Diabetic Kidney Disease

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Joslin Diabetes Center
I have served as a consultant for Boehringer-Ingelheim and have received grant funding from Boehringer-Ingelheim
Numbers of Patients on Dialysis - USA: 1992

1,200+ (1,495)
1,121 to <1,200
1,050 to <1,121
974 to <1,050
below 974 (814)
Numbers of Patients on Dialysis - USA: 2002

www.usrds.org
Geographic variations in adjusted prevalent rates of ESRD per million population, 2011, by HSA

Figure 1.11 (Volume 2)

Common Causes of Chronic Kidney Disease

- Diabetes Mellitus
- Hypertension
- Glomerulonephritis
Incident counts & adjusted rates of ESRD, by primary diagnosis

Figure 1.7 (Volume 2)

Incident ESRD patients.
Adj: age/gender/race; ref: 2010 ESRD patients.
Kidney Disease: 2012 Data

- About 14% of the U.S. 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 408,711 patients on dialysis and 186,303 with a kidney transplant
- Death rates are 20% per year for dialysis population and the number of end-stage patients rises about 1–3% each year
- Medicare spent $28.6 billion in 2012, which is 5.6% of the Medicare budget
DIAGNOSIS:
Diabetic Kidney Disease
Case 1

22 yo white male referred for proteinuria. Patient has had type 1 diabetes for 3 years. History of biopsy proven minimal change disease at age 5. Resolved. Now with albumin/creatinine ratio of 1300.
When to Consider Kidney Diseases Other than Diabetes

- **Type 1 Diabetes Duration of <5 years**
- **Active Urine Sediment**
  - Many RBCs/hpf
  - Many Casts
  - Many WBCs/hpf
- **Rapidly Declining GFR**
- **Rapid Increase or Very High Urine Protein Level**
GFR Decline May Occur with Normal Urine Albumin Levels (DEMAND Study)

<table>
<thead>
<tr>
<th>CKD</th>
<th>n</th>
<th>Normoalbuminuria</th>
<th>Microalbuminuria</th>
<th>Macroalbuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>24,151 (100%)</td>
<td>51%</td>
<td>39%</td>
<td>10%</td>
</tr>
<tr>
<td>Stage 1</td>
<td>3,132 (13%)</td>
<td>56%</td>
<td>36%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Stage 2</td>
<td>5,855 (24%)</td>
<td>56%</td>
<td>36%</td>
<td>8.5%</td>
</tr>
<tr>
<td>Stage 3</td>
<td>2,428 (10%)</td>
<td>41%</td>
<td>47%</td>
<td>12%</td>
</tr>
<tr>
<td>Stage 4</td>
<td>141 (0.6%)</td>
<td>26%</td>
<td>48%</td>
<td>26%</td>
</tr>
<tr>
<td>Stage 5</td>
<td>17 (0.07%)</td>
<td>29%</td>
<td>47%</td>
<td>24%</td>
</tr>
<tr>
<td>Unknown</td>
<td>12,578 (58%)</td>
<td>51%</td>
<td>39%</td>
<td>10%</td>
</tr>
</tbody>
</table>

CKD stage was classified according to MDRD and NKF criteria. Total includes even those patients in whom measures of kidney function were not obtained (categorized as Unknown). In a total of 11,573 patients, data to calculate kidney function were available.
Case 1

22 yo white male referred for proteinuria. Patient has had type 1 diabetes for 3 years. History of biopsy proven minimal change disease at age 5. Resolved. Now with albumin/creatinine ratio of 1300.

Patient Diagnosed with Alport’s Syndrome
Diabetic Kidney Disease: Early Recognition and Diagnosis Essential

- Calculate estimated GFR (eGFR) using the MDRD equation
- Urine albumin level
CKD-EPI Formula is Superior to MDRD Formula in Predicting Outcomes

ALWAYS CALCULATE eGFR
Albuminuria/Proteinuria

- Independent Risk Factor for Progression of Kidney Disease and Cardiovascular Disease
Increasing Albuminuria and Decreasing GFR Correlate with Increased Cardiovascular and Renal Events in Type 2 Diabetes

Excess Mortality in Type 2 Diabetes is Due to Kidney Disease

![Chart showing standardized ten-year cumulative incidence of mortality for different kidney conditions.

