Diabetic Kidney Disease:
An Update

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www.glomerularcenter.org
Apologies for the missing syllabus

- www.columbianephrology.org
  - Teaching->lectures
- jr55@columbia.edu
Objectives

- Prevalence and outcome of diabetic renal disease
- Therapeutic Interventions
Evolution
Adjusted rates of diabetes in the U.S. population, by age

Figure 2.14

Prevalence of Diabetes Mellitus in the US

- 20.8 million children and adults -- 7.0% of the population -- have diabetes

**Estimated age-adjusted total prevalence of diabetes in people aged 20 years or older, by race/ethnicity—United States, 2005**

- American Indians/Alaska Natives
- Non-Hispanic blacks
- Hispanic/Latino Americans
- Non-Hispanic whites

**Source:** For American Indians/Alaska Natives, the estimate of total prevalence was calculated using the estimate of diagnosed diabetes from the 2003 outpatient database of the Indian Health Service and the estimate of undiagnosed diabetes from the 1999-2002 National Health and Nutrition Examination Survey. For the other groups, 1999-2002 NHANES estimates of total prevalence (both diagnosed and undiagnosed) were projected to year 2006.

*Graph and information obtained from CDC (Center for Disease Control and Prevention) website at: [http://www.cdc.gov/diabetes/pubs/estimated05.htm](http://www.cdc.gov/diabetes/pubs/estimated05.htm)* on December 1, 2006.
Incident counts of ESRD patients with diabetes as primary diagnosis

Figure 2.15

Incident ESRD patients.
Stages of (Type 1) Diabetic Renal Disease

- Stage 1
  Hyperfiltration

- Stage 2
  Clinically silent

- Stage 3 (AER: 20-200ug/min)
  Incipient Nephropathy

- Stage 4
  Overt Nephropathy

- Stage 5
  ESRD
Pathology of Diabetic Kidney Disease
Dr. Charles Jennette
A 65-year-old female with HTN and T2DM (+retinopathy) presents with uncontrolled HTN. 3+ edema. Proteinuria of 10g/day (500mg 1 year ago) Creatinine 1.5 10 RBC/HPF in the urine Negative serologies. Would you biopsy her?

- YES
- NO
- ASK Dr. Jennette
Renal Biopsy in Type 2 Diabetics (n=168)
The Columbia Experience

<table>
<thead>
<tr>
<th></th>
<th>Diabetic Nephropathy alone</th>
<th>DN+Non-diabetic renal Disease</th>
<th>Non-Diabetic Renal Disease alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>86 (51)</td>
<td>39 (23)</td>
<td>43 (26)</td>
</tr>
<tr>
<td>Duration DM (yrs)</td>
<td>10.5</td>
<td>9.4</td>
<td>5.2*</td>
</tr>
<tr>
<td>% retinopathy</td>
<td>39</td>
<td>38</td>
<td>17*</td>
</tr>
<tr>
<td>% active sediment</td>
<td>35</td>
<td>69*</td>
<td>38</td>
</tr>
<tr>
<td>% rapid progression</td>
<td>21</td>
<td>38*</td>
<td>19</td>
</tr>
<tr>
<td>% nephrotic prot.</td>
<td>83</td>
<td>62</td>
<td>69</td>
</tr>
</tbody>
</table>

* P < 0.05
DN+Non-diabetic renal disease (group 2; n=39)

- Tubulointerstitial disease (n=20)
  - AIN (10)
  - ATN (6)
  - pyelonephritis (2)

- Glomerular disease (n=13)
  - IgA (3), HSP (3)
  - Membranous GN (2)

- Vascular disease (n=6)
  - Atheroembolic dx (5)
Non Diabetic Renal Disease
(group 3; n=43)

- Glomerular disease (n=28)
  - FSGS (14)
  - MPGN (4)
  - Membranous GN (4)
  - Fibrillary GN (3)
  - Lupus Nephritis (2)

- Vascular disease (n=9)
  - HTN (5)
  - Atheroembolic dx (3), TMA/LAC

- Tubulointerstitial disease (n=8)
  - ATN (2)
  - AIN, lithium, MCN, pyelo
## Definitions of Microalbuminuria and Macroalbuminuria

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Micro-albuminuria</th>
<th>Macro-albuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urine Dip</strong></td>
<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
</tr>
<tr>
<td><strong>Urine AER (μg/min)</strong></td>
<td>&lt; 20</td>
<td>20 - 200</td>
<td>&gt;200</td>
</tr>
<tr>
<td><strong>Urine AER (mg/24h)</strong></td>
<td>&lt; 30</td>
<td>30 - 300</td>
<td>&gt;300</td>
</tr>
<tr>
<td><strong>Urine albumin/Cr# ratio (mg/gm)</strong></td>
<td>&lt; 30</td>
<td>30 - 300</td>
<td>&gt;300</td>
</tr>
</tbody>
</table>
The changing incidence of proteinuria in type 1 diabetes (Steno)

1st positive urine sample in 2/3 collections.

