects of RAS Blockade

• SALT
Sodium Intake Limits Antiproteinuric Effects of RAS Blockade

• Sodium Intake Above 4 grams per day reduces antiproteinuric effects of RAS Blockade by up to 50%-
  (Heeg et.al Kidney International, 1989;36:272)

• Use of thiazide diuretics only partially restores antiproteinuric effect
  (Buter, H. et.al. Nephrol Dialysis & Transpl 1998:16;1682)

• Mechanism for increased sodium on proteinuria is thought to be related to increased oxidant stress (partially) and increases in blood pressure (partially)
Summary of Studies on Nephropathy Progression

All studies that showed significant differences in outcomes had proteinuria >500 mg/d at baseline

2 Phases of AASK

• **Trial with a 2 x 3 factorial design (completed Sept 2001)**
  – 1,094 African-Americans with non-diabetic, hypertensive CKD (GFR of 20-65 ml/min/1.73 m²)

  Initial therapy with:

<table>
<thead>
<tr>
<th>Ramipril</th>
<th>Amlodipine</th>
<th>Metoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>D</td>
<td>E</td>
<td>F</td>
</tr>
</tbody>
</table>

  Low BP Goal: MAP < 92
  Usual BP Goal: MAP 102-7

• **Cohort phase (completed June 2007)**
  – All participants received recommended BP therapy:
    • ACEI (or ARB)
    • BP goal < 130/80 mmHg
  – 1° outcome: composite 2X sCreatinine, ESRD, or death
Composite Clinical Events: Declining GFR Event, ESRD or Death by BP Goal

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

Follow-Up Time (Months)

Wright JT Jr. et al. JAMA 2002
Cumulative Incidence of the Composite Primary Outcome, According to Baseline Proteinuria Status.

What is the Goal BP and Initial Therapy in Kidney Disease or Diabetes to Reduce CV Risk?

<table>
<thead>
<tr>
<th>Group</th>
<th>Goal BP (mmHg)</th>
<th>Initial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian HTN Soc (2010)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>ADA (2010)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>ASH (2008)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>KDOQI (NKF) (2007)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>ESH (2007)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>JNC 7 (2003)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>Canadian HTN Soc. (2002)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>Am. Diabetes Assoc (2002)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor/ARB*</td>
</tr>
<tr>
<td>Natl. Kidney Foundation (2000)</td>
<td>&lt;130/80</td>
<td>ACE Inhibitor*</td>
</tr>
<tr>
<td>British HTN Soc. (1999)</td>
<td>&lt;140/80</td>
<td>ACE Inhibitor</td>
</tr>
<tr>
<td>WHO/ISH (1999)</td>
<td>&lt;130/85</td>
<td>ACE Inhibitor</td>
</tr>
<tr>
<td>JNC VI (1997)</td>
<td>&lt;130/85</td>
<td>ACE Inhibitor</td>
</tr>
</tbody>
</table>

* Indicates use with diuretic
Impact of ACE Inhibition on Blood Pressure and GFR: Acute vs. Chronic Effects

*P<0.05 compared to baseline

N=24

SBP

GFR

*P<0.05 compared to baseline
Complications Associated with CKD

- Hypertension: CKD and CV disease
- Dyslipidemia: CKD progression and CV disease
- Anemia: CKD progression and CV disease
- Cardiovascular disease and mortality
- Diabetes: CKD progression and CV disease
- Osteodystrophy
- Malnutrition
- Metabolic Acidosis
Summary

• Advanced CKD is growing by an alarming degree

• Ideal steps for prevention include a program of CV risk reduction, i.e. glycemic, lipid and BP control. Additionally, avoid dehydration, routine NSAID or Tylenol use.

• In those with established CKD—<3 grams sodium daily, BP <140/90, HbA 1c <7% and LDL <70
If Blood Pressure >130/80 mm Hg in Diabetes (eGFR ≥ 50 ml/min^)

(if systolic BP< 20 mmHg above goal)
Start ARB or ACE Inhibitor titrate upwards

(if systolic BP ≥20 mmHg above goal)
START with ACEI or ARB + thiazide diuretic* or CCB
Recheck within 2-3 weeks

If BP Still Not at Goal (130/80 mm Hg)
Add Long Acting Thiazide Diuretic* or CCB

If BP Still Not at Goal (130/80 mm Hg)
Add CCB or β blocker**
Recheck within 2-3 weeks

If BP Still Not at Goal (130/80 mm Hg)
Consider and Aldosterone Receptor Blocker
If CCB used, Add Other Subgroup of CCB
(ie, amlodipine-like agent if verapamil or diltiazem already being used and the converse)
OR could add alpha blocker is not using vasodilating β blocker with alpha effects
Recheck within 4 weeks

If BP Still Not at Goal (130/80 mm Hg)
Refer to a Clinical Hypertension Specialist#

Bakris GL and Sowers JR, J AM Soc Hypertens, 2010