- No Kidney Disease: 4.1%
- Albuminuria: 17.8%
- Impaired GFR: 23.9%
- Albuminuria & Impaired GFR: 47.0%]
Albuminuria might be a marker for generalized inflammation and endothelial dysfunction.
Prevention of Diabetic Kidney Disease

- **Blood Pressure Control**
  - $<140/80$

- **Blood Glucose Control**
  - A1c $<7$

- **Stop Smoking**
Case 2

76 yo African American male referred for hyperkalemia. Surgical procedure canceled due to high potassium. Patient has had type 2 diabetes for 10 years. History of hypertension – blood pressure 150/90. Currently on hydrochlorothiazide, lisinopril, and amiloride. Potassium 5.5, urine albumin/creatinine ratio 10; creatinine 0.8.
25 Year Follow Up of DCCT/EDIC – 50% Reduction in Microalbuminuria
25 Year Follow Up of DCCT/EDIC – 50% Reduction in eGFR <60 ml/min
Meta-Analysis of Blood Pressure Studies Show 10% Reduction in Microalbuminuria

**Albuminuria progression**

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Change in BP</th>
<th>Odds Ratio (Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD 2010</td>
<td>139</td>
<td>-14.2/-6.7</td>
<td>0.90 (0.83, 0.97)</td>
</tr>
<tr>
<td>ABCD (H) 2001</td>
<td>155</td>
<td>-6/-8</td>
<td>1.07 (0.73, 1.59)</td>
</tr>
<tr>
<td>UKPDS-HDS 1998</td>
<td>159</td>
<td>-10/-5</td>
<td>0.87 (0.66, 1.15)</td>
</tr>
</tbody>
</table>

Overall: -10.1/-6.4

Events/population: 926/2661 versus 998/2563

Favors more intensive BP lowering regimen

BP: blood pressure, SBP: systolic blood pressure (mmHg)
Smoking Increases Chronic Kidney Disease Risk

Table 3 Odds ratio for chronic renal failure by type among regular smokers

<table>
<thead>
<tr>
<th>Type</th>
<th>N (%)</th>
<th>Ever regular use of cigarettes</th>
<th>OR(^\dagger) (CI 95%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No n (%**)</td>
<td>Yes n (%+)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>371(65.2)</td>
<td>120(51.7)</td>
<td>251(74.5)</td>
<td>1 Reference</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>90 (15.8)</td>
<td>59(25.4)</td>
<td>31(9.1)</td>
<td>1.09(0.67-1.78)</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>56 (9.8)</td>
<td>27(11.6)</td>
<td>29(8.6)</td>
<td>2.24(1.27-3.96)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26 (4.6)</td>
<td>11(4.8)</td>
<td>15(4.5)</td>
<td>2.85(1.27-6.39)</td>
</tr>
<tr>
<td>Unknown and other causes</td>
<td>26 (4.6)</td>
<td>15(6.5)</td>
<td>11(3.3)</td>
<td>1.53(0.68-3.44)</td>
</tr>
</tbody>
</table>
Prevention of Diabetic Kidney Disease

- Blood Pressure Control
  - <140/80

- Blood Glucose Control
  - A1c <7%

- Stop Smoking
ACE inhibitors or ARBs should be given to diabetic patients to prevent the development of diabetic kidney disease.

1. True
2. False
No Primary Prevention of Diabetic Kidney Disease by Enalapril or Losartan

Figure 2. Kaplan–Meier Estimates of Time to Microalbuminuria.

No primary prevention of diabetic kidney disease by enalapril or losartan

Table 2. Effects of Enalapril and Losartan on Change in the Mesangial Fractional Volume, Albumin Excretion Rate, and Glomerular Filtration Rate, According to Study Group.*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Enalapril</th>
<th>Losartan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesangial fractional volume</td>
<td>0.201±0.044</td>
<td>0.189±0.041</td>
<td>0.187±0.045</td>
</tr>
<tr>
<td>Mean at baseline</td>
<td>0.005±0.050</td>
<td>0.026±0.054</td>
<td>0.016±0.048</td>
</tr>
<tr>
<td>Mean change at 5 yr</td>
<td>0.011</td>
<td>0.010</td>
<td>0 (reference)</td>
</tr>
<tr>
<td>Change vs. placebo</td>
<td>0.16</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Adjusted change vs. placebo</td>
<td>-0.006</td>
<td>0.008</td>
<td>0 (reference)</td>
</tr>
<tr>
<td></td>
<td>0.38</td>
<td>0.26</td>
<td></td>
</tr>
</tbody>
</table>
There was Primary Prevention with Trandolapril in Type 2 Diabetes

There was No Primary Prevention with Candesartan in Type 2 Diabetes

**Figure 3.** Cumulative proportion of patients with microalbuminuria.

<table>
<thead>
<tr>
<th>Time From Randomization, y</th>
<th>Candesartan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P = 0.60