Diabetes Care 26:1258-1264, 2003
A type 1 diabetic patient has developed microalbuminuria? The risk of developing overt nephropathy is…

- 30%
- 50%
- 100%
Natural History

Type 1 and white type 2 diabetic patients
- Microalbuminuria develops at a rate of 2%–3% per annum.
- The cumulative incidence of microalbuminuria is 50% over a lifetime of diabetes.
- One third of microalbuminuric patients progress to proteinuria.
- Almost all proteinuric patients develop end stage renal disease or die prematurely of cardiovascular disease.

Non-white type 2 diabetic patients
- Microalbuminuria develops at a rate of 4% per annum.
- The cumulative incidence of microalbuminuria is 50% at 20 years’ duration of diabetes.
- Progression from microalbuminuria to proteinuria and end stage renal disease may occur faster than in type 1 diabetes.

Marshal SM. Postgraduate Medical Journal 2004;80:624-633
Progression of Diabetic Nephropathy

Microalbuminuria  Proteinuria  ESRD

Early stage  Late stage  End stage
Proteinuria is the Predominant Risk Marker for Outcome (RENAAL Study)

## Screening for Diabetic Nephropathy

<table>
<thead>
<tr>
<th>Test</th>
<th>When</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Pressure(^1)</td>
<td>Each office visit</td>
<td>&lt;130/80 mm/Hg</td>
</tr>
<tr>
<td>Urinary Albumin(^1)</td>
<td>Type 2: Annually beginning at diagnosis</td>
<td>&lt;30 mg/day</td>
</tr>
<tr>
<td></td>
<td>Type 1: Annually, 5-years post-diagnosis</td>
<td>&lt;20 µg/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;30 µg/mgcreatinine</td>
</tr>
</tbody>
</table>

Current Strategies to Limit Renal Injury in Diabetes

- Blood pressure reduction
- Blood sugar control
- Inhibition of the renin-angiotensin-aldosterone axis
- Metabolic manipulation
- Non-specific reduction of proteinuria
Early Aggressive Antihypertensive Treatment Reduces Rate of Decline in Kidney Function in Diabetic Nephropathy (n=10)

Lower Mean BP Results in Slower Rates of Decline in GFR

MAP (mmHg)

GFR (mL/min/year)

r = 0.69; P < 0.05

# Goal BP Recommendations for Patients with Diabetes or Renal Disease

<table>
<thead>
<tr>
<th>Organization</th>
<th>Year</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Diabetes Association</td>
<td>2001</td>
<td>&lt;130</td>
<td>&lt;80</td>
</tr>
<tr>
<td>National Kidney Foundation</td>
<td>2000</td>
<td>&lt;130</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Canadian Hypertension Society</td>
<td>1999</td>
<td>&lt;130</td>
<td>&lt;80</td>
</tr>
<tr>
<td>British Hypertension Society</td>
<td>1999</td>
<td>&lt;140</td>
<td>&lt;80</td>
</tr>
<tr>
<td>WHO &amp; International Society of Hypertension</td>
<td>1999</td>
<td>&lt;130</td>
<td>&lt;85</td>
</tr>
<tr>
<td>Joint National Committee (JNC VI)</td>
<td>1997</td>
<td>&lt;130</td>
<td>&lt;85</td>
</tr>
</tbody>
</table>
Average Number of Antihypertensive Agents Needed per Patient to Achieve Target BP Goals

**Trial/ SBP Achieved**

- **INVEST** (136 mm Hg)
- **CONVINCE** (137 mm Hg)
- **ALLHAT** (138 mm Hg)
- **IDNT** (138 mm Hg)
- **RENAAL** (141 mm Hg)
- **UKPDS** (144 mm Hg)
- **ABCD** (132 mm Hg)
- **MDRD** (132 mm Hg)
- **HOT** (138 mm Hg)
- **AASK** (128 mm Hg)

