Chronic Kidney Disease and Cardiovascular Risk: Interrelationships and Interventions

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Numbers of Patients on Dialysis-USA: 1992

Map showing the distribution of dialysis patients across the United States in 1992, with different shades indicating the number of patients in each state. The legend shows the number range for each shade, starting from 1,200+ (1,495) down to below 974 (814).
Numbers of Patients on Dialysis-USA: 2002

www.usrds.org
Geographic variations in adjusted prevalent rates of ESRD per million population, 2010, by HSA

Figure 1.11 (Volume 2)
Common Causes of Chronic Kidney Disease

- Diabetes Mellitus
- Hypertension
- Glomerulonephritis
Kidney Disease
2010 Data

- About 14% of the USA Population has chronic kidney disease as defined as GFR of <60 ml/min or elevated urine albumin level
- Most CKD patients die of heart disease before reaching ESRD
- About 593,000 patients on dialysis or with a kidney transplant.
- About 414,000 - Dialysis and 179,000- Transplant; 87,000 on transplant wait list
- Death Rates are 20% per year for dialysis population and the number of end stage patients rises about 1-3% each year.
- Medicare spent 30 Billion dollars in 2010 which is 6.1% of the medicare budget

www.usrds.org
Many Patients Start Dialysis without Seeing a Nephrologist

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>0-12 mo.</th>
<th>&gt;12 mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>43.0</td>
<td>31.7</td>
<td>25.4</td>
</tr>
</tbody>
</table>

Pre-ESRD nephrologist care (column %), 2010

Table 1.f (Volume 2)
Recognize and Diagnose Kidney Disease Early

Glomerular Filtration Rate

Albuminuria/Proteinuria
GFR with Age

Estimated GFR (ml/min/1.73 m²)

Age (years)

Estimated GFR (median, 5th, 95th percentiles)

- Insulin (Davies and Shock, 1950)
- NHANES III Estimated GFR

Joslin Diabetes Center
Cockcroft-Gault and MDRD Equations

Estimated GFR (ml/min/1.73m²)

\[
\text{Estimated GFR} = 186 \times (\text{sCr}) - 1.154 \times \text{(Age)} - 0.203 \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})
\]

\[
= \exp(5.228 - 1.154 \times \ln(\text{SCr}) - 0.203 \times \ln(\text{Age}) - (0.299 \text{ if female}) + (0.192 \text{ if African American})
\]

Cockcroft-Gault Formula – Creatinine Clearance

Estimated Clearance = (140 - age/serum Cr.) x wt (kg)/72 x (0.85 if female)
Estimated Creatinine Clearance

\[
\frac{(140 - \text{age})}{\text{Serum Cr}} \times \frac{\text{Weight (kg)}}{72} \times 0.85 \quad \text{(if female)}
\]
A 70-year-old Woman Who Weighs 55 Kg (121 Lbs.) with a Creatinine of 1.5

Many doctors might think her GFR is about 60–70 ml/min

\[
\frac{(140 - 70)}{1.5} \times \frac{55}{72} \times 0.85 \text{ (for a female)} = 30.3 \text{ ml/min}
\]
Importance of Knowing GFR

- Complications of Kidney Disease (e.g., anemia, hyperparathyroidism) are seen with increasing frequency at GFR <60ml/min
- Increased risk for Contrast Dye Nephropathy
- Drug Dose Adjustments
- Increasing Cardiovascular Disease Risk as GFR Declines
Albuminuria/Proteinuria Are Independent Risk Factors for Progression of Kidney Disease and Development and Progression of Cardiovascular Disease
Albuminuria

- Normal renal excretion is about 200 mg/day of total protein (up to 20 mg is albumin)
- Levels of albumin > 20 mg/24 hours is abnormal
- Microalbuminuria – 30–300 mg/g
- Macroalbuminuria – >300 mg/g
Spot Urine Albumin or Protein/Creatinine Ratio Closely Correlates with 24 Hour Urine

Schwab Arch Int Med 1987
Association of Chronic Kidney Disease with Cardiovascular Disease
Heart Disease is Major Cause of Death in Chronic Kidney Disease

CAD=coronary artery disease
Totals may not add up to 100% due to rounding.

Chronic Kidney Disease Is Prevalent in Cardiovascular Disease

Patient Types

- CAD\(^1\)  CrCl \(\leq 60\) 23%  n = 431
- ACS\(^2\)  GFR <60 33%  n = 14,527
- CHF\(^3\)  GFR \(\leq 60\) 46%  n = 6,800

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Microalbuminuria and Ischemic Heart Disease Risk

General Population

Relative Risk of IHD

10-y follow-up, n = 2,085

High-normal Urine Albumin Levels are Associated with Higher CV Death Risk

Figure 1. Kaplan-Meier curves showing survival free of CVD over follow-up period in individuals above vs those below sex-specific median of UACR.