At risk, n

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Candesartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2618</td>
<td>2613</td>
</tr>
<tr>
<td></td>
<td>2410</td>
<td>2426</td>
</tr>
<tr>
<td></td>
<td>2247</td>
<td>2278</td>
</tr>
<tr>
<td></td>
<td>2092</td>
<td>2150</td>
</tr>
<tr>
<td></td>
<td>1754</td>
<td>1793</td>
</tr>
<tr>
<td></td>
<td>526</td>
<td>540</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>13</td>
</tr>
</tbody>
</table>

## Comparison of Prevention Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>DIRECT-Prevent 1</th>
<th>EUCLID (8)</th>
<th>DIRECT-Protect 2</th>
<th>HOPE Study (16)*</th>
<th>BENEDICT (6)</th>
<th>ADVANCE (17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients, n</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>1662</td>
<td>213</td>
<td>951</td>
<td>1170</td>
<td>601</td>
<td>3931</td>
</tr>
<tr>
<td>Placebo</td>
<td>1664</td>
<td>227</td>
<td>954</td>
<td>1102</td>
<td>603</td>
<td>3946</td>
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<tr>
<td><strong>Type of diabetes</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean age, y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>331</td>
<td>57</td>
<td>65</td>
<td>62</td>
<td>66</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>117/73</td>
<td>122/80</td>
<td>133/78</td>
<td>142/80</td>
<td>151/88</td>
<td>145/81</td>
</tr>
</tbody>
</table>
There is no unique Indication for ACE Inhibitors or ARBs for Primary Prevention of Kidney Disease in Diabetic Patients.

ACE Inhibitors and ARBs are definitely Indicated for Patients with Albuminuria.
Case 2

76 yo African American male referred for hyperkalemia. Surgical procedure canceled due to high potassium. Patient has had type 2 diabetes for 10 years. History of hypertension – blood pressure 130/70. Currently on hydrochlorothiazide, lisinopril, and amiloride. Potassium 5.5, urine albumin/creatinine ratio 10; creatinine 0.8.

I stopped the lisinopril
Treatment of Diabetic Kidney Disease

- Tight Glucose Control - A1c < 7.0%
- Blood Pressure <130/80 or Lower
- Lower Urine Albumin
  - RAAS Inhibitors
  - Blood Pressure Control
  - Blood Sugar Control
- Stop Smoking
CASE 3

49 yo white female with type 1 diabetes and progressive decline in kidney function. Current GFR 25 ml/ min. On lisinopril 20 mg a day, metoprolol 50 mg a day, and furosemide 40 mg a day.

Should the lisinopril be stopped?
GFR Over Time
Early, Aggressive Treatment is Key to Optimal Management
TREATMENT

- Blood Pressure <130/80
- Tight Glucose Control - A1c < 7.0%
- Lower Urine Albumin
- Stop Smoking
Blood Pressure Goal

- Blood Pressure Goal for Kidney Disease <130/80

- American Diabetes Association Now Recommends in General <140/80

- American Heart Association – 120-139 systolic is prehypertension and >140/90 is hypertension
ACCORD Blood Pressures

![Graph showing systolic pressure over years since randomization for Standard and Intensive regimens.](graph.png)

<table>
<thead>
<tr>
<th>Years since Randomization</th>
<th>Standard</th>
<th>Intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>140</td>
<td>120</td>
</tr>
<tr>
<td>1</td>
<td>130</td>
<td>110</td>
</tr>
<tr>
<td>2</td>
<td>120</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>110</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean No. of Medications Prescribed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive</td>
</tr>
<tr>
<td>Standard</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive</td>
</tr>
<tr>
<td>Standard</td>
</tr>
</tbody>
</table>

ACCORD Trial: No Benefit of Tight BP Control on Cardiovascular Outcomes

Lower Systolic Blood Pressure Slows Rate of Decline of GFR

- Viberti GC et al. *JAMA*, 1993
- Bakris GL *Hypertension*, 1997
- Bakris, GL et al. *Arch Intern Med*, 2003

NKF-KDOQI Guidelines
Low Blood Pressures Appear to Increase Cardiovascular Mortality

Cooper-DeHoff RM et al JAMA 304: 61-68 (2010)
Blood Pressure Goal

- Blood Pressure Goal for Kidney Disease
  <130/80

- If no Kidney Disease then <140/80 is reasonable
What is the Initial Drug Choice for Hypertension Control in Diabetic Patients?

- It doesn’t matter unless there is increased urine protein as it often takes multiple drugs to achieve BP goals.