**Number of BP Meds**

Differential effects of calcium antagonist subclasses on markers of nephropathy progression

George L. Bakris, Matthew R. Weir, Michelle Secic, Brett Campbell, and Annette Weis-McNulty

Current Strategies to Limit Renal Injury in Diabetes

- Blood pressure reduction
- Blood sugar control
- Inhibition of the renin-angiotensin-aldosterone axis
- Newer Agents
- Non-specific reduction of proteinuria
T1DM: Diabetes Control and Complications Trial (n=1441, FU 6.5yrs)

Prevention of Microalbuminuria

RR: -39%

Prevention of Macroalbuminuria

RR: -54%

Epidemiology of Diabetes Interventions and Complications (EDIC) study. (DCCT follow up) \textbf{HbA1c}
EDIC study: **Microalbuminuria**

![Graphs showing annual prevalence and cumulative incidence of microalbuminuria in the EDIC study comparing intensive and conventional treatments. The graph indicates a significant difference with a Log-Rank P < 0.001.](graph)

EDIC study: **Overt Nephropathy**

**Figure A**: Annual Prevalence
- **DCCT Closeout**
- **Years 1-2**: Intensive 2%, Conventional 2%
- **Years 3-4**: Intensive 4%, Conventional 4%
- **Years 5-6**: Intensive 8%, Conventional 8%
- **Years 7-8**: Intensive 11%, Conventional 11%

**Figure B**: Cumulative Incidence
- **Log-Rank P < .001**
- **Conventional**
- **Intensive**
- **No. at Risk**
  - **Conventional**: Years 1-2 653, Years 3-4 643, Years 5-6 615, Years 7-8 607
  - **Intensive**: Years 1-2 666, Years 3-4 661, Years 5-6 660, Years 7-8 658

**84%**
Type 2 DM: UK Prospective Diabetes Study: Main Randomization

5102 patients treated with diet (3 months)

4209 patients (82%)

Metformin
Overweight only
n=342

3867 patients
Nonoverweight and overweight

Conventional policy
n=1138
(30%)

Intensive policy
n=2729
(70%)

Sulfonylureas
n=1573

Insulin
n=1156
UKPDS: HbA$_{1c}$ in Glucose Control Study

Cross-sectional, Median Values

![Graph showing the change in Median HbA$_{1c}$ (%)](image)

- **Conventional**
- **Intensive**

- 6.2% = upper limit of normal range

United Kingdom Prospective Diabetes Study (UKPDS): Results

Glucose Control

-12% (P<.0001)
-10% (P=.34)
-25% (P<.01)

Any diabetes-related endpoint
Diabetes-related death
Microvascular endpoints

UK Prospective Diabetes Study Group 38. BMJ. 1998;317:703-713.
# Aggregate Outcomes for Patients during Follow-up

## Table 2. Aggregate Outcomes for Patients during Follow-up.*

<table>
<thead>
<tr>
<th>Aggregate Outcome</th>
<th>Patients with Clinical Outcome</th>
<th>Absolute Risk†</th>
<th>P Value‡</th>
<th>Risk Ratio for Intensive-Therapy Regimen (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea–insulin group</td>
<td>2729</td>
<td>1138</td>
<td>48.1</td>
<td>52.2</td>
</tr>
<tr>
<td>Any diabetes-related end point</td>
<td>1571</td>
<td>686</td>
<td>14.5</td>
<td>17.0</td>
</tr>
<tr>
<td>Diabetes-related death</td>
<td>618</td>
<td>297</td>
<td>26.8</td>
<td>30.3</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>1162</td>
<td>537</td>
<td>16.8</td>
<td>19.6</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>678</td>
<td>319</td>
<td>6.3</td>
<td>6.9</td>
</tr>
<tr>
<td>Stroke</td>
<td>260</td>
<td>116</td>
<td>2.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>83</td>
<td>40</td>
<td>11.0</td>
<td>14.2</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>429</td>
<td>222</td>
<td>10.0</td>
<td>14.2</td>
</tr>
<tr>
<td>Metformin group</td>
<td>342</td>
<td>411</td>
<td>45.7</td>
<td>53.9</td>
</tr>
<tr>
<td>Any diabetes-related end point</td>
<td>209</td>
<td>262</td>
<td>14.0</td>
<td>18.7</td>
</tr>
<tr>
<td>Diabetes-related death</td>
<td>81</td>
<td>120</td>
<td>25.9</td>
<td>33.1</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>152</td>
<td>217</td>
<td>14.8</td>
<td>21.1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>81</td>
<td>126</td>
<td>6.0</td>
<td>6.8</td>
</tr>
<tr>
<td>Stroke</td>
<td>34</td>
<td>42</td>
<td>2.3</td>
<td>3.4</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>13</td>
<td>21</td>
<td>12.4</td>
<td>13.4</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>66</td>
<td>78</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Shown are the numbers of patients who were followed for up to 30 years, including up to 10 years of post-trial monitoring, with aggregate clinical outcomes after assignment in the interventional phase of the United Kingdom Prospective Diabetes Study to the sulfonylurea–insulin group or the metformin group or to the corresponding conventional-therapy group.