Increasing Albuminuria and Decreasing GFR Correlate with Increased Cardiovascular and Renal Events in Type 2 Diabetes

Mortality is directly Associated with GFR and Albumin/Creatinine Ratio

Figure 1. | All-cause mortality rates associated with level of eGFR and age group. eGFR, estimated GFR; PY, person-years; CI, confidence interval. See Supplemental Table 4 for all-cause mortality rates with 95% CIs.

Figure 2. | All-cause mortality rates associated with level of albuminuria and age group. See Supplemental Table 5 for all-cause mortality rates with 95% CIs.
Excess Mortality in Type 2 Diabetes is Due to Kidney Disease

**Chart:**

- No Kidney Disease: 4.1%
- Albuminuria: 17.8%
- Impaired GFR: 23.9%
- Albuminuria & Impaired GFR: 47.0%
Treatment of Kidney Disease
TREATMENT

- Blood Pressure <130/80
- Lower Urine Albumin
- Stop Smoking
- If Diabetic - Tight Glucose Control - A1c < 7.0%
The blood pressure measurement that has been shown to best predict development of complications of hypertension is:

1. Home blood pressure
2. Office blood pressure
3. 24-hour blood pressure monitoring
4. Arterial line blood pressure measurement
Office Blood Pressure

- Considered to be the most accurate
- Usually only taken 1-3 times/year
- White Coat Hypertension may confound data
- Office BP machines are usually accurate but need to be calibrated on a routine basis.
Home Blood Pressure

- Accuracy may be a problem

- Home BP machines may be inaccurate and need to be evaluated at a doctor’s office

- If accurate, likely the best way to diagnose and monitor BP
Home Blood Pressure Monitoring Predicts Events Better than Office Measurements

### Table 1. Prospective Studies Relating Home BP and Office BP to Cardiovascular Events and Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Population Studied</th>
<th>No. of Subjects</th>
<th>Days</th>
<th>AM</th>
<th>PM</th>
<th>Total</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohasama&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Population</td>
<td>1789</td>
<td>28</td>
<td>1</td>
<td>0</td>
<td>26</td>
<td>Strokes and mortality predicted better by HBPM</td>
</tr>
<tr>
<td>SHEAF&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Treated hypertensive patients</td>
<td>4939</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>24</td>
<td>CV morbidity and mortality predicted better by HBPM</td>
</tr>
<tr>
<td>PAMELA&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Population</td>
<td>2051</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>CV and total mortality predicted better by HBPM</td>
</tr>
<tr>
<td>Belgian&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Referred</td>
<td>391</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>Combined CV events predicted better by HBPM</td>
</tr>
<tr>
<td>Didima&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Population</td>
<td>662</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>12</td>
<td>CV events predicted by both HBPM and office BP</td>
</tr>
</tbody>
</table>

CV indicates cardiovascular.

*Hypertension. 2008;52:1-9*

What is the Blood Pressure Goal?
ACCORD Trial: No benefit of Tight BP (120 vs 140 systolic) Control on Cardiovascular Outcomes

New England Journal of Medicine 362:1575-1585; 2010
Low Blood Pressures Appear to Increase Cardiovascular Mortality

Figure 3. Adjusted Risk of All-Cause Mortality

Cooper-DeHoff RM et al JAMA 304: 61-68 (2010)
Lower Systolic Blood Pressure Slows Rate of Decline of GFR

\[ r = 0.39; P < 0.05 \]

- Viberti GC et al. *JAMA*, 1993
- Bakris GL *Hypertension*, 1997

NKF-KDOQI Guidelines
Blood Pressure Goal for Patients with Kidney Disease

- <130/80
- <125/75 if >1 g of urine protein
- Avoid blood pressure of <115 systolic especially if patient has diagnosed cardiovascular disease
Lowering Urine Albumin Level is a Major Goal in Slowing Progression of Kidney Disease and Cardiovascular Disease.
ACE inhibitors and ARBs are ideal medications for protecting kidney function because they lower blood pressure, lower urine albumin level, and increase GFR.

1. True
2. False
The greater the initial decline in GFR after starting Losartan, the slower the rate of decline in long term GFR.