- Choose a medication on the following:
  - Cost
  - Age
  - Co-morbidities
  - Side Effects

- If increased urine protein then consider starting with an ACE Inhibitor or ARB.
Lowering Urine Albumin Level is a Major Goal in Slowing Progression of Kidney 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
Glomerulus

coe.fgcu.edu/.../greenep/kidney/Glomerulus.html
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

Subgroup analyses

(a) Dose
High Dose (n = 44) [17.19]  WMD (95% CI), P-value
Low Dose (n = 125) [16,18,20–25]  −165 (−402 to 71), P = 0.17

(b) Diabetes
Type 1 (n = 61) [16–18]  −134 (−274 to 6), P = 0.06
Type 2 (n = 101) [19–25]  −348 (−625 to 9), P = 0.06

(c) Baseline proteinuria (tertiles)*
4930 (3810 to 6050) mg (n = 40) [21.23.24]  −629 (−1183 to −741), P = 0.03
2850 (988 to 4712) mg (n = 28) [18.22]  −40 (−139 to 69), P = 0.43
867 (−107 to 1842) mg (n = 47) [16,20,25]  −630 (−1019 to −241), P = 0.002

(d) Change in SBP (tertiles)*
−7.7 (−8.3 to −7.0) mmHg (n = 61) [16–18]  −134 (−274 to 6), P = 0.06
−3.0 (−7.2 to 1.2) mmHg (n = 37) [19,20]  −237 (−591 to 117), P = 0.19
2.0 (−0.8 to 4.8) mmHg (n = 19) [23,25]  5 (−16 to 27), P = 0.63

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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.
VA Nephron D and VALID

- **VA Nephron D** – Type 2 Diabetes, GFR 30-90 ml/min, and >300 mg/g of albuminuria

- Stopped due to hyperkalemia and acute kidney injury

- **VALID** – Type 2 Diabetes, Serum Creatinine 1.8 mg/dl to 3.5 mg/dl, >500 mg of urine protein

- To be completed by December, 2014
Use Of ACE Inhibitors/ARBS

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

- In general, avoid combination of ACE-I and ARB.

- Consider using combination in patients with kidney disease and heart failure and possibly in patients with high levels of proteinuria (>1 gram).
Other Medications that Lower Albuminuria/Proteinuria
Renin-Angiotensin-Aldosterone System

Beneficial for both Cardiac and Kidney Disease.

Appears to be safe in combination with ACE-I or ARB.

Spironolactone

Postgraduate Med, 2009
Persistently High Aldosterone has Many Deleterious Effects
(Independent of Effects on Sodium and Potassium)
Other Medications/Treatments that Lower Albuminuria/Proteinuria
Fig. 1. The change in proteinuria and systolic blood pressure. The percentage change in proteinuria, after adjustment for sample size and study length, for dihydropyridine calcium antagonists (DCAs) and nondihydropyridine calcium antagonists (NDCAs) was 2% and −30%, respectively ($P < 0.01$). The percentage change in systolic blood pressure, after adjustment for sample size and study length, for DCAs and NDCAs was −13% and −18.5%, respectively ($P = 0.28$).
CASE 3

49 yo white female with type 1 diabetes and progressive decline in kidney function. Current GFR 25 ml/min. On lisinopril 20 mg a day, metoprolol 50 mg a day, and furosemide 40 mg a day.

Should the lisinopril be stopped?

No
GFR Over Time

Graph showing GFR Value and ALBCREAT RATIO Value over time from 2002 to 2014.
Albumin/ Creatinine Ratio Over Time
Is there a role for Low Protein diets?

- Low Protein Diet (<0.8 g/kg/day)

- In animal studies, a sustained low protein diet lowers glomerular pressures and can slow progression

- Low protein diets have not been shown to be effective in humans. Possibly because it is very hard to stay on a low protein diet

- High protein intake is associated with worse renal disease
Prevention of Diabetic Kidney Disease

- Blood pressure control to at least <140/80
- Hemoglobin A1c of <7%
- Stop Smoking
- Monitor GFR and Urine albumin/creatinine ratio at least once per year (Repeat if Abnormal)
Treatment of Diabetic Kidney Disease

- Blood pressure control aiming for 130/80
  - Lower albuminuria/proteinuria
- Blood glucose control A1c <7%
- Dietary interventions as indicated:
  - Low Salt intake and avoid high protein intake
  - Little to no role for low protein diet
- Stop smoking
Many Patients Start Dialysis Without Seeing a Nephrologist

- None: 42.1%
- 0–12 mo.: 31.6%
- >12 mo.: 26.3%

www.USRDS.org