† The absolute risk is the number of events per 1000 patient-years.

‡ P values were calculated with the use of the log-rank test.
Intensive Control: ACCORD ADVANCE studies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ACCORD</th>
<th>ADVANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
<td>10,251</td>
<td>11,140</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>62</td>
<td>66</td>
</tr>
<tr>
<td>Duration of diabetes (yr)*</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Median glycated hemoglobin at baseline (%)</td>
<td>8.1</td>
<td>7.2</td>
</tr>
<tr>
<td>History of macrovascular disease (%)</td>
<td>35</td>
<td>32</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target glycated hemoglobin value (%)</td>
<td>&lt;6.0</td>
<td>≤6.5</td>
</tr>
<tr>
<td>Median duration (yr)</td>
<td>3.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Medical treatment at study completion (intensive vs. standard) (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>77 vs. 55</td>
<td>41 vs. 24</td>
</tr>
<tr>
<td>Metformin</td>
<td>95 vs. 87</td>
<td>74 vs. 67</td>
</tr>
<tr>
<td>Secretagogue (sulfonylurea or glinide)</td>
<td>87 vs. 74</td>
<td>94 vs. 62</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>92 vs. 58</td>
<td>17 vs. 11</td>
</tr>
<tr>
<td>Incretin</td>
<td>18 vs. 5</td>
<td>Not reported</td>
</tr>
<tr>
<td>Statin</td>
<td>88 vs. 88</td>
<td>46 vs. 48</td>
</tr>
<tr>
<td>Any antihypertensive drug</td>
<td>91 vs. 92</td>
<td>89 vs. 88</td>
</tr>
<tr>
<td>Angiotensin-converting–enzyme inhibitor</td>
<td>70 vs. 72</td>
<td>Not reported</td>
</tr>
<tr>
<td>Aspirin</td>
<td>76 vs. 76</td>
<td>57 vs. 55</td>
</tr>
<tr>
<td><strong>Outcome (intensive vs. standard)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median glycated hemoglobin at study end (%)</td>
<td>6.4 vs. 7.5†</td>
<td>6.4 vs. 7.0†</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>From any cause (%)</td>
<td>5.0 vs. 4.0†</td>
<td>8.9 vs. 9.6</td>
</tr>
<tr>
<td>From cardiovascular causes (%)</td>
<td>2.6 vs. 1.8†</td>
<td>4.5 vs. 5.2</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction (%)</td>
<td>3.6 vs. 4.6†</td>
<td>2.7 vs. 2.8</td>
</tr>
<tr>
<td>Nonfatal stroke (%)</td>
<td>1.3 vs. 1.2</td>
<td>3.8 vs. 3.8</td>
</tr>
<tr>
<td>Major hypoglycemia requiring assistance (ACCORD), or severe hypoglycemia (ADVANCE) (%)/yr</td>
<td>3.1 vs. 1.0†</td>
<td>0.7 vs. 0.4</td>
</tr>
<tr>
<td>Weight gain (kg)</td>
<td>3.5 vs. 0.4</td>
<td>0.0 vs. –1.0†</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>10 vs. 10</td>
<td>8 vs. 8</td>
</tr>
</tbody>
</table>

* Duration of diabetes is the median for the ACCORD trial and the mean for the ADVANCE trial.
† The comparison of the intervention with the standard therapy was significant.
Diabetics on Hemodialysis
Comparison of HbA1c and Glycated Albumin

$P<0.0001$

$P=0.19$
Summary: Tight(er) Sugar Control

- **Type 1 and Type 2:**
  - Less microalbuminuria

- **Type 1:**
  - Less overt proteinuria

- **Unclear:** proteinuria->ESRD

- Higher mortality if HbA1c targets too tight (<6.0%)
Current Strategies to Limit Renal Injury in Diabetes