ACEs and ARBs Appear To Be Synergistic

<table>
<thead>
<tr>
<th>Subgroup analyses</th>
<th>Combination better</th>
<th>ACEI monotherapy better</th>
<th>WMD (95% CI), P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(a) Dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Dose (n = 44) [17,19]</td>
<td></td>
<td></td>
<td>−105 (−402 to 71), P = 0.17</td>
</tr>
<tr>
<td>Low Dose (n = 125) [16,18,20−25]</td>
<td></td>
<td>−193 (−365 to −22), P = 0.63</td>
<td></td>
</tr>
<tr>
<td><strong>(b) Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 (n = 61) [16−18]</td>
<td></td>
<td></td>
<td>−134 (−274 to 6), P = 0.06</td>
</tr>
<tr>
<td>Type 2 (n = 101) [19−25]</td>
<td></td>
<td>−308 (−625 to 9), P = 0.06</td>
<td></td>
</tr>
<tr>
<td><strong>(c) Baseline proteinuria (tertiles)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4530 (3810 to 6050) mg (n = 40) [21,23,24]</td>
<td></td>
<td>−630 (−1019 to −241), P = 0.002</td>
<td></td>
</tr>
<tr>
<td>2850 (988 to 4712) mg (n = 28) [18,22]</td>
<td></td>
<td>−629 (−1183 to −74), P = 0.03</td>
<td></td>
</tr>
<tr>
<td>867 (−107 to 1842) mg (n = 47) [16,20,25]</td>
<td></td>
<td>−40 (−139 to 60), P = 0.43</td>
<td></td>
</tr>
<tr>
<td><strong>(d) Change in SBP (tertiles)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−7.7 (−8.3 to −7.0) mmHg (n = 61) [16−18]</td>
<td></td>
<td>−134 (−274 to 6), P = 0.06</td>
<td></td>
</tr>
<tr>
<td>−3.0 (−7.2 to 1.3) mmHg (n = 37) [19,20]</td>
<td></td>
<td>−237 (−591 to 117), P = 0.19</td>
<td></td>
</tr>
<tr>
<td>2.0 (−0.8 to 4.8) mmHg (n = 19) [23,25]</td>
<td></td>
<td>5 (−16 to 27), P = 0.63</td>
<td></td>
</tr>
</tbody>
</table>

Diabetic Medicine 24:486, 2007
ONTARGET Trial Suggested that ACEs and ARBs are not Synergistic

Figure 1. Kaplan–Meier Curves for the Primary Outcome in the Three Study Groups.
The composite primary outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.
### Little Kidney Disease in Study Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (N = 4733)</th>
<th>Intensive Therapy (N = 2362)</th>
<th>Standard Therapy (N = 2371)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma triglycerides — mg/dl</td>
<td></td>
<td></td>
<td></td>
<td>0.71</td>
</tr>
<tr>
<td>Median</td>
<td>147</td>
<td>147</td>
<td>147</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>98–226</td>
<td>98–227</td>
<td>98–224</td>
<td></td>
</tr>
<tr>
<td>Potassium — mg/dl</td>
<td>4.5±0.7</td>
<td>4.5±0.5</td>
<td>4.5±0.8</td>
<td>0.73</td>
</tr>
<tr>
<td>Serum creatinine — mg/dl</td>
<td>0.9±0.2</td>
<td>0.9±0.2</td>
<td>0.9±0.2</td>
<td>0.98</td>
</tr>
<tr>
<td>Estimated GFR — ml/min/1.73 m²</td>
<td>91.6±28.8</td>
<td>91.6±30.3</td>
<td>91.7±27.1</td>
<td>0.64</td>
</tr>
<tr>
<td>Ratio of urinary albumin (mg) to creatinine (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>14.3</td>
<td>14.6</td>
<td>14.0</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>6.9–44.8</td>
<td>7.0–43.7</td>
<td>6.9–45.8</td>
<td></td>
</tr>
</tbody>
</table>
Use Of ACE Inhibitors/ARBS

- All patients with increased urine albumin (or total protein) should be on ACE-inhibitors or Angiotensin Receptor Blocker even if the patient has excellent blood pressure.

- Avoid combination of ACE-I and ARB in diabetic patients with few complications.

- Combination possibly useful in patients with decreased GFR and increased urine protein.
Treatment of Kidney Disease

- Blood pressure control to at least <130/80
- Blood sugar control if diabetic
- Lower albuminuria/proteinuria

Dietary interventions as indicated:
- Low Salt intake and avoid high protein intake
  - Little to no role for low protein diet
- Stop smoking
Consult Nephrology

For:

- Difficult-to-control hypertension
- Rapidly worsening renal function
- Unexplained urinalysis findings (e.g. proteinuria, hematuria)
- Questions about diagnosis
- Questions about specific treatments
- Questions about diagnosis or management of electrolytes, acid-base, calcium/phosphate, and management of anemia in chronic renal failure
Early Diagnosis and Aggressive Treatment are Essential to Slow the Epidemic of Kidney and Cardiovascular Disease.