- Blood pressure reduction
- Blood sugar control
- Inhibition of the renin-angiotensin-aldosterone axis
- Metabolic manipulation
- Non-specific reduction of proteinuria
Pathologic Processes Leading to Glomerular Injury and Proteinuria

Glycoxidation (glycation) → AGEs → Increased glomerular pressure

Glucose

Urinary protein

= angiotensin AT₁ receptor

Efferent arteriolar constriction

Ang II

www.hypertensiononline.org
Angiotensin II: Role in Renal Injury

Hyperglycemia 

Angiotensin II 

AT$_1$R, AT$_2$R 

NF-$\kappa$B 

Profibrotic cytokines 

Fibroblasts 

Matrix 

FIBROSIONS 

Fibroblasts 

Proliferation and differentiation 

Tubule cells 

Cellular adhesion molecules 

Inflammation 

TNF-\(\alpha\) 

TNFR1, TNFR2 

Angiotensinogen 

Angiotensin II 

+ 

Angiotensin II: Role in Renal Injury 

Angiotensinogen 

Fibroblasts 

Proliferation and differentiation 

Hyperglycemia 

Angiotensin II 

AT$_1$R, AT$_2$R 

NF-$\kappa$B 

Profibrotic cytokines 

Matrix 

FIBROSIONS 

Fibroblasts 

Proliferation and differentiation 

Hyperglycemia
Clinical Trials: Progression of Diabetic Nephropathy

Surrogate end points

Microalbuminuria
Early stage

Clinical end points

Proteinuria
Late stage

ESRD
End stage

Cardiovascular morbidity and mortality
## Progression of Microalbuminuria to Overt Nephropathy

<table>
<thead>
<tr>
<th>REFERENCE</th>
<th>POPULATION</th>
<th>Drug/Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro-HOPE</td>
<td>3,577 diabetics</td>
<td>Ramipril (Vit E) 4.5 years</td>
</tr>
<tr>
<td>IRMA 2</td>
<td>590 DM-2, HTN Microalbuminuria</td>
<td>Usual AHTN vs Valsartan 2 years</td>
</tr>
<tr>
<td>MARVAL</td>
<td>332 DM-2 Microalbuminuria</td>
<td>Valsartan vs Amlodipine 24 weeks</td>
</tr>
</tbody>
</table>
## Progression of Overt Nephropathy

<table>
<thead>
<tr>
<th>REFERENCE</th>
<th>POPULATION</th>
<th>Drug/Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collaborative Study Grp.</td>
<td>419 DM-1 UVPr&gt; 0.5g</td>
<td><strong>Captopril</strong> 3 years</td>
</tr>
<tr>
<td>IDNT</td>
<td>1715 DM-2 UVPR&gt;0.5g</td>
<td><strong>Irbesartan vs Amlodipine</strong> 2.6 years</td>
</tr>
<tr>
<td>RENAAL</td>
<td>1513 DM-2 UVPr &gt;0.9g, Cr 1-3</td>
<td><strong>Losartan</strong> 3.4 years</td>
</tr>
</tbody>
</table>
Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy

**Doubling of Serum Creatinine**

- Risk Reduction: 25%
- p = 0.006

- P (+ CT): 751
- L (+ CT): 762

**ESRD or Death**

- Risk Reduction: 28%
- p = 0.002

- P (+ CT): 751
- L (+ CT): 762

Brenner et al. NEJM 2001;345 (12): 861
RAAS inhibition, yes it works, but…..

- Can it prevent microalbuminuria?
- Are ACE-i/ARB comparable?
- Is proteinuria reduction dose-related?
- Should one discontinue drugs if the creatinine “bumps”?
- Should sequential therapy be standard of care?
Preventing Microalbuminuria?
The BErgamo NEphrologic Diabetes Complications Trial (BENEDICT)

- 1204 subjects with type 2 DM, HTN and normal urine albumin.

- Treatment with at least three years of
  - Trandolapril 2 mg/d + verapamil (SR180mg/d
  - Trandolapril alone 2 mg/d
  - Verapamil SR 240mg/d alone
  - Placebo

- The target blood pressure=120/80 mm Hg.

- The primary end point: development of persistent microalbuminuria

Trough Systolic and Diastolic Blood Pressure According to Treatment Group

Development of Microalbuminuria

ACE Inhibitors

Non-Dihydropyridine CCB’s

Are ACE-I vs. ARB similar?

Proteinuria Reduction

Losartan (■)
Enalapril (○)

Are ACE-I vs. ARB similar?

GFR Change

Diabetics Exposed to Telmisartan and Enalapril (DETAIL) Study

- 252 Patients with mild-to-moderate hypertension and diabetic nephropathy
- Primary end point: GFR change

Are ACE-I vs. ARB similar?

GFR Change

![Graph showing change in glomerular filtration rate (GFR) over years for Enalapril and Telmisartan.](image)

<table>
<thead>
<tr>
<th>Year</th>
<th>No. at Risk</th>
<th>Enalapril</th>
<th>Telmisartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>103 (0)</td>
<td>110 (22)</td>
<td>113 (23)</td>
</tr>
<tr>
<td>1</td>
<td>110 (22)</td>
<td>113 (23)</td>
<td>113 (40)</td>
</tr>
<tr>
<td>2</td>
<td>113 (23)</td>
<td>113 (40)</td>
<td>113 (39)</td>
</tr>
<tr>
<td>3</td>
<td>113 (23)</td>
<td>113 (40)</td>
<td>113 (39)</td>
</tr>
<tr>
<td>4</td>
<td>113 (40)</td>
<td>113 (39)</td>
<td>113 (39)</td>
</tr>
<tr>
<td>5</td>
<td>113 (39)</td>
<td>113 (39)</td>
<td>113 (39)</td>
</tr>
</tbody>
</table>

Impact of ACE-I on BP and GFR: Does the Acute Drop in GFR Persist?

*B P < 0.05 compared to baseline

Ultra high doses of irbesartan in patients with T2DM+microalbuminuria?
Is sequential blocking of the Renin-Angiotensin-Aldosterone system the standard of care for diabetic nephropathy in 2008?

- YES
- NO
- Not sure
ANGIOTENSINOGEN

- t-PA
- Cathepsin G
- Tonin

Renin

ANGIOTENSIN I

- CAGE
- Cathepsin G
- Chymase

Angiotensin Converting Enzyme

ANGIOTENSIN II

AT₁ Receptor

Aldosterone

RENIN INHIBITORS

ACE INHIBITORS

AII ANTAGONISTS

ALDOSTERONE ANTAGONISTS
Escape of Angiotensin II Despite ACE Inhibition

Despite ACE Inhibition


Plasma ACE (nmoL/mL/min)

Plasma Ang II (pg/mL)

*P < .001 vs placebo

Enalapril 20mg bid
ACE-inhibitors+ ARB
Candesartan + Lisinopril in Microalbuminuria

Change in Urinary Albumin: Creatinine Ratio, %

Candesartan 16 mg
Lisinopril 20 mg
Both

* $P = 0.05$ from baseline.
† $P < 0.001$ from baseline.

Direct Renin Inhibitors
Aliskiren Combined with Losartan in Type 2 Diabetes and Nephropathy (AVOID)

Aldosterone Blockade
Eplerenone + Enalapril

Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial

- Age ≥ 55 years
- Established atherosclerotic vascular disease (or)
- Diabetes with endorgan damage.
- SCr < 265 umol/L

Median F/U 56M

---

### Changes in Log Urine Albumin to Creatinine Ratio

<table>
<thead>
<tr>
<th></th>
<th>Ramipril gMean (95% CI)</th>
<th>Telmisartan gMean (95% CI)</th>
<th>Ramipril+telmisartan gMean (95% CI)</th>
<th>Telmisartan vs ramipril p</th>
<th>Telmisartan+ramipril vs ramipril p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UACR, Baseline</strong></td>
<td>0.81 (0.78–0.84)</td>
<td>0.83 (0.80–0.86)</td>
<td>0.81 (0.78–0.84)</td>
<td>0.246</td>
<td>0.923</td>
</tr>
<tr>
<td><strong>2-year ratio to baseline</strong></td>
<td>1.17 (1.13–1.20)</td>
<td>1.08 (1.05–1.12)</td>
<td>1.05 (1.02–1.08)</td>
<td>0.0013</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Final ratio to baseline</strong></td>
<td>1.32 (1.27–1.37)</td>
<td>1.25 (1.20–1.29)</td>
<td>1.22 (1.17–1.26)</td>
<td>0.033</td>
<td>0.0028</td>
</tr>
<tr>
<td><strong>LO ratio to baseline</strong></td>
<td>1.31 (1.26–1.35)</td>
<td>1.24 (1.20–1.28)</td>
<td>1.21 (1.17–1.25)</td>
<td>0.027</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

UACR = urine albumin to creatinine ratio (mg/mmol); Final = study end. gMean = geometric mean. LO = last observation value; for patients with at least one follow-up value, changes from baseline to last observation were compared between groups. All UACR values were log-transformed before analyses; gMean values are back-transformed. Differences were calculated using an ANCOVA model adjusted for baseline values. Number of participants with measurements = 21,076 at baseline, 19,397 at 2 years, 16,098 at study end.
Decrease in eGFR

### End Points

<table>
<thead>
<tr>
<th></th>
<th>Ramipril n (%)</th>
<th>Telmisartan n (%)</th>
<th>Ramipril+ telmisartan n (%)</th>
<th>Telmisartan vs ramipril HR (95% CI)</th>
<th>p</th>
<th>Ramipril+ telmisartan vs ramipril HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All dialysis, doubling, death</td>
<td>1150 (13.4)</td>
<td>1147 (13.4)</td>
<td>1233 (14.5)</td>
<td>1.00</td>
<td>0.968</td>
<td>1.09</td>
<td>0.037</td>
</tr>
<tr>
<td>All dialysis and doubling</td>
<td>174 (2.03)</td>
<td>189 (2.21)</td>
<td>212 (2.49)</td>
<td>1.09</td>
<td>0.420</td>
<td>1.24</td>
<td>0.038</td>
</tr>
<tr>
<td>All dialysis</td>
<td>48 (0.56)</td>
<td>51 (0.60)</td>
<td>63 (0.74)</td>
<td>1.07</td>
<td>0.747</td>
<td>1.33</td>
<td>0.133</td>
</tr>
<tr>
<td>All death</td>
<td>1014 (11.8)</td>
<td>989 (11.6)</td>
<td>1065 (12.5)</td>
<td>0.98</td>
<td>0.641</td>
<td>1.07</td>
<td>0.144</td>
</tr>
<tr>
<td>Doubling</td>
<td>140 (1.63)</td>
<td>155 (1.81)</td>
<td>166 (1.95)</td>
<td>1.11</td>
<td>0.378</td>
<td>1.20</td>
<td>0.110</td>
</tr>
<tr>
<td>Acute dialysis</td>
<td>13 (0.15)</td>
<td>20 (0.23)</td>
<td>28 (0.33)</td>
<td>1.55</td>
<td>0.221</td>
<td>2.19</td>
<td>0.020</td>
</tr>
<tr>
<td>Chronic dialysis</td>
<td>33 (0.39)</td>
<td>31 (0.36)</td>
<td>34 (0.40)</td>
<td>0.94</td>
<td>0.817</td>
<td>1.05</td>
<td>0.854</td>
</tr>
</tbody>
</table>
## Subgroup Analysis

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Percentage incidence of Primary outcome in ramipril group</th>
<th>Relative risk in ramipril and telmisartan group (95% CI)</th>
<th>p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite</td>
<td>17078</td>
<td>13.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>6900</td>
<td>17.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>10178</td>
<td>11.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overt diabetic nephropathy</td>
<td>474</td>
<td>47.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No overt diabetic nephropathy</td>
<td>16604</td>
<td>12.5</td>
<td></td>
<td>0.188</td>
</tr>
<tr>
<td>No diabetes, no hypertension</td>
<td>3786</td>
<td>9.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes or hypertension</td>
<td>13292</td>
<td>14.7</td>
<td></td>
<td>0.019</td>
</tr>
<tr>
<td>Microalbuminuria or macroalbuminuria</td>
<td>2648</td>
<td>27.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No microalbuminuria or macroalbuminuria</td>
<td>12981</td>
<td>10.5</td>
<td></td>
<td>0.131</td>
</tr>
<tr>
<td>eGFR&lt;60 m²/min/1.73 m²</td>
<td>3988</td>
<td>19.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR≥60 m²/min/1.73 m²</td>
<td>12963</td>
<td>11.4</td>
<td></td>
<td>0.804</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>11745</td>
<td>14.6</td>
<td></td>
<td>0.048</td>
</tr>
<tr>
<td>No history of hypertension</td>
<td>5328</td>
<td>10.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Summary RAAS Inhibition

- Decrease risk of progression from
  - Normoalbuminuria to Microalbuminuria
  - Microalbuminuria to Overt Nephropathy
  - Overt Nephropathy to ESRD
- ACE-I are likely comparable to ARB
- GFR drops by ~10% before plateauing
- Sequential therapy is effective in reducing proteinuria; effects on slowing progression is unknown.
Current Strategies to Limit Renal Injury in Glomerular Disease

- Blood pressure reduction
- Blood sugar control
- Inhibition of the renin-angiotensin-aldosterone axis
- Newer Agents
- Non-specific reduction of proteinuria
Metabolic Derangement

Current Strategies to Limit Renal Injury in Diabetic Nephropathy

- Blood pressure reduction
- Blood sugar control
- Inhibition of the renin-angiotensin-aldosterone axis
- Newer Agents
- Others
  - Diet Modification
  - Non-specific reduction of proteinuria
Dietary protein restriction
End point: ESRD or Death

- 82 Type 1 DM pts with GFR decline 7ml/min/yr
- “Usual” protein vs Low protein 0.6g/kg

RR=23%

Additive effects of Simvastatin beyond its effects on LDL cholesterol in 26 diabetic patients with MA & HTN

(a) LDL-Cholesterol

![Bar chart showing LDL-Cholesterol levels with error bars.](image)

(b) AER

![Bar chart showing AER levels with error bars.](image)

Ongoing Trials

- Anti fibrotic agent
  - Pirfenidone
- Metalloproteinase inhibitor
  - XL784
- PPAR
  - Rosiglitazone
- Receptor-AGE inhibitor
  - TTP488
- Glucosaminoglycan
  - Sulodexide (study stopped 2008 for lack of efficacy)
Steno-2: Multifactorial Intervention in T2DM

Multifactorial Intervention in T2DM

- Death from Cardiovascular Causes
- Nonfatal Myocardial Infarction
- Coronary-Artery Bypass Grafting
- Percutaneous Coronary Intervention
- Nonfatal Stroke
- Amputation, or Surgery for Peripheral Atherosclerotic Artery Disease

Development or Progression of Nephropathy, Retinopathy, and Autonomic and Peripheral Neuropathy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephropathy</td>
<td>0.39 (0.17–0.87)</td>
<td>0.003</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>0.42 (0.21–0.86)</td>
<td>0.02</td>
</tr>
<tr>
<td>Autonomic neuropathy</td>
<td>0.37 (0.18–0.79)</td>
<td>0.002</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>1.09 (0.54–2.22)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Intensive Therapy Better vs. Conventional Therapy Better
13.3 years later…

![Graph showing cumulative incidence of death over years of follow-up for intensive and conventional therapy.](image)

- **No. at Risk**
  - Intensive therapy: 80, 78, 75, 72, 65, 62, 57, 39
  - Conventional therapy: 80, 80, 77, 69, 63, 51, 43, 30

- *P* = 0.02
ORIGINAL INVESTIGATIONS

Pathogenesis and Treatment of Kidney Disease and Hypertension

Awareness of Kidney Disease in the US Population: Findings From the National Health and Nutrition Examination Survey (NHANES) 1999 to 2000

Thomas L. Nickolas, MD, MS, Gershon D. Frisch, MD, Alexander R. Opotowsky, MD, MPH, Raymond Arons, DrPH, MPH, and Jai Radhakrishnan, MD
Awareness/CKD Stage

# The Unaware

<table>
<thead>
<tr>
<th></th>
<th>Aware</th>
<th>Unaware</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>54 y</td>
<td>63 y</td>
<td>0.0002</td>
</tr>
<tr>
<td>Black Race</td>
<td>10%</td>
<td>19%</td>
<td>0.03</td>
</tr>
<tr>
<td>HTN</td>
<td>53%</td>
<td>80%</td>
<td>0.001</td>
</tr>
<tr>
<td>SBP</td>
<td>128</td>
<td>144</td>
<td>0.0001</td>
</tr>
<tr>
<td>DM</td>
<td>22%</td>
<td>70%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA1c</td>
<td>5.8</td>
<td>7.4</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Conclusions

- Diabetes is the commonest cause of ESRD and is associated with significant morbidity and mortality.
- Tight blood sugar and BP control, RAA blockade improve outcome.
- Novel approaches to reduce diabetic kidney damage are being actively investigated.
- A multifactorial approach to risk factor reduction is beneficial.